QUANTITATIVE ACOUSTIC ANALYSIS OF INHALER SOUNDS FOR THE OBJECTIVE ASSESSMENT OF INHALER ADHERENCE IN PATIENTS WITH CHRONIC RESPIRATORY DISEASES

A dissertation submitted to the University of Dublin for the degree of

Doctor of Philosophy

by

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Trinity College Dublin, July 2016

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Martin S. Holmes

20th July 2016
Summary

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most prevalent chronic respiratory disorders. Over 800 million people suffer from these diseases and over four million people die annually. Although both asthma and COPD are incurable, symptoms can be effectively controlled through the delivery of medication to the lungs. Inhaler devices are employed to deliver medication to the airways in the treatment of asthma and COPD. An inhalation step is required to extract the medication from the inhaler and deliver it to the airways. However, despite the proven clinical efficacy of inhaler devices, they can be difficult to operate and adherence levels for inhaler medications are subsequently poor (averaging around 50%). Poor inhaler adherence results in reduced clinical outcomes for patients and large financial costs for healthcare providers. Adherence is a critical aspect of inhaler use that should be continually monitored, however, there is currently a lack of objective methods available for this purpose.

In this thesis, an acoustic based approach was taken to objectively monitor inhaler adherence and respiratory health. An acoustic recording device was recently developed for use with the commonly used Diskus inhaler. This electronic device objectively records the audio signal of inhaler use but the analysis and interpretation of the acquired data remains subjective. In the studies detailed in this thesis, acoustic signal processing methods that can objectively and automatically analyse the audio signals of inhaler use are reported. To detect and analyse the sounds generated during inhaler use, several temporal, Fast Fourier Transform (FFT) and Mel Frequency Cepstral Coefficient (MFCC) derived features were employed. The central aim of this thesis was to investigate if the features employed are both sensitive and specific in detecting and analysing the critical steps related to correct inhaler use, and if so, then can an objective and automatic system be developed to assess inhaler adherence.

The main findings of the studies detailed in this thesis were that temporal and spectral features of inhaler inhalation signals can be used to estimate the peak inspiratory flow rate (PIFR) and inspiratory capacity (IC) in the Diskus inhaler. It was also found that temporal and spectral acoustic features can be employed to estimate the quantity of drug extracted from an inhaler device. Furthermore, it was reported that the relationship between temporal and spectral features and PIFR also exists for the common Turbuhaler and Evohaler inhaler devices, once a critical level of turbulent airflow is reached. These findings imply that analysing inhaler adherence using acoustics may be more suited for inhaler devices with medium-to-high levels of airway resistance. It was also found that temporal/spectral features have a low variability within subjects and that the spectral envelope of inhaler inhalations is repeatable across a range of PIFRs. The
effect of exhaling into a Diskus inhaler was quantified for the first time in a study detailed in this thesis. The exhalation factors that influence inhaler drug delivery were also investigated in detail within this thesis. In addition, temporal and spectral acoustic features were used to detect and analyse this critical error. A series of algorithms were developed to detect inhalation sounds, blister sounds and analyse overall inhaler user technique in a further study detailed in this thesis. It was found that the algorithms developed could perform with a high level of accuracy, in comparison with expert human raters. The system described in this thesis is now subsequently being employed in several multi-site clinical trials, encompassing approximately 600 people.

In conclusion, the original contribution to knowledge in this thesis lies in the translation of the signal processing methods to the field of inhaler acoustics. The systems developed can be employed to analyse patients’ adherence to their inhaler medication. The main findings of this thesis help establish the characteristics of sounds generated during inhaler use and demonstrate the potential of using objective signal processing methods in the analysis of inhaler acoustic recordings. Quantitative data on inhaler adherence and subsequent analysis of respiratory health may assist healthcare professionals in monitoring patients’ inhaler use and aid with the effective treatment of asthma and COPD. Improved inhaler adherence may lead to improved clinical outcomes for patients and financial savings for healthcare providers.

**Keywords:** inhaler devices; medication adherence; acoustics; signal processing; chronic respiratory diseases; algorithm development
Acknowledgements

A great number of people have helped me over the last several years and I would like to take this opportunity to offer my thanks to them.

Firstly, I would like to thank my supervisor, Prof. Richard Reilly, for his continuous support and guidance over the past four years. Your advice and wisdom have been invaluable to me and you are a role model not only for me, but also for all students lucky enough to meet you.

I would like to sincerely thank Prof. Richard Costello, for his helpful advice and for providing a clinical perspective to my work. Your enthusiasm for research is contagious and I have learned many important nuggets of information from spending many enjoyable hours in your company.

I would like to thank everyone in the Trinity Centre for Bioengineering, especially those in the Neural Engineering Group for all their help and guidance. I also wish to thank all those I worked closely with in the INCA research group; Mr. Terence Taylor, Dr. Jansen Seheult, Dr. Shona D’Arcy, Dr. Viliam Rapcan, Mrs. Elaine MacHale, Dr. Imran Sulaiman and Dr. Isabelle Killane.

Lastly, I would like to thank my family and close friends for all their love and support during the last number of years. This thesis would not have been possible without you.
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<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Asthma Control Test</td>
</tr>
<tr>
<td>ANN</td>
<td>Artificial Neural Network</td>
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<tr>
<td>AR</td>
<td>Autoregressive</td>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CFC</td>
<td>Chlorofluorocarbon</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>CORSA</td>
<td>Computerised Respiratory Sound Analysis</td>
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<tr>
<td>CoV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>d</td>
<td>Diameter</td>
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<tr>
<td>DCT</td>
<td>Discrete Cosine Transform</td>
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<tr>
<td>DPI</td>
<td>Dry Powder Inhaler</td>
</tr>
<tr>
<td>DUSA</td>
<td>Dosage Unit Sampling Apparatus</td>
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<tr>
<td>DW</td>
<td>Difference Waveform</td>
</tr>
<tr>
<td>F25</td>
<td>Frequency below which 25% of total spectral power lies</td>
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<td>F99</td>
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</tr>
<tr>
<td>FBE</td>
<td>Filter Bank Energy</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FEF50</td>
<td>Forced Expiratory Flow at 50% vital capacity</td>
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<td>FEV1</td>
<td>Forced Expiratory Volume in 1 Second</td>
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<tr>
<td>FIVC</td>
<td>Forced Inspiratory Vital Capacity</td>
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<tr>
<td>FFT</td>
<td>Fast Fourier Transform</td>
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<td>Fmax</td>
<td>Frequency at maximum power</td>
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<td>Fine Particle Fraction</td>
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<td>Forced Vital Capacity</td>
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<tr>
<td>GLS</td>
<td>Generalised Least Squares</td>
</tr>
<tr>
<td>GMM</td>
<td>Gaussian Mixture Model</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>GSD</td>
<td>Geometric Standard Deviation</td>
</tr>
<tr>
<td>HFA</td>
<td>Hydrofluoroalkane</td>
</tr>
<tr>
<td>HFI</td>
<td>Highest frequency during inspiratory breath phase</td>
</tr>
<tr>
<td>HMM</td>
<td>Hidden Markov Model</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IC</td>
<td>Inspiratory Capacity</td>
</tr>
<tr>
<td>INCA</td>
<td>Inhaler Compliance Assessment Device</td>
</tr>
<tr>
<td>( \kappa )</td>
<td>Cohen's Kappa Score</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of Quantification</td>
</tr>
<tr>
<td>LPC</td>
<td>Linear Predictive Coding</td>
</tr>
<tr>
<td>MA</td>
<td>Median Amplitude</td>
</tr>
<tr>
<td>MAD</td>
<td>Mean Absolute Deviation of amplitude</td>
</tr>
<tr>
<td>MEMS</td>
<td>Microelectromechanical System</td>
</tr>
<tr>
<td>MFCC</td>
<td>Mel Frequency Cepstral Coefficient</td>
</tr>
<tr>
<td>MMAD</td>
<td>Mass Median Aerodynamic Diameter</td>
</tr>
<tr>
<td>NGI</td>
<td>Next Generation Cascade Impactor</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
</tr>
<tr>
<td>NRAD</td>
<td>National Review of Asthma Deaths</td>
</tr>
<tr>
<td>( N_{TP} )</td>
<td>Number of True Positives</td>
</tr>
<tr>
<td>( N_{FP} )</td>
<td>Number of False Positives</td>
</tr>
<tr>
<td>( N_{TN} )</td>
<td>Number of True Negatives</td>
</tr>
<tr>
<td>( N_{FN} )</td>
<td>Number of False Negatives</td>
</tr>
<tr>
<td>( P_{ave} )</td>
<td>Average Power</td>
</tr>
<tr>
<td>PDA</td>
<td>Photodiode Array</td>
</tr>
<tr>
<td>PDF</td>
<td>Probability Density Function</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak Expiratory Flow Rate</td>
</tr>
<tr>
<td>PET</td>
<td>Polyethylene Terephthalate</td>
</tr>
<tr>
<td>PIFR</td>
<td>Peak Inspiratory Flow Rate</td>
</tr>
<tr>
<td>pMDI</td>
<td>Pressurised Metered Dose Inhaler</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>PSD</td>
<td>Power Spectral Density</td>
</tr>
<tr>
<td>( \rho )</td>
<td>Density</td>
</tr>
<tr>
<td>RCSI</td>
<td>The Royal College of Surgeons in Ireland</td>
</tr>
<tr>
<td>RIP</td>
<td>Respiratory Inductance Plethysmography</td>
</tr>
<tr>
<td>RMS</td>
<td>Root Mean Square of amplitude</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>SMI</td>
<td>Soft Mist Inhaler</td>
</tr>
<tr>
<td>STFT</td>
<td>Short Time Fourier Transform</td>
</tr>
<tr>
<td>SVM</td>
<td>Support Vector Machine</td>
</tr>
<tr>
<td>TED</td>
<td>Total Emitted Dose</td>
</tr>
<tr>
<td>( u )</td>
<td>Velocity</td>
</tr>
<tr>
<td>UAD</td>
<td>Upper Airway Dose</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>----------------------------------</td>
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<tr>
<td>( \mu )</td>
<td>Viscosity</td>
</tr>
<tr>
<td>VQ</td>
<td>Vector Quantisation</td>
</tr>
<tr>
<td>WAV</td>
<td>Waveform Audio File Format</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WT</td>
<td>Wavelet Transform</td>
</tr>
<tr>
<td>ZCR</td>
<td>Zero Crossing Rate</td>
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</table>
Publications Arising from this Thesis

Peer Reviewed Journal Papers


Peer Reviewed Conference Papers


Peer Reviewed Conference Abstracts


CHAPTER 1: Introduction

Chronic respiratory diseases affect the airways and other structures of the lungs. The most common types of chronic respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome, pulmonary hypertension and occupational lung diseases. Of these chronic diseases, asthma and COPD are two of the most prevalent and cause the greatest number of deaths (WHO, 2007). Hundreds of millions of people of all ages suffer from preventable chronic respiratory diseases, while four million people die annually from these diseases (WHO, 2007). Chronic respiratory diseases create a major burden on people’s quality of life and cause premature deaths. They generate large economic difficulties for countries due to expenditure on screening, diagnosis and treatment of the diseases. In addition to these financial implications, potential revenue is also lost due to people being unable to work and premature mortality. The prevalence of chronic respiratory diseases has been increasing drastically in recent years and this trend is set to continue into the future (Masoli et al., 2004).

A number of the primary risk factors associated with chronic respiratory diseases have been recognised in recent times and many preventive methods have been suggested. Some of the main factors that lead to the development of chronic respiratory diseases include air pollution, tobacco smoke, allergens and occupational agents (US Department of Health, 2006). Although preventive measures have been put in place to stop the rise in people developing chronic respiratory diseases, many people will inevitably develop such diseases and thus treatment is necessary to control patient symptoms. Inhalers are devices that are used to deliver medication in small doses to the airways in the treatment of chronic respiratory diseases. They are small, portable, hand held devices that store medication securely until the patient decides to take their medication. Two of the most common types of chronic respiratory diseases, asthma and COPD, will now be discussed in detail.

1.1 Asthma

Asthma is a chronic inflammatory respiratory disease that affects the airways making it challenging to breathe. In asthma the small airways of the lungs become narrow, constricted and inflamed which in turn leads to reoccurring periods of wheezing, sputum production, coughing and chest tightness (Cruz, 2007). A deterioration of symptoms can cause an asthma attack, which can be life-threatening if not treated swiftly with the correct medication. The World Health Organisation (WHO) estimate that over 235 million people suffer from asthma worldwide while over 250,000 people die annually from this disease (Cruz, 2007). Ireland has the fourth highest
prevalence of asthma in the world (14.6%), behind the United Kingdom (>15.3%), New Zealand (15.1%) and Australia (14.7%) (Masoli et al., 2004). Asthma is also the number one chronic disease suffered by children. Its pathology and pathogenesis are different from that of COPD (Fabbri et al., 2003).

The causes of asthma are not fully understood. Symptoms of asthma are usually initiated when the airways react to irritating substances, more commonly known as triggers. Some triggers are common to all sufferers of asthma while certain triggers are patient specific. The most common asthma triggers include:

- Tobacco smoke (including second hand smoke)
- Allergens such as pollen, dust mites, mould and pet dander
- Chemical irritants from cleaning products

Other less common asthma triggers include physical exercise, cold air, emotional arousal and certain medications such as aspirin (WHO, 2007; Hamad et al., 2004).

There has been a considerable increase in the prevalence of asthma in developed countries over recent decades, particularly in children. The specific causes of asthma are not known although recent increases in prevalence are believed to be associated with increases in atopic sensitisation, and are paralleled by similar increases in other allergic disorders such as eczema and rhinitis (Beasley, 2004). Genetic factors may also be associated with the development of asthma and it is possible that varying environmental factors exert a strong influence on the development of the disease in susceptible individuals (Ober and Yao, 2011).

There is a large economic burden associated with asthma. In developed countries between 1 to 2% of health care budgets are spent on asthma treatment (Masoli et al., 2004). In Europe, approximately €17.7 billion is spent every year treating asthma (Loddenkemper, 2003). The financial burden on individuals who suffer from asthma ranges from US$300 to US$1300 per annum (Sullivan et al., 1996). Patients with severe asthma account for 50% of all costs associated with the disease, despite the fact that this cohort only make up 10-20% of all sufferers (Beasley, 2002). Until there is a better understanding of the factors that cause asthma it is unlikely that the prevalence and thus economic burden of the disease will decline.

Asthma is a chronic disease for which there is no cure. The aim of asthma treatment is thus to control the disease in order to prevent and relieve symptoms. There are two main types of medication used to treat asthma: long-term control medicines and quick relief medication. Long-term control medications aim to reduce airway inflammation and prevent symptoms from developing. Quick relief medications aim to relieve any exacerbations (flare-ups) of asthma.
symptoms that may develop into an asthma attack. Medications to treat asthma are delivered using inhaler devices and these devices are discussed in more detail later in this Chapter.

1.2 COPD

COPD is a heterogeneous disease that is one of the most common causes of mortality and a major contributor to morbidity (Ställberg et al., 2014). It is the fourth leading cause of death in the world, despite the fact that the disease is preventable and treatable (GOLD, 2015). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) define COPD as a disease which is characterised by persistent airflow limitation, that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (GOLD, 2015). GOLD also state that exacerbations and comorbidities contribute to the overall severity in individual patients (GOLD, 2015). COPD is a treatable and preventable disease; however, its prevalence continues to rise due to the worldwide epidemic of smoking.

Several reports in the literature often emphasise the terms ‘chronic bronchitis’ and ‘emphysema’ in relation to COPD. Chronic bronchitis refers to an inflammation in the bronchial airways that leads to cough and sputum production over an extended period of time. Emphysema refers to a breakdown in the gas exchanging surfaces of the lungs (known as the alveoli), meaning that the volume of oxygen capable of reaching the bloodstream is reduced. It is one of several structural abnormalities that can be present in patients with COPD (GOLD, 2015). Emphysema causes patients to have recurring periods of breathlessness or dyspnoea. Patients frequently describe their dyspnoea as a sense of increased effort to breathe, feeling of heaviness or gasping for air (GOLD, 2015).

COPD develops due to the exposure of susceptible individuals to a variety of inhaled noxious gases and particles. Tobacco smoke is by far the number one risk factor associated with COPD. The intensity and duration of exposure to tobacco smoke are known to correlate with the severity of COPD (Burrows et al., 1977). Not all smokers develop clinically significant COPD, but epidemiological studies show that the majority of smokers will develop airflow limitation if they live long enough and continue to smoke often enough (Pena et al., 2000; Mannino et al., 2002). Other risk factors associated with COPD include air pollution, occupational exposure and genetic factors (Varkey, 2004).

Spirometry is the test of choice carried out on patients to diagnose COPD and measure the degree of airflow limitation. Although spirometric tests only measure a small aspect of the effect that COPD has, they remain the gold standard for diagnosis due to their high reproducibility and availability (Pauwels and Rabe, 2004). In spirometry, Forced Expiratory Volume in 1 second (FEV1)
and Forced Vital Capacity (FVC) are measured, in addition to the ratio of these two measurements (FEV1/FVC). In patients who have airflow limitation caused by COPD, the post-bronchodilator FEV1/FVC fixed ratio will be less than 0.7, while the FEV1 result is employed to classify the severity of COPD a patient has. These values are then compared to baseline values corresponding with the patient’s age, sex, height and race. Spirometry readings are primarily employed to help confirm the presence of airway obstruction and provide an index of COPD severity, while they can also be employed to investigate the response to treatment and monitor disease progression.

COPD creates an extremely large economic and social burden due to its high prevalence and effect on patients’ quality of life. COPD is the fourth leading cause of death worldwide and it is the only worldwide leading cause of death that has an increasing prevalence (GOLD, 2015). This is largely due to the increase in the number of people who smoke in low- to middle-income countries. As a result the global burden of COPD is set to increase substantially in the coming years and lead to more cases of acute exacerbations. Prevalence rates for COPD are estimated to range from 4% to 20% in adults over 40 years of age (Viegi et al., 2000; Halbert et al., 2003), with an obvious increase associated with age and in those who smoke. A few countries have attempted to calculate the economic burden of COPD. Data from the US indicates that COPD costs US$23.9 billion per annum, US$14.7 billion towards direct expenditure on medical care and US$9.2 billion related to indirect morbidity and premature death (Chen and Mannino, 1999). Given that the number of people who suffer from COPD in the US is estimated to be roughly 15 million (Singh et al., 1995), the estimated direct cost of COPD would be around US$1500 per patient per annum. Data from the UK indicates a similar cost of COPD to the economy. The cost of COPD in the UK was estimated to be US$1.4 billion per annum and roughly US$1900 per patient per annum (UK Department of Health, 2010). These estimates on the economic burden of COPD are likely to be underestimates, as the full extent of people who suffer from COPD is not accurately reported, and this does not take account of work hours lost and the cost of family carers.

Many other diseases often coexist in patients who suffer from COPD. Patients who suffer from COPD often suffer from cardiovascular diseases, lung cancer, muscle wasting, osteoporosis and mental health deterioration. Depression, anxiety and malnutrition are also common in elderly COPD patients and these factors not only affect quality of life but adherence to COPD medication (Nazir and Erbland, 2009). Similarly to asthma, a number of medications can be employed to control COPD symptoms. These medications are primarily delivered to the airways with the use of inhaler devices. These medical devices will now be discussed in further detail.
1.3 Inhaler Drug Therapy

Inhaler drug therapy is the cornerstone of pharmacological treatment of asthma and COPD. Delivery of medication via the respiratory tract to the lungs offers advantages over systemic therapy, as there is a more rapid onset of symptom relief, a smaller dose of medication and reduced adverse effects (Dulfano and Glass, 1976). Bronchodilators and corticosteroids are the primary drugs used in inhaler devices. Inhaled bronchodilator and corticosteroid medications aim to reduce airway inflammation and hyper-responsiveness, improve lung function and decrease symptoms (Newman and Busse, 2002). There are numerous inhaler devices available which can be employed to deliver medication to the airways in the treatment of asthma and COPD. There are four main categories of inhaler devices used for pulmonary drug delivery: (1) pressurised metered dose inhaler (pMDI), (2) dry powder inhaler (DPI), (3) soft mist inhaler (SMI) and (4) nebuliser. Of these devices, pMDIs and DPIs are by far the most commonly used devices.

1.3.1 Pressurised Metered Dose Inhalers (pMDIs)

The pMDI (Figure 1.1), developed by 3M Laboratories in 1956, delivers medication using a pressurised aerosol canister. The pMDI is a compact, portable, stand-alone metering system for the inhalation of medication, with good dose consistency (Rau, 2006). The pMDI is the cheapest and most frequently prescribed type of inhaler device worldwide (Beaucage and Nesbitt, 2002). In pMDIs, therapeutically active ingredients are dissolved or suspended in a propellant or mixture of propellants. This formulation is stored inside a pressurised canister and when the pMDI is activated, a valve opens which releases a metered volume of drug and propellant. Traditionally a chlorofluorocarbon (CFC) propellant was used to deliver the medication to the airways in pMDIs, but due to Food and Drug Administration (FDA) guidelines to phase out CFCs in recent years, hydrofluoroalkane (HFA) has since become the main propellant used in pMDIs.

A pMDI typically consists of three main components; the main actuator body, a pressurised canister and a metering valve. To actuate the device, users generally press down on the canister, which subsequently releases the medication through the mouthpiece and into the user’s mouth and airways. When medication is inhaled from the pMDI, large diameter droplets are deposited in the mouth, pharynx, and larynx, while smaller diameter droplets travel further towards smaller airways (Beaucage and Nesbitt, 2002). Spacer devices are also frequently used in conjunction with pMDIs, to reduce patient coordination issues. Spacer devices capture the aerosol in a reservoir and allow the patient to take more time to inhale the medication. They have been shown to reduce oropharyngeal drug deposition and increase lung deposition (Lavorini and Fontana, 2009; Newman, 1995). PMDs offer a reliable and effective method of delivering inhaled medication
(Beaucage and Nesbitt, 2002), yet, they also have a number of disadvantages in terms of usability. Many patients make errors in their technique when using pMDIs. For many patients, it can be challenging to get the timing of the inhalation and canister actuation correct. This is the main reason why DPIs were invented.

![Image of pMDI device]

Figure 1.1: pMDI used to control asthma and COPD symptoms; (A) external view and (B) internal components, adapted from Asthma.ca (2015).

1.3.2 Dry Powder Inhalers (DPIs)

DPIs, commercially available since 1969, are portable, hand-held, breath actuated devices that deliver medication in powder format to the lungs. DPIs (Figure 1.2) were originally developed to avoid problems patients had in coordinating the actuation of the pMDI canister with their inhalation (Beaucage and Nesbitt, 2002). However, it is only since the Montreal Protocol of 1987, which aimed to phase out the use of CFCs in pMDIs, that the development of DPIs has grown rapidly (Newman, 2014). Although DPIs are not as widely used as pMDIs, their use has increased greatly in the past number of years (Newman, 2014). As DPIs do not require coordination of the actuation with the inhalation, they are considered easier to use in comparison with pMDIs.

During DPI inhalations, medication is extracted, de-agglomerated and pulled into the airways as a result of turbulent airflow. Peak inspiratory flow rate (PIFR) and inspiratory volume (also referred to as inspiratory capacity (IC)) are two patient dependent factors which determine the ease in which drug particles are extracted from the DPI and delivered to the airways. Technical challenges have resulted in a greater variety of DPI designs and functions compared to pMDIs (FDA, 1998). More than 20 DPIs are commercially available, each with their own unique design and features. Each DPI device also has a specific resistance to airflow and this in turn affects the PIFR required for effective de-aggregation of the powder formulation (Newman, 2003). Typically DPIs require a
‘quick’, ‘forceful’ or ‘fast’ inhalation (optimal PIFR of 60 L/min) with rapid acceleration at onset of the inhalation.

As previously mentioned, DPI devices were designed to overcome patient coordination issues associated with pMDIs. However, despite breath-actuation being one of the advantages of DPIs, it is also one of their disadvantages. If patients are unable to reach the PIFR necessary to successfully remove the medication, then the clinical benefit of using the DPI decreases. Poor inhaler user technique impacts adherence to medication and this topic will now be discussed in detail.

![Diskus DPI](image)

*Figure 1.2: The common Diskus DPI which is manufactured by GlaxoSmithKline. (A) Shows the device in its closed position, while (B) shows the DPI in its open position with the mouthpiece exposed.*

### 1.4 Adherence

Adherence is defined as ‘the degree to which patient behaviours coincide with the clinical recommendations of healthcare providers’ (Newman, 2014). In this thesis, adherence refers to the ability of a patient to use their inhaler at the appropriate prescribed time and also with correct technique. There are numerous studies in the literature indicating that patient adherence to prescribed medications is poor. A recent Cochrane review reported that typical adherence rates are about 50% for prescribed medications and studies in the literature corroborate these findings in relation to prescribed inhaler therapy (Haynes et al., 2008). Poor adherence to inhaler medication leads to unfavourable health outcomes in asthma and COPD patients and creates a large financial burden on societies. Poor adherence results in a large proportion of medication being wasted, while those who are non-adherent to their inhaler medication will also create a burden on the healthcare system due to unnecessary emergency room visits and inpatient hospital care.
The economic impact of non-adherence to medication is estimated to cost between US$77 to US$300 billion per year in the US alone, with asthma and COPD positioned as two of the most prevalent chronic diseases (PWC, 2014). A number of countries (mostly European countries) set a national wholesale price for each inhaler, while other countries such as the United States leave prices open to market competition amongst pharmaceutical companies. This leads to large discrepancies in the prices of inhaler devices worldwide. For example, it has been reported that the common Diskus DPI costs US$250 in the United States, but costs just US$36 in France, while another common DPI, the Turbuhaler, can cost US$175 in the United States and US$20 in the UK (Rosenthal, 2013).

As a result of the documented health and financial impacts of poor adherence to inhaler therapy, a number of researchers have attempted to develop methods to monitor and assess inhaler adherence. A number of subjective and objective methods are detailed in the literature, each with their own advantages and disadvantages. Of the existing methods to assess inhaler adherence, it is reported that electronic monitoring methods have the greatest potential and are the closest to a ‘gold standard’ method (Pritchard and Nicholls, 2015).

The National Institute for Health and Care Excellence (NICE) from the UK published guidelines in 2015 that reviewed the clinical and cost-effectiveness of monitoring adherence to asthma treatment with electronic monitoring devices. They concluded that there is currently not enough evidence available to consider the benefits and harms of monitoring adherence to inhaler devices. The NICE guideline group reported that adherence to inhaler medication is an important area of asthma care and should be regularly monitored in all patients (NICE, 2015). They recommended that research into the clinical and cost-effectiveness of electronic inhaler adherence monitoring devices should be made a high priority (NICE, 2015). These findings are in agreement with a National Review of Asthma Deaths (NRAD) report in 2014 by the UK based Royal College of Physicians that recommended that electronic surveillance of inhaler use should be introduced as a matter of urgency (Levy et al., 2014).

Electronic monitoring devices for inhalers may offer a non-invasive “light touch” method of objectively assessing adherence. Recently published guidelines recommend the introduction of electronic inhaler monitoring devices, however, recent reviews in the literature indicate that there are currently only a handful of devices available that have the potential to assess inhaler adherence in an objective manner. Existing electronic monitoring devices for inhalers employ several differing approaches in adherence assessment, while it is unclear if these devices can objectively assess all errors relating to inhaler adherence.
1.5 Research Goal and Collaborations

The principal goal of this thesis was to examine which objective electronic monitoring methods are best suited for analysing inhaler adherence of patients with asthma and COPD. Based on the existing literature, the method with the greatest potential for monitoring inhaler adherence was examined in significant detail. Studies to further improve the objectivity and scientific depth of this method were conducted as part of this thesis.

This research involved a close collaboration with healthcare professionals in The Royal College of Surgeons in Ireland (RCSI), Beaumont Hospital, Dublin, Ireland and with engineers in Vitalograph Ltd., Ennis, Co. Clare, Ireland. This collaboration enabled a number of clinical trials to take place throughout Ireland. Data collected from clinical trials were employed to investigate the characteristics of real world inhaler adherence on a longitudinal basis. Vitalograph Ltd. manufactured electronic inhaler adherence monitoring devices for clinical trials, while healthcare professionals in RCSI and Beaumont Hospital ensured that the clinical trials were performed ethically, correctly and that all electronic data were transferred to a secure database.

1.6 Impact and Originality of Thesis

The scientific impact of this thesis is that it details new methods that may be employed to objectively analyse inhaler adherence on a longitudinal basis in real world environments. Five journal papers have been published in international peer-reviewed journal papers, five ‘four-page’ conference papers and three conference abstracts have been published in international conference proceedings, while three abstracts have been published in national conferences. A patent application on the signal processing methods developed in Chapter 8 is also in review with the US patents office. The economic impact of this research is that the methods developed may be used to help prevent exacerbations, asthma attacks, hospitalisations and mortality. Preventing these events may have an effect not only at a microeconomic level, but have a macroeconomic effect on national finances and the economy. Methods detailed in this thesis may also assist in potentially reducing the quantity of inhaler medication needed by patients, thus leading to a reduced financial cost for payers of inhaler medications. In terms of social impact, the research detailed in this thesis may be used to improve both the health and quality of life of those suffering from asthma and COPD, in addition to their family and friends. Furthermore, it may also impact the ability of those suffering from asthma or COPD to participate in the labour market or in social settings.
The originality of this research lies in its pluridisciplinary perspective, bringing together the fields of respiratory medicine, signal processing, fluid dynamics, experimental design and pharmaceutical science in a translational medicine environment. Methods to automatically and objectively analyse adherence may be useful for healthcare professionals as it may allow them to monitor those at risk of asthma attacks and exacerbations, educate patients on correct inhaler use, plan future patient treatment courses and understand interactions between inhaler use patterns and patient health outcomes. The research detailed in this thesis can be considered novel in a number of ways, as the signal processing methods detailed have not previously been employed to investigate inhaler use.

1.7 Thesis Organisation

This thesis is organised into a series of Chapters. Chapter 2 – Literature Review describes in detail the problems associated with poor adherence to inhaler therapy. It also focuses on the current literature with regards to the acoustic analysis of breath sounds. Chapter 3 – Research Questions introduces the main hypotheses of this thesis and the specific research questions that were addressed. Chapter 4 – General Methods details the methods employed in this research. It describes the acoustic features employed and the main experimental and statistical methods utilised. Chapter 5 focuses on the development of an acoustic method to estimate inhaler PIFR and inspiratory capacity in a number of in vitro and in vivo experiments. Chapter 6 details research that was conducted to investigate the characteristics of inspiratory inhaler sounds. Chapter 7 aims to quantify the effect of exhaling into the mouthpiece of a dry powder inhaler and it also details an acoustic based method that may be employed to detect and quantify this inhaler user technique error. Chapter 8 describes an algorithm that can be employed to objectively assess inhaler user technique. In Chapter 9 – Discussion, the main findings of the research carried out in this thesis are discussed. The studies conducted are discussed in relation to the research questions posed in Chapter 3, while a series of recommendations for future studies are also given.
CHAPTER 2: Literature Review and Current State of the Art Methods

Chapter 1 introduced the topic of adherence to inhaler therapy for patients with chronic respiratory diseases such as asthma and COPD. This Chapter provides a more comprehensive review of adherence in relation to inhaler devices. In addition, current state-of-the-art methods in assessing inhaler adherence are presented and their specific benefits and limitations are discussed. Acoustic monitoring of patient inhaler use is introduced as a new potential method to assess inhaler adherence. Given the prominence of respiratory breath sounds (inhalations/exhalations) in inhaler acoustic signals, studies in the literature that focus on the acoustic characteristics of respiratory breath sounds are thoroughly discussed. Lastly, studies in the literature describing the feature extraction methods and classification techniques employed in the analyses of breath sounds are presented in detail.

2.1 Adherence to Inhaler Therapy

As long as there have been medication regimes, clinicians have been interested in adherence. Adherence is a term used to describe a patient’s active role in his or her own treatment regime and healthcare. Adherence is defined in the literature as ‘the degree to which patient behaviours coincide with the clinical recommendations of healthcare providers’ (Newman, 2014). Poor adherence to prescribed medication is a challenging problem, for inhaler therapy and additionally for oral drug therapy. Despite the effectiveness of inhaled therapies for asthma and COPD treatment, many patients often fail to adhere to prescribed medications. It has been reported that 50% of adults and children using asthma medication fail to take their inhaler medication as directed at some stage (Boulet et al., 2012). This finding is supported by a recent Cochrane review on the subject of medication adherence, where it is reported that typical adherence rates for prescribed medications are about 50% (Haynes et al., 2008).

Adherence rates have a direct effect on the clinical efficacy of medication. Good adherence to inhaler therapy is associated with better disease control and reduced exacerbation rates in asthma and COPD patients (Toy et al., 2011; Stern et al., 2006). However, adherence to inhaler therapy remains a poorly understood subject, with many different definitions and interpretations existing in the literature. For the purpose of clarity in this literature review, we define adherence to inhaler medication as being comprised of two components; timing (temporal adherence) and technique (technique adherence).
• **Temporal Adherence** – The ability of a patient to follow a dosing regimen as set out by a healthcare professional. Poor temporal adherence can refer to failure to collect the inhaler prescription, overuse of the inhaler, or underuse of the inhaler.

• **Technique Adherence** – The ability of a patient to follow a set of instructions required to operate and store the inhaler device effectively. Poor technique adherence can refer to the failure to complete one or more of the steps critical to correct inhaler use.

Non-adherence to inhaler medication can be intentional, unintentional or a combination of both. Intentional non-adherence occurs when a patient elects not to take their inhaler medication. This typically occurs because a patient is worried about adverse side effects, doesn’t like using an inhaler or feels that they don’t need to continue taking inhaler medication (Newman, 2014). Intentional non-adherence will typically result in poor temporal adherence. Unintentional non-adherence can occur if a patient does not fully understand the role a specific medication plays in treating their asthma or COPD. It will also occur if a patient does not fully understand the instructions on how to use their inhaler correctly as communicated by their healthcare professional. Unintentional non-adherence can result in both poor temporal and technique adherence.

### 2.1.1 Factors that Influence Inhaler Adherence

Adherence is a complex concept, influenced by multiple factors that can be grouped as being social related, patient related and treatment related factors (Bourbeau and Bartlett, 2008). Figure 2.1 illustrates the main factors that influence adherence to inhaler medication.
Figure 2.1: Adherence to inhaler therapy is multifactorial and influenced by the treatment method, the patient and by society (Bourbeau and Bartlett, 2008).

Treatment

The appropriate selection of treatment methods can play an important role in ensuring that inhaler adherence levels are high. A number of different inhaler devices exist, with several different drug delivery methods available. Certain treatment methods may be more suited to certain individuals, so great care must be taken in selecting the most appropriate inhaler device for each person. The internal resistance of each inhaler device to airflow should be taken into account when choosing an inhaler, in addition to the ease of physically operating the device. The number of doses required each day and the time of day that doses should be taken are some of the most important factors which influence adherence (WHO, 2003). Polypharmacy (the use of four or more medications) and drug interactions/side effects also have the potential to affect adherence to inhaler therapy (Bourbeau and Bartlett, 2008).

Patient

There are many patient related factors that influence adherence to inhaler therapy. Some of these factors include health beliefs around taking medication, inhaler device preference, age, cognitive ability, eyesight levels, number of comorbidities present, self-efficacy, level of conscientiousness and psychological profile (Price et al., 2013). A patient’s physical condition should also be taken into account in terms of hand strength, dexterity, lung function, and hand-breath coordination. All of these patient related factors can impact both temporal and technique adherence.
Society

Societal factors have a critical role in ensuring that high levels of inhaler adherence are achieved. The relationship of the patient with the healthcare professional is the most important societal factor. It has been reported that adherence to medication increases if the prescribing healthcare professional is a specialist compared with a general practitioner (Lau et al., 1996). The healthcare professional is responsible for establishing a routine of correct inhaler adherence with the patient from initial diagnosis and in maintaining correct adherence practices over time. The healthcare professional must also ensure that correct inhaler device training is provided to the patient, that the patient understands why they are being given a specific drug and how its use will impact their respiratory health (Tashkin, 1995). The support of friends and family of the patient also play a role in ensuring that adherence levels are high (Tashkin, 1995). Access to medication may affect adherence, as those receiving inhalers through free drug schemes may be more likely to have poor adherence in comparison to those self-financing the treatment. This factor may also be confounded by education level and time spent in the company of a healthcare professional.

2.2 Inhaler Temporal Adherence

2.2.1 Problems Associated with Inhaler Temporal Adherence

Poor temporal adherence to inhaler medication encompasses the underuse or overuse of an inhaler device. Failure to renew an inhaler prescription is also a type of temporal non-adherence that will result in missed doses of medication. Temporal adherence can be quantified; one may compare the number of doses taken to the number of doses prescribed or one may calculate the total number of days in which the correct number of doses was taken as a percentage of the overall days (Newman, 2014). A review paper by Cochrane in 2000 examined studies in which temporal adherence rates to inhaler medication were measured objectively. It was reported that inhaler underuse ranged from 24 – 69 %, while inhaler overuse occurred on 2 – 23 % of the days (see Figure 2.2) depending on the study (Cochrane et al., 2000). This indicates that poor inhaler temporal adherence is a common problem, with inhaler underuse being more prevalent in comparison to overuse. A number of other studies also corroborate these findings (Burnier, 2000; Paes et al., 1997).
2.2.2 Consequences of Poor Temporal Adherence

Adherence is directly related to patient health outcomes. Poor temporal adherence to inhaler medication can result in minor symptoms of asthma and COPD developing, such as wheezing and coughing, and lead to the development of major disease symptoms such as asthma attacks, exacerbations, increased morbidity and premature death (Rau, 2005; Rubin, 2004; Everard et al., 2012). Poor temporal adherence concurrently leads to a reduction in quality of life and an increased use of healthcare resources (Pritchard and Nicholls, 2015). A study by Gamble et al. (2009) found that asthmatic patients with poor inhaler temporal adherence were more likely to have a higher frequency of exacerbations and hospital admissions, be prescribed higher doses of corticosteroids, use bronchodilator reliever medication more frequently, and have lower quality of life scores (Gamble et al., 2009). They also reported that mortality rates were twice as high for non-adherent study participants in comparison to participants with good adherence rates (Gamble et al., 2009).

Poor adherence to inhaler therapy creates a large financial impact on society, since it results in increased hospitalisations and emergency room visits (Melani et al., 2011). The economic impact of non-adherence to medication is estimated to cost between US$77 to US$300 billion per year in the US alone, with asthma and COPD positioned as two of the most prevalent chronic diseases (PWC, 2014).
2.2.3 Current Methods of Monitoring Inhaler Temporal Adherence

As previously reported in the literature, temporal adherence to inhaler medication is poor, many researchers have attempted to monitor this using a variety of methods. Methods of monitoring temporal adherence to inhaler medication can be divided into subjective and objective methods.

Subjective Methods

The most commonly employed methods of monitoring inhaler temporal adherence are subjective based methods. Subjective methods of monitoring inhaler temporal adherence include patient self-reported diaries or evaluation of dose counter inhalers by a healthcare professional. Major problems exist however with these subjective methods, with many patients unwilling to report and admit to poor temporal adherence (Pritchard and Nicholls, 2015). Healthcare professionals can also make errors in assessing adherence and tend to overestimate patients temporal adherence to their inhaler medication, in addition to being susceptible to patient bias.

Objective Methods

A number of objective methods exist which can be employed to monitor inhaler temporal adherence. For pMDIs the canister can be weighed using a digital weighing scale. The aim is to establish how many doses have been taken between two intervals in time. Canister weighing is a simple but costly method that requires skilled professionals to operate the scales. However, this method of monitoring pMDI adherence cannot account for dose dumping or dose sharing (Pritchard and Nicholls, 2015). Dose dumping refers to when patients ‘dump’ their medication in one sitting, while dose sharing refers to when two or more patients share their inhaler medication.

Biochemical monitoring is an alternative method of objectively monitoring inhaler temporal adherence. This method involves monitoring samples of blood, urine or other bodily fluids to measure drug levels. However, it is a very invasive and costly method, and depending on the frequency of monitoring, it may not give an accurate representation of inhaler adherence (Pritchard and Nicholls, 2015).

Dispensed medication can be registered in a pharmacy in order to objectively monitor inhaler temporal adherence. Data recorded can include the dates the medication was dispensed, the dosing schedule and the date in which the inhaler should be replaced. Despite this method being relatively simple and low cost, there is no objective method to detect if the patient is dose dumping or sharing their medication with others (Howard et al., 2014).
Electronic monitoring devices have been reported to offer a ‘gold standard’ method of objectively monitoring inhaler use (Pritchard and Nicholls, 2015). These devices can be used to record and store the exact time and date of inhaler use. The use of electronic monitoring devices to assess temporal adherence can provide detailed data about the patterns of inhaler use. In a phenomenon known as “white-coat adherence”, patients commonly improve their medication taking behaviour in the five days before and after an appointment with a healthcare professional, as compared with 30 days after (Feinstein, 1990; Cramer et al., 1990). In spite of the benefits gained from using electronic monitoring devices to monitor inhaler temporal adherence, they also have a number of shortcomings. They cannot detect dose sharing (i.e. multiple patients sharing the same inhaler), while errors in inhaler user technique, critical for airway drug delivery, are not detected. Despite being somewhat objective, they are not a comprehensive ‘gold standard’ method, as has been claimed in the literature by Pritchard and Nicholls (2015), Howard et al. (2014) and Butz et al. (2005).

Examples of electronic temporal adherence monitoring devices include the Doser [Meditrack Inc., MA/NewMed Corp., USA] and the Diskus Adherence Logger [GlaxoSmithKline, UK]. The Smartinhaler, SmartTrack and SmartTouch AV [Nexus 6, New Zealand] were created to provide audiovisual feedback based on pMDI temporal adherence. Propeller [Propeller Health, USA] records the time and date of inhaler use, in addition to the location the inhaler was used through GPS technology. The adHaler [Evalan, Netherlands] is an adherence monitoring device for pMDIs that can wirelessly transfer data for analysis. However, despite the ability of the aforementioned temporal adherence monitors to detect certain aspects of inhaler use, they all lack the capabilities to fully monitor technique adherence and thus drug deposition in the airways. Inhaler user technique adherence will now be discussed in significant detail.

### 2.3 Inhaler User Technique Adherence

As previously discussed, correct inhaler user technique is critical for the delivery of medication from inhaler devices. A number of steps are required to transport the medication from the inhaler device to the patient’s airways. If one or more of these steps are carried out incorrectly, a patient will have used the inhaler with poor inhaler technique adherence.

#### 2.3.1 Problems Associated with Inhaler User Technique Adherence

Correct inhaler user technique is critical for disease control in asthma and COPD. Using an inhaler with correct technique involves following a predefined set of instructions. Healthcare professionals and patients need to be educated and trained, in order to acquire the skills
necessary to use inhaler devices (Hanania et al., 1994; Duerden and Price, 2001). However, inhalers are complicated devices to use and often require up to eight steps for correct operation (van Beerendonk et al., 1998). Several studies have reported that large numbers of patients are using inhalers with incorrect technique (Melani et al., 2011; van der Palen et al., 1994; Molimard et al., 2003). The percentage of patients using inhalers incorrectly varies, depending on the type of inhaler employed and technique assessment method. In an observational study of 3811 asthma and COPD patients, Molimard et al. (2003) reported that 49% of patients used the Diskus inhaler incorrectly and that 54% used the Turbuhaler incorrectly (Molimard et al., 2003). Undoubtedly many inhaler users are operating their inhalers with poor technique and this poor technique adherence is resulting in a number of adverse outcomes.

Melani et al. (2011) carried out a large study that investigated inhaler technique in a cohort of 1664 adult subjects (mean age 62 years). A total of 843 study participants were using a pMDI, while 1113 participants were using a DPI, which can be broken further into 82 using the Aerolizer, 467 using the Diskus, 505 using the HandiHaler and 361 using the Turbuhaler. The 1664 participants provided 2288 records of inhaler user technique. It was reported that critical errors ranged from 12% for the pMDI, 35% for both the Diskus and HandiHaler and 44% for the Turbuhaler (Melani et al., 2011). It was reported that older age (p = 0.008), lower schooling (p = 0.001) and a lack of instruction from healthcare professionals (p < 0.001), were the main factors that influenced poor inhaler technique adherence, independently of the inhaler device (Melani et al., 2011).

Table 2.1 details the steps required to use a pMDI with correct technique. It also displays the errors in pMDI technique that can be made, in addition to the percentage of participants who made these technique errors in Melani’s observational study (Melani et al., 2011).
Table 2.1: Step-by-step checklist of pMDI technique, most common patient errors and the percentage of technique errors recorded by Melani et al. (2011).

<table>
<thead>
<tr>
<th>Correct Inhaler Technique Step</th>
<th>Error in Inhaler Technique</th>
<th>Errors (% of users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remove mouthpiece cap</td>
<td>Failure to remove cap</td>
<td>0.15</td>
</tr>
<tr>
<td>Shake inhaler</td>
<td>Not shaking inhaler</td>
<td>37</td>
</tr>
<tr>
<td>Exhale before actuating</td>
<td>No exhalation before actuation</td>
<td>50</td>
</tr>
<tr>
<td>Position inhaler upright when</td>
<td>Inhaler not upright</td>
<td>9</td>
</tr>
<tr>
<td>actuating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One actuation for one inhalation</td>
<td>Multiple actuations</td>
<td>19</td>
</tr>
<tr>
<td>Place mouthpiece between lips and over tongue</td>
<td>Mouthpiece placed against lips, teeth or tongue</td>
<td>0.7</td>
</tr>
<tr>
<td>Actuation in the first half of the inhalation</td>
<td>Actuation before, during second half or after inhalation</td>
<td>23</td>
</tr>
<tr>
<td>Actuate while inhaling deeply and slowly to total inspiratory capacity</td>
<td>Inhaling too forcefully</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Stopping inhalation immediately after actuation</td>
<td>10</td>
</tr>
<tr>
<td>Inhalation through mouth only</td>
<td>Inhaling through nose</td>
<td>2</td>
</tr>
<tr>
<td>Hold breath for 10 s</td>
<td>No/Short breath hold</td>
<td>53</td>
</tr>
</tbody>
</table>

Table 2.2 details the steps required to use three common DPIs with correct technique. It also displays the errors in DPI technique that can be made, in addition to the percentage of participants who made these technique errors in some of the most commonly used DPIs in Melani’s observational study (Melani et al., 2011).
Table 2.2: Step-by-step checklist of inhaler technique for three commonly used DPIs, most common patient technique errors and the percentage of technique errors recorded by Melani et al. (2011).

<table>
<thead>
<tr>
<th>Correct Technique Steps</th>
<th>Technique Errors</th>
<th>Errors (% of Diskus users)</th>
<th>Errors (% of Turbuhaler users)</th>
<th>Errors (% of HandiHaler/Aerolizer users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remove or turn cover</td>
<td>Failure to open correctly</td>
<td>0.65</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insert drug capsule</td>
<td>Capsule not inserted</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>Pierce drug capsule</td>
<td>Failure to pierce capsule</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>Load dose</td>
<td>Dose not loaded correctly</td>
<td>7.3</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>Keep inhaler upright</td>
<td>Inhaler not kept upright</td>
<td>NA</td>
<td>23</td>
<td>NA</td>
</tr>
<tr>
<td>Exhale away from mouthpiece</td>
<td>Exhaling into mouthpiece</td>
<td>22</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Inhale deeply and quickly</td>
<td>Inhalation is too slow and not forceful</td>
<td>28</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Stopping inhalation prematurely</td>
<td>29</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Inhale using mouth</td>
<td>Inhalation through nose</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Place mouthpiece between lips and above tongue</td>
<td>Inhaler pressed against lips, teeth or tongue</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Breath hold</td>
<td>No breath hold after inhalation</td>
<td>32</td>
<td>28</td>
<td>25</td>
</tr>
</tbody>
</table>

2.3.2 Consequences of Poor Inhaler User Technique Adherence

Poor inhaler user technique adherence leads to highly variable lung dose in clinical practice, loss of drug efficacy and wastage of economic resources (Newman, 2014). Melani et al. (2011) found that poor adherence to inhaler technique resulted in an increased risk of hospitalisation (p = 0.001), emergency room visits (p < 0.001), courses of oral steroids (p < 0.001), antimicrobials (p < 0.001) and poor disease control evaluated using an Asthma Control Test (ACT) questionnaire based score (p < 0.0001) (Melani et al., 2011). Another study found that 25% of all expenditure on inhalers is wasted due to poor inhaler user technique (Fink and Rubin, 2005). Unfortunately, regardless of the type of inhaler employed, both pMDI and DPI inhaler users frequently use their inhaler devices with incorrect technique. A Cochrane review from 2008 also highlighted the prevalence and clinical consequences of poor adherence and the lack of effective interventions (Haynes et al., 2008). The next Section details some of the most frequently employed methods of monitoring inhaler user technique adherence.
2.3.3 Current Methods of Monitoring Inhaler User Technique Adherence

Similarly to inhaler temporal adherence, technique adherence can be monitored using both subjective and objective methods.

Subjective Methods

The most common method of assessing inhaler user technique is the checklist method. The checklist approach involves a healthcare professional assessing a patient’s inhaler technique based on an inhaler device specific checklist of steps. Healthcare professionals observe patient inhaler use and score inhaler technique based on correct or incorrect performed steps. Basheti et al. (2014) states that the checklist method is the most feasible and accessible method of monitoring inhaler user technique, while other studies have reported that inhaler technique checklists lead to significant improvements in clinical outcomes (Basheti et al., 2014; Basheti et al., 2008; Giraud et al., 2011).

Despite the ease in which inhaler user technique can be evaluated using a checklist, there are many disadvantages associated with this method. The checklist method is susceptible to subjectivity on the part of the healthcare professional. Inhaler checklist evaluations are also primarily performed in a clinical environment and therefore results give no indication of how patients may use their inhaler in their regular home environment. In addition to this, there is a significant Hawthorne effect associated with the inhaler checklist method as patients may improve or alter their technique once they know they are being observed (McCarney et al., 2007).

There is no defined standard for inhaler user technique evaluation using the checklist method. Basheti et al. (2014) report that there are 24 different checklists for the Turbuhaler DPI and 16 different checklists for the Diskus DPI, and that a substantial variation exists in the number of steps listed between checklists (Basheti et al., 2014). It is not clear whether language differences affect checklist evaluation. In translating checklists from one language to another, certain critical words maybe lost or have different meanings. It was also reported by Basheti et al. (2014) that a number of checklists identify a subset of steps as being ‘essential’ or ‘critical’ for the successful delivery of drug to the lungs (Basheti et al., 2014). These findings indicate that the use of the checklist method for monitoring inhaler user technique adherence has a large number of shortcomings. It is for these reasons that researchers have attempted to develop objective methods for monitoring inhaler user technique adherence.

Objective Methods

As previously discussed, there are a number of objective methods that exist to analyse inhaler temporal adherence in both pMDIs and DPIs. Several methods are also detailed in the literature
that attempt to objectively evaluate inhaler user technique adherence. Some methods claim to objectively analyse overall inhaler user technique, while others primarily focus on inhaler inspiratory technique in DPIs, as this is the most crucial step for successful drug delivery.

**Inspiratory Technique in DPIs**

A number of devices have been developed to assess patient inspiratory technique in DPIs. As was previously reported in Table 2.2, incorrect inhalation technique in DPIs is one of the most common errors. DPIs are breath-actuated devices that are dependent on a deep and powerful inspiratory effort to work correctly. During inhalation the PIFR must be large enough (>30 L/min) to de-aggregate the medication from the mouthpiece and transfer it to the airways for deposition. PIFR is dependent on patient effort and also on the internal resistance of the specific DPI to airflow. It has been shown that low PIFRs (<30 L/min) are associated with low levels of airway drug deposition (Vidgren et al., 1988). Patients unable to reach optimal PIFRs (approximately 60 L/min) in DPIs often include children, elderly adults and those with severe airflow obstruction (Newman and Busse, 2002). The size of the drug particles generated during inhalation also influences pulmonary drug deposition, as smaller drug particles, generated as a result of deep and powerful inhalations, can travel further along the respiratory tract to the smaller airways (Lavorini et al., 2008).

Several training devices have been developed as educational aids to train patients to use their inhaler with correct inhalational technique. However, the literature would suggest that these training devices are rarely used outside clinical environments. Some of these training devices are as follows:

The **Mag-Flo** [Fyne Dynamics Ltd., UK] is an inhaler training device that employs a magnetic flow sensor to monitor inhalation technique. It can be attached to a variety of DPIs such as the Diskus, Turbuhaler, Handihaler and Novolizer. In the Mag-Flo, a magnetic field is generated over a cross-section of the inhaler airflow path, from where electrodes record voltage changes during inhaler use. Changes in voltage are directly related to velocity and subsequently to PIFR. Once an adequate PIFR is reached, the electronic device switches on a battery powered green LED light that signifies correct use. This provides real time visual feedback to inhaler users on their inhalation technique.

The **In-Check Dial** [Clement Clarke International Ltd., UK] is a training device that can be employed to teach patients how to inhale effectively. It is a hand-held inspiratory flow measurement device that can simulate the airflow resistance of several popular inhaler devices (Chrystyn, 2003).
The **Turbutest** is an inhaler training device designed specifically for the Turbuhaler DPI. It comprises of a replica Turbuhaler that is connected to an electronic sensor that measures PIFR. The Turbutest uses LED lights to provide visual feedback to patients regarding their PIFR.

The **Aerosol Inhalation Monitor (AIM)** [Vitalograph Ltd., UK] is an electronic device that can be employed to measure PIFR in a variety of placebo DPIs and pMDIs. Visual feedback is provided to patients based on their inhalation technique. The AIM device can be used to train patients on correct inhaler use in a clinical setting.

**Inhalation Manager** is a computer based system that monitors inhalation technique using placebo DPI devices connected to a pneumotachograph. PIFR can be objectively measured using the Inhalation Manager system, in addition to estimated airway drug deposition rates.

Although training can improve the technique of inhaler users, it has been reported that many patients revert back to incorrect inhalation technique within a short period (Crompton et al., 2006; Price and Duerden, 2002). Thus, there is a clear clinical need for longitudinal inhalation technique monitors as none of the aforementioned methods are employed to assess inhalation technique outside clinical environments and over time.

**Overall Inhaler User Technique**

Correct inhaler user technique is critical for the successful delivery of inhaler medication in the treatment of asthma and COPD. There are a limited number of methods available to assess overall inhaler user technique adherence.

**MDILOG**

The MDILog [Westmed Technologies Inc., USA] is a device that can be attached to the casing of a pMDI. It records pMDI actuations through a mechanical beam with a strain gauge. A magnet is used to detect shaking of the pMDI and a heated thermistor is used to detect inhalations (FDA, 1997). It can also monitor the timing of the pMDI actuation in relation to the inhalation. It can record the time and date of pMDI use and wirelessly transmit data to a computer. One of the disadvantages of this device is that it does not provide any feedback on patient inspiratory flow rate, which is a critical factor in successful pMDI drug delivery (Howard et al., 2014).

**SmartMist**

The SmartMist device [Aradigm Corporation, USA] was designed for use with pMDIs only. Actuations in the pMDI are automatically triggered through a plunger once a specific inspiratory flow rate (25 – 60 L/min) and volume (250 – 500 mL) have been reached (Julius et al., 2002). The
SmartMist then records the date and time of actuation in addition to the inspiratory flow rate during use (Julius et al., 2002). It can provide instant feedback to the patient on inhalational technique, indicating if the inhalation was too slow, too fast or correct (Julius et al., 2002). However, according to Pritchard and Nicholls (2015), the SmartMist device was discontinued after the manufacturers decided to focus their attention on the development of a monitoring device for inhaled insulin.

**INCA**

The Inhaler Compliance Assessment (INCA) device [Vitalograph Ltd., UK] was developed to monitor temporal and technique adherence in the Diskus DPI. It employs a miniature microelectromechanical systems (MEMS) sensor to record the acoustic signal associated with Diskus inhaler use. Up to one month of inhaler use audio data can be stored on the devices internal memory and the audio data can be transferred to a computer for analysis via a USB connection. Each time the Diskus DPI is opened the INCA device starts recording audio and saves the audio file with the date and time that the device was operated. This allows a patients temporal adherence to be monitored. Subsequent visual and aural inspection of the audio files allows inhaler user technique adherence to be evaluated. However, one of the current disadvantages of this method is that the manual assessment of the audio files requires a skilled healthcare professional to spend a significant amount of time assessing the audio files. It can take an experienced respiratory clinician 30 minutes on average to analyse recorded audio files from one month of Diskus DPI use from one patient (30 seconds per audio file X 60 audio files per month = 30 minutes). This is a tedious and time-consuming process and the possibility to make errors in classifying inhaler user technique is high. Analyses of patient inhaler technique may also be biased by the subjectivity of the clinician, thus affecting the overall objectivity of the method.

Evidence in the literature suggests that there is currently no effective objective method to monitor overall inhaler user technique. The MDILOG device does not monitor PIFR, which is a crucial component in successful inhaler user technique. The SmartMist device has been discontinued and the INCA device does not currently assess PIFR, while it also lacks complete objectivity and practicality due to the manual over reading process required.

### 2.4 Adherence to Inhaler Therapy: Summary

Inhaler devices are crucial for delivering medication to the airways in the treatment of asthma and COPD. The existing literature suggests that adherence to inhaler medication is quite poor, with many patients failing to take their medication as directed. The consequences of this problem are very substantial, and create a large economic burden on society. Additionally, asthma and
COPD sufferers will continue to have poor health outcomes due to poor adherence to their inhaler medication.

Several subjective and objective methods exist to evaluate temporal and technique adherence. Subjective methods are substantially cheaper to implement in comparison to objective methods, but they are inherently biased and lack the ability to monitor certain critical steps for correct inhaler use, such as PIFR estimation during inhaler use. Of the several methods available for objectively assessing inhaler adherence, it would appear that electronic monitoring methods have the greatest potential. Some disagree with this hypothesis and argue that electronic monitoring methods are expensive and challenging to implement but several others argue that the benefits far outweigh the challenges (Basheti et al., 2014). As previously discussed, the economic costs associated with poor adherence are substantial. The costs of implementing and maintaining an electronic adherence monitoring system could potentially be significantly smaller in comparison to the current expenditure on inhaler drug therapy. This is in addition to the potential clinical benefit to the patient.

An ideal electronic adherence-monitoring device should be capable of monitoring both inhaler temporal and technique adherence with complete objectivity. Unfortunately, the majority of the existing electronic adherence-monitoring devices are not capable of doing this. The INCA electronic monitoring device, with its acoustic sensor, may offer the best method of objectively monitoring inhaler adherence. The INCA electronic monitoring device is attached to the side of the Diskus inhaler, from where it can record the audio signals of inhaler use. Its location on the inhaler does not obstruct or impede the mechanics of inhaler use. The location of the MEMS microphone in relation to the inhaler mouthpiece is shown in Figure 2.3.

Although the INCA device has an objective acoustic data acquisition system, the analysis and interpretation of the data collected is currently subjective and extremely time consuming. Additionally, the INCA device gives no objective information on the PIFR through the inhaler. Acoustic signal processing methods may be capable of objectively analysing and interpreting acoustic data collected from the INCA device. At present, acoustic signal processing methods are primarily employed to analyse normal and abnormal breath sounds, cough sounds, snore sounds and speech sounds amongst others.
A large component of the sounds recorded during inhaler use are breath sounds; both inspiratory and expiratory. It is important to note that these inhaler-based breathing sounds differ to those generated during normal breathing. However, given that there are no studies detailed in the literature which focus on inhaler-based breathing sounds, investigating the characteristics of normal breathing sounds may reveal important information which may be applicable to inhaler-based breathing sounds. The next Section of this literature review will explore the acoustic characteristics of normal breath sounds in further detail.

2.5 Breath Sounds

Breath sounds play an important role in the diagnosis of respiratory diseases and monitoring of respiratory health. Sounds generated during breathing allow healthcare professionals to better understand physiological changes occurring in the lungs. Breath sounds (also referred to in the literature as respiration sounds, respiratory sounds, lung sounds or vesicular sounds) can be defined as those generated during the movement of air in and out of the airways. Normal breath sounds can be defined as the sounds generated during respiration that are free from adventitious (abnormal) components. The stethoscope is the most widely used method of analysing breath sounds. It has contributed to significant advancements in the understanding of breath sounds and how these sounds change during disease (Laennec, 1819). The main advantages of the stethoscope are that it provides the opportunity to listen to breath sounds in a simple and non-invasive manner. However, despite its universal popularity, the stethoscope lacks objectivity.
Auscultation through the stethoscope is inherently limited by inter-listener variability and greatly depends on how the subjective listener interprets abnormal sounds. Another limitation of the stethoscope is low signal intensity due to ambient noises and high frequency attenuation (Gurung et al., 2011). As a result of such limitations, there have been attempts to develop more objective methods of analysing breath sounds. The first electronic systems to record and analyse breath sounds were developed in the 1920s (Cabot and Dodge, 1925). In the past 30 years, advances in digital recording, storage and signal processing have helped improve the objectivity of breath sound analysis studies.

The primary purpose of analysing breath acoustics using signal processing methods is to extract a feature or set of features that can be employed to objectively quantify physiological changes occurring in the lungs. Although the analytical methods of signal processing are developed primarily independent of their application, interpretation of their results in relation to biological data, such as breath sounds, requires a thorough understanding of the physiological system involved (Moussavi, 2006). Therefore, the following Sections discuss how breath sounds are generated in the airways and how such sounds relate to the acoustic features obtained using signal processing methodology.

Another key aspect in the objective analysis of breath sounds is the choice and placement position of acoustic sensor employed to obtain the sounds. In order to have the best opportunity of quantifying physiological changes occurring in the lungs through acoustic features, the most appropriate acoustic sensor must be selected and positioned in an appropriate anatomical site. This topic is discussed in further detail later in this Chapter.

The choice of acoustic features is also of vital importance when analysing breath sounds. Changes in acoustic features during chronic respiratory diseases such as asthma and COPD can provide empirical objective evidence of physiological variations in the lungs, allowing clinicians to monitor disease progression and investigate treatment outcomes. To improve accuracy in analysis, the most appropriate acoustic features must be extracted from the audio data. The acoustic features that can best quantify lung function (i.e. airway obstruction) will also be investigated.

The main aims of Sections 2.5, 2.6 and 2.7 of this Chapter are:

1. To investigate how tracheal and chest wall breath sounds are generated and to investigate what the acoustic characteristics of these respiratory sounds are.
2. To review the acoustic sensors employed to obtain respiratory acoustic measurements.
3. To review the acoustic features that have previously been employed in the literature to objectively quantify physiological changes occurring due to chronic respiratory diseases, primarily in normal breath sounds.

2.5.1 Generation of Breath Sounds

The movement of air in the respiratory airways generates breath sounds. Airflow movement can be described as being either laminar, turbulent, or translational (a mixture of both laminar and turbulent movements).

Laminar Airflow

Laminar flow occurs when a fluid (liquid or gas) flows in smooth parallel layers, with no interference or disruption between the layers (Batchelor, 2000). Laminar flow is associated with low fluid velocities (Batchelor, 2000). A dimensionless quantity, known as the Reynolds number, is employed to describe flow patterns in a fluid. It describes the ratio of inertial forces to the ratio of viscous forces. It can be written as follows for fluid flow through a straight pipe:

$$Reynolds\ Number = \frac{\rho ud}{\mu}$$

Where $\rho$ is the density of the fluid, $u$ is the velocity of the fluid, $d$ is the pipe diameter and $\mu$ represents the viscosity of the fluid. A Reynolds number less than 2000 indicates laminar flow while a Reynolds number greater than 4000 indicates turbulent fluid flow. A Reynolds number between 2000 – 4000 indicates transitional flow, which implies that the flow of the fluid is both laminar and turbulent. Laminar airflow in the lungs is characteristic of small and narrow airways in which the air is travelling at low velocities.

Turbulent Airflow

Turbulent flow occurs when a fluid (liquid or gas) undergoes irregular fluctuations, typically due to the fluid interacting with a structure and as a result the fluids velocity can vary dramatically in magnitude and direction (Batchelor, 2000). Turbulent flow is associated with high fluid velocities and subsequently has a Reynolds number greater than 4000. In the airways, turbulent airflow generally occurs in the larger airways such as the trachea and bronchi. Turbulent airflow in the upper airways is generally associated with noisy breathing (Mangione, 2012). The link between turbulent airflow and noise intensity is well established (Gavriely and Cugell, 1996). Increasing values of airflow velocity will increase the Reynolds number and thus turbulence. Other factors will also contribute to turbulent airflow, such as roughness and length of the channel through which the fluid is flowing (Fuchs et al., 2010). Bifurcation of the large airways in the lungs will also
contribute towards the generation of turbulent airflow, and thus the intensity of sound during breathing.

2.5.2 Normal Tracheal Breath Sounds

Tracheal sounds are a subset of bronchial sounds that attract a lot of interest in the field of respiratory acoustic monitoring. They can easily be recorded and are known to contain important information regarding upper airway obstructions. Tracheal sounds are typically recorded from locations on the suprasternal notch or the lateral neck. Sounds recorded from these locations are considered pure and less filtered, as the quantity of lung tissue that the sounds pass through before reaching an acoustic sensor is small, in comparison with other chest based respiratory sounds (Pasterkamp et al., 1997).

The generation of tracheal breath sounds is related to the flow of turbulent air in the upper airways, including pharynx, glottis and subglottic regions (Pasterkamp et al., 1997). An early study on bronchial sounds reported that they were produced in airways with diameters of 4 mm or larger, and that the glottis also plays a role in generating these sounds (Fahr, 1927). Beck et al. (2005) states that it is vibration of the tracheal wall that is detected when a surface sensor is used. The tracheal wall vibrates due to pressure forces acting on the inside surface. The quantity of tracheal wall motion is determined by the magnitude and frequency content of the pressure force, but also by the mass, elasticity and resistance of the wall (Beck et al., 2005).

![Conducting Passages](image)

**Figure 2.4:** Upper and lower respiratory tract. Tracheal breath sounds are generated in the upper respiratory tract (National Cancer Institute, 2015).

A strong relationship exists between airflow rate and tracheal sound intensity. Many researchers have reported that an increase in inspiratory and expiratory airflow rate is accompanied with a
corresponding increase in tracheal sound intensity (Yadollahi and Moussavi, 2007; Beck et al., 2005; Gavriely and Cugell, 1996). Regression models employing time and frequency based features have been developed to estimate respiratory airflow rates from tracheal breath sounds. An important point to note however, is that although airflow rate will affect sound intensity, Beck et al. (2005) reported that the airflow rate does not affect the pattern and position of resonance peaks in the tracheal spectral curve.

Tracheal sounds cover a broad energy spectrum, starting from below 100 Hz and going up to more than 1,500 Hz in some cases (Pasterkamp et al., 1997). A drop off in power has been reported to occur above 850 Hz (Gavriely et al., 1981). The spectral profile of tracheal sounds has many peaks and troughs, and these have been reported to be related to subject height and gas density (Sanchez and Pasterkamp, 1993; Pasterkamp and Sanchez, 1996). The implications for this are that the peaks and troughs seen in the spectral profile of tracheal breath sounds are dependent on resonances created in the airways. In a study on tracheal breath sounds at standardised airflow rates, it was reported that children, having short tracheal lengths, had significantly louder sounds and higher quartile and spectral edge frequencies in comparison to adults with longer tracheas (Sanchez and Pasterkamp, 1993). These significant differences in loudness and frequency may imply that the length of the trachea is involved in the generation of tracheal sounds.

Tracheal sounds have been studied in great detail in relation to upper airway obstruction. The main hypothesis adopted by researchers is that the narrowing of the upper airways may cause alterations in the acoustic signal and that this may be quantified using acoustic features. Greater sound power at high frequencies is frequently associated with upper airway obstructions (Pasterkamp and Sanchez, 1992). Inversely, it has been reported that a decrease in power in low frequencies may highlight upper airway obstruction (Pasterkamp et al., 1997). Tracheal sound intensity has been related to physiological changes in the trachea, the principal bronchi and their lobar segmental branches. The degree of narrowing in the central bronchi can be closely related to the loudness and pitch of abnormal inspiratory sounds (Forgacs et al., 1971). This has been employed previously to distinguish changes in the spectral profile due to airway obstruction (Malmberg et al., 1995). The clinical implications for this are that acoustics may be employed as a tool to objectively study airway obstruction.

Use of tracheal sounds for clinical applications is dependent on their intra-subject repeatability. Sanchez and Vizcaya (2003) investigated the repeatability of tracheal breath sounds in seven healthy subjects over a period of 30 days. They reported that frequencies below which 25% (F25), 50% (F50), 75% (F75) and also 99% (F99) of the spectral power between 100 and 200 Hz were not
statistically significantly different, and that all these features had variations below 20% (Sanchez and Vizcaya, 2003). This implies that the within subject variation of tracheal sounds are relatively repeatable over time. Sanchez and Vizcaya (2003), however, reported a significant variation between subjects and postulated that such variations could be as a result of gender, height and anatomical characteristics. Mahagnah and Gavriely (1994) reported that within subject tracheal breath sounds were significantly repeatable in a cohort of five healthy adult males. Since the variability of the spectral features during normal breathing has been reported as being low, this would suggest that spectral features may be employed to study changes in breathing during periods of illness, or to monitor patients’ respiratory function longitudinally.

2.5.3 Normal Chest Wall Breath Sounds

Chest wall breath sounds are those that originate in the lungs and are heard through the chest wall. They are soft low frequency murmurs that can be heard as air enters and leaves the airways. Chest wall sounds can be recorded from locations on both the anterior and posterior chest wall. In comparison to tracheal sounds, chest wall sounds have a lower signal-to-noise ratio and are susceptible to heart and muscle sounds. Nonetheless, researchers have investigated the possibility of using chest wall sounds as a diagnostic tool in demarcating normal and abnormal breath sounds.

Inspiratory lung sounds are hypothesised to originate in the lobar and segmental airways, while the expiratory lung sounds are generated in more proximal larger central airway locations (Pasterkamp et al., 1997; Malmberg et al., 1995). Inhalations have been reported as having a higher pitch, longer duration and greater intensity in comparison with exhalations (Gavriely et al., 1995; Pasterkamp et al., 1997). Air turbulence has been frequently postulated as the origin of chest wall sounds, however, turbulence is a density dependent phenomenon and the behaviour of chest wall sounds in response to low density gas is not easily explained. In a study where subjects breathed a low density He-O2 gas, tracheal sound amplitude decreased by 45% whereas sounds recorded on the chest wall were observed to only decrease by 13-16% (Austrheim and Kraman, 1985). Another study also reported that lung sounds decreased 17% below 300 Hz but 40% above 300 Hz when subjects breathed a low density He-O2 gas (Pasterkamp and Sanchez, 1996). This would suggest that lung sounds at higher frequencies are turbulence dependent. However the mechanism that generates lung sounds below 300 Hz is still not fully understood.

Chest wall sound energy peaks below 100 Hz and then drops off significantly between 100-200 Hz (Gavriely et al., 1995). However, it can still be detected at or above 1000 Hz in quiet recording environments (Pasterkamp et al., 1996). Unlike bronchial sounds, chest wall sounds have a relatively flat spectral profile without any discrete peaks (Pasterkamp et al., 1997). Chest wall
sound intensity is dependent on a number of factors such as the individual subject and the location of recording on the chest wall. Similar to tracheal breath sounds, chest wall sounds are also highly dependent and closely correlated with airflow rate (Shykoff et al., 1988; Gavriely et al., 1995; Kraman, 1984).

Normal breath sounds of healthy subjects recorded on the chest wall are known to be quite stable over time. In a study on five healthy males, it was reported that the spectral pattern of lung sounds was significantly stable (Mahagnah and Gavriely, 1994). Another study also reported similar findings, in that the spectral profile lacked variation within and between subjects (Ploysongsang et al., 1991). Sanchez and Vizcaya (2003) recorded the lung sounds of 10 healthy adults. By analysing the F25, F50, F75 and F99 frequency features, it was observed that there were no significant differences between the measurements obtained longitudinally (Sanchez and Vizcaya, 2003).

A number of factors may have the potential to influence chest wall breath sounds. Some of these factors are:

**Body Size**

Pasterkamp et al. (1996) investigated differences in lung sound spectra in 10 new-born infants, nine children between 6 to 8 years old and 10 adults between 25 to 37 years old. They reported that the new-born infants breath sounds contained less power below 300 Hz in comparison with the other two groups. This resulted in statistically significantly higher F25, F50, F75 and F99 values in the infant group (Pasterkamp et al., 1996). However, it is likely that age was also a factor in these differences.

**Sex**

Differences in the frequency spectra of chest wall breath sounds have been observed between healthy adult males and females (Gavriely et al., 1995). It was reported that females had higher maximal frequencies (Fmax) in comparison with males. Inspiratory Fmax values were 12.19 % higher in females in comparison with males (767±246 Hz versus 667±246 Hz, p<0.001) at all chest wall recording locations. Expiratory Fmax values were 32% higher in females only at the right anterior chest in the mid clavicular line in the second intercostal space. The results of this study therefore suggest that healthy females have higher frequencies during breathing in comparison with healthy males. Another separate study also found significant differences in the normal chest wall breath sounds of healthy people, with a larger proportion of higher frequencies observed in females in comparison with males (Gross et al., 2000).
Age

Studies have shown that infants have higher median frequencies (F50) while breathing in comparison with older children and adults (Kanga and Kraman, 1986; Hidalgo et al., 1991). Reasons for this may lie in the fact that infants have a thinner chest wall which may result in less filtering of high frequency lung breath sounds. Smaller sized lungs and narrower airways may also contribute to high frequency components of the acoustic signal, and as previously mentioned, subject height is also a factor. Gross et al. (2000) recorded lung sounds from 162 subjects and computed a ratio (Q) of relative power in two frequency bands, 330 to 600 Hz and 60 to 330 Hz. Using linear regression methods they reported a small but significant correlation ($R^2 = 0.1$, $p < 0.05$) between Q and age. For both men and women, an increase in the relative power was observed with a corresponding increase in age in the 330-600 Hz frequency band (Gross et al., 2000). Importantly however, they concluded that the percentage changes observed in Q (5 %) were too small to be clinically relevant.

The results of the aforementioned studies would indicate that although normal chest wall breath sounds are consistent among individuals, body size, sex and age are important factors that influence the frequency content of the sounds. Such considerations must be taken into account when listening to and analysing breath sounds recorded from the chest wall.

2.5.4 Adventitious Breath Sounds

Adventitious (or abnormal) breath sounds are those that are heard as air enters and leaves the airways that are different to normal breath sounds. Two common examples of adventitious breath sounds include wheezes and crackles. The presence of adventitious breath sounds typically indicates that problems exist in the airways.

Wheeze

Wheezees are continuous musical sounds that are heard during breathing. They are normally longer in duration than 80 to 100 ms, while their frequency range extends from below 100 Hz to more than 1000 Hz (Akasaka et al., 1975). The pathophysiological mechanisms that generate wheezes are not fully understood, with many researchers hypothesising that the movement of airway secretions and the flutter of airway walls generates wheeze sounds (Pasterkamp et al., 1997). Forced expiratory wheezes have been found to be repeatable in normal subjects (Beck and Gavriely, 1990), however the presence of wheezes in normal subjects indicates that forced expiratory wheezes lack specificity and are not useful in the clinical diagnosis of asthma (King et al., 1989; Marini et al., 1979; Schreur et al., 1994).
Spontaneous wheezes are occasionally heard during inspiration in patients with asthma (Shim and Williams, 1983), a phenomenon that cannot be reproduced in healthy subjects. However, the presence of spontaneous wheeze sounds can be unpredictable and they can appear at different stages of disease progression. Nevertheless, wheeze sounds are useful clinical indicators of airway obstruction and as a parameter to gauge the severity of asthma (Pasterkamp et al., 1997).

Crackles

Crackles are discontinuous, non-musical, short duration breath sounds that can be heard during inspiratory or expiratory respiration. Crackles are more predominately heard during inspiration (Forgacs, 1967). Crackle sounds can be divided into fine and coarse categories. Fine crackles are shorter in duration compared with coarse crackles. Many researchers have used the temporal features of the crackle sounds to develop objective methods to distinguish fine crackles from coarse crackles, however, such objective based methods are rarely used in clinical practice.

2.6 Acoustic Sensors Used in Respiratory Sound Acquisition

The selection of acoustic sensors and their placement position are of vital importance in recording breath sounds. There have been two popular choices of commercially available sensors employed in acoustic based studies of chronic respiratory diseases; electret condenser microphones and piezoelectric contact sensors. Given the requirement of non-invasiveness in many studies, non-contact acoustic sensors are often selected to acquire respiratory sounds.

2.6.1 Electret Condenser Microphone

The electret condenser microphone detects acoustic signals from sound waves displacing an electret diaphragm which converts a varying capacitance into an electrical signal (Paajanen, 1996). The sensor is usually mounted in a chamber. Conically shaped chambers are popular and are more sensitive to higher frequencies (Pasterkamp et al., 1997). The electret condenser microphone accompanied with a coupling chamber has been a popular choice of acoustic sensor for chest wall and tracheal sound analysis due to their low weight and sensitivity in several studies (Malmberg et al., 1995; Murphy, 2008; Kraman et al., 2006). Due to their light weight, low cost and practicality, researchers have also previously employed miniature electret sensors in a sensor array placed on the posterior chest wall surface to analyse lung sounds (Murphy, 2008). These acoustic sensors tend to have a flat frequency response within the frequency ranges of chest wall and tracheal sounds. This means that the sensor does not attenuate or amplify specific frequencies. The main disadvantage of electret condenser microphones is that there are additional components required, such as a mounting chamber, which may alter the frequency
characteristics depending on the chamber shape. One must have prior knowledge of the frequency range of interest in order to design the electret sensor set-up efficiently.

2.6.2 Piezoelectric Contact Accelerometer

Piezoelectric contact accelerometers capture surface vibrations and convert them into electrical signals, while they are also insensitive to air vibrations. They are typically mounted on the skin, on the trachea for tracheal sound recordings and on the posterior and/or anterior chest wall surface for chest wall recordings. They are normally attached to the chest wall with rubber belts and/or adhesive rings (Earis and Cheetham, 2000; Paajanen, 1996). Unlike electret condenser microphones piezoelectric sensors generally do not need an air-coupled chamber (Vannuccini et al., 2000). It has been reported that piezoelectric microphones are robust to ambient background noise and also have a high sensitivity in ambient environments (Kraman et al., 1998). Piezoelectric contact accelerometers are sensitive at high frequencies and this makes them an appealing choice of sensor to collect respiratory acoustic data (Sanchez and Vizcaya, 2003; Pasterkamp et al., 1993). However, it has been reported that contact piezoelectric accelerometers tend to be heavy and fragile sensors (Earis and Cheetham, 2000; Vannuccini et al., 2000). They can also resonate at frequencies close to those of lung sounds which may introduce noisy artefacts into respiratory acoustic data (Vannuccini et al., 2000; Pasterkamp et al., 1997).

2.6.3 Non-Contact Acoustic Sensors

From the literature reviewed it appears that electret condenser microphones are the microphones of choice for non-contact based acoustic studies. True condenser cardioid microphones have been widely used to record cough sounds and snore sounds (Abeyratne et al., 2013a; Abeyratne et al., 2013b; Swarnkar et al., 2013). In these studies microphones were placed 50 cm from the patient’s mouth, but this distance varied from 40 – 70 cm due to patient head movement.

Ben-Israel et al. (2012) employed a condenser transducer microphone with a cardioid polar pattern to estimate patient’s obstructive apnea hypopnea index but placed the microphone a distance of 1 m from patients’ heads. This setup was also used by Dafna et al. (2013) to record whole night snore sounds. Lapel microphones have also been used to record cough sounds (Larson et al., 2012; Barry et al., 2006). Despite the success in which non-contact condenser microphones have been used to record cough and snore sounds, the majority of these microphones are too large and invasive to be used to record respiration sounds longitudinally. It is for this reason that smaller non-contact acoustic sensors are required.
Microelectromechanical systems (MEMS) microphone technology is a new category of miniature condenser microphone that may be employed in non-contact acoustic recording environments. MEMS microphones are comprised of a miniature flexible suspended diaphragm that sits above a fixed back plate on a silicon wafer. Compared to electret condenser microphones, MEMS microphones are smaller, more lightweight, have lower power consumption, have excellent stability and have an identical frequency response (Lewis and Moss, 2013). They therefore offer an excellent choice of acoustic sensor if size and non-invasiveness are a priority. The INCA electronic monitoring device previously discussed in this Chapter employs a MEMS microphone to record sounds generated during inhaler use.

2.7 Role of Acoustics in Assessing Patients with Chronic Respiratory Disorders

2.7.1 Role of Acoustics in Assessing Patients with Asthma

Automated respiratory sound analysis approaches have frequently been postulated as methods to objectively diagnose asthma, guide asthma management and make more accurate anatomical diagnoses. Asthma can result in narrowing of the airways and it is this narrowing that may cause variations in time and/or frequency features of respiratory sounds during breathing. In addition to identifying the presence of adventitious respiratory sounds, it has also been hypothesised that asthma can be detected and monitored from normal breath sounds. In the area of normal breath sounds, researchers have typically conducted studies with one or more of the following aims:

(i) To discriminate asthmatic individuals from healthy individuals and those with other variations of chronic respiratory illnesses.
(ii) To estimate the degree of airflow limitation.
(iii) To investigate regional variations caused by asthma.

A study by Malmberg et al. (1995) employed both chest wall and tracheal inspiratory breath sounds to investigate differences between asthma participants (n=10), COPD participants (n=17) and healthy participants (n=11). It was reported that recordings at the chest wall (10 cm below the margin of the scapula and 15 cm to the right of the spine) of individuals with stable asthma had a median frequency (F50) higher to that of the COPD and healthy subjects (p<0.001). The F50 feature from the normal breath sound spectra was 239±19 Hz for asthma subjects, while it was 201±21 Hz for COPD subjects and 206±14 Hz for healthy subjects. They also reported that the root mean square (RMS), employed to analyse intensity of the normal breath sounds recorded at the chest, was higher in stable asthmatics than in subjects with COPD.
Regarding airway obstruction level, Malmberg et al. (1994) observed a significant correlation between F50 and FEV1 from both normal tracheal and chest wall recordings during a histamine challenge test. Twelve asthmatic subjects and six healthy subjects participated in the study. It was reported that the normal tracheal expiratory sounds F50 feature had the best correlation with FEV1 ($r = -0.853$, $p<0.0001$). They also noted that the increase in F50 was significantly larger in asthmatic subjects compared with healthy subjects ($p<0.005$). In a later study Malmberg et al. (1995) again observed that F50 recorded at the trachea on the right side of the cricothyroid cartilage was significantly correlated to the forced FEV1 during normal breathing ($r = -0.77$, $p<0.01$) in asthmatics. However, FEV1 was not significantly correlated with F50 for the chest wall recordings during normal breathing ($r=-0.50$, $p<0.1$) (Malmberg et al., 1995). Several other groups have also reported a relationship between decreasing FEV1 and increasing F50, while it has also been reported that the sound intensity from asthmatic breath sounds correlates with FEV1 (Li and O’Connell, 1996). These findings support the hypothesis that airway obstruction levels may be estimated using the acoustics of normal asthmatic breath sounds from the trachea.

The frequency distribution of tracheal breath sounds has a high inter-subject variation that is dependent on resonant frequencies generated in the trachea. Intra-subject variations of healthy subject’s frequency distribution have been reported to be very repeatable, when recorded from the trachea and chest wall (Sanchez and Vizcaya, 2003). Although normal breath sounds at the chest wall contain lower frequencies in comparison to tracheal breath sounds, an increase in pitch and sound intensity has been observed at these low frequencies in asthmatic lung sounds (Schreur et al., 1995). This suggests that it is possible to record from the chest wall and detect regional ventilation changes, as with the stethoscope, in addition to recording at the trachea.

The baseline spectral profile from asthmatic normal breath sounds may differ from that of healthy breath sounds without airway obstruction occurring (Pasterkamp et al., 1997; Schreur et al., 1995). This is an interesting observation as it highlights how asthma can alter the shape of the airways without completely obstructing the airflow. It has been reported that asthmatic normal breath sounds tend to be higher in intensity due to higher levels of turbulence in the airways. Recently, it was shown that an increase in the highest frequency during the inspiratory phase (HFI), recorded at the right upper anterior chest at the second intercostal space in the mid-clavicular line, correlated with a decrease in forced expiratory flow at 50% vital capacity (FEF50) in 131 asthmatic children ($r=-0.45$, $p<0.001$) (Habukawa et al., 2009). According to Malmberg et al. (1995), the increase in frequency directly relates to an increase of flow velocity through the narrowed bronchi which results in increased kinetic energy and turbulence (Malmberg et al., 1995). This subsequently causes a higher pitched sound to be heard on the trachea and chest wall. The ability to detect changes in acoustic features from asthmatic normal breath sounds
demonstrates the feasibility of using such methods as a tool in objectively diagnosing and monitoring asthma.

Acoustic based methods have previously been employed to detect adventitious respiratory sounds associated with asthma. Wheezes are a common example of an adventitious respiratory sound caused by bronchoconstriction or secretions in the airways. Adventitious breath sounds have distinctive temporal and spectral features, and therefore it has been possible to detect adventitious sounds using time-frequency analysis methods (Taplidou and Hadjileontiadis, 2007). However, adventitious respiratory sounds are not present in each asthmatic subject and they may only be audible at different stages of airway obstruction in different people.

2.7.2 Role of Acoustics in Assessing Patients with COPD

Similarly to asthma, researchers have investigated if there are unique objective acoustic features in COPD normal breath sounds that allow them to be differentiated from other breath sounds. Malmberg et al. (1995) reported that although asthmatic respiratory acoustic features were significantly different from healthy subjects, COPD quartile frequency features (F25, F50 & F75) from chest wall and tracheal recordings were not significantly different from healthy subjects. However, it was found that F50 from the chest wall recordings was significantly lower for COPD subjects in comparison with asthmatic subjects (p<0.0001). A recent study with a large cohort of COPD subjects investigated if COPD could be detected using a multichannel lung sound analyser (Vyshedskiy and Murphy, 2012). They reported that the ratio of inspiratory duration to expiratory duration was lower in COPD patients (n=100) than a cohort of age-matched healthy subjects (n=100). It was also observed that the ratio of low frequency inspiratory energy to high frequency inspiratory energy was greater in COPD subjects than in healthy subjects.

Malmberg et al. (1995) reported that F50 from tracheal and chest wall recordings from COPD patients did not correlate with FEV1, indicating that there is no relationship between airway obstruction levels and normal breath sounds from COPD subjects. One could argue that the insignificant relationship that occurs between COPD and FEV1 is due to the heterogenic nature of COPD. Emphysema and chronic bronchitis often coexist in COPD patients and this may result in a greater variability of F50 values. Airway structural change and the site of disease in the bronchi and lung parenchyma may also differ between COPD and asthma, and this may account for the differences in the acoustic frequency content of breath sounds (Malmberg et al., 1995).

COPD symptoms may alter with time and disease progression, factors which potentially have a direct effect on acoustic features. The noisy breathing of bronchitis patients, uncontaminated by crackles or wheezes, has a wide spectrum of frequencies, with its energy evenly distributed over a
range of 200 to 2,000Hz. Breath sounds at the mouth relate to turbulence in the upper airways, the trachea and the first two or three generations of the bronchi (Forgacs et al., 1971). Therefore an increase in breath sound intensity from chronic bronchitis patients may mirror those from asthmatic patients. This could potentially make it difficult to discriminate COPD from asthma solely based on breath sounds. The F50 feature, calculated from averaged spectra, may not be the answer to aid COPD diagnosis but may however be partnered with adventitious sound detection to collect more information regarding the pathology of an individual’s COPD symptoms.

2.8 Acoustical Respiratory Airflow Estimation

The relationship between respiratory airflow and acoustic features has been of particular interest to acoustic researchers. In clinical settings, respiratory airflow can be measured using spirometry devices, such as a pneumotachograph, nasal cannulas connected to pressure transducers, heated thermistor or anemometry (Yadollahi and Moussavi, 2007). Other indirect methods of measuring airflow rate also exist such as monitoring chest wall movements using respiratory inductance plethysmography (RIP), strange gauges and magnetometers. The most common method of measuring respiratory airflow rate is with the use of a mouthpiece or facemask connected to a pneumotachograph.

Difficulties and inaccuracies in the previously mentioned flow rate measurement techniques have prompted some researchers to estimate flow from respiratory sounds. Acoustic signals are typically recorded on either the chest wall or trachea. Some common features investigated in respiratory flow rate estimation include mean amplitude, average power, mean frequency and the multiplication of mean frequency and mean amplitude. Some studies have suggested that polynomial and power models best describe the relationship between tracheal sound intensity and flow rate (Yadollahi and Moussavi, 2011; Hossain and Moussavi, 2004; Yadollahi et al., 2013; Gavriely and Cugell, 1996), while other studies have suggested that exponential models are more suited for this task (Hossain and Moussavi, 2002). The wide variation in models to describe the relationship between flow rate and acoustic features demonstrates the challenges in using a general flow-sound model in large populations of subjects. Multiple sources contribute to tracheal and chest sound generation during respiration, and results vary significantly between individuals.

Respiratory sounds are stochastic signals and non-stationary in nature. Temporal and spectral signal analysis methods only represent the first- and second order- moments of the signal and thus they do not represent all statistical properties of respiratory sounds. To deal with this fact Yadollahi and Moussavi (2006) reported the use of an entropy measure of tracheal sounds to estimate respiratory flow rate. Entropy is a measure of uncertainty of a signal and it involves
calculating a probability density function (PDF) of a signal. Results from this study indicated that the model created was capable of estimating flow rate with an error of 9%. Previous studies using temporal and spectral analyses methods have found that flow can be estimated with an average error of more than 10% (Soufflet et al., 1990; Golabbakhsh et al., 2005).

With the INCA technology described earlier in this Chapter, there exists an opportunity to use acoustic based flow rate estimation methods to analyse inhaler inhalation technique. A patient’s PIFR through their inhaler device is a vital metric that describes a patient’s ability to use their inhaler and directly relates to drug deposition in the airways.

A review of respiratory flow estimation based studies involving acoustics was conducted in March 2015. A PubMed (US National Library of Medicine, National Institutes of Health), Science Direct and Web of Knowledge search was performed using the search details: “Respiratory Flow Estimation” AND “Acoustic”. Only studies that directly investigated respiratory flow estimation through the use of acoustic parameters were included. Review, validation and conference papers studies were excluded. Results revealed two studies that investigated the relationship between respiratory airflow and acoustic features. The references cited in these two studies were also investigated for details on other studies in the literature. This process revealed a further eight studies. A summary of these studies is displayed in Table 2.3.
Table 2.3 Summary of respiratory flow estimation studies involving acoustic analysis.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Journal</th>
<th>Microphone Details</th>
<th>Acoustic Features</th>
<th>Number Subjects</th>
<th>Findings Reported</th>
<th>Additional Comments</th>
</tr>
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<tbody>
<tr>
<td>(Yadollahi et al., 2013)</td>
<td>Ann Biomed Eng.</td>
<td>Electret tracheal microphone, Fs=16kHz, Bit Depth=16 bits/sample</td>
<td>Sound energy</td>
<td>18 (3 females)</td>
<td>Results show that during wakefulness and sleep, flow–sound relationship follows a power law but with different parameters.</td>
<td>Results show that acoustical respiratory flow estimation parameters change from wakefulness to sleep.</td>
</tr>
<tr>
<td>(Beck et al., 2005)</td>
<td>Ann Biomed Eng.</td>
<td>Piezoelectric contact sensor positioned on trachea, Fs=4.8kHz, Bit Depth = 12 bits/sample</td>
<td>Amplitude and averaged spectra</td>
<td>8 male subjects</td>
<td>Tracheal breath sounds are proportional to airflow (inspiratory and expiratory). Relationship follows a power law model.</td>
<td>Tracheal breath sounds consist primarily of direct turbulent eddy pressure fluctuations that are perceived as sound during auscultation.</td>
</tr>
<tr>
<td>(Huq and Moussavi, 2012)</td>
<td>Med Biol Eng Comput.</td>
<td>Electret tracheal microphone, Fs= 10.24kHz</td>
<td>Duration, volume and shape of sound envelope</td>
<td>93</td>
<td>Reported method showed accuracy of 95.6% with 95.5% sensitivity and 95.6% specificity for breath-phase identification.</td>
<td>Breath phase detection method using tracheal breath sounds only.</td>
</tr>
<tr>
<td>(Yadollahi and Moussavi, 2011)</td>
<td>IEEE Trans Biomed Eng</td>
<td>Electret tracheal microphone, Fs=16kHz, Bit Depth=16 bits/sample</td>
<td>Average Spectral Power</td>
<td>93</td>
<td>Results show that airflow estimation error based on the group-calibrated</td>
<td>Low estimation errors confirm the possibility of defining a general flow estimation</td>
</tr>
<tr>
<td>Year</td>
<td>Journal/Media</td>
<td>Methodology</td>
<td>Model Features</td>
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<tr>
<td>Harper et al., 2003</td>
<td>IEEE Trans Biomed Eng</td>
<td>Piezoelectric contact accelerometer positioned on trachea, Fs=10.24kHz, Average Spectral Power</td>
<td>Relationship exists between tracheal breath sounds average spectral power and airflow rate.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Que et al., 2002</td>
<td>J App Physiol.</td>
<td>Electret microphone positioned on trachea, Fs=3kHz, Bit Depth = 12 bits/sample, Sound Amplitude</td>
<td>Relationship between breath sound amplitude and flow rate. Linear regression model best fits the data.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yadollahi and Moussavi, 2006</td>
<td>IEEE Trans Biomed Eng.</td>
<td>Chest microphone, Fs= 10.24kHz, Entropy</td>
<td>Overall estimation error was found to be 8.3± 2.8% and 9.6±2.8% for inspiration and expiration phases</td>
<td>Novel method for estimating flow using entropy of the band pass filtered tracheal sounds is proposed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gavriely and Cugel, 1996</td>
<td>J App Physiol.</td>
<td>Not given, Average power spectrum</td>
<td>Areas under the spectral curves of the breath sounds found to have power</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Soufflet et al., 1990)</td>
<td>IEEE Trans Biomed Eng</td>
<td>Tracheal Microphone, Fs=5.12kHz</td>
<td>Average power spectrum</td>
<td>9</td>
<td>Reported method capable of estimating airflow with an error of 15%</td>
<td></td>
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<td>------------------------</td>
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<td></td>
<td>Reported relationship existed between sound and airflow and was thus reflected by the variations of certain acoustic parameters</td>
<td></td>
</tr>
<tr>
<td>(Lessard and Wong, 1986)</td>
<td>IEEE Trans Biomed Eng</td>
<td>Electronic stethoscope placed on trachea, Fs=4.096kHz</td>
<td>Spectral features – max power, mean frequency</td>
<td>12</td>
<td>Mean frequency of power spectrum increases linearly with flow up to 45L/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Expiratory spectra have higher mean frequencies than inspiratory spectra</td>
<td></td>
</tr>
</tbody>
</table>
2.9 Breath Sounds: Summary

The main observations from Sections 2.5, 2.6, 2.7 and 2.8 of this Literature Review can be summarised as follows:

(i) Tracheal and chest wall breath sounds are primarily generated due to air turbulence in airways, are closely related to airflow rate and are repeatable within individuals over time.

(ii) There are two main types of acoustic sensors employed in respiratory sound acquisition, with many researchers choosing the most appropriate sensor based on their specific needs.

(iii) The frequency content of asthmatic breath sounds are statistically significantly different to that of both COPD and healthy breath sounds, while there is no statistical difference between COPD derived breath sounds and healthy breath sounds. These findings would suggest that frequency based acoustic features are suitable for objectively analysing physiological changes in asthma.

(iv) It is possible to use acoustically derived features to estimate airflow rate during breathing on both the trachea and the chest wall, with time and frequency based features being the most commonly used in the literature.

The acoustic characteristics of tracheal and chest wall normal breath sounds have been extensively investigated in the literature. Researchers have endeavoured to understand how the sounds generated at these locations relate to physiological changes in the airways. Turbulence of airflow is frequently proposed as the primary source of audible tracheal and high frequency chest wall sounds. Tracheal normal breath sounds are known to have a broad frequency spectrum, with many peaks and troughs, in comparison with normal chest wall sounds that have a narrow and flat frequency spectrum. Both tracheal and chest wall normal breath sounds can be used to estimate airflow rate and are quiet repeatable over time. In spite of this, however, there are a lack of studies in the literature focusing on how normal breath sounds behave longitudinally in chronic respiratory diseases such as asthma and COPD. This may be due to a lack of suitable acoustic sensors that can record sounds from the trachea and chest wall longitudinally.

From the literature reviewed, there is no obvious acoustic sensor that should be employed to record respiratory sounds from the trachea and chest wall. The choice of acoustic sensor typically depends on a number of factors including the frequency response desired, cost, complexity and utility. Each sensor also has a different sensitivity to ambient environmental noise and this should be taken into account when choosing the appropriate acoustic sensor (Rossi et al., 2000;
From the literature reviewed, electret condenser microphones and piezoelectric contact sensors were the two most prevalent acoustic sensors. These sensors can be fragile and somewhat uncomfortable for the subject and there is a strong need for a less invasive, more useable and durable method of monitoring respiratory sounds, particularly if such sounds are to be studied longitudinally. The INCA electronic monitoring device utilises a MEMS microphone, which is a suitable choice of acoustic sensor, given that inhaler use is to be measured longitudinally.

Asthmatic chest wall breath sounds are known to contain higher frequency content in comparison to breath sounds obtained from COPD and healthy subjects. The acoustic features where this can be seen include the quartile frequencies (F25, F50, F75) and the total spectral power of chest wall sounds (Malmberg et al., 1995). Interestingly there are no statistical differences for the same spectral features for recordings from the trachea. COPD breath sounds have been reported to lack any distinct acoustic features that allow them to be distinguished from the breath sounds of healthy subjects. However, given the number of factors that are known to affect breath sounds and the small sample sizes of previous studies, one cannot conclude that the same results would be achieved with larger sample populations.

The literature suggests that acoustically derived spectral features (specifically inspiratory F50) may be employed to estimate the level of airway obstruction in asthma. A statistically significant relationship was reported between F50 and FEV1 from an inspiratory signal obtained from the trachea’s of asthmatic subjects (Malmberg et al., 1995). A statistically significant relationship was not reported in chest wall recordings of asthmatic subjects or for the COPD subjects, regardless of the recording location. Physiologically, the heterogenic nature of COPD may explain the lack of a statistically significant relationship, while obstruction of the larger upper bronchioles in asthmatic patients, close to the placement of the tracheal microphone, may explain the significant relationship observed in tracheal recordings.

In addition to analysing normal breath sounds, acoustic methods can also be employed to objectively detect and classify adventitious respiratory sounds that occur as a result of asthma and COPD. However, adventitious respiratory sounds have also been reported to occur in healthy people. This makes it challenging to use an acoustic based approach in this area as adventitious sounds behave somewhat unpredictably.

Recent systematic review articles on respiratory sounds in healthy people and COPD patients report that there is a lack of standardization in studies concerning the acoustic analysis of respiratory sounds (Jacome and Marques, 2014; Oliveira and Marques, 2014; Gurung et al., 2011). This lack of standardization is in relation to recording procedures, analysis methods and feature
selection. Attempts to standardize acoustic studies relating to respiratory sounds have been made in the last 15 years. The Computerised Respiratory Sound Analysis (CORSA) guidelines were developed to standardize the acoustic sensor technology used, the signal processing analysis methods and the acoustic features extracted, in addition to the nomenclature in relation to breath sounds (Sovijarvi et al., 2000). However, despite these guidelines being introduced, a lack of standardization still exists and this makes it challenging to interpret the results of breath sound studies.

2.10 Automatic Detection of Breath Sounds using Acoustic Signal Processing Methods

2.10.1 Introduction

Acoustic methods, such as the INCA technology, have the potential to objectively monitor inhaler adherence; however, such methods are currently restricted by the subjective and time-consuming nature of the data analysis method. Quantitative signal processing approaches may offer the solution to this problem, as they can be both objective and automatic. Up until now this Chapter has reviewed adherence to inhaler medication, methods to monitor adherence, how breath sounds are generated, the locations breath sounds are typically recorded from, what the characteristics of breath sounds are, what acoustic sensors are typically employed to record breath sounds, how breath sounds can be employed to analyse asthma and COPD and also how they can be employed to estimate airflow rate. It is clear that breath sounds contain important information that relates to the physiological condition of the airways and that they have unique features that may be analysed using acoustic signal processing based approaches. As previously mentioned in this thesis, the INCA electronic monitoring device is limited in that a human rater is required to manually analyse each audio recording and classify breath sounds. Acoustic signal processing methods could potentially be employed to automatically and objectively carry out this task.

In order to investigate what features and classification methods are best suited for the detection of inhaler breath sounds, a review of the current literature on breath sound detection was conducted. Findings indicate that there are no studies in the literature that use acoustic signal processing methods to detect/classify the breath sounds generated during inhaler use. However, there are numerous studies in the literature that employ signal processing methods to detect breath sounds (both normal and adventitious), snore sounds, cough sounds and also differentiate inspiration/expiration breath phases. Typically, in breath detection systems the signal is framed
and windowed, before a set of features are extracted from the signal and finally a classifier is used to identify the breath sound. Figure 2.5 below details this process.

![Audio Signal Processing Diagram]

*Figure 2.5: Typical classification system used to detect the presence of breath sounds in audio signals.*

2.10.2 Framing & Windowing

The audio signal is firstly divided into small time frames (~20ms) so that each frame can be analysed separately and a feature vector can be calculated. It is assumed that there is stationary behaviour in each frame. Frames are typically overlapped in order to get a good estimation of how a feature vector changes over time. A window function is typically applied to each frame in order to reduce the effect of discontinuities at the edges of the frame.

2.10.3 Feature Extraction

Feature extraction is a process employed to transform high dimensional vectors into lower dimensional vectors (Bahoura, 2009). In feature extraction, the aim is to capture the main characteristics of the signal, while also reducing the dimensionality of a signal. Before features can be extracted from a signal, the signal is typically divided into a number of overlapping frames, from where a window function is applied (Figure 2.5). For breath sound classification, the goal is to use a feature or set of features which will allow the breath sounds to be classified successfully and separated from other sounds (such as background noise) in the signal. Table 2.4 details the features that have previously been extracted in studies related to breath sound detection.

2.10.4 Statistical Modelling/Classification

After feature extraction, the final stage involves classifying the frames in the signal. Training data were first employed to create a model which best discriminates the events of interest from other noises in the signal. After this model is created, testing is carried out to validate the performance of the model on new unseen data. Supervised and unsupervised classification approaches are frequently used, with the former being the most commonly used approach. Table 2.4 details the classification methods that have been used in previous breath sound detection studies.
Table 2.4: Summary of studies in the literature that use signal processing approaches to detect breath sounds in audio signals. If motivation is given for the features extracted or classification methods, then it is also included.

<table>
<thead>
<tr>
<th>Authors &amp; Journal</th>
<th>Objectives/Results</th>
<th>Number subjects</th>
<th>Microphone Details</th>
<th>Features Extracted</th>
<th>Classification Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abushakra and Faezipour (2013) – IEEE Journal of Biomedical &amp; Health Informatics</td>
<td>Classification of breathing movements; employing a linear threshold, could classify inhales and exhales within 90-100% accuracy.</td>
<td>2 male lung cancer patients and 123 healthy subjects.</td>
<td>SONY VAIO VPCEB42FM microphone (Realtek High Definition Audio). The microphone was placed approximately 10cm away from the speaker. Sampling frequency of 44.1 kHz.</td>
<td>Voice Activity Detection (VAD) – Fast Fourier Transform (FFT), 13 Mel Frequency Cepstral Coefficients (MFCCs), inhale and exhale differentiated using 6th MFCC (2200-3100 Hz)</td>
<td>Linear Thresholding</td>
</tr>
<tr>
<td>Abushakra and Faezipour (2012) – IEEE conference on Bioinformatics &amp; Bioengineering</td>
<td>Estimation of lung capacity via acoustic analysis of breath sounds</td>
<td>20 healthy subjects</td>
<td>SONY VAIO VPCEB42FM microphone (Realtek High Definition Audio). The microphone was placed approximately 10cm away from the speaker. Sampling frequency of 44.1 kHz.</td>
<td>Voice Activity Detection (VAD) - FFT (Motivation: the spectrum of the speech signal changes quickly, but the background noise is relatively stationary and changes slowly); The VAD algorithm is fine-tuned for the acoustic signal of breath to differentiate the silence and breathing phases; It is implemented by first filtering the signal to remove the undesired low- frequency components, and second, calculating the power with different window sizes of the FFT of the input signal. Energy feature also</td>
<td>None reported</td>
</tr>
<tr>
<td>Authors &amp; Year</td>
<td>Description</td>
<td>Subjects</td>
<td>Equipment</td>
<td>Features</td>
<td>Classification Method</td>
</tr>
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</tr>
<tr>
<td>Bahoura and Pelletier (2003) - IEEE CCECE</td>
<td>Respiratory sound classification</td>
<td>Not Given, 12 normal sounds</td>
<td>Not Given</td>
<td>20 MFCCs</td>
<td>Vector Quantification based system</td>
</tr>
<tr>
<td>Bahoura and Pelletier (2004) - IEEE CCECE</td>
<td>Respiratory sound classification</td>
<td>Not given, 12 normal sounds</td>
<td>Not given</td>
<td>MFCC and Subband Based Cepstral (SBC) parameters</td>
<td>Gaussian mixture models (GMM)</td>
</tr>
<tr>
<td>Baydar et al. (2003) - IEEE EMBS</td>
<td>Classification respiratory sounds (52%-11)</td>
<td>Two sites on the chest: left basilar and right basilar. The sound signals as well as the flow signal were digitized</td>
<td></td>
<td>Signal coherence (FFT) - measure of spectral stability of signals both in terms of amplitude and phase; compares a Euclidean distance classifier, called the nearest mean classifier with leave-one-out method.</td>
<td></td>
</tr>
<tr>
<td>Chuah and Moussavi (2004) - IEEE EMBS</td>
<td>76-93% of phase detection accuracy and 100% of breath onset detection accuracy</td>
<td>11 healthy subjects</td>
<td>Tracheal sounds and chest sounds were recorded</td>
<td>Power spectrum (FFT): average chest power spectra to detect the respiratory phases; average tracheal power spectra are used to determine the breath onsets. A frequency band of 150-300 Hz was chosen to calculate the average power of the chest signals; the slope at each sample is calculated by taking the differences between adjacent points; inspiration peaks are expected to be much higher than expiration peaks. Motivation: With an appropriate frequency range, the peaks of average power spectra of chest signals match with the midpoints of respective inspiration phases; chest signals can be used to detect the peaks of inspiration phases; tracheal signals require a lower minimum critical airflow to produce detectable breath sounds during expiration; tracheal signals can be used</td>
<td>None reported</td>
</tr>
<tr>
<td>Authors</td>
<td>Methodology</td>
<td>Participants</td>
<td>Measurement Devices</td>
<td>Features</td>
<td>Classification Method</td>
</tr>
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<tr>
<td>Dafna et al. (2013) – PLoS One</td>
<td>Automatic Detection of Whole Night Snoring Events Using Non-Contact Microphone</td>
<td>67 adults</td>
<td>Non-contact directional microphone (RØDE, NTG-1) and handy Olympus LS-5</td>
<td>127 features relating to temporal signal (periodicity, duration/sample scattering and energy) and the spectrum (spectral parameterisation, bio-characteristic frequencies, dynamic frequencies)</td>
<td>AdaBoost Classifier</td>
</tr>
<tr>
<td>Dokur and Ölmez (2003) – International journal of pattern recognition and artificial intelligence</td>
<td>Classification of respiratory sounds</td>
<td>20 subjects</td>
<td>Electronic stethoscope (Cardionics Inc.)</td>
<td>Wavelet transform</td>
<td>Artificial Neural Network</td>
</tr>
<tr>
<td>Folland et al. (2004) - Artificial intelligence in medicine</td>
<td>Classification of tracheal-bronchial breath sounds by respiratory auscultation</td>
<td>Not given</td>
<td>Not given</td>
<td>FFT</td>
<td>Constructive Probabilistic Neural Networks (CPNNs) method was compared to multi-layer perceptron (MLP) method and radial basis function network (RBFN).</td>
</tr>
<tr>
<td>González et al. (2014) - Ubiquitous Computing and Ambient</td>
<td>Noise-robust algorithm for segmentation of breath events (inhalations and exhalations)</td>
<td>Not given</td>
<td>Smartphone microphone (model not given)</td>
<td>FFT and MFCC</td>
<td>Template matching approach</td>
</tr>
<tr>
<td>Intelligence</td>
<td>exhalations during continuous speech</td>
<td>18 chronic obstructive patients, 19 restrictive lung disease patients and 20 healthy subjects</td>
<td>Two air-coupled electret microphones were used to record respiratory sounds from the basilars. The signal was amplified with a low noise amplifier and bandpass-filtered between 80 to 2000 Hz. The signal was sampled with a 12-bit analog-to-digital converter at 5000 Hz.</td>
<td>AR (autoregressive) parameters and cepstral coefficients obtained directly from linear prediction coefficients.</td>
<td>Multilayer perceptron (MLP) – the simplest and most popular ANN.</td>
</tr>
<tr>
<td>Güler et al. (2005) - Computers in biology and medicine</td>
<td>Classification of respiratory sound pattern</td>
<td>Siemens (EMT25C) accelerometer placed on five locations at chest wall.</td>
<td>Log variance. Once breath phases are detected: extraction of peak intensity or amplitude of the breath phase in decibels (dB), duration, proportion of the area under the log variance curve in the first half of the phase, the difference between the percentage of the area under the log variance curve between the 1/3rd and 3/3rd sections of each phase, the falling gradient of the breath phase (calculated</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Hossain and Moussavi (2002) – IEEE EMBS</td>
<td>Respiratory airflow by mean of acoustic features</td>
<td>10 healthy subjects</td>
<td>FFT - Average power was calculated within 100-300 Hz frequency band.</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Huq and Moussavi (2012) - Medical &amp; biological engineering &amp; computing</td>
<td>Acoustic phase detection using tracheal breath sounds - accuracy of 95.6% with 95.5% sensitivity and 95.6% specificity for breath-phase identification.</td>
<td>93 healthy subjects</td>
<td>Sony Condenser microphone (ECM-77B) – embedded in an air coupled chamber and placed over the suprasternal notch on the trachea.</td>
<td>Specificity, sensitivity: Two majority-vote approaches, 5VOTE and 3VOTE.</td>
<td></td>
</tr>
<tr>
<td><strong>Huq et al. (2007) - IEEE International Symposium on Signal Processing and Information Technology</strong></td>
<td>Pilot study before 2012: comparison of respiratory phase with flow signal recorded with spirometer</td>
<td>9 healthy subjects</td>
<td>Siemens Accelerometer (EMT25C) – placed over suprasternal notch on the trachea.</td>
<td>Two intensity related features of tracheal breath sounds: the average power (FFT) and log variance between various frequency ranges from 50 to 1,800 Hz.</td>
<td>None reported</td>
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</tr>
<tr>
<td><strong>Huq and Moussavi (2010) - IEEE EMBS</strong></td>
<td>Pilot study before 2012 – Breath phase detection using tracheal breath sounds.</td>
<td>6 healthy subjects</td>
<td>Sony Condenser (ECM-77B)</td>
<td>Variety of features derived from the log variance feature – intensity, duration, volume, area under curve ratio, falling gradient.</td>
<td>Majority vote approach – 5VOTE and 3VOTE</td>
</tr>
<tr>
<td><strong>Hult et al. (2000) – Medical Engineering and Physics</strong></td>
<td>Timing of the different phases of the breathing cycle and monitoring of breathing frequency</td>
<td>Study 1: 10 healthy subjects Study 2: 2 healthy subjects Study 3: 2 patients</td>
<td>To measure the tracheal sound from breathing, a microphone (Siemens Elema no. 6919328, Solna, Sweden) was used. An external microphone (Siemens Elema no. 6919328, Solna, Sweden) was also used to detect noise disturbances.</td>
<td>Temporal and spectral features, such as maximum amplitude of the tracheal sound, its root mean square (RMS) value, duration of the phase and peak, median (F50) and maximum frequencies. Motivation: Great importance to capture fast changes in intensity over small time periods.</td>
<td>Threshold</td>
</tr>
</tbody>
</table>
| **Igras and Ziolko (2013) - IEEE ICME** | Algorithm for automatic detection of | 24 healthy subjects | Not given | Temporal & spectral features. First stage: length & energy. Second stage: Mel-scale discrete wavelet | Dynamic time warping algorithm (time-series analysis measuring similarity between two temporal sequences which}
<table>
<thead>
<tr>
<th>Conference</th>
<th>breath events in a speech signal</th>
<th>transform parameters (12 wavelet frequency subbands; from 125 Hz to 8 kHz)</th>
<th>may vary in time or speed to establish final recognition: similarity to breath template: distance measure between the two signals of different lengths; 94.7% accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahya et al. (2003) – IEEE EMBS</td>
<td>Respiratory sound classification</td>
<td>Air coupled electret microphone, record from four locations on chest wall.</td>
<td>AR model coefficients, percentile frequencies, first 3 principal components obtained by projection of AR feature vectors onto 3D space using eigenvector projection method.</td>
</tr>
<tr>
<td>Lei et al. (2014) – Neurocomputing</td>
<td>Breath sound classification</td>
<td>Digital voice recorders</td>
<td>Support vector machine (SVM) and artificial neural network (ANN) classification approach. Motivation: Both methods can achieve high accuracy and have more variability for solving practical problems.</td>
</tr>
<tr>
<td>Nakano et al. (2008) – ICMPC</td>
<td>Acoustic analysis of breath sounds in singing</td>
<td>Songs taken from RWC Music database</td>
<td>HMMs; Average recall rate of 97.5% and precision rate of 77.7%</td>
</tr>
<tr>
<td>Pesu et al. (1998) – Technology Health Care</td>
<td>Respiratory sound classification</td>
<td>Not given</td>
<td>Wavelet packet decomposition</td>
</tr>
<tr>
<td>Price et al. (1989) – Workshop on speech and</td>
<td>Automatic breath detection method (speech)</td>
<td>Not given</td>
<td>Cepstral coefficients</td>
</tr>
</tbody>
</table>

Gaussian Mixture Model classifier; 93% accuracy.
<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Methodology</th>
<th>Data description</th>
<th>Features</th>
<th>Approach</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruinskiy and Lavner (2007) – IEEE Transactions on Audio, Speech, and Language Processing</td>
<td>Automatic breath detection method (speech/song)</td>
<td>24 voices of professional singers/narrators</td>
<td>Not given – Sampling rate of 44 kHz MFCCs, short-time energy, zero crossing rate (ZCR), spectral slope, duration</td>
<td>Template matching approach</td>
<td>Motivation: Not to choose more complicated method (SVM, GMM) but template-matching approach: it is simple and computationally efficient, and yet very accurate and reliable. In contrast, both SVM and GMM require more complex models with multiple parameters and assumptions, and therefore with higher time and space complexity (Burges, 1996) Precision/recall rate 97.6%/95.7% Hybrid classification method</td>
</tr>
<tr>
<td>Sankur et al. (1994) – Computers in Biology and Medicine</td>
<td>Respiratory sound classification</td>
<td>Not given</td>
<td>Not given</td>
<td>AR vectors</td>
<td>Two classifiers were used: k-nearest neighbour (k-NN) and a quadratic classifier</td>
</tr>
<tr>
<td>Snider and Kain (2013) – IEEE ICASSP</td>
<td>Classification of breathing sounds produced during sleep.</td>
<td>4 adults with sleep disordered breathing</td>
<td>Audio-Technica AT8035 microphone with 16-bit resolution and 16 kHz sampling rate. 13 cepstral coefficients (CC), MFCCs, and reflection coefficients from linear predictive coding (LPC). The first coefficient from the resulting CC and MFCC feature vectors were excluded, to make the features energy-independent. (LPC reflection coefficients already model</td>
<td>Hidden Markov models</td>
<td></td>
</tr>
</tbody>
</table>
the spectrum in an energy-independent manner.) In addition, the first-order delta features were derived from the static features. (Note: the CC features represent the spectrum smoothly, while the LPC features focus on modelling the spectral peaks)

**Motivation:** The use of LPC features generally resulted in the highest accuracy at each level versus cepstral and Mel-frequency cepstral coefficient features, yielding 86–90% accuracy in the SD experiment and 76–87% accuracy in the SI experiment.

<table>
<thead>
<tr>
<th>Research</th>
<th>Method/Description</th>
<th>Participants</th>
<th>Equipment</th>
<th>Features</th>
<th>Classifier/Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wightman and Ostendorf (1991) - IEEE ICASSP</td>
<td>Automatic breath detection method (speech)</td>
<td>1 professional radio announcer</td>
<td>Not given</td>
<td>Cepstral coefficients</td>
<td>Bayesian classifier; 91% accuracy</td>
</tr>
<tr>
<td>Yahya and Faezipour (2014) - IEEE ASEE</td>
<td>Detection and classification of respiratory phases into expirations and inspirations: accuracy 95%.</td>
<td>9 healthy subjects</td>
<td>Samson C01U USB microphone placed 2-4 cm from nose</td>
<td>VAD algorithm for voice/unvoiced segments. For breathing phase detection: The sum of the peaks in the signal per phase is calculated.</td>
<td>SVM with linear kernel training function</td>
</tr>
</tbody>
</table>
than other signal processing techniques, making this technique highly attractive for hardware implementations. The number of desired peaks was calculated as it gives an estimation of the phase duration by giving the number of frames for each phase. After these calculations, the respiratory phases can be detected which also indicate the airflow direction.
In addition to detecting breath sounds and discriminating inhalations and exhalations, a number of studies have attempted to classify and differentiate normal breath sounds and adventitious breath sounds (i.e. wheezes and crackles). A review by Bahoura (2009) reported that the features most commonly employed to differentiate wheeze sounds and normal sounds were based on the Fourier transform, linear predictive coding, wavelet transform and MFCCs. It was also reported that vector quantisation, GMMs and ANNs are frequently used to classify the different breath classes (Bahoura, 2009). Other classifiers that have been used in the literature for normal/abnormal breath detection include SVMs (Jin et al., 2014; Serbes et al., 2011), HMMs (Yamamoto et al., 2010) and Bayesian classifiers (Wightman and Ostendorf, 1991).

2.10.5 Discussion

From the literature reviewed in Table 2.4, it appears that the most commonly employed feature extraction approaches in breath detection studies are:

1. Fast Fourier Transforms (FFT)
2. Mel Frequency Cepstral Coefficients (MFCCs)
3. Linear Predictive Coding (LPC) / autoregressive (AR) modelling
4. Wavelet Transform (WT)

While the most frequently employed classification methods are:

1. Gaussian Mixtures Models
2. Artificial Neural Networks
3. Vector Quantisation
4. Support Vector Machines
5. Hidden Markov Models
6. Thresholding
7. k-nearest neighbour

Experimental results from Bahoura (2009) reported that MFCCs offered the best performance in detecting breath sounds, compared with FFT, LPC and WT based approaches. It was also reported that using MFCCs in combination with a GMM classifier produced the best performance in detecting breath sounds (Bahoura, 2009). The motivation for using MFCCs is originally due to the need to separate glottal speech sounds from the vocal tract response (Noll, 1967). In the cepstral domain, lower coefficients describe the envelope structure (vocal tract response), while the higher coefficients describe the harmonic structure (glottal speech response) (Bahoura and Pelletier, 2003).
Breath sounds are often regarded as having acoustic characteristics similar to broadband noise (Wold et al., 1996). Lei et al. (2014) explain that feature extraction may be the most important part of the breath sound feature classification stage and that the effectiveness of breath sound detection depends on a classifier's ability to classify sound data properties or contents. For clinical diagnostic purposes, a reliable, accurate, fast and content-based method for breath sound classification is essential (Lei et al., 2014). Similarly to breath sounds, it is also necessary to understand inhaler breath sounds unique time and frequency features before classifying or detecting the signal. The characteristics of inhaler breath sounds will thus be investigated in subsequent Chapters of this thesis.

Table 2.4 provided details on the most commonly employed feature extraction and classification approaches for breath detection. The results of this review of the literature will be used as motivation for selecting features in this thesis. As there has been no previous research in the area of inhaler acoustics, the focus of this thesis will be on feature extraction, not on the selection of the classifier. FFT based feature extraction methods present a method of understanding the fundamental properties of the sounds and are frequently employed to successfully detect breath events. MFCC based methods are the current state-of-the-art in detecting breath sounds and Table 2.4 demonstrates that there are many studies in the literature that successfully use MFCCs to detect breath sounds (typically with accuracies greater than 90%). In this thesis, FTT and MFFC derived features will be used to detect breath sounds generated during inhaler use. It was hypothesised that these feature extraction methods may be capable of detecting the breath sounds generated during inhaler use in this thesis. The theory behind FFT and MFCC feature extraction will be discussed in Chapter 4.

Both FFT and MFCC features will be used in this thesis to detect the presence of breath sounds in inhaler audio signals obtained from INCA electronic monitoring devices. To conclude this literature review Chapter, an example of the time and frequency characteristics of Diskus inhaler use will be provided, in addition to the steps necessary for correct Diskus inhaler user technique.

### 2.11 Inhaler Sound Generation and its Potential for Assessing Inhaler Adherence

An extensive search of the literature indicates that there are no studies detailing the acoustic characteristics of inhaler use. It remains to be seen how the acoustic signals of inhaler use are represented in the time or frequency domains. There are also no studies in the literature detailing how inhaler breath sounds are generated. It can be hypothesised that inhaler breath sounds share similar characteristics with normal breath sounds. However, the design of the inhaler and also the
resistance of the inhaler to airflow will modulate inhalations through an inhaler mouthpiece. These important differences imply that the acoustic features employed in the analyses of normal breath sounds and relationships observed, may not be observed for inhaler-based breath sounds. Later sections of this thesis will investigate if the features employed in the analyses of normal breath sounds are applicable for inhaler-based breath sounds.

At present, the INCA electronic monitoring device can be used with the commonly used Diskus DPI. Figure 2.6 below illustrates Diskus inhaler use in the time domain, while Figure 2.7 shows the audio signals corresponding spectrogram. The INCA device records audio signals at a sampling rate of 8000 Hz and resolution of 8 bits/sample. The audio signal was obtained from the INCA device in a quiet recording environment. It shows the drug being released at 2.2 s and an inhalation beginning at 5 s. This sequence of events would indicate that the Diskus DPI was used with correct user technique. As the Diskus DPI is employed in several studies in this thesis, the steps for correct user technique will now be explained for this specific inhaler.

![Figure 2.6: Typical Diskus DPI use as recorded from the INCA device. Blister event takes place at 2.2 s and the inhalation begins at approximately 5 s.](image_url)
Blister event takes place at 2.2 s and the inhalation begins at approximately 5 s.

### 2.11.1 Correct Diskus Inhaler User Technique

**a) Turn Cover to Expose Inhaler Mouthpiece**

The first step to using the Diskus inhaler involves sliding the cover to reveal the mouthpiece. To do this the outer case should be held with one hand, whilst the other hand should be used to push the thumb grip until the mouthpiece is revealed and a click sound is heard. It is at this point in time that the INCA device powers on. Audio is recorded from now until the thumb grip is moved back to its closed position. If the inhaler is not closed, the INCA device will automatically stop recording audio after 90 seconds. A graphical representation of this step can be seen in Figure 2.8.
(b) Load Dose

This Diskus DPI should now be held horizontally with the mouthpiece facing towards the user. Holding the inhaler firmly in one hand, the other hand should be used to push the lever until a sharp click noise is made. This sharp click indicates that the blister foil in the Diskus has been pierced and that drug powder has been loaded into the mouthpiece, in preparation for inhalation. The mechanics of this step are displayed in Figure 2.9. Its representation in the time and frequency domain can be seen in Figure 2.6 and Figure 2.7 at time 2.2 s.

(c) Exhale Away from Mouthpiece

The next step for correct Diskus DPI use is to exhale away from the mouthpiece of the inhaler to functional residual lung capacity. This is to ensure that no moisture is introduced into the mouthpiece of the inhaler that may cause the drug to clump together. Exhaling into the mouthpiece may also cause the drug to be dispersed, resulting in a reduced amount of medication available for delivery. Depending on the proximity of the INCA device to the patient’s mouth, in addition to the flow rate and the volume of the exhalation, this event may or may not be detected in the audio signal.

(d) Inhale Deeply and Quickly

The Diskus DPI is a breath-actuated inhaler. Drug deposition in the airways is dependent on the peak inspiratory flow rate at the inhaler mouthpiece. Diskus DPI users are instructed to inhale deeply and quickly. The mouthpiece should be positioned between the lips and sealed tightly. The tongue or teeth must not obstruct the path the drug will take during the inhalation. The inhalation should be through the mouth only and not through the nose. In order to effectively remove the drug particles from the mouthpiece and de-agglomerate the particles before they are
transported to the airways, the PIFR should be greater than 30 L/min (Pauwels et al., 1997). This is
to ensure that the drug has a clinical benefit to the user. The recommended PIFR for the Diskus is
60 L/min, and larger PIFRs are associated with higher levels of lung drug deposition (Pauwels et
al., 1997). The correct position of the Diskus during inhalation is displayed in Figure 2.10. The
inhalation event in the time and frequency domain can be seen in Figure 2.6 and Figure 2.7 at 5 s.

Figure 2.10: Inhaling through the Diskus DPI.

(e) Breath Hold

After the inhalation manoeuvre the Diskus mouthpiece should be removed from the lips and
breath should be held. Most checklists recommend that patients hold their breath, although the
duration of breath holding can be variable. The general recommendation for clinical practice is
that the breath should be held for as long as is comfortable (Basheti et al., 2014). A 10 second
breath hold was originally suggested for pMDIs, based on lung deposition studies (Newman et al.,
1981). Diskus DPI guidelines state that breath should be held for about 10 seconds, or for as long
is comfortable (GSK, 2015). After breath hold, the Diskus can be closed by sliding the Diskus
thumb grip back to its original position (see Figure 2.9). It is at this point in time that the INCA
device will power off and the microphone will cease recording.

2.12 Chapter Conclusion

In conclusion, several research questions emerge from this review of the literature. There is a lack
of research on the use of acoustic signal processing methods to detect and analyse the breath
sounds generated during inhaler use. It is unclear what feature extraction methods would be best
suited in this area. It remains unclear what the acoustic characteristics of inhaler breath sounds
are. Knowledge of the characteristics of inhaler breath sounds may assist in the selection of the
most appropriate acoustic features for classification purposes. Research is also lacking into the
relationship between inhaler inhalations and airflow rate, and in particular how acoustically
derived features may vary with airflow rate. Finally, it remains to be seen if acoustic signal processing approaches can be utilised to automatically and objectively assess inhaler adherence at a level comparable to human raters. Further research in these areas may contribute to a more objective and scientific approach in analysing inhaler audio signals and thus evaluating inhaler adherence. The central hypothesis of this thesis is that acoustics may be employed to analyse inhaler use and assess patient adherence. The next Chapter of this thesis establishes the main aims of this thesis, in addition to the specific research questions that were derived from the review of the literature in this Chapter.
CHAPTER 3: Research Questions

Following a review of the existing literature regarding adherence to inhaler drug therapy and the various methods to monitor it, it appears that the INCA electronic monitoring device offers the greatest potential of the currently existing methods. A number of signal processing methods exist which may improve the objectivity, speed and thoroughness of this adherence monitoring method. It was seen in Chapter 2 that signal processing approaches have previously been employed to detect and analyse breath sounds in speech and song signals. However, a number of questions still beset the literature in relation to breath sounds generated during inhaler use:

• Can a patient’s adherence to their inhaler therapy be objectively assessed using acoustic signal processing analyses methods?
• What are the most appropriate acoustic features needed to analyse inhaler adherence using signal processing methods?
• Do inhaler inhalation sounds, recorded from an inhaler, contain pertinent information that relates to physiological changes in airway function?
• Will objective data on patient adherence to inhaler medication assist clinicians in educating patients on correct inhaler use, planning future patient treatment courses and understanding interactions between inhaler use patterns and patient health outcomes?

It was hypothesised that the sounds generated during inhaler use contain pertinent information needed to automatically and objectively assess inhaler user technique adherence using signal processing methods. To test this hypothesis a number of specific research questions were derived.

3.1 Relationship between Inhaler Inspiratory Airflow and Acoustic Features

1. Can temporal and/or spectral acoustic features of inhaler inhalations be used to estimate PIFR in an inhaler device?
2. Can temporal and/or spectral acoustic features of inhaler inhalations be used to estimate inspiratory volume through an inhaler device?
3. Which regression model best describes the relationship between PIFR/inspiratory volume and acoustic features of inhaler inhalation?
4. Which acoustic features demonstrate the best correlation values with PIFR and inspiratory volume?

5. Can temporal and/or spectral acoustic features of inhaler inhalations be used to estimate the quantity of drug removed from an inhaler device?

6. Is the relationship between PIFR/inspiratory volume and acoustic features of inhaler inhalations consistent, regardless of age, sex, height, weight and respiratory function?

3.2 Characteristics of Inspiratory Sounds during Inhaler Use

7. What are spectral acoustic features of inhaler inspiratory sounds?
8. Does the spectral envelope of inhaler inhalations vary with PIFR?
9. Are temporal and spectral acoustic features of inhaler inhalations repeatable within subjects, between subjects and over time?
10. How are the sounds of inhaler inhalations generated?
11. How does the microphone sampling rate affect the relationship between acoustic features and PIFR?

3.3 Exhalation into a DPI Mouthpiece

12. What factors associated with exhalation into a DPI mouthpiece are detrimental to the efficacy of the medication?
13. Which exhalation factor has the biggest impact on subsequent drug delivery?
14. Can temporal and spectral acoustic features associated with expiratory breath sounds be used to detect exhalations into a DPI mouthpiece?
15. Can temporal and spectral acoustic features associated with expiratory breath sounds be used to quantify the effect of exhaling into a DPI mouthpiece?

3.4 Development of Objective Methods to Assess Inhaler Adherence

16. Can temporal and spectral based feature extraction methods be employed to successfully detect the blistering of the drug foil during Diskus inhaler use, in audio recordings of inhaler use, at a level comparable to that of expert human raters?
17. Can MFCC and temporal based features be used to detect inhalation sounds in audio recordings of Diskus inhaler use, at a level comparable to that of expert human raters?
18. What are the differences in the inhalation onset and offset time classification for an algorithm versus human rater?
19. Can a system be developed to automatically and objectively classify inhaler user technique adherence using the results of blister, inhalation and exhalation acoustic detection algorithms? If so, then can this algorithm perform at a level comparable to that of expert human raters?

20. Are there any differences in the performance of inhalation detection and inhaler user technique classification algorithms in asthma patients versus COPD patients?

21. Does manual aural and visual assessment of audio recordings from the INCA device provide a true gold standard method of assessing inhaler user technique or are there differences in opinion between human raters?

22. Can a low quality acoustic sensor provide data capable of being used to monitor inhaler adherence using signal processing methods?

To address these research questions, this thesis is organised into a number of Chapters, which describe several studies focusing on the use of acoustic analysis methods in the assessment of Diskus inhaler adherence. To undertake these studies a number of signal processing methodologies need to be developed. The next Chapter, Chapter 4, details the development of these signal processing methods.
CHAPTER 4: General Methods

In order to address the specific research questions presented in Chapter 3, a number of advanced methods are required. This Chapter provides a detailed overview of the main methods (both signal processing and experimental) employed in this thesis.

In Chapter 2, Table 2.4 summarised a review of the literature and provided details on the most commonly employed feature extraction and classification approaches for breath detection in audio signal processing. The results of this review will be used as motivation for feature selection in this thesis, as there has been no previous research in the area of inhaler acoustics. The focus of this thesis will be on the feature extraction, not on the selection of the classifier. Threshold based methods will be used to classify breath sounds and to differentiate inhalations and exhalations. FFT based feature extraction methods present a method of understanding key characteristics of the sounds and are frequently employed to successfully detect breath events (see Table 2.4). MFCC based methods are the current state-of-the-art in detecting breath sounds and Table 2.4 demonstrated that there are many studies in the literature that successfully use MFCCs to detect breath sounds (typically with accuracies greater than 90%). In this thesis, FTT and MFFC derived features will be employed to detect breath sounds generated during inhaler use. It was hypothesised that these feature extraction methods may be capable of detecting the unique characteristics of the breath sounds generated during inhaler use. The theory behind FFT and MFCC feature extraction will now be discussed.

4.1 FFT

FFT based approaches are frequently employed to detect breath sounds in speech and song signals (Table 2.4). In non-stationary signals, such as inhaler audio recordings, it is important to window the signal and look at the frequency components of short-time periods. The short-time Fourier transform (STFT) can be obtained by applying the Fourier transform by a fixed size moving window to a signal. The STFT of a discrete time signal $x[n]$ can be estimated as:

$$X[m, k] = \sum_n x[n] w[n - m] e^{-j2\pi nk/N}$$  \hspace{1cm} (4.1)

Where $w[n]$ is a short-time window function, with its centre at time location $m$ and $N$ is the total number of discrete frequencies. As the Fourier transform is a complex function, the power spectral density (PSD) can be estimated as:

$$P[m, k] = \frac{1}{N} |X[m, k]|^2$$  \hspace{1cm} (4.2)
At a sampling frequency $F_s$, each windowed frame is represented by $N$-points power spectrum for the frequency range $[-F_s/2, F_s/2]$. FFT based methods are frequently employed to extract the average power of the audio signal, in addition to other features relating to the signals frequency components. FFT methods are utilised in Chapters 5, 6, 7 and 8 of this thesis.

### 4.2 MFCC

As seen in Table 2.4, MFCCs are features that are frequently used in automatic breath sound detection systems. Originally, cepstral based analysis was motivated by the need to separate the signal content of glottal speech $g[n]$ to that of the vocal tract response $v[n]$ (Noll, 1967).

$$x[n] = g[n] * v[n]$$  \hspace{1cm} (4.3)

In the frequency domain, the convolution relationship becomes a multiplication relationship:

$$X(e^{j\Omega}) = G(e^{j\Omega})V(e^{j\Omega})$$  \hspace{1cm} (4.4)

In order to separate these signals, one can get the log transform in the frequency domain:

$$\log\left(X(e^{j\Omega})\right) = \log\left(G(e^{j\Omega})\right) + \log\left(V(e^{j\Omega})\right)$$  \hspace{1cm} (4.5)

To calculate the cepstral coefficients, the inverse transformation of the amplitude spectra is calculated:

$$c[n] = DFT^{-1}\log\left(|G(e^{j\Omega})|\right) + DFT^{-1}\log\left(|V(e^{j\Omega})|\right)$$  \hspace{1cm} (4.6)

The mel-cepstrum uses physiological features of the auditory system, in addition to the decorrelating properties of cepstral analysis methods (Bahoura, 2009). It is motivated by the fact that the human cochlea is much better at processing small changes in pitch at low frequencies (linear below 1000 Hz), compared to changes in pitch at higher frequencies (logarithmically above 1000 Hz) (Muda et al., 2010). The use of the mel-scale in breath sound detection is carried out in order to potentially provide greater discriminatory capability, compared with a purely linear scale. The steps typically taken to calculate MFCCs are displayed in Figure 4.1 below. MFCC based methods are employed in Chapter 8 of this thesis.
Both FFT and MFCC features will be used in this thesis to detect the presence of breath sounds in inhaler audio signals obtained from INCA electronic monitoring devices.

### 4.3 Algorithm Assessment

In the studies detailed in this thesis, algorithm performance was evaluated using sensitivity, specificity and accuracy based measurements. Sensitivity, specificity and accuracy can be calculated using the following equations:

\[
Sensitivity = \frac{N_{TP}}{N_{TP} + N_{FN}} \quad (4.7)
\]

Where \( N_{TP} \) is the number of true positives and \( N_{FN} \) is the number of false negatives.

\[
Specificity = \frac{N_{TN}}{N_{TN} + N_{FP}} \quad (4.8)
\]

Where \( N_{TN} \) is the number of true negatives and \( N_{FP} \) is the number of false positives.

\[
Accuracy = \frac{N_{TP} + N_{TN}}{N_{TP} + N_{TN} + N_{FP} + N_{FN}} \quad (4.9)
\]

A detailed explanation on the interpretation of true/false positives/negatives in relation to breath sounds is given in Table 4.1.
Table 4.1: Interpretation of the different events that affect sensitivity, specificity and accuracy of an algorithm. Note: Breath sounds are used as an example in this table.

<table>
<thead>
<tr>
<th>Event</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positive</td>
<td>Breath sound correctly labelled as a breath sound.</td>
</tr>
<tr>
<td>False Positive</td>
<td>Noise incorrectly labelled as a breath sound. i.e. false detection.</td>
</tr>
<tr>
<td>True Negative</td>
<td>Noise correctly labelled as noise.</td>
</tr>
<tr>
<td>False Negative</td>
<td>Breath sound incorrectly labelled as noise. i.e. missed detection.</td>
</tr>
</tbody>
</table>

4.3.1 Cohen’s Kappa Score for Interrater Agreement

In studies described in this thesis, there are several studies where two human raters classified different events in inhaler audio files. Cohen’s kappa score was employed to investigate the level of agreement between raters for a particular test. The kappa score, also known as the kappa statistic, is a measure of interrater reliability. It is advantageous over percentage agreement measures as it accounts for the possibility that raters may guess the score for certain tests when faced with uncertainty. Cohen’s kappa can range from -1 to 1, with 0 representing the amount of agreement that can be expected from random chance. A Cohen’s kappa of 1 will occur if perfect agreement exists between raters. Cohen’s kappa may be calculated using the following equation:

\[ \kappa = \frac{Pr(a) - Pr(e)}{1 - Pr(e)} \]  

(4.10)

Where \(Pr(a)\) is the actual observed agreement and \(Pr(e)\) represents the chance agreement.

The interpretation of the kappa score in relation to the agreement between raters is displayed in Table 4.2 below.

Table 4.2: Interpretation of Kappa scores and their interpretation in relation to interrater agreement.

<table>
<thead>
<tr>
<th>Kappa Score</th>
<th>Level of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 0.2</td>
<td>None</td>
</tr>
<tr>
<td>0.21 – 0.39</td>
<td>Minimal</td>
</tr>
<tr>
<td>0.40 – 0.59</td>
<td>Weak</td>
</tr>
<tr>
<td>0.60 – 0.79</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.80 – 0.90</td>
<td>Strong</td>
</tr>
<tr>
<td>Above 0.90</td>
<td>Almost Perfect</td>
</tr>
</tbody>
</table>
4.4 Extraction of Inspiratory and Expiratory Inhaler Acoustic Features

The previous Sections of this Chapter have discussed methods that can be used to detect the presence of blister sounds and breath sounds (inhaled/ exhaled) in inhaler audio recordings. This Section describes the time and frequency based features that were employed to investigate the variations of inhaler breath sounds with airflow rate. These features will be employed in Chapters 5, 6 and 7 of this thesis.

4.4.1 Temporal

Median amplitude (MA) of the inhaler audio signals was computed in several studies described in this thesis. MA was selected instead of mean amplitude in order to limit the effects of short duration noise spikes in the inhalation signal. MA was estimated by calculating the median value of the absolute value peaks in the inhalation signal.

\[ MA = \frac{1}{2} (n + 1)^{th\ value} \]  

(4.11)

Where \( n \) is the total number of values in the data set.

Mean absolute deviation (MAD) of the amplitude signal is commonly used as a temporal feature to calculate the mean of the absolute values of a sinusoidal signal. It can be calculated using the following equation:

\[ MAD = \frac{1}{n} \sum_{i=1}^{n} |x_i - \bar{x}| \]  

(4.12)

Where \( n \) is the total number of values in the data set, \( x_i \) is the \( i^{th} \) value of the signal and \( \bar{x} \) represents the mean of the signal.

Root mean square (RMS) or quadratic mean is a statistical measure of the effective value of a signals amplitude, including the mean value. It takes into account sinusoidal waveforms and gives the equivalent non-varying power of a varying waveform. It is the square root of the mean of the squares of the values of either a discrete or continuously varying function. RMS has been used in a previous study, which investigated the volume-dependent changes in regional lung sound amplitudes (Kiyokawa and Pasterkamp, 2002). It was calculated using the following equation:

\[ RMS = \left[ \frac{1}{n} (x_1^2 + x_2^2 + x_3^2 + \ldots + x_n^2) \right]^{1/2} \]  

(4.13)
4.4.2 Spectral

FFT based features are extracted from the inhaler audio signals in order to investigate the distribution of the power in the signal across a frequency range of interest. Welsh’s method of estimating PSD is a nonparametric method that estimates the PSD from the signal itself. In this method the signal can be divided into overlapping segments, before a periodogram is computed for each segment and the PSD estimates are averaged. Averaging the periodograms decreases the variance of the PSD estimate, compared to estimating a single periodogram for the entire signal. Estimating the PSD involves calculating the discrete-time Fourier transform of the signal and squaring the result. The periodogram estimate of PSD for a signal \( x(n) \) of length \( L \) is

\[
P_{xx}(f) = \frac{1}{L F_s} \left| \sum_{n=0}^{L-1} x(n) e^{-j2\pi fn/F_s} \right|^2
\]

(4.14)

Where \( F_s \) is the sampling frequency.

For Welch’s PSD estimation, audio recordings are typically divided into 256 segments with 50% overlap between segments. A Hanning window was applied to each segment and the Welch PSD estimate was computed using 1,024 Discrete Fourier Transform points. The above method was employed to calculate the average power of inhalation signals in this thesis. A number of features derived from the FFT are also estimated.

The frequency below which 25%, 50% and 75% of the total spectral power lie (\( F_{25} \), \( F_{50} \) and \( F_{75} \)) are employed as features to investigate changes in the frequency characteristics of inspiratory inhaler sounds. These features are often referred to as the quartile frequencies, while \( F_{50} \) is sometimes referred to as the median frequency in the literature. These features are frequently employed in the literature to investigate changes in the frequency characteristics of inhalations sounds during breathing. The quartile frequency features will be employed in this thesis to investigate changes in frequencies due to inhaler PIFR.

4.5 Objective Measurement of PIFR

This Section describes the airtight adapter and spirometer employed in this thesis. This equipment was employed extensively in Chapters 5 and 6.

4.5.1 Airtight Adapter

In this thesis an airtight container/adapter was used in conjunction with an inhaler and a spirometer to obtain objective measurements of PIFR during inhaler use. This method has been used previously in the literature to measure inhaler PIFR (Azouz et al., 2015). The airtight
container ensures that all inspired air through the mouthpiece of the inhaler flows through the spirometer, from where it can be measured objectively. Clear PET (Polyethylene Terephthalate) containers were used in this thesis to act as airtight adaptors between an inhaler and a spirometer. Figure 4.2 shows an example of one such airtight adapter, with an empty Diskus™ inhaler placed into the container. This specific airtight adapter had a custom aperture cut for the mouthpiece, the INCA device and the spirometer connector.

![Image of a custom airtight adapter](image)

Figure 4.2: Example of a custom airtight adapter, which was built for use with the Diskus DPI and INCA recording device.

For the Diskus inhaler the mouthpiece was extended out 1 cm in length in order for subjects to get a good seal around the mouthpiece. The aperture for the INCA device was cut so that the position of the INCA device resembled that of real world use i.e. sitting flush on the Diskus inhaler; this limited the damping of the acoustic signal. Steinel Hybond 86 adhesive was used to seal any gaps and prevent any unintentional air from going in or out of the container. The container was submerged in a water bath before each test in order to verify that it was airtight. The end result was that air could only enter or exit via the inhaler mouthpiece and through the spirometer connector. This setup allows for the objective measurement of inhaler PIFR, with the spirometer acting as the gold standard measurement method.

### 4.5.2 Spirometer

A Vitalograph Pneumotrac 6800 spirometer was employed for a number of studies in this thesis. The spirometer uses a Fleisch pneumotachograph to record airflow/volume measurements. The spirometer can be connected to an airtight adapter, such as the one described previously in Section 4.5.1. In addition, the spirometer can also be employed to measure study participants’
l lung function. The specifications of the spirometer used in studies detailed in this thesis are as follows:

- Flow detection principle: Fleisch type pneumotachograph
- Volume detection: Flow integration sampled at 100 Hz
- Accuracy:
  - Volume: Better than ± 3 %
  - Flow: Better than ± 5 %
  - Linearity: ± 1 % in range 0.1 L/s to 16 L/s
- Resistance: < 1.2 cm H₂O/L s⁻¹ at 14 L/s
- Calibrated to perform in line with BS EN ISO 23747: 2009 standards

4.6 INCA Audio Recording Device

The INCA electronic inhaler monitoring device, manufactured by Vitalograph Ltd., was employed in several studies in this thesis. The INCA device enables the acoustics of Diskus DPI use to be recorded for analysis (Figure 4.3).

![INCA device](image)

*Figure 4.3: INCA electronic monitoring device which records the acoustics of Diskus DPI use.*

The INCA device contains a microphone, microcontroller and battery. The microphone is a Knowles Acoustics SPU0414HR5H-SB MEMS microphone (see Appendix A for microphone specifications). The audio files are stored on the INCA device from where they can be subsequently uploaded to a computer via a USB connection. The INCA device can be used in conjunction with the common Diskus inhaler. The INCA device can be bonded securely to the side of the Diskus inhaler, from where it does not impact on the mechanics of inhaler use. The INCA device starts recording once the Diskus inhaler is opened and switches off when the Diskus is
The acoustics of inhaler use are recorded as mono WAV files, at a sampling rate of 8000 Hz and resolution of 8 bits/sample. The INCA device has sufficient battery life to record patient inhaler use for a period of one month.

4.7 Summary

This Chapter presented acoustic features that may be employed to detect and analyse inhaler based breath sounds. The feature extraction methods described in this Chapter will be employed in studies presented in the following Chapters of this thesis. Methods to objectively measure PIFR through inhaler devices were also presented (airtight adapter and spirometer), while the acoustic recording device (INCA) employed to record inhaler audio signals was also discussed. The next Chapter, Chapter 5, will describe studies that investigated the relationship between acoustic features of the inhalation signal with objective measures of inspiratory flow rate.
CHAPTER 5: Investigation into the Relationship between Inspiratory Inhaler Acoustic Signals and Inspiratory Flow Rate, Volume and Drug Delivery in the Diskus Inhaler

The studies described in this Chapter examine research questions 1-6 as posed in Section 3.1 of Chapter 3. As was discussed in Section 2.3 of Chapter 2, adherence to correct inhaler technique is low (typically around 50%). The studies presented in this Chapter investigate the relationship between acoustic features of inhaler inspiratory signals with objective measurements of PIFR, inspiratory volume and drug delivery. Based on previous research in the field of tracheal and chest wall breath sounds, it was hypothesised that the sounds generated as air is inhaled through an inhaler device may be correlated with the PIFR and inspiratory volume (or inspiratory capacity). Furthermore, it was also hypothesised that since drug delivery in DPIs is dependent on PIFR, acoustic methods may also be employed to estimate the level of drug deposition in the airways. It was hypothesised that as PIFR through an inhaler device increases, a similar increase may be observed in temporal and spectral features of the inhaler inhalation signal. The studies presented in this Chapter examine the aforementioned hypotheses, which have not been investigated in the literature previously.

5.1 An In Vitro Investigation into the Feasibility of Using Acoustic Features to Estimate Inspiratory Flow Rate and Drug Removed from a Dry Powder Inhaler

5.1.1 Introduction

Despite the fact that a full inspiratory effort leads to effective disease management (Horne et al., 2005), many patients fail to reach the minimum inspiratory effort or PIFR necessary to remove medication from their inhaler (Janssens et al., 2008). This minimum PIFR threshold is 30 L/min for DPIs. Failure to reach this PIFR means that patients may fail to obtain the intended total emitted dose (TED) from their inhaler, leading to decreased levels of drug lung deposition and clinical efficacy (Chrystyn, 2003). As up to 28% of patients are unable to inhale with adequate PIFR, there exists a strong need to monitor patients PIFR and TED levels in order to objectively analyse their ability to correctly use their inhaler.

Previous studies have demonstrated a relationship exists between airflow and breath sounds (Hossain and Moussavi, 2004; Gavriely and Cugell, 1996; Kraman, 1984). Most of the previous
research in this area has focused on respiratory sounds originating at the chest wall and trachea. However, this relationship has not previously been investigated in relation to inspiratory inhaler sounds. The primary aim of this study was to investigate if acoustic measurements of inhaler use could be used to predict the flow rate and drug removed from a commonly used DPI in an in vitro based environment.

The primary hypotheses tested in this study were:

1. Temporal and spectral features of a simulated inhalation signal contains important information regarding the PIFR through a Diskus DPI
2. TED can be determined from temporal and spectral features of the simulated inhalation signal
3. Analysis of (1) and (2) may be employed to demonstrate that inhaler inhalation user technique adherence may be determined using acoustics.

The ability to predict PIFR and TED may provide clinicians with objective measurements that may be useful in determining if a patient is capable of using their inhaler with correct technique.

5.1.2 Methods

Experimental Test Setup

A novel test rig was designed to simulate inhalations in an in vitro environment (Figure 5.1). The test rig employed an air vacuum to replicate patient inhalations. The flow rate of each inhalation was varied by controlling the power to the vacuum through a variable power supply. An on/off valve was used to vary the duration of each inhalation. PIFR was measured using a rotameter, while a specially designed fixture was used to hold the inhaler securely in place. The inhaler used was the Diskus DPI. The INCA device, was bonded securely to the side of the Diskus in order to record the audio signal of each simulated inhalation. To measure the percentage of TED achieved for each inhalation a milligram scale was used to weigh the Diskus before and after each trial.
Figure 5.1: Experimental test setup employed to remove drug from Diskus DPI.

Simulated inhalations were carried out from 100 L/min to 40 L/min in steps of 10 L/min and from 40 L/min to 10 L/min in steps of 5 L/min. This is the flow range typically achieved by patients during Diskus inhaler use. Tests were carried out for all of the aforementioned flow rates for inhalations of duration 0.5 s, 1 s, 2 s and 3 s, durations typical of Diskus inhaler use. A total of 52 trials were carried out (13 simulated inhalations x 4 inhalation durations). To address the issue of drug residue remaining in the mouthpiece of the Diskus and leading to inaccurate TED measurements, the device was cleaned out after every four trials using an air compressor gun.

Data Analysis

The inhalation audio signals were divided into frames of length 1,024 samples with 50% overlap between successive frames. The window used to analyse each segment was a Hamming window, while an FFT was used to calculate the power spectrum of each segment. The MA of the inhalations was calculated using a relative peak detection method. This method was chosen over calculating the mean value of the inhalation signal in order to reduce the effect of noise artefacts in the analysis. In addition to calculating the MA of the inhalation signals, MAD and RMS of the signal was also calculated using methods discussed in Chapter 4.

The average power of each inhalation was calculated over the frequency bands: 20-40Hz, 40-70Hz, 70-150Hz, 150-300Hz, and 300-600Hz, in addition to the frequency bands 70-300Hz, 70-450Hz, 100-300Hz, 100-450Hz and 150-450Hz respectively. These frequency bands were chosen as they were previously used in a study by Hossain and Moussavi (2004), investigating the relationship between flow rate and average power in respiratory sounds. It was hypothesised that these frequency bands may relate to vibrations in the Diskus inhaler at low frequency levels (i.e. below 600 Hz).
5.1.3 Results

Experimental results indicate that there is a strong correlation between simulated flow rate and acoustic features. The relationship between MA, MAD and RMS to PIFR was best described using quadratic regression models. The coefficient of determination ($R^2$) was found to be 0.9767 between MA and PIFR, 0.9675 between RMS and PIFR and 0.9784 between MAD and PIFR. Similarly there was a strong relationship between the average power of the simulated inhalations at the selected frequency bands and PIFR. The results of these correlations are demonstrated in Table 5.1 below. All correlations were found to be statistically significant ($p < 0.01$). Overall, it was found that MAD represented the best method of predicting PIFR, based on its $R^2$ value in this experimental in vitro based study (Figure 5.2).

Table 5.1: Correlation of $R^2$ values with various frequency bands.

<table>
<thead>
<tr>
<th>Frequency Band (Hz)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>0.9725</td>
</tr>
<tr>
<td>40-70</td>
<td>0.9720</td>
</tr>
<tr>
<td>70-150</td>
<td>0.9630</td>
</tr>
<tr>
<td>150-300</td>
<td>0.9757</td>
</tr>
<tr>
<td>300-600</td>
<td>0.9740</td>
</tr>
<tr>
<td>70-300</td>
<td>0.9732</td>
</tr>
<tr>
<td>70-450</td>
<td>0.9772</td>
</tr>
<tr>
<td>100-300</td>
<td>0.9720</td>
</tr>
<tr>
<td>100-450</td>
<td>0.9720</td>
</tr>
<tr>
<td>150-450</td>
<td>0.9779</td>
</tr>
</tbody>
</table>

Figure 5.2: Relationship between PIFR and MAD.
The Diskus inhaler was weighed before and after each simulated inhalation in order to calculate the percentage of TED removed. The available weight in each dose of the inhaler was 13.05 mg, which represented a TED of 100%. When PIFR was plotted against TED it was found that for a PIFR of 30 L/min at least 77% of the TED was extracted from the inhaler (i.e. 10.04 mg of drug). For PIFR values of 35L/min or greater the percentage of the TED removed through the simulated inhalations remained consistently high (92-109%). It was possible to remove more than 100% of the TED if drug remained in the mouthpiece from previous inhalations. Below 30 L/min there was a dramatic decrease in percentage of TED removed (25% TED for a PIFR of 10L/min). It was found that the duration of the inhalations did not impact the amount of drug removed from the inhaler. The acoustic features employed in this study provide a method of estimating PIFR in this simulated experiment. As the acoustic features employed can be related to PIFR and since TED is PIFR dependent, it is therefore possible to predict TED by employing acoustic analysis methods. To demonstrate this, a MAD value of 0.0049 would imply that 77% of the drug is removed from the mouthpiece of the inhaler, as this is the MAD value that corresponds with a PIFR of 30 L/min. To visualise this, MAD was plotted against TED as can be seen in Figure 5.3.

![Figure 5.3: Total emitted dose (TED) versus mean absolute deviation (MAD).](image)

### 5.1.4 Discussion

The aim of this in vitro study was to investigate if acoustic measurements could be used to predict the inspiratory flow rate and drug removed from a dry powder inhaler in an experimental test setup. Results indicated that MA, RMS, MAD and $P_{ave}$ are strongly correlated with PIFR ($R^2>0.96$). It was found that quadratic regression models best described the relationship between MA, MAD and RMS to PIFR, while linear regression models best described the relationship between average power and PIFR. MAD represented the best overall method of predicting PIFR. It was also demonstrated that TED is PIFR dependent, which indicates that it is possible to consequently predict TED using acoustic measurements. The strong level of correlation between the variables is
a promising result as it proves the hypotheses that acoustics can be used to predict PIFR and TED, and that these variables may be used to assess inhaler user technique.

As discussed in Chapter 2, a number of previous studies have been carried out into the relationship between respiratory sounds (tracheal and chest wall) and airflow rate. However, this study differs from previous studies in that the sounds analysed are inhaler sounds. Inhaler sounds are a mixture of both respiratory sounds and sounds created by the inhaler device. The results support previous research which established that variations in flow rates affect the intensity and frequency distribution of sounds (Gavriely and Cugell, 1996; Kraman, 1984). A study by Hossain and Moussavi (2004) indicated that $P_{ave}$ had the strongest correlation with the airflow generated by subjects breathing, and that a power model best described this relationship in healthy adults and children. The same study also found that the optimum frequency band to calculate $P_{ave}$ to be 150-450 Hz. The experimental study presented here found that MAD exhibited the strongest correlation with simulated inspiratory flow ($R^2=0.9784$). Of the frequency bands investigated in this present study, it was established that the 150-450 Hz frequency band provided the strongest correlation with inspiratory flow through an inhaler device. In the study presented here, quadratic regression models best described the relationship between MA, MAD and RMS to PIFR (based on $R^2$ values). A number of studies have indicated that a power regression model best describes the relationship between spectral power and flow in respiratory sounds (Gavriely and Cugell, 1996; Hossain and Moussavi, 2004), however, in this study it was found that a linear model best described the spectral power data in inhaler sounds. Reasons for this variation may be due to the turbulence created by the inhaler device, the fact that the current study employed an experimental model to simulate inhalations opposed to actual patients, and that this study investigated flow values between 10-100L/min (typical inhaler flow range), as opposed to the flow of breaths which range between 30-180L/min (Gavriely and Cugell, 1996; Hossain and Moussavi, 2004).

A number of previous in vitro studies have been carried out investigating the relationship between PIFR and TED (De Boer et al., 1996; Hindle and Byron, 1995). These studies reported that for a PIFR of 30L/min as little as 50% of TED is delivered while this can drop as low as 25% at a PIFR of 20L/min. The results of the current study are in agreement with previous research in this area. In the current study TED was found to be 77% at a flow rate of 30L/min, while TED dropped to 25% for a flow rate of 10 L/min. Inhalations are judged to be clinically effective above a flow rate of 30L/min. U.S. FDA guidelines require all inhalers to deliver 75%-125% of the claimed label dose (FDA, 1998). This study proves the hypothesis that acoustic measurements such as MAD, RMS, etc. can be used to predict TED.
This study has some limitations due to its experimental nature. Inhalations were simulated using an air vacuum, while PIFR was controlled using a variable power supply. A number of factors can influence the amount of drug removed from a DPI and the probability of the medication reaching the distal pathways of the lung. Such factors include PIFR, rise or ramp rate of the inhalation and total air volume inhaled. In this study an instantaneous ramp rate is used which is not fully representative of actual inhalations which have a more gradual ramp rate. There may also have been slight variations in the PIFR measured by the rotameter, and the actual PIFR at the mouthpiece of the Diskus inhaler. However despite these limitations, this study has a number of important findings.

The ability to estimate PIFR and TED values from an inhaler using acoustics may have a number of benefits for both clinicians and inhaler users. Current methods of assessing patients’ inhaler technique are limited in that clinicians make subjective decisions on a patient’s ability to use their inhaler. Effective inhalations are primarily dependent on the flow rates achieved which cannot be measured during inhaler use. Therefore a method of estimating PIFR during inhaler use may be highly beneficial. Actively measuring TED would also help clinicians understand if patients are getting the full amount of medication from their inhaler and if they are capable of using their inhaler device. This type of quality feedback may encourage patients to improve their inhaler technique, which in turn may improve the clinical efficacy of the inhaler medication.

5.1.5 Conclusions

In conclusion, it has been demonstrated that it is possible in an experimental trial to estimate airflow rate and drug removed from an inhaler device using acoustic based features. Being able to predict such values provides clinicians with important objective measurements on patients inhaler use. Acoustic monitoring of inhaler use is beneficial as it is a non-invasive method of observing patient inhaler technique. The next Section of this Chapter will focus on estimating inspiratory flow rate and volume from a Diskus DPI during actual inhaler use.

5.2 A Method of Estimating Inspiratory Flow Rate and Volume from an Inhaler using Acoustic Measurements

5.2.1 Introduction

In Section 5.1 of Chapter 5 it was found that there was a relationship between temporal and spectral acoustic features of simulated inspiratory inhaler sounds and PIFR. This Section will
investigate the relationship between acoustic features of actual inhaler inhalations and PIFR, in addition to inspiratory volume (or inspiratory capacity).

This study aims to investigate if a relationship exists between inhaler inhalation sounds and airflow during inhaler use. Inhaler inhalation sounds are a mixture of both respiratory sounds and sounds created from turbulence in the inhaler. It is well known that a relationship exists between airflow and respiratory sounds. Most of the previous research in this area has examined the relationship between respiratory sounds generated at the trachea and on the chest wall to airflow.

The main objectives of this study were to investigate the relationship between temporal and spectral features of the inhalation sound and inspiratory flow rate and volume measurements in healthy subjects. It was hypothesised that features obtained from the inhalation sound could be used to estimate PIFR and IC. Three measurements of amplitude were used, in addition to the $P_{ave}$ feature at a range of different frequency bands, in order to investigate which acoustic measurement had the best correlation with PIFR and IC. Using the inhalation signal to estimate such inspiratory values would establish the feasibility to provide clinicians with new objective measurements on patient inhaler use.

### 5.2.2 Methods

**Participants**

Fifteen healthy volunteers between the ages of 18-40 years were recruited. Subjects were excluded if they had any cardiac, respiratory, hepatic, renal dysfunction, recent respiratory tract infection in the last six weeks, a greater than ten pack/year smoking history, a history of drug/alcohol abuse or a known sensitivity to Salmeterol or Fluticasone. Baseline Spirometry was performed according to ATS recommendations (Miller et al., 2005) to confirm that subjects had normal lung function.

**Flow Experimental Design**

A spirometer is a device that is capable of measuring the flow rates and volume of air inspired and expired by the lungs. Several studies have previously employed an airtight container to connect an inhaler to a spirometer in order to obtain flow measurements through an inhaler device (Magnussen et al., 2009; Malmberg et al., 2010). The airtight container ensures that all inspired air through the mouthpiece of the inhaler comes through the spirometer where it can be measured. In this study a clear PET (Polyethylene Terephthalate) container was used to act as an airtight adaptor between a Diskus inhaler and a spirometer. An empty Diskus inhaler was placed into the container (Figure 4.7), which had a custom aperture cut for the mouthpiece, the INCA
device and the spirometer connector. The mouthpiece was extended out 1cm in length in order for subjects to get a good seal around the mouthpiece. The aperture for the INCA device was cut so that the position of the INCA device resembled that of real world use i.e. sitting flush on the Diskus inhaler; this limited the damping of the acoustic signal. Steinel Hybond 86 adhesive was used to seal any gaps and prevent any unintentional air from going in or out of the container. The container was submerged in a water bath before each test in order to verify that it was airtight. This produced a system in which air could only enter or exit via the inhaler mouthpiece and through the spirometer connector.

**Spirometer Employed**

The spirometer used was the Vitalograph Pneumotrac (Model 6800) supplied by Vitalograph Ltd. The specifications of this spirometer were presented in Chapter 4.

**Test Procedure**

The airtight container described previously was connected to the spirometer. Patients were instructed to exhale gently (to functional residual capacity) and then inhale at a variety of flow rates and volumes. Each patient performed this manoeuvre six to eight separate times. The airtight container was sterilized after each patient performed the test to ensure that no infections were passed between subjects. A graphical representation of the overall test set up can be seen in Figure 5.4.

![Spirometer and Inhaler Diagram](image)

*Figure 5.4: Preliminary experiment design showing the interaction between subject, inhaler, airtight container and spirometer. Note: Final container design shown previously in Figure 4.7.*
Inhalation Signal Analysis

The inhalation audio signals were divided into frames of length 1,024 samples with 50% overlap between successive frames. A Hanning window was used to analyse each segment, while an FFT was used to calculate the power spectral density. Three measures of amplitude were employed in this study; MA, MAD of the amplitude and RMS of the amplitude. These three measures of amplitude were chosen in order to investigate which had the best correlation with PIFR and IC.

The average power \( P_{ave} \) of each inhalation was calculated in the frequency bands: 20-40 Hz, 40-70 Hz, 70-150 Hz, 150-300 Hz, and 300-600 Hz, in addition to 70-300 Hz, 70-450 Hz, 100-300 Hz, 100-450 Hz and 150-450 Hz. These frequency bands were chosen as they were previously used in a study by Hossain and Moussavi (2004) which investigated the best frequency band to estimate flow rate from respiratory sounds obtained from the chest wall. They were also employed in the first study of this Chapter, where they achieved high \( R^2 \) values (> 0.97).

In spirometry, the area under a PIFR – time curve equates to the volume of an inhalation or IC. Since acoustic measurements were used to predict the PIFR, integration could not be used to determine IC. Instead it was noted that the area under the curve of the inhalational sound waveform (inhalation volume) approximates that of the area of a semi-ellipse, described by the following equation:

\[
\text{Inhalation Volume} = \frac{1}{2} \pi \cdot A \cdot \frac{B}{2}
\]  

(5.1)

Where \( A = \text{PIFR} \) and \( B = \text{Duration} \). Values for MA, MAD, RMS and \( P_{ave} \) for each inhalation were employed to obtain predicted values for the mean PIFR. These predicted mean PIFR values and the actual duration of the inhalation were used to calculate a predicted IC value. The predicted values for IC were then compared to the actual IC values for each inhalation, as obtained from the spirometer.

Figure 5.5: Area of semi-ellipse from which the volume or inspiratory capacity (IC) of an inhalation can be calculated.
Statistical Analysis

Analysis was carried out using the statistical software Stata SE Version 12. This study was designed as a repeated measures study due to the fact that the samples were not independent. A Generalised Least Squares (GLS) regression model, which accounts for random effects intercept at the subject level, was used to compare the acoustic parameters of MA, MAD, RMS and $P_{a\text{ve}}$ with measured PIFR and IC. The GLS model takes into account the correlation between the observations when calculating the regression model and was thus deemed appropriate for analysis of the data in this study.

5.2.3 Results

Table 5.2 presents the demographics and baseline lung function of the 15 healthy volunteers enrolled in this study. The ethnic origin of subjects was Caucasian for 93.3% (14/15) and Hispanic for the remaining 6.7% (1/15). All subjects had an FEV1/FVC ratio >0.7 and a predicted FEV1 > 89%, confirming normal baseline lung function according to ATS standards.
Table 5.2: Summary of demographics and baseline lung function data from all subjects (n=15).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.9</td>
<td>4.2</td>
<td>22-35</td>
</tr>
<tr>
<td>Gender (Males)</td>
<td>(9/15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.5</td>
<td>6.4</td>
<td>164-185</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.8</td>
<td>9.0</td>
<td>56-91</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;a&lt;/sup&gt; (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>23.86</td>
<td>2.21</td>
<td>20.8-29.7</td>
</tr>
<tr>
<td>FEV1&lt;sup&gt;b&lt;/sup&gt; (L)</td>
<td>3.98</td>
<td>0.58</td>
<td>2.79-4.85</td>
</tr>
<tr>
<td>FEV1&lt;sup&gt;b&lt;/sup&gt; (%) Predicted</td>
<td>99.33</td>
<td>5.33</td>
<td>92-110</td>
</tr>
<tr>
<td>FVC&lt;sup&gt;c&lt;/sup&gt; (L)</td>
<td>4.90</td>
<td>0.73</td>
<td>3.41-6.24</td>
</tr>
<tr>
<td>FEV1/FVC Ratio</td>
<td>0.81</td>
<td>0.06</td>
<td>0.70-0.91</td>
</tr>
<tr>
<td>PEFR&lt;sup&gt;d&lt;/sup&gt; (L/min)</td>
<td>547.6</td>
<td>103.7</td>
<td>384-744</td>
</tr>
<tr>
<td>FIVC&lt;sup&gt;e&lt;/sup&gt; (L)</td>
<td>4.56</td>
<td>0.67</td>
<td>3.34-5.76</td>
</tr>
<tr>
<td>PIFR&lt;sup&gt;f&lt;/sup&gt; (L/min)</td>
<td>402.1</td>
<td>82.1</td>
<td>276-535</td>
</tr>
</tbody>
</table>

<sup>a</sup> BMI – Body Mass Index
<sup>b</sup> FEV1 – Forced Expiratory Volume in 1 second
<sup>c</sup> FVC – Forced Vital Capacity
<sup>d</sup> PEFR – Peak Expiratory Flow Rate
<sup>e</sup> FIVC – Forced Inspiratory Vital Capacity
<sup>f</sup> PIFR – Peak Inspiratory Flow Rate

A total of 120 audio files were obtained from the 15 subjects. 17 audio files were discarded due to corrupted signals. In this study the PIFR range of interest was between 0-100 L/min and a subsequent 17 audio files were omitted that had PIFR values greater than 100 L/min, leaving a total of 86 observations from the 15 subjects. For each inhalation the spirometer provided values for PIFR and IC. PIFR was compared to MA, MAD and RMS of the inhalation signal, while P<sub>ave</sub> at several select frequency bands (described earlier) was also compared to PIFR.

It was found that MA, MAD and RMS were all highly correlated with PIFR (P < 0.00001) at a significance level of α= 0.05. The coefficients of determination were found to be $R^2 = 0.8386$ for MA, $R^2 = 0.8340$ for MAD and $R^2 = 0.8320$ for RMS. $P_{ave}$ for a range of select frequency bands was
also calculated. Using a GLS regression model to compare PIFR to $P_{\text{ave}}$ it was found that the relationship was also highly correlated for all of the frequency bands ($P < 0.00001$, $\alpha = 0.05$). It is worth noting that at higher powers, the GLS regression model will give PIFRs exceeding the maximum possible flow rate through the inhaler (i.e. >150 L/min). The $P_{\text{ave}}$ in the frequency band 300-600 Hz had the strongest correlation with PIFR, as the GLS regression model for this frequency band had an $R^2$ value of 0.9079. A complete analysis of the relationship between $P_{\text{ave}}$ and PIFR for each of the frequency bands analysed is presented in Table 5.3. The overall results demonstrating the relationship between MA, MAD, RMS, $P_{\text{ave}}$ and PIFR can be seen in Figure 5.7. Individual plots of acoustic parameters versus PIFR for each subject with the associated GLS regression can be found in Appendix B.

Table 5.3: Correlation scores between $P_{\text{ave}}$ and PIFR.

<table>
<thead>
<tr>
<th>Frequency Band (Hz)</th>
<th>Coefficient of Determination ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>0.7865</td>
</tr>
<tr>
<td>40-70</td>
<td>0.7018</td>
</tr>
<tr>
<td>70-150</td>
<td>0.8067</td>
</tr>
<tr>
<td>150-300</td>
<td>0.8461</td>
</tr>
<tr>
<td>300-600</td>
<td>0.9079</td>
</tr>
<tr>
<td>70-300</td>
<td>0.8427</td>
</tr>
<tr>
<td>70-450</td>
<td>0.8746</td>
</tr>
<tr>
<td>100-300</td>
<td>0.8431</td>
</tr>
<tr>
<td>100-450</td>
<td>0.7018</td>
</tr>
<tr>
<td>150-450</td>
<td>0.8807</td>
</tr>
</tbody>
</table>

With the analysis of MA, MAD, RMS and $P_{\text{ave}}$ it is possible to estimate IC. Figure 5.6 demonstrates that it is possible to estimate values for PIFR from analysis of the inhalation signal.

GLS regression demonstrated that IC can be estimated using MA, MAD, RMS and $P_{\text{ave}}$ ($P < 0.0001$, $\alpha = 0.05$). The coefficients of determination ($R^2$) for predicting IC were 0.9020 for MA, 0.9047 for MAD, 0.8989 for RMS and 0.9245 for $P_{\text{ave}}$ in the frequency band 300-600 Hz. Figure 5.7 presents plots of actual IC versus IC estimated from MA (ICma), MAD (ICmad), RMS (ICrms) and $P_{\text{ave}}$ (IC$P_{\text{ave}}$).
GLS Regression outputs for each acoustic parameter and individual plots of calculated versus measured IC for each subject can be found in Appendix C.

Figure 5.6: PIFR versus (a) MA, (b) MAD amplitude, (c) RMS amplitude and (d) average power ($P_{ave}$) in the frequency band 300-600Hz. Plotted points are calculated PIFRs based on regression equation for each subject. Black line represents overall regression model equation.
5.2.4 Discussion

The aim of this study was to investigate whether acoustic features of inhalations could be used to estimate PIFR and IC in 15 healthy subjects. The main results reveal that MA, MAD and RMS of the amplitude and $P_{\text{ave}}$ at a range of different frequency bands all provided a robust method of estimating PIFR and IC. These findings are in agreement with the results reported in Section 5.1 of this Chapter. The high level of correlation between PIFR and IC from the acoustic measurements to the “gold standard” method using spirometry is a promising result, suggesting that this approach may be used in future validation studies.

As was discussed in Chapter 2, several previous studies have investigated the relationship between respiratory sounds and airflow. Unlike studies that have investigated respiratory sounds recorded on the chest wall and trachea, this study focused on sounds generated during inhaler use. Inhaler sounds are a mixture of both respiratory sounds and sounds from the inhaler itself. The microphone was located in the INCA device, which was securely bonded to the inhaler in a location less than 5cm from the mouth. The results of this study are in accordance with previous research which established that variations in flow are reflected in the intensity and frequency distribution of the sounds generated (Kraman, 1984; Gavriely and Cugell, 1996). A study by Hossain and Moussavi (2004) indicated that $P_{\text{ave}}$ had the strongest correlation with flow rate from
respiratory sounds. The results of the present study found that $P_{\text{ave}}$ had the strongest correlation with flow rate from inhaler sounds. The same study by Hossain and Moussavi (2004) also reported that the optimum frequency band to calculate $P_{\text{ave}}$ was 150-450 Hz for healthy subjects, while in the present study we found this optimum frequency band to be 300-600 Hz for inhaler sounds. It is therefore clear to see that the sounds created by the inhaler are different in comparison to normal respiratory sounds. Inhaling through the narrow opening of the Diskus inhaler has created a shift in sound intensity towards higher frequencies.

The additional dead space volume of the airtight container adds additional airway resistance to the overall pathway of the spirometer. This means that a slightly greater patient effort is required in order to obtain PIFR and IC values that would have been reached without the airtight container. This could lead to values of MA, MAD, RMS and $P_{\text{ave}}$ obtained being slightly higher than they should be for the corresponding PIFR and IC values. However, for the purposes of this study it was decided that the effects of the containers dead space is small enough to be negligible, given that the ranges studied were quite large (range of 100L/min for PIFR and 3.54L for IC). The additional dead space of the container also met ATS 2005 requirements for spirometry, in that the total dead space of the circuit was less than 350 ml. One point to consider in this study also is that if the sound is generated by the flow through the inhaler, the frequency content of the sound may be proportionally shifted to higher frequencies at higher flows. Further research is required to better interpret this effect on the results of this study and this topic will be investigated further in Chapter 6.

The current methods of assessing patients’ inhaler technique are limited. At present clinicians make a subjective decision on whether a patient’s inhalation is sufficiently adequate for their medication to reach their airways. However an effective inhalation is dependent on inspiratory flow rate, which cannot be measured subjectively. PIFR can be measured using training devices such as a Clement Clarke In-Check Dial™ device (Janssens et al., 2008; Amirav et al., 2005), although this device is not widely used and when it is used, it is primarily in clinical environments. Additionally, the effort patients exert in front of the clinician may not correlate to the effort they put into using their inhaler on a day-to-day basis. The method we propose in this paper allows PIFR values from real world patient inhaler use to be acquired, in addition to IC values.

The objective of this study was to demonstrate the feasibility of using acoustic measurements to estimate PIFR/IC from inhalers. The regression models are inherently biased to the dataset used and hence cannot be used to estimate the 95% CI for a population of individuals. Nonetheless, the regression outputs in Appendix B show that the 95% CIs for the variables are actually relatively small, suggesting potential clinical benefit in carrying out a validation study on a large population
of inhaler users. There are numerous potential clinical applications for a system that can accurately predict PIFR and IC from patients’ inhalations during inhaler use. A standard threshold could be put in place to inform clinicians whether a patient performed an effective or ineffective inhalation. PIFR and IC could also be monitored on a day-to-day basis, providing the opportunity to assess patients’ respiratory condition over time. Monitoring PIFR and IC longitudinally may provide the opportunity to predict and prevent exacerbations before they take place. The method of calculating PIFR and IC as described in this study is independent of age and thus has many benefits for monitoring inhaler therapy. Analysis of PIFR may also show when narrowing of the airways occurs, while analysis of IC variations might be used to study dynamic hyperinflation, and monitor the drop in IC associated with exacerbations. Informing patients of their day-to-day PIFR and IC values may also encourage them to take better control of their respiratory disease, as they may come to realise that a greater effort is required on their part, in order to help deliver the medication to their airways. Such active feedback may provide the opportunity to improve the efficacy of the medication, reduce exacerbations and lower the frequency of admissions to hospital emergency departments.

5.2.5 Conclusion

In conclusion, it has been shown that acoustics can be employed to estimate the PIFR and IC values of healthy subjects’ inhalations through a DPI device. It was found that $P_{\text{ave}}$ in the frequency band 300-600 Hz provided the best acoustic measurement to predict PIFR, while $P_{\text{ave}}$ in the same frequency band also represented the best method of predicting IC. The ability to use acoustic measurements to estimate PIFR and IC provides clinicians with new objective measurements that reveal the quality of a patient’s inhaler inhalation effort. Such objective measurements may allow clinicians to reach a decision on a patient’s ability to use their inhaler and also to provide feedback to a patient concerning their technique. Quality active feedback may encourage patients to improve their inhaler technique, which in turn may improve the clinical efficacy of inhaler medication, reduce the number of exacerbations, hospital admissions and ultimately reduce mortality rates.

5.3 Chapter Summary

This Chapter examined the relationship between inspiratory inhaler acoustic signals and inspiratory flow rate, volume and drug delivery in the Diskus DPI. The first study found that in an in vitro experiment, acoustic features of the inhalation sound were highly correlated with PIFR. In addition to this, it was found that acoustic features of the inhalation sound are related to the quantity of drug removed from a Diskus DPI. In the second study, it was observed that in 15
healthy individuals, a clear relationship exists between PIFR and inspiratory capacity with acoustic features of the inhaler inhalation sound. These findings would indicate that it is possible to use acoustics to model the clinical efficacy of inhaler inhalations.
CHAPTER 6: Characteristics of Ambient Inspiratory Inhaler Sounds

This Chapter examines research questions 7-11 which were posed in Section 3.2 of Chapter 3. As discussed previously in Chapter 2, the acoustical characteristics of inspiratory inhaler sounds have not previously been defined. Chapter 5 demonstrated that acoustic based features can be employed to estimate PIFR, IC and TED from a Diskus DPI, however, the specific characteristics of the sounds were not fully quantified. The effect of PIFR on the frequency content of inhalation sounds was not investigated thoroughly in Chapter 5. It is essential to define the time/frequency characteristics of normal inspiratory inhaler sounds, in order to establish a baseline against which future inhaler acoustic studies may be compared. The main aim of the study detailed this Chapter was to investigate the temporal and spectral characteristics of normal inspiratory inhaler sounds. The variations in acoustic features were investigated in relation to PIFR. The repeatability of the sounds was also investigated.

6.1 Introduction

Many patients are unable to reach the recommended PIFR in inhaler devices (Jarvis et al., 2007). Regardless of what inhaler device a patient uses, PIFR is a critically important metric and should be monitored. There is currently a lack of objective methods to monitor PIFR longitudinally in non-clinical environments. In Chapter 5, it was reported that acoustic methods may be employed to estimate PIFR and inspiratory capacity (IC) in healthy participants using the Diskus. One of the current limitations of the acoustic device employed (INCA) is that the acoustic monitoring device can only be used with the Diskus inhaler. There has recently been a surge in the popularity of wearable technologies (i.e. smart watches) and the potential to use non-contact (i.e. not attached to the patient’s skin or the inhaler device) acoustic methods to monitor inhaler use is a promising opportunity. In this study, the feasibility of using non-contact acoustic methods to estimate PIFR in three commonly used inhalers will be investigated.

The main objectives of this study are to use non-contact acoustic methods to estimate PIFR in three commonly used inhalers (Diskus DPI, Turbuhaler DPI, and Evohaler pMDI). The variability of temporal and spectral acoustic features at an intra-subject level will be investigated to determine the reliability of acoustic features in analysing inhaler inhalation sounds. Finally, the repeatability of the acoustic spectral profile will be analysed to determine if the position of the peaks and troughs of the profile remain unchanged within participants across a range of PIFRs. This will provide a baseline for future development of feature extraction methods for inspiratory inhaler acoustic analyses.
6.2 Methods

6.2.1 Participants

There are a number of factors that affect the acoustic properties of breath sounds such as sex (Gavriely et al., 1995), age (Kanga and Kraman, 1986) and height (Pasterkamp et al., 1993; Pasterkamp and Sanchez, 1996). Therefore, a cohort of males with a narrow age, weight and height range were chosen to characterize the inspiratory inhaler sounds in this study. Eleven healthy young (age range: 22-31) adult males were recruited. All participants were free from respiratory tract infections and were non-smokers. Baseline spirometry was performed to ATS/ERS recommendations to confirm that all participants had normal lung function.

6.2.2 Inhaler Recording Setup

Three custom-built polyethylene terephthalate (PET) airtight containers were assembled for three commonly used inhalers; Diskus, Turbuhaler and Evohaler. The airtight containers were connected to a Vitalograph Pneumotrac 6800 spirometer to obtain PIFR measurements. Several previous studies have reported using an airtight container as a method to calculate PIFR during inhaler inhalations (Malmberg et al., 2010; Magnussen et al., 2009). The airtight container design ensured that all air inhaled through each inhaler flowed through the spirometers pneumotachograph from where flow rate can be measured objectively.

An Earthworks TC30 [Earthworks Inc., New Hampshire, USA] omnidirectional microphone was employed to record the sounds associated with inhaler inhalations through the airtight container. The microphone has a flat frequency response from 9 Hz to 30 kHz. The microphone was positioned 5 cm away from the edge of the inhaler mouthpiece in the airtight container. A Novation nio 2/4 [Novation, UK] was employed as an audio interface and Adobe Audition V6.0 was used to record audio data with a sampling rate of 44.1 kHz and resolution of 32 bits/sample in a data acquisition laptop. The complete experimental setup is demonstrated graphically in Figure 6.1.
6.2.3 Test Procedure

Study participants were instructed to exhale gently (to functional residual capacity), before inhaling through the inhaler mouthpiece and airtight container at maximum PIFR. Participants were asked to inhale at maximum PIFR for 10 recordings. Based on the maximum PIFR achieved, participants were then asked to subjectively lower their PIFR. For the two DPIs, participants were generally able to inhale with maximum PIFR between 80-90 L/min. Once 10 inhalations were recorded for this PIFR band, participants were asked to inhale 10 times at the next lowest PIFR band i.e. 70-80 L/min. This procedure was repeated until 10 inhalations were achieved for each PIFR band as low as the 20-30 L/min PIFR band.

For the pMDI, the participants were capable of inhaling with PIFR up to 300 L/min. For this inhaler, participants were asked to inhale 10 times in the PIFR band 250-300 L/min. Participants were then asked to subjectively lower their PIFR and inhale 10 times for the PIFR band 200-250 L/min. This was repeated for all PIFR bands greater than 100 L/min. Below 100 L/min, participants were asked to inhale 10 times for PIFR bands 75-100 L/min, 50-75 L/min and 25-50 L/min. All recordings were aurally and visually assessed by an expert reviewer using Adobe Audition software. If participants did not inhale for at least two seconds in duration or had coughed, the audio recording would be discarded and participants were asked to repeat the inhalation. Each airtight container was disinfected after each recording session to ensure no infections were passed between participants.

6.2.4 Inhalation Acoustic Analysis

Baseline correction was performed on all inhalation audio recordings by removing any DC offset present in the audio signal. This was done by subtracting the mean amplitude from each audio recording.
6.2.5 Acoustic Feature Selection

Six features were selected to analyse the acoustical characteristics of the inspiratory inhaler sounds. The first, second and third quartile frequencies of the power spectrum, which correspond to the frequencies below which 25%, 50% and 75% of the total power lie (F25, F50 and F75), were employed. \( P_{\text{ave}} \), MAD and RMS were also employed as features. Acoustic feature analysis was divided into two groups: (1) Group A (F25, F50 and F75) and (2) Group B (\( P_{\text{ave}} \), MAD and RMS). Quartile frequencies have been previously employed in breath sound analysis to distinguish physiological differences between healthy individuals and those with asthma and COPD, in particular measuring severity of airway narrowing (Malmberg et al., 1994). It has yet to be reported how quartile frequencies change with PIFR in inhaler inhalation sounds. \( P_{\text{ave}} \) has been previously employed to estimate flow rate from chest wall (Hossain and Moussavi, 2004) and tracheal (Yee Leng and Moussavi, 2002) respiratory sounds.

6.2.6 Acoustic Feature Extraction

Each inhalation audio recording was divided into frames of length 1024 samples with 50% overlap between each frame. A Hanning window was applied to each segment and the Welch PSD estimate was computed using 2048 Discrete Fourier Transform points. All inhalation sounds were high-pass filtered above 200 Hz to remove low frequency noise. A five second sample of background noise was estimated during periods of breath hold for each participant. The PSD was estimated for each participant’s breath hold and then removed from each participant’s audio recordings using spectral subtraction. This method has been previously employed in breath sound analysis and has been a recommended method for noise removal (Malmberg et al., 1995; Gavriely et al., 1995; Rossi et al., 2000).

The PSD was calculated for all 10 inhalation audio recordings at each PIFR band for each participant. The average PSD was then computed over all 10 recordings in order to obtain a single reliable estimate of the true spectral profile of each participant at each PIFR band. This resulted in one PSD spectral curve for each PIFR band. Figure 6.2 shows an example of the inhalation averaged power spectra from one participant for all PIFR bands for the Diskus, Turbuhaler and Evohaler. Once the average PSD was calculated, Group A features (F25, F50 and F75) and \( P_{\text{ave}} \) were calculated from the average power spectrum at each PIFR band.

The MAD and RMS features were calculated for each inhalation audio signal. All 10 values for each feature were then averaged for each PIFR band.
Figure 6.2: Spectral curves for the Diskus, Turbuhaler and Evohaler.
6.2.7 Statistical Analysis of Inhaler Inhalation Sounds

A Generalised Least Squares (GLS) regression model, which accounts for random effects intercept at the subject level, was employed using Stata SE Version 12 to study the relationship between the six selected acoustic features and PIFR.

A Coefficient of Variation (CoV) was calculated for all acoustic features at each PIFR for each participant. The CoV values were then averaged across all participants to compute the average CoV of acoustic features. The CoV was calculated as a percentage ratio of the standard deviation ($\sigma$) to the mean ($\mu$) of acoustic features at each PIFR band.

$$CoV = \frac{\sigma}{\mu} \times 100$$  \hspace{1cm} (6.1)

Pearson’s linear correlation coefficient was employed to correlate all power spectral envelopes for all PIFR bands and this was repeated for all participants. This was done to assess if the power spectral envelope remained consistent regardless of PIFR.

6.3 Results

Table 6.1 presents demographics and baseline lung function of the 11 healthy participants enrolled in this study. All participants had an FEV1/FVC ratio > 0.7 and a predicted FEV1 > 89%, confirming normal baseline lung function according to ATS standards.

A total of 2,150 inhaler inhalation recordings were obtained for this study for inspiratory acoustic analysis consisting of 750 (10 inhalations for each PIFR band for each participant) recordings from the Diskus, 730 recordings from the Turbuhaler and 670 recordings from the Evohaler. One participants’ data were discarded from Evohaler analysis as the data were corrupt.
Table 6.1: Summary of participant demographics and baseline lung function data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.36 ± 2.50, (22-31)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.36 ± 7.86, (167-190)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.36 ± 8.66, (65-93)</td>
</tr>
<tr>
<td>BMI $^a$ (kg m$^{-2}$)</td>
<td>23.79 ± 2.77, (21.2-28.7)</td>
</tr>
<tr>
<td>FEV1$^b$ (L)</td>
<td>4.48 ± 0.47, (3.92-5.18)</td>
</tr>
<tr>
<td>FEV1 predicted (%)</td>
<td>99.27 ± 5.74, (89-112)</td>
</tr>
<tr>
<td>FVC$^c$ (L)</td>
<td>5.50 ± 0.72, (4.63-6.87)</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>0.82 ± 0.04, (0.72-0.88)</td>
</tr>
<tr>
<td>PEFR$^d$ (L min$^{-1}$)</td>
<td>615.09 ± 72.06, (538-640)</td>
</tr>
<tr>
<td>FIVC$^e$ (L)</td>
<td>5.12 ± 0.59, (4.55-6.13)</td>
</tr>
<tr>
<td>PIFR$^f$ (L min$^{-1}$)</td>
<td>487.54 ± 46.45, (405-540)</td>
</tr>
</tbody>
</table>

$^a$BMI - Body Mass Index. $^b$FEV1 - Forced Expiratory Volume in 1 second. $^c$FVC - Forced Vital Capacity. $^d$PEFR - Peak Expiratory Flow Rate. $^e$FIVC - Forced Inspiratory Vital Capacity. $^f$PIFR - Peak Inspiratory Flow Rate.

6.3.1 Relationship between PIFR and Acoustic Features

It was found that all acoustic features employed correlated with PIFR ($p < 0.00001$) at a significance level of $\alpha = 0.05$. Table 6.2 presents the coefficient of determination $R^2$ values for each acoustic feature for all three inhalers. The results suggest that time and frequency based acoustic features have a significant relationship with PIFR. It was noted that F50 generated the strongest correlation with PIFR for the Diskus ($R^2 = 0.85$), F75 for the Turbuhaler ($R^2 = 0.80$) and $P_{ave}$ for the Evohaler ($R^2 = 0.75$). Figure 6.3 demonstrates the relationship between $P_{ave}$ and PIFR for each inhaler. The $P_{ave}$ feature was selected to present in Figure 6.3 as it was observed to generate the highest consistent $R^2$ values across all inhalers. An example of 10 inhalations from one participant for each inhaler is shown in Figure 6.4.

Table 6.2 Correlation scores between acoustic features and PIFR

<table>
<thead>
<tr>
<th></th>
<th>F25</th>
<th>F50</th>
<th>F75</th>
<th>$P_{ave}$</th>
<th>MAD</th>
<th>RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskus</td>
<td>0.80</td>
<td>0.85</td>
<td>0.84</td>
<td>0.77</td>
<td>0.59</td>
<td>0.55</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>0.64</td>
<td>0.58</td>
<td>0.80</td>
<td>0.70</td>
<td>0.54</td>
<td>0.56</td>
</tr>
<tr>
<td>Evohaler</td>
<td>0.41</td>
<td>0.37</td>
<td>0.18</td>
<td>0.75</td>
<td>0.60</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Figure 6.3: Generalised Least Squares (GLS) regression models displaying the relationship between $P_{ave}$ (i.e. Mean Power) and PIFR for all 11 subjects. (A) Diskus, (B) Turbuhaler and (C) Evohaler.

Figure 6.4: 10 inhalations with PIFR 40-50 L/min from one participant for (a) Diskus, (b) Turbuhaler and 150-200 L/min for (c) Evohaler.
6.3.2 Power Spectral Envelope Consistency with PIFR

$R^2$ values from all participants’ data were divided into PIFR bands to assess the consistency of the peaks and troughs of the power spectral envelope. Figure 6.5 displays the distribution of $R^2$ values relating to how each power spectral envelope correlates with all other PIFR power spectra for each inhaler. All $R^2$ values for both Diskus and Turbuhaler were statistically significant ($p < 0.001$). However, the error bars in Figure 6.5 indicate that the inspiratory acoustic profile of the Evohaler is not as repeatable across the entire PIFR range as it is in the Diskus and Turbuhaler. This is due to limited acoustic power at lower flow rates in the Evohaler.

![Boxplot displaying 95% confidence interval notches of the median (red), the 25th and 75th percentile, and the 95% population (error bars) of $R^2$ values demonstrating spectral envelope consistency across all PIFR bands within each participant in (a) Diskus, (b) Turbuhaler and (c) Evohaler.](image)

6.3.3 Acoustic Feature Variation

The results of the CoV analysis for all acoustic features for each inhaler are shown in Figure 6.6. The average CoV of Group A features remain at approximately 20% in the Diskus and Turbuhaler across the entire PIFR range. This range of repeatability in respiratory sounds is in agreement with Sanchez and Vizcaya (2003), who also reported repeatability in the range of 20%.

Group A and Group B CoV values for the Evohaler are substantially higher below 100 L/min. This is due to minimal acoustic power generated at inhalations below 100 L/min. The average MAD and
RMS CoV values tend to increase with PIFR in the Diskus and increase at 40-50 L/min in the Turbuhaler. Notably, $P_{\text{ave}}$ (referred to as Mean Power (MP) in Figure 6.6) generated the least CoV within participants across all inhalers.

Figure 6.6: Average CoV ± standard error of Group A (top) and Group B (bottom) features across 11 participants for (a) Diskus, (b) Turbuhaler and (c) Evohaler.

### 6.4 Discussion

All acoustic features employed were observed to be significantly correlated with PIFR ($p<0.001$). $P_{\text{ave}}$ was noted to be the most consistent predictor of PIFR across all inhalers. It was observed that
the $P_{ave}$ feature generated the least variation in each inhaler across all PIFRs compared to other acoustic features. This implies that it a reliable feature for PIFR estimation through inhalers. The Turbuhaler generated the highest acoustic power, within the recommended PIFR ranges, followed by the Diskus and Evohaler. This can be observed in Figure 6.2. It also suggests how the airflow resistance of inhaler designs may affect the acoustic power.

It was noted that correlations between acoustic features and PIFR were stronger within participants. This may suggest that acoustic features may vary from person to person even when the effects of sex, age and height are limited. Therefore personalising future algorithms for PIFR estimation based on acoustic measurements may be more suitable if these methods are to be translated to a wearable device for inhaler users.

Temporal acoustic features (MAD and RMS) generated higher variability compared to spectral features ($F_{25}$, $F_{50}$, $F_{75}$ and $P_{ave}$), particularly in the Diskus and Turbuhaler. DPIs require more inspiratory effort to reach the required inspiratory flow rates. This may lead to instantaneous bursts of noise at the mouthpiece or within the oral cavity at higher flow rates and may skew acoustic features even when averaged over multiple inhalations. Therefore spectral features may be more suitable for PIFR estimation in DPIs.

There was a noticeable difference between the variability of quartile frequency features (Group 1) in the Evohaler below 100 L/min and above 100 L/min. This is due to limited turbulent airflow existing in the Evohaler at PIFRs below 100 L/min. Therefore, the inhalation sounds were inaudible at lower flow rates resulting in poor acoustic measurements. This finding highlights the inability of acoustic methods to objectively measure PIFR below 100 L/min in the Evohaler. This is an important finding considering that the recommended PIFR to obtain maximum therapeutic effect from pMDIs is <90 L/min. Hence, non-contact acoustics may not be a suitable method to monitor patients’ inhalation technique in pMDIs.

It was demonstrated that acoustic spectral profiles of inspiratory inhaler sounds are repeatable for all PIFRs. This is an interesting finding as it builds on previous findings from studies that characterised normal breath sounds from the trachea and chest wall (Sanchez and Vizcaya, 2003; Beck et al., 2005). This information may assist building future feature extraction methods to analyse inspiratory inhaler sounds.

The INCA device is currently the only acoustic monitoring device available for monitoring inhaler use. However, at present it is designed for the Diskus only, it must be attached to the inhaler, and is limited to an 8 kHz sampling rate (D'Arcy et al., 2014). In order to gain a greater understanding of the acoustic properties of inhaler inhalation sounds, a greater sampling rate was required. In this study, a non-contact high quality microphone was employed to record ambient inhalation
sounds near the mouthpiece of the inhalers. The experimental setup aimed to simulate a wearable non-contact acoustic recording device for inhaler users. In this way, there may be no need to design inhaler-specific monitoring devices in future. Activation of new wearable devices may be through proximity sensors on the inhaler rather than relying on the mechanical function of the inhaler to turn on a recording device.

Monitoring inhaler user technique in patients currently relies heavily on subjective checklists from healthcare professionals, quality of life questionnaires and self-reports from patients regarding their inhaler use (Burgess et al., 2011). The clinical significance of this study lies in developing new novel objective methods to monitor patients’ inhalation technique during inhaler use. Objective monitoring of inhaler user technique may allow inhaler users and healthcare professionals to become more aware of technique errors and this may help improve adherence to inhaler medication. It may also assist healthcare professionals in selecting appropriate inhalers for patients depending on their PIFR through an inhaler. This may improve overall quality of life for asthma and COPD patients.

6.5 Conclusion

To conclude, it has been shown that non-contact acoustic methods are suitable for objectively measuring PIFR through DPIs but may not be suitable for pMDIs. DPIs generate more turbulent energy than pMDIs at the clinically effective PIFRs. Spectral acoustic features were observed to generate low variability. It was also observed that the acoustic spectral profile of inhaler inhalation sounds is repeatable regardless of PIFR. This is an important finding for future feature extraction methods in inhaler acoustics. Non-contact methods may limit the need to design monitoring devices for specific inhalers. The methods presented in this study may translate to a wearable inhaler monitoring device for patients which may be used to monitor patient inhaler technique in non-clinical environments. This may lead to an improvement in inhaler user technique and greater clinical effectiveness from inhaler devices.
CHAPTER 7: Quantifying the Effect of Exhaling into a Dry Powder Inhaler and an Acoustic Based Method to Detect this Critical Error

This study described in this Chapter will focus on answering research questions 12-15, which were presented in Section 3.3 of Chapter 3. Chapters 5 and Chapter 6 of this thesis primarily focused on the acoustic features of inspiratory inhaler sounds and how they can be employed to objectively assess inspiratory inhaler technique adherence problems. The study reported in this Chapter will focus on another critical error that patients make whilst using DPIs; exhaling into the mouthpiece. It has previously been reported that up to 22% of DPI users exhale into their mouthpiece before inhalation (Melani et al., 2011). There are currently a lack of studies in the literature that report the consequences of this critical error, although several papers firmly suggest that this error influences drug delivery to the airways. This Chapter will attempt to quantify the effect of exhaling into a DPI mouthpiece by investigating the influence of a number of factors on drug delivery. It was also hypothesised that acoustic based methods could be employed to objectively detect and analyse this critical inhaler user technique error.

7.1 Introduction

One frequently observed error for dry powder inhalers (DPIs) is that patients exhale into the inhaler mouthpiece after loading the drug (Basheti et al., 2011; Melani et al., 2011; Lavorini et al., 2008; Basheti et al., 2014). Exhaling into a DPI mouthpiece can cause medication to become dispersed, leading to a reduced quantity of drug available for pulmonary administration. A study carried out by Engel et al. (1992) first demonstrated this finding, reporting that inhalations which were preceded by exhalations into the Turbuhaler’s mouthpiece resulted in poor bronchodilation for patients (Engel et al., 1992). However to the best of the author’s knowledge, this is the only study in the literature that investigated the effect of this critical inhaler user technique error and little is known on how the dry powder formulation is affected. In addition, there currently exists no objective method to detect this critical error when it occurs during unsupervised inhaler use.

It has been reported that between 14-22% of patients exhale into their DPI mouthpiece prior to the inhalation step (Melani et al., 2011; Li et al., 2014). A recent study by our research group reported that in unsupervised environments, 16% of subjects exhaled into the Diskus inhaler mouthpiece after loading the drug in more than 20% of cases, despite receiving training (D’Arcy et al., 2014). Exhaling into a DPI mouthpiece can cause medication to clump and stick to the sides of the mouthpiece (Figure 7.1). The inability of many patients to correctly use their inhaler device may be a direct consequence of insufficient or poor inhaler technique instruction (Lavorini et al., 2014).
In a study on pharmacists’ knowledge of correct DPI user technique, it was reported that the vast majority were unaware of the requirement to exhale away from the device mouthpiece prior to inhalation (Basheti et al., 2011). The outcomes of this error in user technique include a lack of improvement in respiratory symptoms. This may cause clinicians to prescribe higher doses of medication to patients, who consequently may then suffer from adverse reactions and incur higher medication costs.

![Figure 7.1: Clumping and attachment of salmeterol and fluticasone drug around the mouthpiece of a Diskus DPI obtained from a patient who was exhaling into their inhaler over a one month period.](image)

The objective of this study was to quantify the effect of exhaling on drug delivery from the Diskus DPI. It was hypothesised that the flow rate of the exhalation, distance between mouth and inhaler mouthpiece, exhalation duration and relative air humidity of the exhalation impact the amount of medication available for delivery. Having shown that exhalations prior to the inhalation step may compromise drug delivery, we then set out to develop a method to detect this critical error. An acoustic approach was taken as it was thought to be best placed to analyse this error. The acoustic sound associated with an exhalation may convey important information on the expiratory flow rate, distance from mouth to the inhaler and exhalation duration. It was hypothesised that the energy of exhalation sounds would differentiate this important event from other sounds during inhaler use. Providing objective information to clinicians and patients on the effect that exhaling into a DPI has on drug delivery may encourage patients to modify their inhaler technique and improve their clinical outcomes.
7.2 Methods

The methods Section consists of two main parts. The first part focuses on the simulation of exhalations with the in vitro test rig, while the second part focuses on the acoustic signal processing of exhalation sounds.

7.2.1 Impact of Exhalation on Delivered Dose

To recreate the effect of an exhalation with dry air, a high capacity airflow pump and critical flow controller (air valve) were connected in series to a glass adaptor (mouthpiece) that mimicked the oropharynx (Figure 2 – Path A). A salmeterol/fluticasone 50 µg/250 µg Diskus DPI was tested. Relative air humidity was determined using a Testo 410 Humidity Meter (Testo, Hampshire, UK).

Dry air (relative humidity of 28%) was blown at the inhaler at flow rates of 30, 60, 90, 120 L/min, for durations of 2, 4, 6 seconds and at distances of 0, 5, 10 cm from the inhaler. Each trial was completed three times for all of the conditions specified (36 variations x 3 runs). After each trial, the inhaler was connected to a dosage unit sampling apparatus (DUSA) [Copley Scientific, Nottingham, UK] and the delivered dose was determined. This corresponds with Path A as shown in Figure 7.2. For humid air (relative humidity of 80%) air travelled on Path B and the above procedure was repeated. The DUSA apparatus was connected to a high capacity vacuum pump (HCP4, Copley Scientific) and Critical Flow Controller (TPK 2000, Copley Scientific). The Flow Controller was operated at 60 L/min (optimal PIFR) at a pressure drop of 4 kPa for a duration of 4 seconds. Pictures of the main components employed in testing are shown in Figure 7.3.

![Figure 7.2: Experimental setup used to investigate the impact of exhalations on drug delivery in a dry powder inhaler. Air was propelled at various flow rates and durations through variable flow paths. Path A represents dry air at a relative humidity of 28% and Path B included a round bottom flask filled with boiled water.](image)
water to bring the humidity of the air to 80% relative humidity. Finally the distance between the artificial mouthpiece and the inhaler mouthpiece was also varied.

![Figure 7.3: Equipment used in in vitro testing (A) Artificial Mouthpiece, (B) Air Humidifier and (C) Diskus inhaler with attached INCA acoustic recording device.](image)

### 7.2.2 Dosage Uniformity Analysis

To validate our *in vitro* method of removing drug from the Diskus DPI, a DUSA was used to determine the delivered-dose uniformity from a salmeterol/fluticasone 50 µg/250 µg Diskus DPI (GlaxoSmithKline, London, UK) (US Pharmacopoeia 601) (The United States Pharmacopeial Convention, 2013). The Diskus DPI was not subject to any exhalations. Ten replications were performed. The target dosage uniformity was 9 of 10 results between 75% and 125% and no more than 1 of 10 results between 65% and 135% (The United States Pharmacopeial Convention, 2013).

### 7.2.3 Particle Size Distribution of Emitted Dose

Testing was carried out to investigate the effect of humid air exhalations on the particle size distribution of the total emitted dose (TED) for the Diskus DPI. To investigate this, the TED and fine particle fraction (FPF) from one Diskus post-exhalation was compared to TED and FPF obtained from one Diskus that was not subject to an exhalation. This testing was carried out using a Next Generation Impactor (NGI) cascade impactor.

The NGI was used with a pre-separator and cups 1-8. A high capacity vacuum pump (HCP4, Copley Scientific) and critical flow controller (TPK 2000, Copley Scientific) were attached to the air intake.
Simulated inhalations were performed at a flow rate of 60 L/min, pressure drop of 4 kPa and duration of 4 seconds. NGI impaction cups 1-5 were lined with filter papers and with 2 mL of a mixture of methanol: acetonitrile: water (25:25:50). Cups 6-8 were coated only with 2 mL of solvent. This was to prevent particle bounce and re-entrainment.

To investigate the effect of exhalations on drug delivery in a DPI, the test setup was employed to exhale air at a flow rate of 60 L/min, for a duration of 4 seconds and using air with a relative humidity of 80% at a Diskus DPI. Exhalations were carried out on five separate Diskus DPIs in order to preserve the possible humidity effect from each trial. A regular Diskus DPI that was not subjected to any exhalations was used to compare the effects of the exhalations.

Total emitted dose (TED) was determined as the sum of the total drug recovered from the throat, pre-separator, and cups 1-8 of the NGI. This was averaged for each study condition. The Fine Particle Dose (FPD), i.e. cumulative drug dose less than particle size 5 μm, was calculated by interpolation on a log-probit plot using pre-specified stage cutpoints at each flow rate. The Upper Airway Dose (UAD) corresponded to the cumulative drug dose above an aerodynamic particle size of 5 μm. Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) were also calculated at each study condition for both formulations using published methods. The TED, FPD and UAD for the standard emitted dose and the post-exhalation emitted dose were compared.

### 7.2.4 Measurement of Salmeterol and Fluticasone

High performance liquid chromatography (HPLC) analysis was performed using a Waters Alliance Separations module equipped with a temperature programmable auto sampler and Waters 2996 Photodiode Array (PDA) detector. Chromatographic data were recorded and integrated using Waters Empower chromatography software and quantified using external standards. Analytical method validation was demonstrated for both methods with regard to accuracy, precision, specificity and linearity as per established guidelines. The limits of detection for fluticasone and salmeterol peaks were 0.032 μg/mL and 0.014 μg/mL, respectively, while the limit of quantification (LOQ) values for the same two peaks were 0.101 μg/mL and 0.042 μg/mL, respectively. HPLC conditions for fluticasone propionate/ salmeterol xinafoate are presented in Table 7.1.
Table 7.1: Details of High Performance Liquid Chromatographic (HPLC) techniques used for quantification of fluticasone propionate and salmeterol xinafoate.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Mobile Phase (per 1 L)</th>
<th>Flow Rate (mL/min)</th>
<th>Column Details</th>
<th>Injection Volume</th>
<th>Detection Wavelength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone Propionate / Salmeterol Xinafoate</td>
<td>500mL - 50mM ammonium phosphate pH2.4 1mL - triethylamine 250mL - methanol 250mL - acetonitrile</td>
<td>1.2</td>
<td>Varian Pursuit XRs C18 3µm 4.6 x 150 mm,</td>
<td>200 µL</td>
<td>252nm</td>
</tr>
</tbody>
</table>

7.2.5 Relationship between Exhalation Factors and Acoustic Features

The INCA acoustic recording device was attached to the Diskus inhaler during experimentation to investigate the effect of different exhalation factors on delivered dose, and whether acoustic features could be used as a means to analyse exhalations. Temporal and spectral features of the exhalation signal were analysed to investigate the feasibility of using acoustics to analyse exhalations during inhaler use. The MAD and $P_{ave}$ features of the exhalation signal were computed and compared to the flow rate of the exhalations and to the distance of the exhalations from the inhaler mouthpiece. Exhalations were divided into 1024 data samples with 50% overlap between successive frames. A Hanning window was used to analyse each frame, while an FFT was used to calculate the PSD. $P_{ave}$ was calculated for frequencies between 300 – 600 Hz. Previous studies have reported that this frequency band shows the best correlation between airflow rate and sound power. MAD is the mean of the absolute deviations from the central value.

7.2.6 Acoustic Method of Automatically Detecting Exhalations

An acoustic recording device (INCA) was employed to investigate the acoustic profiles associated with exhalations during DPI use. A training database of inhaler audio files was employed to develop an algorithm to automatically detect exhalation events from non-exhalation events in inhaler audio signals.

Filter bank energies (FBEs) obtained from calculation of the MFCCs were employed as features to detect exhalations in the audio signals in this study. FBEs are physically meaningful quantities that are known to correlate with human auditory processing (Paliwal, 1999). Audio events (exhalation and non-exhalation events) were automatically detected using an adaptive energy threshold in this study. Exhalations were segments with higher energy in certain frequency regions compared to other background noises in the audio signals (Figure 7.4). To detect exhalation sounds the
average energy in the three filter banks 8-10 is calculated. It was found from empirical observations in a test set of inhaler audio files that the energy in these three filter banks was higher for exhalations in comparison to inhalations and other audio sounds obtained during inhaler use (Figure 7.4). These filter banks correspond with triangular filters starting at 620Hz and ending at 1197Hz. Comparing the average energy in filter banks 8-10 to the average FBE in all 20 channels provides a Difference Waveform (DW) that can be used to automatically detect exhalations:

\[ DW = FBE_{8-10} - FBE_{1-20} \]  

(7.1)

![Figure 7.4: (A) Inhaler audio signal containing exhalation at 5 s and inhalation at 9-11 s, (B) average Filter-Bank Energies (FBE) for channels 1-20 (blue) and channels 8-10 (red), (C) difference waveform (FBE 8-10 – FBE 1-20) and adaptive threshold (dashed red line) and (D) inhaler audio signal with automatically detected exhalation coloured in fuchsia.](image)

The training database consisted of 50 audio files obtained from 10 asthmatic patients using a Diskus DPI in uncontrolled real world environments. The training database was employed to calculate which specific FBE channels contained the largest amount of energy for exhalations and in the design of the adaptive energy threshold. The validation dataset comprised of a random cross-section of inhaler audio files obtained from 22 separate asthma patients. Similar to the training database, the audio files were obtained in uncontrolled real world environments. Five
audio files were randomly selected from each patient to give a total of 110 audio files in the validation dataset.

Two experienced respiratory clinicians independently classified each audio file in the validation dataset using visual and aural methods (Audacity software). The classification of the audio files by the respiratory clinicians was used as the gold standard method of exhalation detection. Exhalation detection performances of the algorithm were compared to that of the gold standard method and calculated using sensitivity, specificity and accuracy values.

7.2.7 Acoustic Method of Assessing Exhalations during Inhaler Use

A Diskus inhaler with an INCA device attached was clamped to a stand. Healthy subjects performed subjectively variable exhalations at distances of 0 cm, 5 cm and 10 cm from the mouthpiece of the inhaler, in locations above, below and directly at the mouthpiece of the Diskus inhaler. Exhalations were also performed with a mouth seal at subjectively variable flow rates. Forty exhalations from three healthy subjects were analysed (training dataset) to develop an algorithm for determining the distance of the exhalation from the inhaler mouthpiece and the expiratory flow rate of the exhalation.

Exhalations were divided into 1024 data samples with 50% overlap between successive frames. A Hanning window was used to analyse each frame, while an FFT was used to calculate PSD. $P_{ave}$ in the frequency bands 20-40 Hz (P1), 40-70 Hz (P2) and 70-150 Hz (P3) was calculated. The MAD of the amplitude of the exhalation signals was also calculated.

The following three equations were derived from the training dataset of forty exhalations to classify different aspects of exhalations:

$$Mouth\ seal\ Test = MAD > 0.002 & \frac{P_2}{P_3} > 0.91 & \frac{P_1}{P_3} > 0.91$$  \hspace{1cm} (7.2)

$$Significant\ Exhalation\ at\ 0cm = MAD > 0.003 \ or\ Mouth\ seal\ test = 1$$  \hspace{1cm} (7.3)

$$Significant\ Exhalation\ at\ 5cm = MAD > 0.002 & \frac{P_1}{P_2} < 0.975$$  \hspace{1cm} (7.4)

Significant exhalations were defined in this study as any exhalation performed at a distance of 0 cm or 5 cm from the inhaler mouthpiece, directly at the inhaler mouthpiece or any exhalation performed with a mouth seal. The term ‘significant’ was employed to imply that the exhalations were significantly detrimental towards the quantity of drug available for inhalation. Any
exhalation directly at the acoustic recording device was also classified as being significantly detrimental. The sensitivity and specificity of the method in distinguishing between exhalations performed at 0 cm and exhalations performed at 5 cm was also tested.

To test the robustness of the algorithm in classifying exhalations, a validation dataset of fifty exhalations from four new healthy subjects was acquired. Classification results were compared with documented conditions for the exhalations in the validation dataset to obtain sensitivity and specificity values of the method in determining significantly detrimental exhalations.

### 7.3 Results

#### 7.3.1 Impact of Exhalation on Delivered Dose

The impact of four exhalation factors (exhalation flow rate, distance to inhaler mouthpiece, exhalation duration and relative air humidity level) on drug delivery was investigated. It was found from multivariate regression analysis that all four exhalation factors had a statistically significant effect on both salmeterol and fluticasone drug delivery ($P < 0.05$, significance level $\alpha = 0.05$). From the multivariate regression model, the adjusted $R^2$ values were 62.67% for salmeterol and 63.4% for fluticasone. Figure 7.5 (A and B) details the total percentage of salmeterol and fluticasone delivered as a percentage of the Diskus inhaler manufacturer’s claim (nominal dose). Interaction plots are also presented to illustrate the differences between both relative air humidity levels (Figure 7.5 C).

Exhalations were found to have an overall negative effect on drug delivery. At a distance of 0cm from the inhaler mouthpiece, less than 50% of drug available is delivered on average for all flow rates using humid air (relative air humidity = 80%). In the worst case scenario, an average of 2.44% of drug was delivered from the Diskus DPI when the preceding exhalation was at an expiratory flow rate of 120 L/min and 0 cm from the inhaler mouthpiece (Figure 7.5 B). Delivered dose was more consistent when dry air was used, but more variable and unpredictable when humid air was used. It was observed that less drug is delivered on average when humid air is used in comparison to dry air (Figure 7.5 C).
Figure 7.5: Effect of exhalations on delivered dose as percentage of label claim. (A) Salmeterol delivered dose after exhalation with dry air, (B) salmeterol delivered dose after exhalation with humid air, and (C) interaction plot detailing differences between salmeterol delivered dose for different factors. Results for fluticasone were correspondingly similar.

To investigate the effects of each of the four factors on drug delivery, measures of effect size (eta-squared and partial eta-squared) were obtained from the multivariate regression model for each independent variable (Table 7.2 and Table 7.3). Results established that distance from the inhaler mouthpiece was the single most influential factor in reducing the percentage of drug delivery from a DPI. Exhalation flow rate and air humidity level were the next most influential factors with similar effect sizes. Although its effect was statistically significant, exhalation duration was the least influential factor in determining drug delivery for the multivariate regression model.
Table 7.2: Effect size for each of the four factors on drug delivery for salmeterol.

| Variable            | P > |t|  | Eta-squared | % Change in Eta-squared | Partial Eta-squared |
|---------------------|-----|-----|--------------|-------------------------|---------------------|
| Exhalation flow rate| 0.00001 | 0.1223 | 18.8898 | 0.2577 |
| Distance            | 0.00001 | 0.3578 | 55.2553 | 0.5039 |
| Duration            | 0.006 | 0.0420 | 6.49827 | 0.1067 |
| Air humidity        | 0.000 | 0.1253 | 19.3564 | 0.2624 |

Table 7.3: Effect size for each of the four factors on drug delivery for fluticasone.

| Variable            | P > |t|  | Eta-squared | % Change in Eta-squared | Partial Eta-squared |
|---------------------|-----|-----|--------------|-------------------------|---------------------|
| Exhalation flow rate| 0.00001 | 0.1160 | 17.7232 | 0.2514 |
| Distance            | 0.00001 | 0.3719 | 56.8191 | 0.5185 |
| Duration            | 0.006 | 0.0420 | 6.4255 | 0.1085 |
| Air humidity        | 0.00001 | 0.1245 | 19.0320 | 0.2651 |

7.3.2 Dosage Uniformity Analysis

The dosage uniformity analysis on the Diskus DPI demonstrated that the dose delivered from the Diskus was uniform and repeatable. 9 of the 10 test results fell between 75% - 125% and 1 of the 10 test results was between 65-135% of the delivered dose label claim, in accordance with US Pharmacopeial standards (The United States Pharmacopeial Convention, 2013). Results for this testing can be found in Table 7.4 below.
Table 7.4: Dosage uniformity analysis of salmeterol/fluticasone Diskus inhaler over 10 trials (DUSA 1-10).

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol Delivered Dose (mcg)</th>
<th>Salmeterol Delivered Dose (% label claim)</th>
<th>Fluticasone Delivered Dose (mcg)</th>
<th>Fluticasone Delivered Dose (% label claim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUSA 1</td>
<td>37.14</td>
<td>74.28</td>
<td>200.73</td>
<td>80.29</td>
</tr>
<tr>
<td>DUSA 2</td>
<td>43.79</td>
<td>87.58</td>
<td>225.66</td>
<td>90.27</td>
</tr>
<tr>
<td>DUSA 3</td>
<td>40.86</td>
<td>81.73</td>
<td>207.45</td>
<td>82.98</td>
</tr>
<tr>
<td>DUSA 4</td>
<td>47.55</td>
<td>95.11</td>
<td>231.39</td>
<td>92.56</td>
</tr>
<tr>
<td>DUSA 5</td>
<td>47.43</td>
<td>94.87</td>
<td>238.31</td>
<td>95.32</td>
</tr>
<tr>
<td>DUSA 6</td>
<td>47.07</td>
<td>94.14</td>
<td>239.23</td>
<td>95.69</td>
</tr>
<tr>
<td>DUSA 7</td>
<td>46.56</td>
<td>93.13</td>
<td>238.56</td>
<td>95.42</td>
</tr>
<tr>
<td>DUSA 8</td>
<td>46.46</td>
<td>92.93</td>
<td>218.92</td>
<td>87.57</td>
</tr>
<tr>
<td>DUSA 9</td>
<td>48.37</td>
<td>96.75</td>
<td>245.06</td>
<td>98.02</td>
</tr>
<tr>
<td>DUSA 10</td>
<td>47.95</td>
<td>95.90</td>
<td>242.10</td>
<td>96.84</td>
</tr>
<tr>
<td>Average</td>
<td>45.32</td>
<td>90.64</td>
<td>228.74</td>
<td>91.50</td>
</tr>
</tbody>
</table>

7.3.3 Particle Size Distribution of Emitted Dose

An NGI cascade impactor was employed to investigate the effect that exhaling into a DPI has on particle distribution. Diskus DPIs that had been subject to an exhalation using humid air at a flow rate of 60 L/min, a distance of 5 cm from the mouthpiece and for a duration of 4 seconds were compared to Diskus DPIs that were not subject to exhalations. It was found that there were no differences in the total emitted doses but that the FPF was significantly reduced for inhaler devices subjected to an exhalation. This result demonstrates that exhaled air humidity most probably cause particles to clump together and has a detrimental effect on particle size distribution. Results for this are displayed in Figure 7.6. Detailed results for particle size distribution are reported in Table 7.5.
Figure 7.6: Analysis of particle size distribution of salmeterol and fluticasone from Diskus dry powder inhaler as obtained from a Next Generation Impactor (NGI). (A) Total drug recovered from all sections of the NGI and (B) Fine Particle Fraction (FPF) drug recovered demonstrating a reduction due to exhalations.
Table 7.5: Particle size distribution of emitted dose data for no exhalation (standard dose) versus exhalation with humidified air (post humidified-air exhalation) in NGI cascade impactor.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Salmeterol</th>
<th>Fluticasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Condition</td>
<td>Standard Dose</td>
<td>Post humidified-air exhalation</td>
</tr>
<tr>
<td>Throat (µg)</td>
<td>5.60</td>
<td>11.90</td>
</tr>
<tr>
<td>PSA (µg)</td>
<td>26.40</td>
<td>25.68</td>
</tr>
<tr>
<td>S1 (µg)</td>
<td>2.03</td>
<td>1.03</td>
</tr>
<tr>
<td>S2 (µg)</td>
<td>3.35</td>
<td>1.19</td>
</tr>
<tr>
<td>S3 (µg)</td>
<td>3.42</td>
<td>1.43</td>
</tr>
<tr>
<td>S4 (µg)</td>
<td>2.68</td>
<td>1.37</td>
</tr>
<tr>
<td>S5 (µg)</td>
<td>1.52</td>
<td>0.93</td>
</tr>
<tr>
<td>S6 (µg)</td>
<td>BLOQ</td>
<td>1.13</td>
</tr>
<tr>
<td>S7 (µg)</td>
<td>BLOQ</td>
<td>BLOQ</td>
</tr>
<tr>
<td>MOCb (µg)</td>
<td>BLOQ</td>
<td>BLOQ</td>
</tr>
<tr>
<td>TEDc (µg)</td>
<td>45.82</td>
<td>45.06</td>
</tr>
<tr>
<td>FPDd (µg)</td>
<td>11.53</td>
<td>6.63</td>
</tr>
<tr>
<td>UADe (µg)</td>
<td>34.29</td>
<td>38.42</td>
</tr>
<tr>
<td>MMADf (µm)</td>
<td>3.85</td>
<td>2.92</td>
</tr>
<tr>
<td>GSDg</td>
<td>1.97</td>
<td>2.40</td>
</tr>
</tbody>
</table>

* PS – Pre-separator
* MOC – Micro-orifice Collector
* TED – Total Emitted Dose
* FPD – Fine Particle Dose
* UAD – Upper Airway Dose
* MMAD – Mass Median Aerodynamic Diameter
* GSD – Geometric Standard Deviation
* BLOQ – Below Limit of Quantification

7.3.4 Relationship between Exhalation Factors and Acoustic Features

A relationship was observed between the exhalation flow rate and the acoustic features obtained from the exhalation audio signal. As the expiratory flow rate increased, a corresponding increase was seen in both $P_{ave}$ in the 300-600 Hz frequency band and in the MAD of the amplitude. Distance between the inhaler and the artificial mouthpiece was also related to both acoustic power and acoustic amplitude of the exhalation signal. The smaller this distance, the greater the power and amplitude of the signal. Results for the correlations between acoustic features with both flow rate and distance are illustrated in Figure 7.7.
Figure 7.7: Relationship between exhalation flow rate and distance from inhaler mouthpiece with acoustic features for humid air in vitro. Each data point represents mean ± standard error for three trials. (A) Mean Absolute Deviation (MAD) of the exhalation signal plotted versus exhalation flow rate and distance from inhaler mouthpiece. (B) Average power ($P_{ave}$) in the 300-600 Hz frequency band of the exhalation signal plotted versus exhalation flow rate and distance from inhaler mouthpiece.

### 7.3.5 Acoustic Method of Automatically Detecting Exhalations

Cohen’s kappa statistic ($K$) was calculated to measure the level of agreement between the two respiratory clinicians who manually classified the presence of exhalation events in each audio file in the validation dataset. $K$ was 1, indicating perfect agreement between the two raters. Using the FBE feature to automatically detect exhalations, performance was evaluated on the 110 audio files from 22 patients in the validation dataset. The overall detection rate (accuracy) on the 22 patients in the validation dataset was found to be 89.1% compared to the gold standard method of classification. Sensitivity (detecting exhalations as exhalations) was 82.2%, and specificity
(detecting noise as noise) was 91.6% compared to the gold standard method. $K$ was also calculated to compare the level of agreement between the proposed algorithm and the gold standard method of classification. Taking the classification of the algorithm as one output and the classification of respiratory clinicians as the gold standard output, $K$ was 0.6638, indicating substantial agreement between the two classification methods.

### 7.3.6 Acoustic Method of Assessing Exhalations during Inhaler Use

Exhalations occurring at a distance of 5 cm or less, into the DPI mouthpiece or directly at the INCA device were classified as significantly detrimental. This was chosen because the distance to the inhaler mouthpiece was the single most influential factor in impacting drug delivery from the in vitro testing. It was found that the threshold developed to classify a significantly detrimental exhalation had a sensitivity of 72.22% and a specificity of 85.71% when tested on the validation dataset. Positive predictive values (PPV) and negative predictive values (NPV) were also calculated. Results for detecting exhalations at 0 cm or a mouth seal and exhalations at 5 cm are presented in Table 7.6.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant exhalation</td>
<td>72.22</td>
<td>85.71</td>
<td>92.86</td>
<td>54.55</td>
</tr>
<tr>
<td>Exhalation at 0 cm/mouth seal</td>
<td>88.89</td>
<td>70.73</td>
<td>40.00</td>
<td>96.67</td>
</tr>
<tr>
<td>Exhalation at 5 cm</td>
<td>81.25</td>
<td>88.24</td>
<td>76.47</td>
<td>90.91</td>
</tr>
</tbody>
</table>

### 7.4 Discussion

Several authors in the literature have argued that exhaling into a DPI prior to inhalation has a detrimental impact on the dose available for pulmonary delivery (Melani et al., 2011; Basheti et al., 2011; Lavorini et al., 2008; Engel et al., 1992; Basheti et al., 2014). There are very few studies that have been carried out to clearly delineate and quantify the impact of this effect; nonetheless, exhalation into a DPI has been widely reported as a critical error in the assessment of inhaler user technique.

Results showed that exhalation into the Diskus DPI had a significant effect on the subsequent delivered dose and that the main determining factors were distance of the exhalation from the DPI mouthpiece, flow rate of exhalation and humidity of exhaled air. The most important of these
was distance of the exhalation from the mouthpiece. The duration of the exhalation had a negligible effect on drug dispersal, even though it was a statistically significant variable in our regression model. On average, more than 50% of salmeterol and fluticasone were dispersed from the DPI after exhalation from a distance of 0 cm using humid air. At 10 cm, less than 25% of drug was found to be lost.

Results demonstrated that the relationship between flow rate, distance and duration of exhalation using humidified air is less predictable than that using dry air. Drug agglomeration provides a plausible explanation for these results. Particles which have clumped together may either remain inside the DPI or be emitted as a large mass; this accounts for the greater variability in total delivered dose seen with humidified air. To clarify the effect of air humidity, experiments were performed using an NGI. Results from this test indicated that even though the TED may remain constant after an exhalation with humid air, the fine particle fraction is almost halved, meaning that the majority of the TED may be deposited in the upper airways.

In the second part of this study, an acoustic monitoring device was employed to record the audio signals of patients using a Diskus DPI. An algorithm was developed to automatically detect exhalations prior to inhalations. The exhalation detection algorithm was successful in detecting exhalations in unsupervised real world inhaler audio signals in comparison to expert raters. Its overall accuracy was demonstrated to be 89.2% in detecting exhalations events from non-exhalation events, while its corresponding sensitivity and specificity values were also high. These results are encouraging if such an algorithm is to be used longitudinally to automatically detect the critical error of exhaling into a DPI.

Furthermore, our calculations based on acoustic power in various frequency bands and MAD of the amplitude was found to be very sensitive and specific for detecting significant exhalations and for differentiation of an exhalation at 0 cm from one at 5 cm. Our in vitro studies clearly showed that distance was the single most important factor accounting for drug dispersal or loss from the DPI. The acoustic based method is therefore a suitable means of not only automatically detecting exhalations but of objectively quantifying the impact of these exhalations on drug delivery.

A shortcoming of this study is that we were limited by the in vitro design. The individual variability in inhaler user technique and the confounding factors of physiological variation, inhalation flow rate, volume and additional errors mean that the impact of exhalations is difficult to measure accurately in an in vivo clinical study.

Clearly results indicate that exhaling into a DPI has a negative effect. This critical error needs to be addressed by designers of DPIs as its impact on drug delivery is paramount. Future DPIs need to have a system in place to prevent users from exhaling into the mouthpiece or instructions for
inhaler use need to be modified to ensure that inhaler users are told exhale prior to releasing the drug, instead of after as is the current practice.

The current gold standard in assessing inhaler user technique is the checklist method. This method is fraught with limitations; it is subjective and it cannot be employed to monitor patients’ technique longitudinally. There is also a significant Hawthorne effect where patients change their behaviour because they know they are being assessed. Acoustic analysis of both the inhalation and any critical errors associated with inhaler use, can be used to quantify, drug delivery from dry powder inhalers in a more objective manner. Such data can be employed to provide clinicians and patients with objective evidence on how inhalers are being used for the first time.

The studies described in the next Chapter of this thesis will focus on the design of a series of algorithms that can objectively assess Diskus inhaler user technique, using acoustic based methods. This Chapter aims to bring together the findings of the studies reported in Chapters 5, 6 and 7, in order to best analyse adherence to inhaler therapy.
CHAPTER 8: Development of Objective Methods to Assess Inhaler Adherence

This studies detailed in this Chapter describe the development of methods to automatically and objectively assess inhaler technique adherence. It builds on the studies described in Chapters 5, 6 and 7, which focused on the acoustic characteristics of inspiratory and expiratory breath sounds during inhaler use. This studies reported in this Chapter investigate if acoustic signal processing methods can be employed to detect the events critical for successful drug delivery during inhaler use, and employ the presence of these events to evaluate inhaler adherence. Research questions 16-22, which were posed in Section 3.4 of Chapter 3, will be answered in this Chapter.

8.1 Blister Detection Algorithm

8.1.1 Introduction

The presence of a blister sound in an audio recording of inhaler use indicates that the lever has been activated. Drug becomes available for inhalation in the Diskus DPI once the lever has been pushed back fully. This manoeuvre assists in moving the previous blister foil and drug residue away from the mouthpiece and transporting a newly opened blister foil into the mouthpiece chamber. Failure to blister the Diskus DPI device before inhalation will result in no drug becoming available for inhalation. Therefore this step is crucial for successful Diskus inhaler use.

Recent studies have shown that 7.3% of patients fail to blister the foil correctly in the Diskus DPI (Melani et al., 2011). This can be due to patients forgetting to blister the inhaler or by blistering the inhaler too many times (overdosing). Up until now, human over readers have used visual and aural methods to detect the presence of blister sounds in the audio signals obtained with the INCA device. As discussed extensively throughout this thesis however, this method is both a subjective and tedious task. Acoustic signal processing methods may be capable of automatically detecting the blister event in the audio signal. This may improve the objectivity of assessing inhaler use and help identify errors in user technique related to this important step.

The objective of this study is to use acoustic signal processing methods to detect blister sounds in inhaler audio signals. It is hypothesised that blister sounds contain unique time and frequency characteristics that allow them to be distinguished from other sounds. Features based on the intensity, duration and frequency characteristics of the blister sound will be utilised in this study. The motivation for selecting the features in this study arises from the unique characteristics of the blister sound, which will now be discussed in detail.
8.1.2 Methods

Study Design

To evaluate the performance of the blister detection algorithm, data were recorded from 12 community dwelling asthma patients (6 female & 6 male). The age range of recruited patients was 20-83 (mean 49 ± SD 18) years. All patients had experience in using the Diskus DPI. It was communicated to patients before they began the study that an acoustic recording device that could monitor their temporal and technique adherence would be attached to their Diskus inhaler.

Each patient was provided with an individual INCA equipped Diskus inhaler by their doctor for a period of one month. Patients were instructed to use their inhaler as normal and they were not given any extra advice or special training. After using their INCA enabled inhaler for one month the patients returned to their clinic, where their INCA device was removed from their inhaler and the audio files were uploaded to a database for analysis.

Blister Characterisation

The algorithm designed to detect blister sounds initially went through a characterisation training phase. The 12 patients recruited in this study provided 609 audio files in total. Each of these audio files represented a unique record of inhaler use. There was a great quantity of variation between subjects (inter-subject variability) and also within subjects (intra-subject variability), in terms of recording environment and patient user technique. 202 (33% of total files available) audio files were randomly selected and employed in the characterisation training phase of the algorithm.

Blister Detection Algorithm Design

In the Diskus inhaler, blister events occur when the lever is turned and the drug foil is pierced. As this manoeuvre is carried out, a short burst of acoustic energy is emitted from the inhaler. Detecting blister events during Diskus inhaler use is critical as this step is necessary for successful drug delivery. Failure to release the medication via the blistering of the drug foil results in no medication becoming available for inhalation. To detect blister events during Diskus inhaler use, a number of time and frequency based signal processing methods were employed.

Average power was estimated using an FFT based approach. The audio signal was framed and windowed before the PSD feature was extracted. The signal is segmented into frames of 100 ms that overlap every 10 ms. This frame length was deemed adequate to capture the frequency characteristics of the blister sound, given the short duration of the sound. The PSD was calculated using a one-sided periodogram estimate given by the following equation:

\[
P(i, j) = k |S(i, j)|^2
\]

(8.1)
where $S$ denotes the input signal and $k$ is given by:

$$k = \frac{2}{F_s \sum_{n=1}^{L} |w(n)|^2}$$

(8.2)

where $W(n)$ denotes the window function (Hanning), $F_s$ is the sampling frequency (8000 Hz) and $L$ is the length of the input signal. A Hanning window was used as it provides good frequency resolution and reduced spectral leakage (NI, 2015). The commercial INCA electronic monitoring device samples audio at 8000 Hz and it was for this reason that the 8000 Hz sampling frequency was chosen.

The PSD is first estimated for frequencies between 2000-3000 Hz. It was hypothesised that power levels are high for blister sounds in this frequency range and that low frequency noise components would have low power at this range. If the mean PSD is greater than -65 dB (threshold $\theta_1$) in a frame then the frame is marked as a potential blister sound. It was observed that in a characterisation dataset of 202 inhaler audio recordings from 12 asthma patients that the mean PSD of blister frames was greater than -65 dB, in comparison to non-blister frames. To remove false positive blister detections, a number of additional steps are performed. Any potential blisters that have a maximum amplitude less than 0.7 are discarded (threshold $\theta_2$). Any potential blister sounds that are greater than one second in duration are also rejected (threshold $\theta_3$). An additional PSD calculation is then performed to estimate the power in the frequency range 20-200 Hz. Potential blister sounds with power less than -62 dB are discarded (threshold $\theta_4$). The selected thresholds were set as they gave the highest sensitivity/specificity in the characterisation dataset of 202 inhaler audio recordings. A flow diagram of the steps detailed is shown in Figure 8.1.
To test the algorithm’s performance in detecting blister sounds, 407 new audio files were selected from the 12 asthma patients recruited in this study (67% of total audio files obtained). Two human raters, trained by an experienced respiratory clinician to identify inhalation events during Diskus inhaler use, independently classified each of the 407 audio files using the audio tool Audacity®. Each human rater manually examined the audio files using visual and aural methods. Results comparing the performance of the blister detection algorithm (new proposed method) in comparison to the human raters (gold standard method), are detailed in Table 8.1.

*Table 8.1: Performance of blister detection algorithm in detecting blister sounds in 407 audio files obtained from real-world inhaler use.*

<table>
<thead>
<tr>
<th>Inhaler Event</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister Sound</td>
<td>98.3</td>
<td>86.8</td>
<td>92.1</td>
</tr>
</tbody>
</table>
8.1.4 Discussion

This study detailed the development of an algorithm that can detect blister sounds in inhaler audio recordings. It was found that the feature extraction methods proposed allowed blister sounds to be detected with a high level of accuracy. The unique temporal and spectral characteristics of the blister sound during Diskus inhaler use made this possible. The algorithm developed offers an automatic and objective method of detecting blister sounds in the audio recordings of Diskus inhaler use.

When listening to inhaler audio recordings with the INCA device, it can be challenging to manually detect the presence of blister sounds. Often there are a number of additional sounds that share similar characteristics to the blister event. For example, the patient fumbling with their inhaler device, shaking their inhaler, placing it down on a hard surface or banging the inhaler mouthpiece against their teeth can cause blister-like sounds. As well as being short in duration (< 1 s), such sounds also share similar frequency characteristics to the blister event. Oftentimes the human rater will not be able to distinguish true positive blister events from false positive blister events. This is a cause for concern given that human raters were employed as the gold standard method of blister detection in this study. Future studies in this area should thus strive to use a true gold standard method in detecting blister sounds.

In this study it was observed that blister sounds have high levels of energy in frequency bands 2000-3000 Hz and 20-200 Hz. The former frequency band is at a frequency range higher than that of the fundamental frequency of speech based sounds (Tan and Karnjanadecha, 2003), while the latter frequency band is at a frequency range in which inhaler inhalations have low levels of energy i.e. 20-200 Hz. Combining these FFT based approaches with two intensity and duration based features was found to give high levels of blister detection accuracy in this study. Blister sounds typically have a high maximum amplitude, which sets them apart from other common inhaler sounds such as breath sounds and speech sounds. Their unique short duration also enables them to be distinguished from other longer duration sounds in the audio signal. One limitation of this study is that the same cohorts of patients were used in both the training and testing phases. It is possible that individual patients have a unique method of blistering the Diskus inhaler. Future studies should employ separate cohorts of patients in the training and testing phases. Overall, the feature extraction steps detailed in this study allowed Diskus blister sounds to be detected with a high level of accuracy on audio recordings of 12 asthma patients.
8.2 Inhalation Detection Algorithm

The inhalation step is critical for drug delivery to the lungs during inhaler use. Without a successful inhalation manoeuvre, the drug contained in the inhaler will not leave the device, de-agglomerate and deposit in the central and peripheral airways. Technique errors related to the inhalation are quite common. It was recently reported that over one in every four patients make an error related to the inhalation step when using the Diskus DPI, while one in every two patients make an error related to the inhalation step in the pMDI (Melani et al., 2011). In Chapters 5 and 6 it was reported that acoustic methods can be employed to analyse the inhalation step during inhaler use. In these Chapters, the temporal and spectral characteristics of the inhalation signal were discussed in detail. Results indicated that it may be possible to use signal processing methodologies to detect the inhalation, given its unique characteristics. At present, human raters employ visual and aural methods to detect the presence of the inhalation in Diskus audio signals, recorded from the INCA device. However, this is a very time consuming and tedious process for the human raters, while the opinion of the human raters is also subjective in nature. An objective and automatic method of detecting inhalation sounds in the audio signals is required. This Section presents three studies that were performed in the development of an automatic inhalation detection algorithm.

8.2.1 Investigation into the Feasibility of Using Acoustic Feature Extraction Methods to Detect Inhalation Sounds

Introduction

In the literature review (Chapter 2), it was observed that MFCCs are features that are frequently employed to detect breath sounds. MFFCs are one of the most widely used features in speech recognition systems, due to their good discrimination capabilities and low computational complexity (Dimitriadis et al., 2011). Temporal features such as ZCR and MA have also been previously used in breath sound detection studies. The aim of this study was to investigate the feasibility of using such features to identify inhalation sounds in audio recordings of inhaler use. Data collected from an early prototype version of the INCA device, which sampled data at 7913 Hz, were employed in this study.

Methods

Study Participants

Twenty asthma patients (11 female & 9 male) who attend an outpatient’s respiratory clinic were recruited for this study. The age range was 20 – 68 (mean 43.5 ± standard deviation 14.2). All
patients had previously used the Diskus DPI and were very familiar with the mechanics of using such inhalers. Patients were each given a Diskus DPI with the prototype INCA monitoring device attached and instructed to use the DPI as normal in their home environment. Each patient’s inhaler use was recorded for a period of one month, with each patient returning to the clinic at the end of the month to have their inhaler recordings uploaded to a database.

**Inhalation Detection Algorithm Design**

A two-step algorithm was designed to identify inhalation sounds and detect their temporal onset/offset time. The first step involves identifying and demarcating potential inhalation events in the recordings, while the second step involves removing false positives.

MFCCs were employed as features in step one of the algorithm. Extracting MFCCs is a common parameterisation method for vocalisation, due to the fact that MFCCs model the known variation of the human ears critical bandwidth with frequency. It is known that breath sounds have a characteristic pattern which allows them to be distinguished from other sounds (Ruinskiy and Lavner, 2007). Based on this observation an algorithm was designed to detect this pattern.

The algorithm firstly went through a training procedure using a set of 20 randomly selected inhaler audio recordings (from 20 different patients). Each signal was separated into frames of length 700ms which overlapped every 20ms. A frame length of 700ms was selected as this was the length of the shortest inhalation in the training dataset. 13 MFCCs (0th MFCC and MFCCs 1-12) were estimated for each frame in the signal, forming a short-time cepstrogram. Using Singular Value Decomposition (SVD), a normalised singular vector was computed from the cepstrogram of the signal. Singular vectors can be used to capture the most important characteristics of inhalation sounds obtained from MFCC calculations. A threshold approach was used to classify the inhalation sounds. In the characterisation dataset, a threshold that was 14% higher than the lowest singular vector in the inhaler recording produced the greatest number of true positives and lowest number of false positives. Singular vectors above the threshold were marked as potential inhalation events, while those below it were discarded. This threshold was found to produce the most accurate detection of inhalation sounds in the characterisation dataset.

In the second stage of the algorithm, the ZCR and MA features were computed to reduce the number of false positives detected by the algorithm, i.e. artefacts classified as inhalations. Inhalations were empirically found to have a characteristically high ZCR compared to non-inhalations in the training set. A fixed threshold of 0.17 zero crossings per frame was therefore introduced to reflect this observation. In the characterisation dataset, inhalations consistently had a ZCR above this threshold value, while false positives were successfully removed.
The MA of the proposed inhalation frames was also calculated. Similar to the ZCR threshold, a fixed threshold was introduced to remove false positives based on empirical observations from the characterisation dataset. Frames with inhalations present were found to have a MA value higher than 0.012, while non-inhalation frames consistently had a MA lower than this threshold. This was due to the energy generated during the inhalation. This combination of threshold values was empirically found to produce the most accurate detection of inhalations, and was applied to a new validation set of 255 audio files.

Results

The inhalation detection algorithm was validated on acoustic signals obtained from asthmatic outpatients who attended a respiratory clinic. A total of 255 audio files were selected at random from the inhaler recordings database. Of the 20 prototype INCA devices, 8 failed while in use, resulting in a high percentage of corrupt audio files in 8 of the devices. Audio files were therefore randomly selected from only 12 out of 20 patients who were part of the study. Two human raters, trained by an experienced respiratory consultant on how to identify inhalation sounds, independently classified each of the 255 audio files using visual and aural inspection methods. The human raters firstly identified if an inhalation was present and secondly demarcated the onset and offset time of the inhalation. The human raters agreed on the presence of inhalations in 100% of the audio files. The average difference between raters in the detection of the inhalations onset time was ±19 ms, while the average difference in the offset times was ±15 ms.

Table 8.2 below shows the performance of the algorithm in detecting inhalations, compared to that of the human raters. Results were classified as True Positive (TP), False Positive (FP), True Negative (TN) and False Negative (FN), according to the classification of the human raters. It was found that the algorithm had a sensitivity (Sen) of 94.9%, specificity (Spe) of 93.7% and accuracy (Acc) of 94.3% in detecting inhalations.

<table>
<thead>
<tr>
<th>Inhaler Recordings</th>
<th>Total Number Inhalations</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Sen</th>
<th>Spe</th>
<th>Acc</th>
</tr>
</thead>
<tbody>
<tr>
<td>255</td>
<td>255</td>
<td>242</td>
<td>16</td>
<td>239</td>
<td>13</td>
<td>94.9%</td>
<td>93.7%</td>
<td>94.3%</td>
</tr>
</tbody>
</table>

The performance of the algorithm in accurately identifying the onset and offset of the inhalations is shown in Table 8.3 and Table 8.4 respectively. For this analysis only the true positive inhalations were considered. For inhalation onset time, the average difference between the human raters was ±57 ms and ±61 ms respectively. For inhalation offset time, the average difference was ±104 ms and ±107 ms. Taking into consideration that an average inhalation duration was found to be
1.8 s in this study, the algorithms inhalation onset time classification varied by ±3.16-3.38%, compared to that of the human raters classification. Furthermore, the algorithms inhalation offset time was found to vary by ±5.77-5.94%, compared to that of the human raters’ classification.

Table 8.3: Inhalation onset time accuracy.

<table>
<thead>
<tr>
<th></th>
<th>Inhalation Onset Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rater 1 V. Algorithm</td>
</tr>
<tr>
<td>Average Difference (+/-)</td>
<td>57ms</td>
</tr>
</tbody>
</table>

Table 8.4: Inhalation offset time accuracy.

<table>
<thead>
<tr>
<th></th>
<th>Inhalation Offset Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rater 1 V. Algorithm</td>
</tr>
<tr>
<td>Average Difference (+/-)</td>
<td>104ms</td>
</tr>
</tbody>
</table>

Discussion

This study describes an algorithm that can automatically detect and demarcate inhalations from recordings of inhaler use in real world environments. Results indicated that the algorithm was able to detect, on average, inhalations in 94.9% of the audio recordings that contained inhalations according to the human raters. The algorithm had a specificity of 93.7%, while accurate identification of inhalations took place, on average, in 94.3% of audio files. This high level of accuracy is a promising result if this approach is to be included in a fully automated system for identifying inhalations from audio recordings.

For the inhalations that the algorithm detected successfully, it was observed that the algorithm identified the onset/offset times of inhalations with a high degree of accuracy. In comparison to the human raters, the algorithm differed in inhalation onset time by ±57 ms and ±61 ms and in inhalation offset time by ±104 ms and ±107 ms. A possible explanation as to why the algorithm was not as accurate in detecting the inhalation offset time, compared to that of the onset time can be found in the mechanics of inhaler use.
Inhalation of the drug from the Diskus DPI requires a hard, fast and long inhalation from the patient, in order to inhale the drug successfully into the small airways of the lungs. When patients follow the correct inhalation technique, inhalation sounds have a characteristic pattern, in both the time and frequency domains. The onset of an inhalation is commonly accompanied by a period of silence in the period before the inhalation takes place. Although artefacts can occasionally interfere with the accuracy of the inhalation onset time identification, the algorithm achieved quite good correlation compared to that of the human raters in this study.

The accurate identification of the offset time of inhalations from inhaler recordings represents a more challenging task. As patients inhale the drug from the Diskus inhaler there is a tendency to gradually reduce inspiratory flow rate in the last few hundred milliseconds of the inhalation. At the end of the inhalation the patient will remove their lips from the mouthpiece of the inhaler device before clapping their mouth shut and holding their breath. The reduction in the flow rate of the inhalation towards its completion, the sound artefacts produced by the removal of the lips from the mouthpiece, in addition to artefacts associated with the fumbling of the inhaler as it is removed from the area of the mouth, are a number of factors which contribute to making the accurate identification of inhalation offset times challenging.

As the inhalations analysed by the algorithm in this study were from asthma patients in real world environments, the accurate detection of inhalations onset and offset time was always going to be challenging. The accuracy and specificity results are slightly lower than those achieved by Ruinskiy and Lavner (2007); however the recording environments were very different for these two studies. Ruinskiy and Lavner (2007) employed recordings of speech and song signals in a controlled environment while the recordings for this study were recorded in the real world and thus much less controlled. In conclusion, it was found that the MFCC, ZCR and MA features allowed inhalations to be detected with a high level of accuracy in this study. This automatic and objective method may be of clinical benefit in analysing inhaler user technique, in conjunction with the INCA electronic monitoring device.

8.2.2 Inhalation Detection in Audio Signals Obtained from a New INCA Device

Introduction

The previous study demonstrated the feasibility of using MFCCs, ZCR and MA as features to detect and demarcate inhalation sounds. However, a prototype version of the INCA device was used in that study. A new INCA device was subsequently introduced by Vitalograph Ltd., in which the location and orientation of the microphone was changed. In addition, a different MEMS
microphone was employed and the sampling rate was increased from 7913 Hz to 8000 Hz. The changes to the new INCA device affected the acoustic characteristics of inhalation sounds and it was found from preliminary testing, that the sensitivity and specificity of the inhalation detection algorithm described in the previous study decreased with the new INCA device. This study set out to adapt the previously described inhalation detection algorithm, in order to accurately detect inhalation events with the new INCA device. A larger number of audio files were employed in the training and testing datasets of this study, in comparison to the previous study.

Methods

Study Background & Instrumentation
To evaluate the performance of the inhalation detection algorithm on the new INCA device, data were recorded from 12 community dwelling asthmatic patients (6 female & 6 male). The age range of recruited patients was 20-83 (mean 49 ± SD 18) years. All patients had experience in using the Diskus DPI. It was communicated to patients before they began the study that an acoustic recording device that could monitor their temporal and technique adherence would be attached to their Diskus inhaler.

Each patient was given an INCA equipped Diskus inhaler by their doctor for a period of one month. Patients were instructed to use their inhaler as normal and they were not given any extra advice or special training. After using their INCA enabled inhaler for one month the patients returned to their clinic, where the INCA device was removed from the inhaler and the audio files were uploaded to a database for analysis.

Inhalation Detection Algorithm Design
The algorithm designed to detect the inhalation events initially went through a training phase. The 12 patients recruited in this study provided 609 audio files in total. Each of these audio files represented a unique record of inhaler use. There was a great quantity of variation between subjects (inter-subject variability) and also within subjects (intra-subject variability), in terms of recording environment and patient technique. 202 (33% of total files available) audio files were randomly selected and employed in the training phase of the algorithm. As in the previous study, an MFCC feature extraction approach was employed to detect inhalations in this study, due to the fact that inhalations are known to have a characteristic MFCC pattern that allows them to be distinguished from other sounds (Ruinskiy and Lavner, 2007).

Unlike the previous study, there were a number of exhalations present in the audio recordings in this study. The algorithm was designed to detect breath sounds (both inspiratory and expiratory), before inhalations were separated from exhalations. Each signal is separated into frames of length
700ms with an overlap of 20ms. The 0th MFCC and MFCCs 1-12 are calculated for each frame, forming a short-time cepstrogram of the signal. SVD was subsequently employed to obtain a normalised singular vector from the cepstrogram of the signal. Singular vectors have been reported to capture the most important characteristics of breath sounds obtained from MFCC calculations (Ruinskiy and Lavner, 2007). An adaptive threshold ($\theta_3$) is set that is 7% higher than the lowest singular vector in the inhaler recording. Singular vectors above this adaptive threshold are marked as potential breath events. This adaptive threshold was found empirically to produce the most accurate detection of breaths in the characterisation dataset. The mean ZCR is then computed to reduce the number of false positive breaths detected by the algorithm. 

Breaths were found to have a characteristically high ZCR compared to that of non-breaths in the characterisation dataset. A fixed threshold ($\theta_6$) constant of 0.1 was therefore introduced to reflect this fact. Breaths also consistently had a ZCR above this threshold value, while false positives were successfully removed. A flow chart of the steps employed to detect breath events can be seen in Figure 8.2.

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**Figure 8.2: Flow chart demonstrating how breath events were detected.**

**Inhalation/Exhalation Differentiation**

Breath sounds are finally differentiated into inhalations and exhalations. To do this the mean PSD of identified breaths is calculated for frequencies between 2.52-4 kHz in the original unfiltered signal. It was found from empirical observations in the training dataset that inhalations had a greater power in this specific frequency band compared to exhalations. Based on this fact a fixed threshold ($\theta_7$) was put in place. Inhalations were found to have a $P_{ave}$ greater than -80dB in the
training dataset and exhalations were found to have a \( P_{ave} \) below this value. The standard deviation of the ZCR was also found to be higher for inhalations in comparison to exhalations in the training dataset. A fixed threshold \( (\theta_4) \) of 0.045 was put in place with inhalations having a value greater than this threshold and exhalations a value below this threshold. A flow chart of the processing steps the algorithm employed to differentiate inhalations and exhalations is displayed in Figure 8.3.

![Flow chart](Figure 8.3: Flow chart illustrating how inhalations and exhalations are separated.)

**Results**

To test the algorithm's performance in detecting inhalation sounds, 407 new audio files were selected from the 12 asthmatic patients recruited in this study (67% of total audio files obtained). Two human raters, trained by an experienced respiratory clinician to identify inhalation events during Diskus inhaler use, independently classified each of the 407 audio files using the audio tool Audacity®. As in the previous studies, each human rater manually examined the audio files using visual and aural methods. In this study the onset and offset times were not compared between the human raters and the algorithm.

Cohen’s kappa statistic is a measure of interrater agreement and takes into account the prior probability of a specific class occurring (Redmond and Heneghan, 2006). The overall kappa agreement (Cohen’s Kappa Statistic) between Rater 1 and Rater 2 in classifying inhaler user technique was found to be 0.58, indicating moderate agreement between the two human raters. Patients were divided into two subgroups based on the kappa agreement scores between the human raters; Group A consisted of patients for whom the raters had almost perfect agreement
(kappa > 0.81) and Group B consisted of patients for whom the kappa agreement was below this score (kappa < 0.81). For Group A (n=8), the overall accuracy of the algorithm in detecting inhalation sounds was 91.7%. Table 8.5 details the classification performance of the algorithm in detecting inhalation sounds for Group A in comparison to the human raters.

**Table 8.5: Inhalation detection algorithm performance.**

<table>
<thead>
<tr>
<th>Inhaler Event</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation Sound</td>
<td>84.8</td>
<td>98.4</td>
<td>91.7</td>
</tr>
</tbody>
</table>

**Discussion**

MFCCs and ZCR were employed as features to detect inhalation sounds in this study. These features have previously been used to successfully detect breath sounds in speech and song signals (Ruinskiy and Lavner, 2007). A previous study in this Chapter (8.2.1) investigated the feasibility of using MFCCs and ZCR to detect inhalation sounds in inhaler audio recordings. The findings of that study indicated that the features can be successfully applied to inhaler audio recordings (Accuracy = 94.3%). However, the previous study was performed using a prototype version of the INCA device. The INCA electronic monitoring device employed in this study differed from the prototype device and had a different microphone, sampling rate and recording location.

It was found in this present study that MFCCs and ZCR detected inhalation sounds in inhaler audio signals with an accuracy of 91.7%. This accuracy is slightly lower than the previous study, however, given the small sample sizes in both studies (20 patients and 12 patients), this discrepancy may be negligible. The 12 patients who took part in this study were the first 12 patients to use the new model of the INCA electronic inhaler monitoring device. Compared with the previous study, the patients in this study generated more noise during inhaler operation. This may explain why the algorithm sensitivity was lower in this study (84.8%), in comparison to the sensitivity attained in the previous study (94.9%). Nevertheless, the results of the present study are encouraging and indicate that MFCC and temporal based acoustic signal processing methods can be employed to automatically and objectively detect inhalation sounds in inhaler audio recordings.

Cohen’s Kappa score was employed to assess the agreement between the two human raters in classifying inhaler user technique in this study. The Kappa score between the two human raters in this study was 0.58, indicating moderate agreement between raters. Given that the level of agreement was far from perfect, it is clear that the human raters are not a true gold standard.
Therefore, there may be some discrepancies in attempting to compare an objective method versus an imperfect subjective based method. A better gold standard method is needed for future studies, instead of more subjective human raters.

8.2.3 A Filter Bank Energy (FBE) Approach to Detecting Inhalation Sounds

Introduction

MFCCs 1-12 were employed as features in the previous studies to detect inhalation sounds. However, given the broadband spectral nature of the inhalation sounds (as was observed in Chapter 6), it was hypothesised that the FBE may adequately capture the most important characteristics of the inhalation. MFCCs 1-12 are successfully employed to detect breath sounds in speech and song signals, however, the spectral characteristics of these sounds differ from inhaler inhalation sounds. A study by Drugman et al. (2011) reported that of 105 different audio features, the FBE contained the most intrinsic information in relation to cough sounds. It can be argued that cough sounds share similar characteristics to inhaler inhalations, given the velocity of air passing through the oral cavity. It was thus hypothesised that removing MFCCs 1-12 would not impact on the performance of the inhalation detection algorithm and that the FBE could be employed as a feature to successfully detect the inhalation sounds. Compared with frame energy, the FBE contains more information relating to specific sub-bands of frequency. The FBE feature is more sensitive to low frequencies and less sensitive to high frequencies in comparison to typical frame energy. This is similar to the hearing characteristics of the ear (Zheng et al., 2001). Zheng et al. (2001) also reported that including the FBE feature with MFCC features improved the performance of a speech classifier, compared to using MFFCs on their own. These results would suggest that the FBE is a useful feature that can be employed to detect acoustic respiratory events.

In the previous studies detailed in this Chapter, the ZCR feature was employed to remove false positive inhalation events. Inhalations were observed to have a high ZCR in comparison to non-inhalations. However, a number of short duration artefacts were still being classified as inhalation events. It was decided that a temporal duration threshold would be better suited at removing short duration noise artefacts, in comparison to the ZCR feature. There is no information in the literature on what the minimum duration of inhalation should be for inhaler use. It is known that for DPIs, like the Diskus, the drug is removed from the inhaler in the first 200ms of the inhalation. However, the fine particle fraction dose is determined by the PIFR and the duration of the inhalation. Recent studies (El Larhrib et al., 2015) have reported that instructing patients to inhale for longer (5 seconds) improves the fine particle fraction dose.
This study investigates what combination of thresholds (FBE and duration) produces the highest sensitivity and specificity in detecting inhalation sounds in a dataset of audio recordings obtained from 50 asthma and 50 COPD patients.

**Methods**

**Asthma Patients**

A total of 1000 audio recordings were selected at random from 50 asthmatic patients who were part of a 3-month multi-centre clinical trial in Ireland. Approximately 20 audio files were selected at random from each of the 50 patients. There were a total of 18 males and 32 females in the study. The average age of the asthma study participants was $53.45 \pm 16$.

**COPD Patients**

A total of 1000 audio files were also selected at random from 50 COPD patients. The COPD patients were part of a 1-month clinical trial in Beaumont Hospital Dublin. As with the asthma patients, 20 audio recordings were randomly selected from each patient to produce the 1000 audio files. The number of males in this study was 24 and the number of females was 26. The average age of the COPD study participants was $70.93 \pm 9.21$.

**Inhalation Detection Algorithm**

To detect inhalation sounds in the inhaler audio signals, FBE is extracted as a feature. The MFCC derived FBE is known to contain a significant amount of unique information regarding respiratory events and has previously been reported as the most intrinsic feature in detecting other respiratory based sounds (Drugman *et al.*, 2011). It was hypothesised that this feature may be useful in detecting inhaler inhalation sounds. FBE was computed using the following steps:

The audio signal is first epoched into frames of length 25ms ($N_w$), which overlap every 10ms.

Calculation of energy spectrum:

$$y(k) = \sum_{n=0}^{N_w-1} x(n)W(n)e^{-j\frac{2\pi nk}{N_w}} ; \quad 0 \leq k \leq N_w$$  \hspace{1cm} (8.3)

where $x(n)$ is the input inhaler signal and $W(n)$ is a Hamming window. The energy spectrum is subsequently given by:

$$X_k = |y(k)|^2; \quad 0 \leq k \leq K$$  \hspace{1cm} (8.4)

where $K$ is taken equal to $N_w/2$, as only half the spectrum is considered.
Using a lower frequency limit of 0 Hz and an upper frequency limit of 4000 Hz (limited due to INCA device), 20 filter banks were estimated using a mel-scale. The following equation (described by Quatieri (2002)) was employed to map the triangular FBEs to the mel-scale:

\[ M(f) = 2595 \log_{10}(1 + f/700) \]  

(8.5)

The energy in each filter bank is then calculated:

\[ E_J = \sum_{k=0}^{K-1} \theta_J(k)X_k ; \quad 0 \leq j < J \]  

(8.6)

where \( J \), which equals 20, is the number of triangular filters (\( \theta_j \)) used.

FBE channels are then normalised between 0 and 1. To smooth the signal and remove short duration noise artefacts in the signal, the root mean square (RMS) amplitude of 50 ms frames which overlap every 10 ms are calculated. The triangular FBE as mapped to the mel-scale from 0 – 4000 Hz is displayed in Figure 8.4. Table 8.6 details the frequency ranges employed to create Figure 8.4. An example of a final FBE signal is displayed in Figure 8.5.

![Diagram of triangular filter banks](image)

*Figure 8.4: Illustrative example of the spacing and overlap of the 20 mel spaced triangular filter banks.*
<table>
<thead>
<tr>
<th>Channel</th>
<th>Frequency Range (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 – 139.18</td>
</tr>
<tr>
<td>2</td>
<td>66.44 – 218.84</td>
</tr>
<tr>
<td>3</td>
<td>139.18 – 306.05</td>
</tr>
<tr>
<td>4</td>
<td>218.84 – 401.54</td>
</tr>
<tr>
<td>5</td>
<td>306.05 – 506.10</td>
</tr>
<tr>
<td>6</td>
<td>401.54 – 620.57</td>
</tr>
<tr>
<td>7</td>
<td>506.10 – 745.92</td>
</tr>
<tr>
<td>8</td>
<td>620.57 – 883.16</td>
</tr>
<tr>
<td>9</td>
<td>745.92 – 1033.43</td>
</tr>
<tr>
<td>10</td>
<td>883.16 – 1197.96</td>
</tr>
<tr>
<td>11</td>
<td>1033.43 – 1378.11</td>
</tr>
<tr>
<td>12</td>
<td>1197.96 – 1575.36</td>
</tr>
<tr>
<td>13</td>
<td>1378.11 – 1791.32</td>
</tr>
<tr>
<td>14</td>
<td>1575.36 – 2027.79</td>
</tr>
<tr>
<td>15</td>
<td>1791.32 – 2286.71</td>
</tr>
<tr>
<td>16</td>
<td>2027.79 – 2570.19</td>
</tr>
<tr>
<td>17</td>
<td>2286.71 – 2880.59</td>
</tr>
<tr>
<td>18</td>
<td>2570.19 – 3220.45</td>
</tr>
<tr>
<td>19</td>
<td>2880.59 – 3592.56</td>
</tr>
<tr>
<td>20</td>
<td>3220.45 – 4000</td>
</tr>
</tbody>
</table>
Figure 8.5: Final average FBE signal for an inhaler audio signal. The inhalation sound occurs between 6-8 s.

**Adaptive Noise Threshold**

To detect inhalation events in the inhaler audio signals an adaptive noise threshold is estimated. The elements of the smoothed FBE signal are first sorted in ascending order. The mean of the smoothed FBE is then estimated from the sorted matrix from the lower 50% of values only. This adaptive mean value is then added to 0.02 to give a final noise floor threshold. A value of 0.02 was selected based on results detailed later in this Chapter.

**Inhalation Detection Step**

To detect inhalation sounds, smoothed FBE indices above the adaptive noise threshold are marked as potential inhalation sounds. Potential inhalation sounds are examined and any less than 500 ms in duration are discarded. This threshold was selected as inhalations shorter than this are regarded as insufficient for successful drug delivery (decided by two experienced Respiratory Physicians). To improve the accuracy of the inhalation offset time further, a gradient descent algorithm is employed.

**Gradient Descent Algorithm for Inhalation Offset Demarcation**

To select the correct inhalation sound offset time a gradient descent algorithm was constructed to examine the smoothed FBE in a discrete period of time after the proposed offset. Mean smoothed FBE is computed for 150 ms frames after the proposed offset time and these frames overlap every 10 ms. If the mean smoothed FBE in a frame is less than the previous five frames, then the gradient of the FBE is judged to be descending. This iterative process is repeated to estimate a more accurate inhalation offset time until the mean smoothed FBE value is greater than or equal to any one of the previous five frames. If 100 overlapping frames (equal to 1000 ms
in duration) have been estimated or the inhaler audio signal ends before the gradient of the mean smoothed FBE stops descending, then the end time of the last time frame is judged to be the end of the inhalation signal.

Over Reading and Statistical Analysis

Each of the 1000 audio recordings in the asthma and COPD cohorts were manually overread by an expert human rater, who was trained to identify inhalations. The total number of inhalations in each audio file was noted, in addition to their onset time, duration and offset time.

A receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal combination of FBE and inhalation duration thresholds. The ROC curve is frequently used as a method of visualising the performance of different classifiers (Bahoura, 2009).

Results

The performance of the inhalation detection classifier was evaluated by comparing it to that of an expert human rater (gold standard). The inhalation duration threshold was varied from 0.3 s to 1 s in steps of 0.1 s. The FBE thresholds employed were 0.01, 0.02 and 0.03. Sensitivity and specificity values were calculated by estimating the number of true positives and negatives, in addition to false positives and negatives. For the cohort of 50 asthmatic patients it was found that using a FBE threshold of 0.02 and an inhalation duration threshold of 0.5 s produced the best balance between sensitivity (88.84%) and specificity (91.46%). This combination of thresholds was the closest point on the ROC curve to the upper left corner, where the ideal classifier would lie (i.e. 100% sensitivity and 100% specificity). Figure 8.6 shows the ROC curves with the varying combination of thresholds for the 50 asthmatic subjects.
Figure 8.6: ROC curve detailing the performance of the inhalation detection algorithm in classifying inhalation sounds in a cohort of 50 asthma patients.

As in a previous study in this Chapter, differences between the onset time and offset time were calculated for the 50 asthma patients. The results of this analysis are detailed in Table 8.7 below, while a graphical representation is provided in Figure 8.7.

Table 8.7: Differences in onset, duration and offset time of inhalation sounds for human rater versus algorithm.

<table>
<thead>
<tr>
<th>Mean Onset Difference (ms)</th>
<th>Mean Duration Difference (ms)</th>
<th>Mean Offset Difference (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>±110</td>
<td>±253</td>
<td>±342</td>
</tr>
</tbody>
</table>
For the cohort of 50 COPD patients, it was found that using a FBE threshold of 0.02 and an inhalation duration threshold of 0.4 s produced the best balance between sensitivity (63.83%) and specificity (77.36%). The ROC curve for the COPD patients is displayed in Figure 8.8 below.

To investigate if age would impact the selection of optimum thresholds, the asthma patients were divided into those aged less than 60 years (n=29 patients) and those aged greater than 60 years (n=21 patients). There was no statistically significant difference in gender, height, weight or BMI
between these two cohorts of patients (\( p > 0.05 \)). It was found that for older asthma patients (age > 60 years), the thresholds reported previously in this Chapter are the most appropriate. This corresponds with a FBE threshold of 0.02 and an inhalation duration threshold of 0.5 s. This produces a sensitivity of 86.74% and a specificity of 91.54%. For the younger asthmatic patients (age < 60) it was found that a FBE threshold of 0.01 and an inhalation duration threshold of 0.7 s produced a classifier with a sensitivity of 90.88% and specificity of 93.9%. ROC curves for the two asthma age based cohorts are shown in Figure 8.9 and Figure 8.10. Histogram plots are also given which illustrate the start time (after opening the Diskus) and duration of inhalations in both the asthma and COPD cohorts (Figures 8.11 – 8.14).

![ROC curve](image)

*Figure 8.9: ROC curve detailing the performance of the inhalation detection algorithm in classifying inhalation sounds in a cohort of asthmatic patients greater than 60 years in age (n=21).*
Figure 8.10: ROC curve detailing the performance of the inhalation detection algorithm in classifying inhalation sounds in a cohort of asthmatic patients less than 60 years in age (n=29).

Figure 8.11: Inhalation start time for 50 asthmatic patients. Mean start time is 10.38 s and median start time is 7.74 s.
Figure 8.12: Inhalation duration for 50 asthmatic patients. Mean duration is 2.16 s and median duration is 1.78 s.

Figure 8.13: Inhalation start time for 50 COPD patients. Mean start time is 10.89 s and median start time is 6.97 s.
A Mann-Whitney U test was employed to investigate differences between the characteristics of the asthma and COPD patients’ inhalations. The Mann-Whitney U test is used to determine differences between two unrelated groups on an independent variable, and it can be used to analyse non-normal distributions. It was found that there was a statistically significant median increase in inhalation duration for asthma patients, compared with the COPD patients (p < 0.00001). It was also found that there was a statistically significant difference between the inhalation start time between asthma and COPD patients (p = 0.0206), with asthma patients taking slightly longer to inhale after opening the inhaler compared with COPD patients. The results of this analysis imply that asthmatic patients have longer inhalation durations, compared with COPD patients in unsupervised real world settings. It also implies that asthma patients take longer to begin the inhalation through their inhaler after opening the device, in comparison to COPD patients.

Discussion

In comparison with the previous studies described in this Chapter that focused on inhalation detection, this study employed a greater number of patients and audio files. A total of 1000 audio files were randomly selected from 50 asthma patients (20 audio files per patient), while an additional 1000 audio files were selected from 50 COPD patients (also 20 audio files per patient).
This varied cohort of patients was a robust test of algorithm performance and results obtained are a good estimate of how the algorithm would perform in real world asthma and COPD patients.

It was observed that different combinations of the FBE and inhalation duration thresholds produced different results between asthma and COPD patients, in addition to young versus old asthma patients. It is no surprise that for young asthma patients (< 60 years), the highest sensitivity and specificity values were achieved (90.88% and 93.9%). Young patients will typically have large PIFRs and long inhalation durations in comparison to older patients suffering from asthma and COPD. The FBE threshold was smaller (0.01 v 0.02) and the inhalation duration threshold was longer (0.7 v 0.5 s) for young asthmatic patients compared to older asthmatic patients. It can be hypothesised that a lower FBE threshold produces a greater sensitivity in detecting inhalations, while also maintaining a high level of specificity given that younger patients will have less noise artefacts in the audio recordings. The inhalations of younger adults will also be longer in duration compared with older adults. This study demonstrated that taking a personalised approach may thus improve the performance of the inhalation detection algorithm.

The inhalation detection algorithm performed poorest on the cohort of COPD patients with a sensitivity of 63.83% and specificity of 77.36%. The primary reason for this is that COPD patients frequently inhale with low PIFRs and short durations. Given that the features employed to detect inhalations in this study were FBE and inhalation duration, the detection of low energy and short duration inhalations remains challenging. COPD patients also generate a large number of artefacts that are similar in acoustic characteristics to inhalation sounds. Future studies should investigate the use of acoustic features that are independent of energy and duration, as they may be better suited in detecting inhalations in COPD patients.

In this study the FBE feature was employed, and unlike previous inhalation detection studies in this Chapter MFCCs 1-12 were not utilised. Removing MFCCs 1-12 did not impact significantly on the performance of the inhalation detection algorithm in this study and high sensitivity and specificity values were achieved. The inhalation duration feature was found to be a more appropriate choice of feature, in comparison to the ZCR feature, in removing short duration noise artefacts. Although the ZCR feature could have been used to remove false positives, it does not take the duration of the false positives into account and is similar to the FBE feature. Overall, it was found that the FBE and inhalation duration features are a good choice in detecting inhalation sounds from inhaler recordings, and in particular for asthmatic patients.
8.3 User Technique Score Algorithm

8.3.1 Introduction

The purpose of this algorithm is to automatically and objectively assess inhaler user technique adherence. Previous studies described in this Chapter have detailed algorithms to detect blister and inhalation sounds in audio signals generated during Diskus inhaler use. In Chapter 7, an algorithm to detect exhalation sounds during inhaler use was reported. In this study, the information on the presence of these events (i.e. blister, inhalation and exhalation), their frequency and their sequence in each audio file will be employed to calculate a technique score for each audio file.

At present, human raters assess inhaler audio files and score each audio file as one of three outcomes: used correctly, used incorrectly (also referred to as ‘Technique Error’) or not used. The same scoring scheme will be used to classify inhaler audio files in this study. The primary objective is to use the algorithms developed previously to automatically and objectively score each inhaler audio file. The performance of the algorithm in deciding a user technique score will be compared to that of expert human raters, and described in terms of sensitivity, specificity and accuracy.

8.3.2 Methods

Inhaler User Technique Score

The algorithms described previously in this Chapter and Chapter 7 allow for the development of a system to objectively assess inhaler technique adherence. Using data from the blister detection, inhalation detection and exhalation detection algorithms, it is possible to calculate an objective inhaler user technique score. An inhaler user technique classification algorithm was designed and developed to classify inhaler audio files obtained from the INCA audio device. Audio files could be classified as either (a) used correctly, (b) used incorrectly or (c) not used. To decide an inhaler user technique score the algorithm checks to see what events have taken place, the frequency of each type of inhaler event and the order in which these events have taken place (Figure 8.15).

![Figure 8.15: Overview of the steps taken by the user technique score algorithm.](image-url)
The Diskus inhaler is deemed to have been used correctly if a patient first blisters the foil and secondly inhales the medication. Exhalations can take place before the blister or after the inhalation, still leading to a ‘used correctly’ score from the algorithm. However, if the patient exhales in the time between the blister and inhalation then they are judged to have committed a ‘technique error’ as they may have exhaled into the mouthpiece of the inhaler and dispersed some of the medication. Such a scenario is viewed as a critical error. Although instructions for Diskus inhaler use specify that patients should exhale between the blister and inhalation steps (as explained in Section 2.11.1), this should be in a direction away from the mouthpiece. Such exhalations will not be detected by the algorithm, however, those in the direction of the mouthpiece will be detected and classified as errors in inhaler user technique. Any other sequence of inhaler events is deemed to be a user technique error. For example: An inhalation event followed by a blister event, a blister event but no inhalation present, exhalation event but no inhalation event etc. If the algorithm detects multiple inhalations or multiple blisters then a user technique error will also be judged to have taken place. These combinations of events and outcomes were decided based on the opinions of two experienced Respiratory Physicians in Beaumont Hospital, Dublin. Examples of how the algorithm classifies inhaler audio recordings are displayed in Table 8.8.

Table 8.8: Interaction between inhaler steps and inhaler technique score with the INCA for the Diskus inhaler.

<table>
<thead>
<tr>
<th>Inhaler User Technique Step</th>
<th>Blister</th>
<th>Exhale</th>
<th>Inhale</th>
<th>Multiple Inhalations</th>
<th>Multiple Blisters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incorrect</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incorrect</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Not Used</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Inhaler Used Incorrectly – Error Type**

If the Diskus inhaler is deemed to have been used incorrectly, then the cause of the error can be one of seven possible results. These seven specific error types were decided by two respiratory consultants, who spent a great quantity of time overreading audio files from the INCA device. The seven error types are as follows:
• **Multiple Inhalations** – If two or more inhalations are detected in the audio signal.

• **Multiple Blisters** – If two or more blister sounds are detected in the audio signal.

• **Multiple Inhalations & Multiple Blisters** – A combination of the above two error types.

• **Exhaling into the Mouthpiece** – Blowing into the mouthpiece of the inhaler in between the blister step and the inhalation step. It is at this time when the drug dose is sitting in the mouthpiece of the inhaler and is susceptible to exhalations.

• **No Blister, Inhalation Present** – No blister therefore no drug was released.

• **No Inhalation, Blister Present** - Drug released but no inhalation to deliver it to the lungs.

• **No Inhalation and No Blister Present** – No inhalations or blisters but exhalation present.

Using this information, it is possible to develop an algorithm that can automatically classify inhaler user technique errors and execute the same logical steps that a respiratory consultant would. The algorithm for this procedure is based on the following table (Table 8.9), from where the combination of events that leads to each of the seven user technique errors is detailed.

*Table 8.9: Inhaler user technique steps and their interaction with the seven technique errors.*

<table>
<thead>
<tr>
<th>Inhaler User Technique Error</th>
<th>Blister</th>
<th>Exhale</th>
<th>Inhale</th>
<th>Multiple Inhalations</th>
<th>Multiple Blisters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Inhalations</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple Blisters</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Multiple Inhalations &amp; Multiple Blisters</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exhaling into Mouthpiece</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No Blister, Inhalation Present</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No Inhalation, Blister Present</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No Inhalation &amp; No Blister Present</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
A complete overview of the possible outcomes for an inhaler audio recording is displayed in Figure 8.16 below.

![Diagram showing possible outcomes for an audio signal of inhaler use as recorded by the INCA device.]

### Figure 8.16: Possible outcomes for an audio signal of inhaler use as recorded by the INCA device.

**Validation of User Technique Score Algorithm**

To validate the performance of the user technique score algorithm, data were analysed from two clinical trials that used the INCA electronic monitoring device. The first of these clinical trials involved a cohort of asthma patients while the second involved a cohort of COPD patients. As in the previous studies in this Chapter, patients used an INCA equipped Diskus inhaler as they normally would in their home environment. At the end of each month the patients returned to a respiratory outpatient’s clinic, from where the audio data were downloaded from the INCA devices. Two expert respiratory consultants then proceeded to manually overread the audio files in the database. They marked each audio file as one of three outcomes: used correctly, used incorrectly or not used. If there was any audio file in which they were unsure what the technique score should be, they would flag it and a second opinion would be given by the second respiratory consultant. Overreading was carried out for a number of files in both the asthma and COPD...
clinical trials. The results of the manual overreading were then compared against the results from the automatic algorithm.

### 8.3.3 Results

**Asthma Patients**

There are a total of 22,907 audio files in a database from a clinical trial involving asthma patients. A total of 19,932 audio files (from 145 study participants) were overread by the two respiratory consultants. The performance of the inhaler user technique score algorithm in correctly deciding the correct technique score versus human raters is given below (Table 8.10 and Figures 8.17-8.20).

*Table 8.10: Number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) for the technique score algorithm in deciding how inhaler was used by asthma patients, in comparison to human raters.*

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaler Used Correctly</td>
<td>13759</td>
<td>842</td>
<td>3222</td>
<td>1967</td>
</tr>
<tr>
<td>Inhaler Technique Error</td>
<td>1636</td>
<td>2162</td>
<td>15143</td>
<td>849</td>
</tr>
<tr>
<td>Inhaler Not Used</td>
<td>1293</td>
<td>98</td>
<td>18113</td>
<td>286</td>
</tr>
</tbody>
</table>

*Figure 8.17: Algorithm performance versus human rater in calculating if inhaler was used or not used in asthma patients.*
There were 849 false negatives for inhaler user technique errors. This implies that the algorithm missed the detection of errors that the human raters were capable of detecting. This is why the sensitivity value for detecting when the inhaler is used with incorrect technique is 65.8%. The technique errors that the algorithm missed are represented in Figure 8.19 below.
Figure 8.19: Technique errors that the algorithm missed for the asthma patients. The most common errors missed were exhaling into the mouthpiece (n=489) and low PIFR (n=142).

There were 2162 false positives for inhaler user technique errors. This implies there were 2162 occasions when the inhaler was used with correct user technique (as classified by the human raters), but the algorithm calculated that the inhaler was used with incorrect user technique. A detailed distribution of these errors are presented in Figure 8.20.
Figure 8.20: Technique errors that the algorithm output, when the inhaler was used with correct technique in asthma patients. The most common errors given by the algorithm were multiple inhalations (n=832), no blister detected, inhale present (n=633) and blister detected, no inhalation present (n=457).

The fact that no inhalations were detected on 457 occasions would imply that the algorithm is not sensitive to detecting all inhalations. Previous investigation indicates that these inhalations have PIFRs less than 50 L/min. Adjustments to the thresholds may improve the sensitivity of inhalation detection. However, it should also be noted that the number of multiple inhalations detected was quite high (n=832). Blisters were not detected on 633 audio files, in which the human raters detected blister events.

A Kappa score of interrater agreement was calculated for the asthma patients. Of the 19,932 audio files that were overread, 1,735 were overread by the two respiratory consultants. The kappa score for these files was 0.66, indicating 86.16% agreement between raters (Table 8.11). The interpretation of this result is given in Figure 8.21.
Table 8.11: Cohen’s Kappa score estimation for the 1,735 audio files that were overread by more than one overreader.

<table>
<thead>
<tr>
<th>Expected Agreement</th>
<th>Kappa</th>
<th>Std. Err.</th>
<th>Z</th>
<th>Prob&gt;</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>86.16%</td>
<td>59.29%</td>
<td>0.6600</td>
<td>0.0192</td>
<td>34.33</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Figure 8.21: Interpretation of Kappa scores. A score of 0.666 in this study indicated substantial agreement (as highlighted by the box in red).

COPD Patients

There are a total of 11,453 audio files in a database from a clinical trial involving COPD patients. Of these audio files, 7,583 audio files were overread by the two respiratory consultants from 92 COPD study participants. The performance of the inhaler user technique score algorithm in correctly deciding the correct technique score versus the human raters is given below (Table 8.12 and Figures 8.22-8.25).

Table 8.12: Number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) for the technique score algorithm in deciding how inhaler was used by COPD patients, in comparison to human raters.

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaler Used Correctly</td>
<td>2612</td>
<td>502</td>
<td>3248</td>
<td>871</td>
</tr>
<tr>
<td>Inhaler Technique Error</td>
<td>2496</td>
<td>1052</td>
<td>3145</td>
<td>540</td>
</tr>
<tr>
<td>Inhaler Not Used</td>
<td>497</td>
<td>74</td>
<td>6445</td>
<td>217</td>
</tr>
</tbody>
</table>
Figure 8.22: Algorithm performance versus human rater in calculating if inhaler was used or not used for the COPD patients.

Figure 8.23: Algorithm performance versus human rater in calculating if inhaler was used correctly or incorrectly for COPD patients.
Figure 8.2: Technique errors that the algorithm missed for COPD patients. The most common errors missed were blister present, no inhalation detected.

- Blister present, no inhalation detected (n=38)
- Exhaling into mouthpiece (n=137)
- Low PIFR (n=210)
- Multiple blisters (n=8)
- Multiple inhalations (n=117)
- Multiple inhalations & multiple blisters (n=7)
- No blister & no inhalation detected (n=6)
- No blister detected, inhale present (n=2)

Figure 8.25: Technique errors falsely detected by the algorithm for COPD patients.

- Blister present, no inhalation detected (n=446)
- Exhaling into mouthpiece (n=12)
- Multiple blisters (n=96)
- Multiple inhalations (n=184)
- Multiple inhalations & multiple blisters (n=52)
- No blister detected, inhale present (n=262)
8.3.4 Discussion

For asthma patients, results suggest that the technique score algorithm can differentiate audio recordings into those that were used versus not used with a high level of accuracy (>98%). In differentiating asthma audio files that were used correctly versus incorrectly, the algorithm can classify inhaler user technique with an accuracy greater than 84% in comparison to the expert human raters. This is a promising result if this algorithm were to be used to replace the current manual overreading method. In the asthma clinical trial, the most common error that the algorithm missed was exhalations into the mouthpiece (n=489). The two respiratory consultants would mark an exhalation event if they detected an exhalation event in the time between the blister and the inhalation. However, they were not able to discriminate between exhalations that occurred in the direction of the mouthpiece and exhalations that were aimed away from the mouthpiece. In addition, they could not differentiate exhalations close to the mouthpiece versus those far away. Given the inadequacies in the human raters detection method, it is unclear if the exhalations they detected were truly detrimental to inhaler user technique. Multiple inhalations were also a common missed error by the algorithm, however the human raters did not take the energy and duration of the inhalations into account when classifying inhalation sounds. As energy and duration based acoustic features were employed to detect the inhalations sounds, certain low energy and short duration inhalations may be missed. Given that these types of sounds correspond with low PIFR and reduced drug deposition, it is unclear if the automatic algorithm is correct in classifying these audio files as having weak/missing inhalations or the human raters are correct in classifying the audio files as having multiple inhalations.

For the COPD patients, the technique score algorithm differentiated audio recordings into those that were used versus not used with an accuracy greater than 95%. The algorithm could differentiate inhaler user technique (used correctly versus used incorrectly) with an accuracy greater than 78%, in comparison to the human raters. There are a number of reasons the performance of the algorithm was lower for the COPD patients compared with the asthma patients.

In the COPD dataset, there were 446 occasions when the algorithm indicated that there was no inhalation present, but the human raters indicated that they heard an inhalation in the audio signal. As the audio files were recorded from COPD patients, it can be assumed that their PIFR was quite weak and that their inhalation duration was short. As was reported in Section 8.2.3 of this Chapter, the inhalation detection algorithm performs poorest on COPD patients. Nevertheless, these patients have low PIFR and short duration inhalations which are not ideal. The fact that the algorithm is capable of objectively classifying these events is of clinical benefit given that they will
impact drug delivery to the airways. COPD patients who frequently have audio files where no inhalation is detected (as judged by the objective algorithm) should be retrained on how to inhale with correct technique. Just because the human raters heard an inhalation sound, it does not imply that the PIFR or duration was adequate.

The gold standard method used to evaluate the technique score algorithm in this study was the subjective classification of inhaler audio files by two independent human raters. The two human raters were experienced respiratory consultants who had a significant amount of experience in assessing Diskus inhaler audio recordings and classifying user technique. Overall the two raters agreed with each other at a substantial level (Kappa = 0.66). The fact that the agreement between the human raters, who independently classified audio files, was far from perfect demonstrates the subjective nature of analysing patient inhaler user technique. The identification of common Diskus inhaler events from acoustic signals, namely blisters, inhalations and exhalations, can be challenging. Oftentimes it can be difficult to distinguish blister events as they can have similar characteristics to other background artefacts in the audio signal. The human raters also found it problematic to differentiate inhalations from exhalations when using visual and aural analysis methods.

Given that there was some disagreement between the two human raters in this study, additional methods (besides aural assessment) of classifying inhaler user technique will be needed for future studies. Device specific checklists are currently used as the gold standard to assess inhaler user technique in clinical settings (as discussed in Chapter 2), and may provide a better method of assessing the accuracy of future inhaler user technique score algorithms. However, such checklist methods are subjective in nature and are limited in that they can only be performed in controlled clinical environments. At present there is no gold standard method of objectively assessing inhaler user technique. This makes the interpretation of results from new objective methods (like presented in this study) challenging.
CHAPTER 9: Discussion

9.1 Thesis Summary

The studies detailed in this thesis aimed to investigate the use of acoustic based methods in objectively assessing inhaler adherence. Adherence to inhaled medications is consistently poor and there are several ways in which patients can make errors when using inhaler devices. Although correct inhaler adherence is critical for successful drug delivery, there are a shortage of reliable objective methods to monitor inhaler adherence. Of the existing methods, the electronic INCA acoustic adherence monitoring device offers the greatest potential. The integration of objective signal processing analysis methods with the electronic recording device may help improve the performance and reliability of the INCA system.

The literature contains numerous examples of how acoustic based signal processing methods can be employed to objectively detect and analyse breath sounds. Breath sounds are known to contain important information relating to physiological lung condition and researchers have utilised the objectivity of sound recording and digital signal processing methods to extract pertinent features. In order to further improve the objectivity of the INCA adherence monitoring system, a number of experiments were carried out in studies described in this thesis to investigate the use of signal processing based methods in analysing inhaler audio recordings. The motivation for the features extracted from the acoustic inhaler signals stem from features previously employed to detect inhalations and exhalations during breathing. A number of temporal, FTT and MFCC based features were employed throughout studies reported in this thesis. All thesis objectives and aims were examined by the studies and are further outlined within this Discussion Chapter.

9.2 Main Findings of the Thesis

The studies detailed in this thesis demonstrate that acoustic methods may be employed to objectively assess inhaler adherence. This finding was established from carrying out a number of studies that probed different aspects of inhaler technique and investigated the use of acoustic based methods in detecting/analysing events crucial for successful inhaler use. The importance of the research findings and the lessons learnt from this thesis will now be critically discussed in relation to the research questions previously posed in Chapter 3. Interpretation of the main findings will also be discussed in the light of the previous literature as detailed in Chapter 2.
Temporal and spectral features of inhaler inhalation signals can be employed to estimate the inspiratory airflow (PIFR) through an inhaler device.

The inhalation is the single most crucial step during inhaler use (Lavorini et al., 2008). At present, however, no method exists to objectively monitor inhaler PIFR on a longitudinal basis during real world use. In Section 2.3.3.2.1 of Chapter 2, a number of methods that can be employed to assess PIFR in clinical settings were introduced. Such methods are primarily used as training aids and it is likely that patients improve their technique when they are being supervised by a healthcare professional in clinical based settings. In the review of breath sounds in Chapter 2 (Sections 2.5-2.9), it was reported that acoustic based methods have previously been employed to estimate airflow rate from tracheal and chest wall recording locations during breathing. Typically, a set of features is extracted from the breath signals and these features are then compared to airflow rate using regression models. In Chapter 5, it was hypothesised that airflow rate through the Diskus DPI (i.e. PIFR) is related to the acoustic inhalation signals. It was postulated that time and frequency based acoustic features could be employed to accurately describe the relationship via regression models, given that these features perform highly in tracheal and chest wall based studies.

Results from Chapter 5 indicate that both temporal and spectral features of the inhalation signal are highly correlated with PIFR. In Section 5.1 of Chapter 5, it was reported that for simulated inhalations, $R^2$ values up to 0.97 were achieved when temporal and spectral features were used to estimate PIFR. In Section 5.2 of Chapter 5, 15 healthy subjects inhaled at a range of PIFRs while the acoustics of their inhalations were recorded with the INCA device. Again it was found that both temporal and spectral features could be used to estimate PIFR. $R^2$ values as high as 0.90 were reported for spectral based features. These results are highly promising as they establish the practicality of employing acoustics to monitor PIFR. With the INCA device, it is possible to record inhalations on a use-to-use basis. Therefore, it may be possible to monitor PIFR on a use-to-use basis also and assist healthcare professionals in monitoring patients’ inhaler use longitudinally.

Drug delivery from a DPI can be estimated using temporal and spectral features of the inhalation signal.

In DPIs drug delivery is dependent on the PIFR achieved by the patient (Broeders et al., 2001; Chrystyn, 2007). High PIFRs lead to high levels of drug deposition in the airways, while low PIFRs lead to low levels of lung drug deposition (Chrystyn, 2007). In Chapter 5 Section 5.1, it was demonstrated that acoustic based methods could be employed to estimate PIFR. Given the link
between PIFR and drug delivery, it is consequently possible to also estimate drug delivery using acoustic based methods. The feasibility of this was established in Chapter 5 Section 5.1, where TED was measured using a high precision weighing scales. It was observed that as the average power and MAD of the inhalation signal increased, so too did the TED. This finding was important, as it was the first study to demonstrate that acoustic based methods may be used to estimate drug delivery in an inhaler. However, these results were limited due to the in vitro design of the study. Inhalations were simulated using an air vacuum and thus had a square wave profile, unlike real world inhalations which have a more gradual ramp rate. Using the findings reported in Section 5.1 as motivation, an experiment was conducted using an NGI to further quantify the relationship between temporal/spectral acoustic features and drug deposition in the Diskus DPI (not detailed in this thesis). The advantages of using a cascade impactor are that the FPF and throat deposition levels can be estimated, in addition to the TED. The results of that study corroborate the findings obtained in Chapter 5 Section 5.1, in that acoustic methods are a useful tool in estimating drug deposition levels. The importance of this work lies in the fact that it provides healthcare professionals with a new metric for analysing inhaler inhalations and drug delivery in an objective and longitudinal basis, during real word inhaler use.

**Temporal and spectral features of inhaler inhalation signals can be used to estimate the volume of air inhaled through an inhaler device.**

Another important metric related to the inhalation event during inhaler use is inspiratory volume. Although PIFR is the most widely used metric to describe inhaler inhalations, it does not provide any information about the duration of the inhalation or the slope of the flow-time curve before and after PIFR is reached. The inspiratory volume is the area under the flow-time curve and this metric is frequently used in spirometry as a measure of lung function. In Chapter 5 Section 5.2, it was hypothesised that the acoustic signal of the inhalation, from the INCA device, could be employed to estimate inspiratory volume during inhaler use. In spirometry, the area under a PIFR – time curve equates to the volume of an inhalation or IC. Since acoustic measurements were used to predict the PIFR, integration could not be used to determine IC. Instead it was noted that the area under the curve of the inhalational sound waveform (inhalation volume) approximated to that of the area of a semi-ellipse in the subjects tested. Using the PIFR of the inhalation in combination with the duration, a value for inspiratory volume was estimated using the equation for the area of a semi-ellipse. Estimated inspiratory volume measurements were compared to actual volume measurements recorded by the spirometer for 15 healthy adult subjects. $R^2$ values greater than 0.90 were achieved in the estimation of inspiratory volume, using the methods proposed in Chapter 5 Section 5.2. It is possible that in a larger populations or in diseased
patients, a semi-ellipse may not best approximate the area of the inhalation. A study by Azouz et al. (2015) reported that asthma patients inhalation characteristics differ to that of COPD patients. More research is needed to define the true shape of inhaler inhalation flow-profiles, in order to improve the accuracy of volume prediction models. Monitoring inspiratory volume longitudinally may be important as it may indicate when patient’s capacity to inhale becomes reduced. This may potentially help healthcare professionals predict asthma attacks/exacerbations before they occur.

The ability to predict inspiratory flow rate, volume and drug delivery during real world inhaler use provides clinicians with objective measurements regarding how inhalers are used.

Until now, healthcare professionals have no way of knowing how patients inhale when using their inhaler devices outside clinical environments. Training devices exist but they are primarily used in clinical environments. Healthcare professionals will typically assume that patients, who demonstrate correct technique in the clinic, will be able to use their inhaler with correct inhalational technique in their home environments. However, many patients will make mistakes in their technique once they use their inhaler in unsupervised environments. This is analogous to passing a driving test in the company of an instructor, but later failing to follow the correct rules of the road and having an accident as a result. PIFR, inspiratory volume and drug delivery are three very important metrics that relate to a patient’s ability to use their inhaler with correct inhalational technique. The INCA electronic monitoring device uses acoustic methods to record patients’ inhaler use longitudinally. Presently, human raters analyse the inhaler audio recordings but similarly to healthcare professionals in a clinic, they have no objective method of knowing how the inhalation sound they hear relates to correct technique. The methods reported in Chapter 5 provide new objective methods of analysing inhalation technique in real world environments. This objective data can provide healthcare professionals with quantifiable data on how their patients are really using their inhaler devices.

Temporal and spectral features of ambient inhaler inhalation signals can be used to estimate the inspiratory airflow through the Diskus, Turbuhaler and Evohaler.

In Chapter 5, it was demonstrated that temporal and spectral features of inhalation signals can be employed to estimate inhaler PIFR. In Chapter 5, the INCA device was used to record the inhalation signals. However, the sampling rate was limited to 8 kHz in the commercial INCA device employed in this study and the plastic shell that contains the microphone may affect the frequency characteristics. To acquire a better understanding of the frequency characteristics of inhaler use, Chapter 6 describes a study in which a high quality measurement microphone was
employed to record ambient inhaler inspiratory sounds (at a distance of 5 cm from inhaler mouthpiece). In addition to the Diskus DPI, the acoustic characteristics of inhalations from the Turbuhaler DPI and the Evohaler pMDI were also investigated.

Results reported in Section 6.3.1 of Chapter 6 indicated that temporal and spectral features of ambient inspiratory inhaler sounds are significantly correlated with PIFR. For the Diskus inhaler, the correlation coefficients reported were lower (MAD $R^2=0.59$, RMS $R^2=0.55$), in comparison with the correlation coefficients reported in Section 5.2.3 of Chapter 5 (MAD $R^2=0.83$, RMS $R^2=0.83$). This may be due to the microphone being non-contact in Chapter 6, while in Chapter 5, the INCA microphone records vibrations directly from the Diskus device. Results also imply that there is a level of inter-subject variability in the acoustic features of inhaler inspiratory sounds. Interestingly, it was found that frequency based features (quartile frequencies and $P_{ave}$) were most highly correlated to PIFR for the Diskus inhaler. The quartile frequencies (F25, F50 and F75) were highly correlated with PIFR, a finding that was not reported in Chapter 5 Section 5.1 and 5.2.

A number of noteworthy findings were obtained for the Evohaler pMDI. At the recommended PIFR range for this inhaler, which is between 30-90 L/min, minimal acoustic energy was generated during inhalations. This is an important finding as it implies that acoustic methods may not be suitable for detecting/analysing inhalations in this specific inhaler device. The generation of turbulent acoustic energy during inhaler use is thus related to the airflow resistance of the inhaler. The pMDI has a low airflow resistance ($0.0135 \text{ (V cm H}_2\text{O)/(L/Min})$), the Diskus has a medium airflow resistance ($0.078 \text{ (V cm H}_2\text{O)/(L/Min})$) and the Turbuhaler has a high airflow resistance to airflow ($0.110 \text{ (V cm H}_2\text{O)/(L/Min})$) (Al-Showair et al., 2007; Azouz et al., 2014). The airflow resistance of an inhaler is an important factor that should be taken into account when analysing the acoustic signals of inhaler inhalations. High airflow resistance inhaler devices will generate more turbulent sound energy and thus the inhalation sounds will subsequently have a higher signal-to-noise ratio.

The spectral envelope of ambient inspiratory inhaler sounds is repeatable across a range of PIFRs.

In Chapter 6 Section 6.3.2, the spectral envelope of ambient inspiratory inhaler sounds was estimated for three inhalers. Study participants were asked to inhale at a range of PIFR bands and inhalations were repeated ten times for each PIFR band. A robust estimate of the spectral envelope was obtained for each PIFR band, in a within-subject analysis. Results revealed that within subjects, the spectral envelope was highly repeatable across PIFR bands for all three inhalers. This is an important finding for future acoustic based inhaler studies. The repeatability of
the peaks and troughs in the spectral profiles demonstrates that if frequency based features were to be employed in the analysis of inhalations, then it could be expected that the characteristics of the sound would be observed for all PIFRs. Given the high repeatability of the spectral envelopes within subjects, the opportunity exists to monitor spectral envelope longitudinally. It may be hypothesised that the spectral envelope could alter in shape during airway obstruction or respiratory infection. Future studies could investigate this hypothesis further and use the results reported in Section 6.3 of Chapter 6 as a baseline.

Temporal and spectral features of ambient inspiratory DPI sounds have a low variability.

In Chapter 6, the within subject variation of the inhalation sounds was calculated using the CoV equation. It was found that for the Diskus and Turbuhaler, frequency based features had variability at approximately 20%. The $P_{ave}$ of inhalation sounds had the lowest variability, with results less than 5%. Temporal features had variations slightly greater than 20% for the Diskus and Turbuhaler also, apart from the 80-90 L/min PIFR band in the Turbuhaler which had high variations. Reasons for high variability in this flow band are most likely due to subjects attempting to inhale at their maximum capacity, and thus introducing vocal cord noise artefacts into the inhalation signal. Variability in the Evohaler pMDI was high, especially for the quartile frequencies and temporal features. The most variability was observed in the quartile frequencies at PIFRs less than 100 L/min. Given the lack of acoustic energy at these PIFRs, it is of no surprise that the frequency curve is affected and the variability is high. Surprisingly, the $P_{ave}$ feature variability was low for the Evohaler. This finding suggests that $P_{ave}$ is a good choice of feature, if the variability of the inhalation sound were to be monitored longitudinally.

The fact that spectral features of DPI inspiratory sounds have a low variability is an important finding. The within subject repeatability of the features implies that the methods proposed are useful for monitoring inhaler inhalations. The repeatability of tracheal and chest wall breath sounds over the course of one month have been reported in the literature (Sanchez and Vizcaya, 2003). Studies in the literature also show that the acoustic characteristics of breath sounds change due to impairment in the upper airways (Forgacs et al., 1971; Malmberg et al., 1994). However, one of the major limitations of these findings is that it is currently unfeasible to expect patients to attach a microphone to their chest wall or trachea on a daily basis. These limitations are overcome with inhaler use, as patients prescribed oral steroids will typically use their inhaler at least once a day. Attaching an acoustic recording device to an inhaler (i.e. INCA) or using ambient/wearable acoustic sensors creates the opportunity to monitor inhaler inhalations longitudinally. Results in Section 6.3.3 of Chapter 6 demonstrated the repeatability of
temporal/spectral features in healthy subjects. If the features were to change during airway obstruction, then this would demonstrate the feasibility of using acoustic methods to monitor airway obstruction.

**Ambient inspiratory inhaler sounds may be composed of sounds associated with the airways and the inhaler design.**

Results obtained in Chapter 6 Section 6.3.1 clearly indicate that the design of the inhaler modulates the inhalation sounds. Three inhalers with varying levels of airflow resistance were employed in Chapter 6 and it was observed that the acoustic sounds generated are dependent on the airflow resistance of the inhaler device. This is an important finding in the field of inhaler acoustics as it indicates the importance of inhaler design on time/frequency based acoustic features. In Chapter 2 Section 2.5.1 of this thesis, the mechanisms that generate breath sounds were discussed in detail. It was reported that the movement of air in the respiratory airways generates the breath sounds heard at the trachea and chest wall. Turbulent breath sounds are heard in large diameter airways such as the trachea and bronchus (Mangione, 2012). Given that it is likely that airflow in the mouth and trachea is turbulent during inhaler inhalations, it can be assumed that sounds originating from the airways are generated. Further experiments are needed to separate out physiological respiratory sounds from inhaler specific sounds. Future studies should investigate the behaviour of acoustic features of inhaler inhalations during airflow obstruction. If the inhaler inhalation sounds vary due to airflow obstruction levels, it would confirm that inhaler sounds contain acoustic information specifically generated in the airways.

**A number of factors associated with exhaling into a DPI mouthpiece prior to the inhalation step influence drug delivery; namely exhalation airflow rate, distance from mouth to inhaler, exhalation duration and relative air humidity.**

Exhaling into the mouthpiece of a DPI is a common technique error. In Section 2.3.1 of Chapter 2, it was reported that over one in every five Diskus inhaler users exhale into the mouthpiece prior to the inhalation step (Melani et al., 2011). The primary aim of the study presented in Chapter 7 was to quantify the effect of four factors, all related to the exhalation, on drug delivery in the Diskus inhaler. The factors investigated were exhalation flow rate, distance from the mouth to the inhaler, exhalation duration and relative air humidity. It was hypothesised that these four factors would influence the amount of drug subsequently available for delivery. Results revealed that all four factors influenced subsequent drug delivery (P<0.05). It was found that the distance from the
mouth to the inhaler was the most influential factor influencing drug delivery. The duration of the exhalation was the least influential factor.

From the literature reviewed, many studies exist which claim that DPI users should not exhale into the mouthpiece of their inhaler prior to the inhalation step (Basheti et al., 2011; Melani et al., 2011; Lavorini et al., 2008; Basheti et al., 2014). However, it appears that this advice is based solely on one study (Engel et al., 1992). The effect of exhaling into the Diskus inhaler is unclear and the study presented in Chapter 7 set out to quantify the effect of this critical technique error. The importance of this study is that it is the first study to be carried out which investigates the effects of different exhalation factors on drug delivery. The results reported in Chapter 7 may help guide the design of future inhaler devices and improve future inhaler users’ technique.

The humidity of exhaled air has a significant detrimental effect on the amount of medication available for delivery in a DPI.

In the study reported in Chapter 7, the effect of humidity levels on exhalations into the Diskus DPI was investigated. Simulated exhalations with dry air (relative humidity of 28%) and humid air (relative humidity of 80%) were performed on a Diskus inhaler. After these simulated exhalations, inhalations were performed using common pharmacopeial-based methods (DUSA Apparatus). It was found that the delivered dose was more consistent when dry air was used, but more variable and unpredictable when humid air was used. It was also observed that less drug was delivered, on average, when humid air was used in comparison to dry air. These findings are important, as they are the first to demonstrate the detrimental effect of air humidity on exhalations into a dry powder inhaler. There are no studies in the literature that investigate the impact of this exhalation factor, to the best of the author’s knowledge.

An NGI cascade impactor was also employed to investigate the effect that exhaling into a DPI has on particle distribution. It was found that there were no differences in the total emitted doses (TED) but that the FPF was significantly reduced for inhaler devices subjected to an exhalation. This result demonstrates that exhaled air humidity most probably cause particles to clump together and has a detrimental effect on particle size distribution. Again this is an important finding given how common it is for inhaler users to exhale into the mouthpiece of their inhaler device. The findings reported in Chapter 7 indicate that more research is needed to design an inhaler better equipped to prevent humid exhalations from affecting the drug. Any future in vitro based DPI studies focusing on the impact of the exhalation should strive to use exhalations with humidity levels similar to real world exhalations.
Temporal and spectral features associated with exhalation sounds can be employed to automatically detect the occurrence of exhalations prior to inhalations during inhaler use.

As exhaling into a Diskus DPI has a detrimental effect on subsequent drug delivery, it is important to develop objective methods to detect this critical technique error. An algorithm detailed in this thesis can assess data from the INCA device and detect this exhalation sound when it occurs during use. At present, human rater’s overread audio recordings and look for the presence of exhalation events taking place prior to the inhalation step. However, this procedure is both tedious and subjective, and a better method is needed if the INCA system is to be employed in large-scale studies. Results from Chapter 7 indicate that the distance from the inhaler mouthpiece, the expiratory flow rate and the exhalation duration all influence the integrity of the drug. These factors can be detected using signal processing based methods and audio signals of inhaler use obtained from the INCA device.

MFCC based methods were employed to detect the presence of exhalation events in audio recordings. Specifically the FBE feature was employed to detect exhalation events in Chapter 7. It was found that the FBE in channels 8-10 contained more energy for exhalations in comparison to inhalations. Using this finding, a difference waveform and adaptive threshold were used to automatically detect exhalation events. In a cohort of 22 asthma patients, the exhalation detection algorithm was able to detect exhalation sounds with an accuracy of 89%, compared to expert human raters. This is an important finding, given the difficulty human raters often experience in overreading audio recordings.

Temporal and spectral features can be employed to assess the impact of an exhalation on the medication dose available for delivery.

Studies detailed in Chapter 7 indicated that the distance between the artificial mouth and the inhaler mouthpiece during exhalation was the single most important factor accounting for drug dispersal from the Diskus DPI. Based on this finding, exhalations occurring at a distance of 5 cm or less, into the DPI mouthpiece or directly at the INCA device were classified as significantly detrimental. FFT and MAD features were employed to detect when these significantly detrimental events occur. It was found that the threshold developed to classify a significant exhalation had a sensitivity of 72.22% and a specificity of 85.71% when tested on a small validation dataset. There are a number of difficulties in trying to determine if an exhalation has a significant detrimental effect on drug delivery, when acoustic methods are used. It can be difficult to determine if the exhalation takes place in the direction of the inhaler mouthpiece or directly at the acoustic
recording device. It can also be challenging to determine at what angle the exhalation is taking place in relation to the inhaler mouthpiece. Nevertheless, the method developed had moderately high sensitivity and specificity values. This area remains challenging and future work in this area is described later in this Chapter.

FFT, intensity and duration based acoustic features can be employed to automatically and objectively detect the blistering of the drug foil during Diskus inhaler use.

The blistering of the drug foil is an important event during Diskus inhaler use. The presence of the blister sound indicates that the drug has been transported to the inhaler mouthpiece and is available for inhalation. When assessing Diskus audio recordings from the INCA device, human raters will search for this event to ensure that the patient is following the correct technique. Human raters look for a burst of power, in combination with a short time duration, in order to detect the blister sound. The features reported in this thesis to automatically detect blister sounds (Section 8.1 of Chapter 8) were motivated by the method in which the human raters detect these sounds. FFT, intensity and duration-based features were calculated and in Chapter 8 Section 8.1, a training dataset was used to decide on the optimum selection of thresholds that produce the highest number of true positive events. FFT based features were deemed suitable for detecting the short burst of power from the blistering of the Diskus device. Wavelet based features may provide better time resolution at high frequencies, however, given a sampling rate of 8 kHz in the commercial INCA device, FFT based features were considered suitable. Results revealed that the features employed were able to classify blister sounds with a high degree of accuracy. The importance of this study is that the algorithm developed may be used to replace the human raters, thus providing more objectivity to the method.

MFCC and temporal based acoustic features can be employed to automatically and objectively detect inhalation sounds in Diskus inhaler audio recordings.

In Chapter 2, the current state of the art in automatic breath sound detection was reported. A wide range of features are described in the literature, which can be employed to detect breath sounds (Table 2.4). MFCC based methods are frequently postulated as superior features in the detection of breath sounds and several recent studies have reported good levels of classification performance with these features (Ruinskiy and Lavner, 2007; Bahoura and Pelletier, 2003; Abushakra and Faezipour, 2012). One recent review reported that MFCCs outperform all other features in detecting breath sounds in speech and song signals (Bahoura, 2009). The selection of MFCCs as features in this thesis was motivated by their reportedly high performance in detecting
breath sounds in previous studies. It was hypothesised that using these features in combination with temporal features would enable the accurate classification of inhalation sounds generated during inhaler use. MFCCs 0-12 and ZCR were successfully employed as features to detect inhalation sounds in two preliminary studies in Chapter 8 (Sections 8.2.1 and 8.2.2). High accuracy levels were reported in these studies, although these studies did have small sample numbers. In a third study, the FBE feature was used in place of all 13 MFCCs. The motivation for this step was based on the findings of a recent study that reported the capacity of the FBE feature to capture the unique properties of a cough sound, in comparison to over 100 other features (Drugman et al., 2011). Given the similarities between cough sounds and forced inspiratory sounds through an inhaler (in terms of energy, airflow rate, ramp rate, volume and duration), it was hypothesised that the FBE feature would capture the intrinsic characteristics of inhaler inhalations. The FBE feature was used in combination with a duration-based feature to detect inhalation sounds in a large cohort of both asthma and COPD patients. ROC curve analysis was performed to determine the optimum selection of thresholds for the asthma/COPD patients.

Results from this thesis demonstrate that MFCC features are a good choice of features in detecting inhalation sounds in audio recordings of Diskus DPI use. In particular, the FBE feature is a good choice of feature, particularly for asthmatic patients. When visually and aurally assessing inhaler audio recordings, human raters look for the inhalation based on its intensity and duration. The FBE feature replicates the same process taken by the human raters and given its calculation of energy levels based on a mel-scale, it models the human raters’ aural discriminatory ability. The importance of the studies reported in Chapter 8 is that the algorithms developed are the first that can automatically and objectively detect inhalation sounds in inhaler audio signals. These algorithms have a number of clinical benefits and their clinical value will be discussed at a later stage in this Chapter.

A system was developed to automatically and objectively analyse Diskus inhaler technique.

Analysis of audio recordings from the INCA device allows for the investigation of inhaler user technique. Based on the presence of various events in the audio signals, the frequency of the events and the order in which they take place, respiratory clinicians have devised a scoring system for assessing inhaler technique in each audio recording. As previously mentioned in Section 8.3 of this thesis, an audio file can be either (a) used correctly, (b) used incorrectly or (c) not used. The objective of the algorithm developed in Section 8.3 of Chapter 8, was to replicate the same decision process taken by human raters in classifying audio recordings. Objective data from the blister, inhalation and exhalation detection algorithms made this process possible. Results
reported in Section 8.3 revealed that the technique score algorithm developed could decide the inhaler technique score with a relatively high degree of accuracy. This algorithm was tested on 19,932 audio recordings from 145 asthma patients and on 7,583 audio recordings from 92 COPD patients. It was found that the algorithm performed better for asthma patients, compared with COPD patients. This finding is related to the inhalation manoeuvre, which will shortly be discussed in more detail. The benefits of the algorithm reported in Section 8.3 of Chapter 8 are that it can be employed to automatically and objectively classify inhaler user technique. This system has the potential to replace the current subjective manual overreading system, and it may potentially save time and money for healthcare professionals. The clinical benefits of this system will be outlined at a later stage in this Discussion Chapter.

It is easier to analyse asthma patients’ inhaler audio recordings in comparison to COPD patients, as COPD patients tend to have lower PIFR and shorter duration inhalations.

In Chapter 8, it was reported that asthma patients typically have higher PIFRs and inhale for longer in comparison to COPD patients (also reported by Azouz et al. (2015)). An inhalation detection algorithm was developed using MFCC derived FBE and inhalation duration as features. The inhalation detection algorithm had greater sensitivity and specificity results for a cohort of 50 asthma patients, in comparison to a cohort of 50 COPD patients. This is an important finding for future research in the field of inhaler acoustics. COPD is a heterogeneous disease that causes airflow limitation (Ställberg et al., 2014). It is this airflow limitation that makes it challenging for COPD patients to reach an adequate PIFR and to inhale for a sufficient duration. As energy and duration based features were employed to detect the inhalation sounds in the audio signals, this task was always going to be challenging for COPD patients. Acoustic features that are independent of energy and duration may have higher sensitivity and specificity in detecting inhalation sounds for COPD patients. Nevertheless, if the PIFR is low (<50 L/min) then the turbulence generated in the patients inhaler device and oral cavity will have a low signal-to-noise ratio.

An inhaler that can generate turbulent energy at low PIFRs may help improve the performance of future inhalation detection algorithms. The amount of turbulent energy generated is a factor of both the patients PIFR and the intrinsic resistance of the inhaler device to airflow. The Diskus inhaler is a medium airflow resistance device. If low airflow resistance inhaler devices were to be employed, such as the pMDI, then it would be an even greater challenge to extract pertinent features from the audio signal at low PIFRs. This finding was observed in Chapter 6, where minimal acoustic energy was emitted in the Evohaler pMDI during inhalations in the recommend
airflow range (30 – 90 L/min). It is therefore unlikely that the inhalation detection algorithm designed in this thesis would accurately work with acoustic data recorded from the Evohaler pMDI. This is an important finding in the context of developing acoustic methods to accurately detect the inhalation sound in inhaler audio recordings. It cannot be assumed that a method developed for one specific type of inhaler will work for another inhaler, unless the inhaler devices airflow resistance and recommended PIFR range is taken into account. This point was emphasised at a recent International Society of Aerosol Medicine (ISAM) conference (June 2015), where it was reported that power is a more accurate way of comparing different inhaler devices and drug de-agglomeration, not PIFR (Haidl et al., 2015).

Disagreement levels between human raters are high, and thus a better gold standard method of analysing inhaler use is needed for future studies.

Several studies detailed in this thesis employed human raters to overread audio recordings from the INCA device. The human raters were employed as the gold standard method in detecting inhaler events (i.e. breath sounds, blister sounds) and in classifying inhaler technique. The objective methods developed were compared to the results of the human raters, in order to generate sensitivity, specificity and accuracy scores. However, results obtained in Chapter 8 indicate that agreement levels between the human raters are far from perfect. There are a number of reasons for disagreements between human raters and it is important to understand the limitations of this method, so that future research can improve on this limitation. Firstly, classifying audio files obtained during inhaler use can be difficult due to the limited amount of information in the audio signals. Human raters assessed audio files by visually assessing the signals, while at the same time listening to the signal. Although it can be assumed that patients typically blister the drug and inhale, the detection of these events can be challenging in the presence of background noise. In addition, low energy breath sounds (with correspondingly low PIFRs) can be challenging to detect with human raters, depending on the signal-to-noise ratio. It is clear that a better gold standard method of classifying inhaler audio files is needed for future studies. Recommendations for future studies in this area are discussed in Section 9.5 of this Chapter.

9.3 Limitations of Research

Acoustic analysis of inhaler sounds in real world environments is subject to noise

One of the limitations of using acoustic methods is that they are susceptible to noise interferences. Although rare in occurrence, the majority of inhaler noise interferences are due to
speech noise and adventitious breath sounds. These types of noise interferences primarily take place at low frequencies, i.e. less than 4000 Hz. However, in the study presented in Chapter 6, it was reported that the inhaler inhalation sounds have power at frequencies up to 20 kHz. The commercial INCA device records audio with a sampling rate of 8000 Hz and thus frequencies greater than 4000 Hz cannot be analysed. Future developments may focus on using acoustic recording devices that sample the data with sampling rates greater than 8000 Hz, and subsequently employing features that focus on the high frequency characteristics of the breath sounds. This may help reduce the effect of noise interferences on the audio signals. Ruinskiy and Lavner (2007) employed a spectral slope feature to differentiate breath sounds from speech sounds. The motivation for this was that in voiced speech, the spectrum is expected to be flat between 11-22 kHz, whereas the spectral slope would be steeper at this frequency range in breath sounds (Ruinskiy and Lavner, 2007). These findings suggest that electronic acoustic monitoring devices with sampling rates of 44.1 kHz would be useful in the differentiation of breath sounds from speech sounds. With regards to respiratory sound signal processing, one of the main areas of interest to researchers has been the cancellation of heart sounds from lung sound recordings (Iyer et al., 1986; Pourazad et al., 2003; Pourazad et al., 2006). However, heart sounds are not recorded by acoustic inhaler monitoring devices. Noise interferences in inhaler audio signals are not too common during real world inhaler use and thus the focus of this thesis was to primarily investigate the use of different features in the analysis of common inhaler events. Future work could investigate the use of noise removal methods in inhaler audio recordings, which may further improve the accuracy of the algorithms described in this thesis.

Differences exist in onset and offset time inhalation detection, between human raters and algorithm

In Section 8.2.3.3 of Chapter 8, it was found that the average difference in onset time between the inhalation detection algorithm and the human rater was 110 ms, while the average difference in offset time was 342 ms. These differences in inhalation onset and offset times may introduce errors in the estimation of PIFR and IC, if these metrics were to be employed by healthcare professionals. However, these differences may not be completely accurate given that the objective algorithm was being compared to a subjective human rater. Estimating inhalation offset time is a challenging step for human raters, given that it can be difficult to assess when the inhalation stops from listening to the acoustic signals. It is therefore difficult to interpret the results of the onset and offset analysis. Future studies could use a flow sensor to accurately demarcate the onset and offset time of inhalations.
Drug delivery was estimated from in vitro data

Results presented in Chapter 5 detailed how drug delivery from inhaler devices can be estimated from analysing the acoustic features of the inspiratory sound. However, these studies were performed in vitro in a lab environment. In Section 5.1 of Chapter 5, drug delivery was estimated by weighing the inhaler device before and after the simulated inhalation, while in the study reported in Chapter 7 drug delivery was estimated using a cascade impactor. Both of these methods have limitations as they do not entirely represent how much drug would be delivered in vivo. The cascade impactor is the current industry standard in testing inhaler drug delivery, and was therefore deemed a suitable method in estimating drug delivery in the study reported in Chapter 7.

To control the factors related to the inhaler inhalation, a vacuum pump was employed to simulate real world inhalations. Due to the design of the vacuum pump valves, the onset and offset of the simulated inhalations were instantaneous (thus producing a square wave). This is in contrast to real world inhalations, where the ramp rate (or time to PIFR) can vary widely and is rarely instant. In addition, the inhalation offset is typically preceded by a gradual decrease in airflow rate. These differences may cause limitations in estimating drug delivery from simulated inhalation signals.

The design of the INCA device could be improved

A number of studies in this thesis were limited by the design of the commercial INCA device. The MEMS microphone employed in the INCA device has a sampling rate of 8000 Hz. In comparison, the majority of studies in the literature in the field of respiratory acoustics use a sampling rate of 44,100 Hz. It could be argued that if the INCA device had a higher sampling rate, then the algorithms described in Chapter 8 would be able to classify inhaler events and estimate PIFR with greater accuracy. The MEMS microphone in the commercial INCA device is also enclosed in a plastic shell with a thickness of 4 mm. This plastic shell acts as a filter, as it dampens the true sounds of inhaler use as they travel to the microphone. Despite the fact that the MEMS microphone has a flat frequency response between 50-4000 Hz, the plastic shell of the INCA device may attenuate or accentuate certain frequencies. This limitation may influence the true spectral characteristics of the inhaler breath sounds and thus affect the interpretation of any spectral based features.

No true gold standard which to compare algorithms

A number of studies in this thesis described the performance of algorithms in comparison to human classifiers. These studies were inherently limited due to the lack of complete agreement between the human classifiers. This finding illustrates the subjective nature of detecting breath
sounds during inhaler use in audio recordings. It is a challenging task to evaluate the performance of an algorithm when it is being compared to an imperfect gold standard. Despite this limitation, agreement was still substantial (as judged by Cohen’s Kappa Statistic analysis) between the human raters. In a number of respiratory event detection studies in the literature, only one human classifier is employed to mark the respiratory events (Amrulloh et al., 2015) or agreement between two human classifiers is not reported (Vizel et al., 2010; Ruinskiy and Lavner, 2007). In a study by Barry et al. (2006), two human classifiers counted the number of cough sounds present in audio recordings from 33 subjects. Significant differences were reported between the human classifiers, in the number of cough sounds counted (p < 0.05). Agreement between human classifiers in the differentiation of wet and dry coughs has also been reported to be moderate (Cohen’s Kappa = 0.54) (Swarnkar et al., 2013). The literature implies that the detection of respiratory events in audio recordings can be challenging for human classifiers, and the differences observed are not unique to the identification of events in inhaler audio recordings.

A number of studies focused only on healthy individuals

In Chapters 5 and Chapter 6, healthy participants were recruited to investigate the characteristics of breath sounds and also establish the PIFR-sounds models. As was detailed in Chapter 2 - Literature Review, the characteristics of breath sounds are known to vary due to respiratory diseases, such as asthma and COPD. However, as there have been no prior studies concerning inhaler breath sounds reported in the literature, it was important to establish the characteristics of inhaler breath sounds from healthy participants to use as a baseline for future studies. As inhaler users primarily suffer from asthma and COPD, certain results in this thesis may be limited and not applicable to those with chronic respiratory diseases.

Other features and classification methods may be more accurate

In Chapter 2 – Literature Review, a number of features and classification approaches were presented as potential methods to classify inhaler breath sounds (Table 2.4). In the studies detailed in this thesis, temporal, FFT and MFCC based features were primarily employed. However, other combinations of features and classification methods may provide higher performance in classifying inhaler breath sounds. Acoustic features that capture the complexity of the inhaler signal or are more energy-independent may be worth investigating in future studies. A template matching classification approach may also be useful in creating more personalised algorithms for inhaler breath detection.
Limitations due to airtight adapter

In a number of studies in this thesis, inhalers were placed inside airtight containers and connected to a spirometer. This was done to objectively measure PIFR through the inhaler device. A limitation of this method is that the spirometer measures PIFR at the pneumotachograph, not at the inhaler mouthpiece. The PIFR at the mouthpiece may differ from that at the pneumotachograph, due to airflow resistance created by the inhaler device and the airtight adapter. It is probable that the PIFR at the inhaler mouthpiece is higher than the PIFR measured by the spirometer. Nevertheless, the alternative method of positioning a flow sensor in an inhalers airflow channel would increase airflow resistance and thus modify the acoustic profile of any inhalation sounds. This limitation may influence the accuracy of the PIFR estimation method described in this thesis.

Another limitation concerning the airtight adapters employed in this thesis relates to the volume of dead space in the airtight adapter. As the airtight adapter and spirometer tubing will contain a volume of dead space, this air will be inhaled prior to any air being inhaled through the spirometers pneumotachograph. This may lead to slight inaccuracies in the PIFR and IC estimation. However, ATS standards published in 2005 state that a spirometers dead space should be less than 350 ml, which implies that the airtight adapter employed in this study is within limits (Miller et al., 2005).

Exhalations remain difficult to detect

Unlike inhalation sounds, where the mouth is positioned directly on the inhaler mouthpiece, the acoustic characteristics of exhalation sounds can vary greatly. Exhalation sounds may take place at any distance from the inhaler, the flow of air may be directed in any direction and these variables may also dynamically change over time. This makes it challenging to detect exhalation sounds during inhaler use with acoustic monitoring methods such as the INCA device. Despite this, results reported Chapter 7 demonstrated the feasibility of detecting such sounds when they occur in close proximity to the INCA device or inhaler mouthpiece. A limitation of using acoustic methods for this task is that it is difficult to discriminate between exhalations aimed at the microphone versus those directly into the inhaler mouthpiece.

Inhalations with low PIFRs are difficult to detect

One limitation of using acoustic methods to detect inhalations is that at low PIFRs, little turbulent energy is created, making it difficult to distinguish inhalation signals from background noise. Depending on the airflow resistance of each inhaler device, the PIFR at which inhalation signals can be detected using signal-processing based methods will vary. In Chapter 6, it was reported
that this threshold is close to 100 L/min for the Evohaler, but closer to 30 L/min for the Diskus. This limitation may be overcome by creating additional turbulent sound energy at low PIFRs.

9.4 Clinical Impact of Research

A system that can objectively analyse inhaler adherence has a number of clinical benefits. The system described in Chapter 8 is a time saving tool for healthcare professionals. As previously mentioned, manually classifying inhaler audio files is a time consuming and monotonous process. A task that would have previously taken 30 minutes can now be automatically completed in less than 5 minutes. Making this process automated frees up time for healthcare professionals, allowing them to concentrate on other important tasks.

The system developed to classify inhaler adherence in this thesis is objective. Any subjectivity on the part of the healthcare professional that over reads the audio files is removed. The system developed is not biased towards certain patients or patient groups, and thus objectively assesses each audio signal independently.

Until now, healthcare professionals had no quantifiable method of understanding what a patient’s PIFR through their inhaler device was during use in real-world settings. In addition, they could not access any quantitative data regarding a patient’s inspiratory volume during inhaler use. Methods reported in this thesis (Chapters 5 and 6) have established the feasibility of employing acoustic based features to objectively complete this task. Furthermore, the amount of drug deposition in the airways can also be estimated from the acoustic signal. There are a number of clinical benefits related to this work. Firstly, it allows healthcare professionals to objectively determine if patients are capable of successfully using their inhaler device. This could be used as a decision tool to determine which inhaler device is best suited for each patient. Metrics pertaining to the inhalation could also be employed to longitudinally monitor performance. Patients may be able to successful inhale in the clinic, but their performance over time may give a more accurate reflection of their ability to use their inhaler. In addition, metrics associated with the inhalation may offer insights into lung function and may be indicative of detrimental respiratory events.

Another important clinical benefit of this research is that it allows healthcare professionals to understand interactions between the treatment and the progression of the disease. Until now, most healthcare professionals assume that patients are adherent to their inhalers. It can be challenging to interpret how patients with asthma and COPD develop symptoms of illness, when their inhalers are designed to prevent such symptoms from developing. By using the algorithms developed in this thesis, healthcare professionals have objective evidence on how their patients’
Inhalers are really being used. The data presented to them may assist in helping them to understand how inhaler use influences disease symptoms.

The methods reported in this thesis can be used as an educational tool in clinical settings. The methods provide healthcare professionals access to a wide variety of objective data on real-world inhaler use. For example, clinicians can easily see what the most frequent technique error that a patient makes. They can then re-educate the patient on how to avoid making such technique errors and track their progress in the subsequent weeks and months. The system reported in this thesis provides healthcare professionals with confidence to make informed decisions on patient’s health. Up until now, they had no way of knowing exactly how someone is using their inhaler outside the clinic.

There are a number of studies in the literature that report on the prevalence of user technique errors during inhaler use (Melani et al., 2011; Basheti et al., 2011; Lavorini et al., 2008). The majority of these studies were carried out in clinical based settings and are therefore not indicative of the user technique errors that patients make outside the clinic. In addition the frequency of user technique errors may differ outside of clinical environments. The methods developed in Chapter 8 of this thesis allow data on user technique errors to be recorded outside clinical settings. It can therefore be used to obtain real world data and may also reveal new user technique errors, not previously described in the literature. This data may influence future inhaler designs and help create new guidelines on inhaler user technique.

Inhaler devices are expensive and large sums of money are being spent on these devices in order to treat asthma and COPD (PWC, 2014). Furthermore, large quantities of healthcare budgets are being spent on treating non-adherence to inhaler medication. A system that monitors and prevents non-adherence in inhaler devices could potentially save money. As a result, money could be reallocated to other areas of importance in the healthcare system, thus increasing healthcare efficiency.

The system described to assess adherence in this thesis is currently being employed in five clinical trials in Ireland, encompassing approximately 600 people. These trials are being undertaken to investigate true adherence levels amongst different inhaler user groups. Four of the clinical trials are investigating if inhaler adherence can be improved with the use of the system developed in this thesis. Preliminary results from these trials indicate that adherence levels are poor across all groups, and that when inhaler technique errors are taken into account, actual rates of adherence are significantly lower than attempted adherence rates (Figure 9.1). These trials have also helped establish the technique errors that inhaler users are making in real-world settings (Figure 9.2).
Figure 9.1: Percentage of correct adherence for four clinical trials using the INCA device. The attempted rate of adherence is shown (considering temporal adherence only), in addition to the actual rate of adherence (i.e. once user technique errors are taken into account).

Figure 9.2: Mean number of user technique errors reported in four clinical trials with the use of the INCA device.
9.5 Future Research Directions

Acoustic analysis of further inhaler devices

In Chapter 6, the acoustic characteristics of three commonly employed inhalers (Diskus, Turbuhaler and Evohaler) were recorded. Acoustic signals were recorded from a non-contact acoustic sensor, positioned 5 cm from the inhalers mouthpiece, in order to investigate the potential of using acoustic based methods in the analysis of inhaler sounds. In Chapters 5, 7 and 8, the commercial INCA electronic monitoring device was employed in studies relating to the Diskus DPI only. In its current commercial design, the INCA device can only be attached to the Diskus DPI. Additional research is needed to develop commercial acoustic monitoring devices for other inhalers. Future developments of acoustic monitoring devices for inhalers should consider employing dynamic microphones. This could potentially improve the signal-to-noise ratio and also increase the battery life of devices, in comparison to condenser based microphones. More than 20 different DPI devices are sold commercially, each with their own unique design (Newman, 2003). In addition to DPI devices, there is a need to develop an acoustic monitoring device for pMDIs. pMDIs, such as the Evohaler, are the most frequently employed inhaler devices worldwide (Terzano, 2001; Lavorini, 2013). Their design does not change hugely, in comparison to DPIs. Therefore, designing an acoustic monitoring device for the pMDI, would be the most logical future development in the field of acoustic inhaler monitoring.

Currently, the greatest limiting factor in developing an acoustic device to monitor inhalers is the activation of the electronic device before use. In the INCA device, this task is achieved using magnets. When the Diskus DPI is opened for use, a magnet aligns with a reed switch in the INCA device. This powers the circuit and allows the MEMS sensor to record audio, until such a time that the inhaler is closed or a time of 90 seconds has passed. However, in other inhalers it is not as straightforward to use magnets to activate an electronic monitoring device.

Inhaler users could potentially power on an electronic monitoring device with the use of a simple switch. However, this would create problems as it introduces an additional step into using an inhaler and it would be highly likely that inhaler users would forget to activate the electronic monitoring device at some stage. It is also highly probable that those with poor adherence would be the group most likely to not switch on an electronic monitoring device before inhaler use. There is a clear need for a device that can automatically power on before inhaler use.

There are a number of potential methods to automatically activate an electronic monitoring device attached to an inhaler. Focusing on the common pMDI, this could be achieved with the use of an accelerometer that activates an acoustic sensor when the patient handles, or even shakes
the device as recommended in the instructions for correct pMDI use. A capacitor based pressure sensor could be placed on top the of the pMDIs canister, from where activation of the canister could start an audio recording. Additionally, new materials that are responsive to touch could be positioned on the pMDI and assist in activating an acoustic sensor (Barrett and Omote, 2010).

Despite the fact that acoustic signal processing methods can be applied to DPIs such as the Diskus and Turbuhaler, results reported in Section 6.3 of Chapter 6 indicated that the acoustic power generated during a correct pMDI inhalation has a poor signal-to-noise ratio. It is recommended that users inhale with a PIFR less than 90 L/min when using a pMDI, however, because the airflow resistance of the MDI is low (0.0135 (Vcm H2O)/(L/Min)), little turbulent energy is generated at PIFRs below this threshold. If acoustic electronic monitoring methods, such as the INCA device, were to be adapted for pMDI devices, then a system is needed to increase the turbulent energy created during inhalation. This could be achieved by introducing a device that creates an acoustic signature (i.e. whistle sound) at PIFRs less than 90 L/min. Until a system like this is developed, it is unfeasible to use acoustic methods to assess pMDI adherence.

The INCA recording device was designed for use with GSK’s Diskus inhaler only. The patent on both the Diskus device design and the drug used (Seretide) has recently expired (Tobin, 2012). As a result, a number of generic drug manufacturers will inevitably attempt to replicate the Diskus inhaler and the combination drug it contains. To counteract losses in sales figures, GSK have recently launched a new inhaler device and drug combination. The Ellipta DPI, containing the combination drug Breo, has recently been marketed as the next generation Diskus inhaler by GSK (Chamberlin, 2014). Without GSK actively promoting its Diskus inhaler brand, the number of asthma and COPD patients using the Diskus DPI may decrease. As the INCA device can only currently be used with the Diskus, it will need to be able to adapt to new types of DPI device designs.

**Development of personalised acoustic models for inhaler PIFR estimation**

In Chapter 5, it was reported that a number of temporal and spectral features of the inhalation sound could be employed to estimate PIFR. The generalised least squares regression model generated takes all subjects into account when selecting the model of best fit. It is therefore inevitable that the model will not be suitable for the entire population, given that it is biased towards the subjects tested. A possible future approach would be to personalise the PIFR – acoustic model on a subject-by-subject and inhaler-by-inhaler basis. Calibrating the model to each subject and each inhaler may have the potential to increase future accuracy in estimating PIFR. In clinical settings, a calibration procedure with an acoustic monitoring device could be carried out prior to an inhaler being prescribed by the healthcare professional. To test this hypothesis,
asthma and COPD subjects could be asked to inhale for a range of PIFRs (between 15-120 L/min). Large R² coefficients at a within-subject level would indicate the benefit of using personalised regression models in place of a general population model for inhaler acoustic-PIFR estimation.

**Speech and adventitious breath sound removal**

The presence of noise in the signals recorded during inhaler use can reduce the performance of algorithms used to classify inhaler events such as breaths and blisters. By far the two most common types of unwanted noise observed from the INCA device during Diskus inhaler use are: speech noise and adventitious breath noise. Speech noise in the audio signals can originate from the inhaler user engaging in conversation with others before inhaler use. If the Diskus is opened, the INCA device can record the speech signals of other non-inhaler users, in addition to speech sounds from entertainment systems (i.e. radio, televisions, etc.). As discussed in Section 2.5.4 of Chapter 2, adventitious breath sounds can be crackles and wheezes, but the majority of adventitious breath noises recorded with the INCA device are cough sounds and throat clearing sounds. Both speech noise and adventitious breath noise increase the number of false positives detected by an inhalation/exhalation algorithm. There are a number of possible future studies that could be carried out to reduce the effect of unwanted noise in inhaler audio signals. Steps could be introduced to eliminate the effect of unwanted noise in the inhaler audio signals by detecting and removing unwanted noise sounds. A number of speech-based classifiers are detailed in the literature, in addition to several adventitious sound detection algorithms. Introducing such classifiers into a system that analyses the acoustic sounds of inhaler use may prove beneficial, so long as they do not increase the processing time significantly.

**Development of a gold standard method to assess inhaler adherence**

Results presented in Chapter 8 revealed that it is challenging to manually assess inhaler adherence using the audio signals recorded from an electronic acoustic recording device. Human raters do not always agree in the classification of inhaler adherence, as it can be sometimes difficult to distinguish sounds using visual and aural overreading methods. This is an inherent limitation of using acoustic methods to analyse inhaler adherence. Studies are needed to establish a gold standard method of assessing inhaler adherence, and subsequently compare manual and automated adherence assessment methods to the gold standard. There are a number of ways a gold standard adherence assessment method could be introduced. Sensor technology could be employed to objectively detect airflow at the device mouthpiece. Sensors could also be employed to objectively detect the actuation or movement of any drug release mechanisms during inhaler use. This type of a system could act as a gold standard, against which future acoustic analysis methods could be compared.
Redefinition of inhaler adherence

Adherence to medication is typically expressed as a percentage of the expected adherence rate. Patients are deemed to be adherent to their medication if their adherence rates are greater than 80% (Ho et al., 2009). However, inhaling medication from an inhaler device is not the same as simply ingesting a tablet. In pMDIs the actuation of the canister must be coordinated with the inhalation. In addition, the inhalation must be slow and steady, with a PIFR less than 90 L/min. In flow dependent DPI devices, several steps are required to successfully de-agglomerate the drug formulation and transport it to the airways. Despite the intricacies associated with inhaler use, a number of studies in the literature only report on the temporal aspect of inhaler adherence, while errors in technique are ignored (Burnier, 2000; Paes et al., 1997). Given the complexities associated with correct inhaler use, future studies are needed to redefine how adherence is measured for inhaler users. Possible approaches to this may investigate a patients attempted adherence and their true adherence rate (i.e. when inhaler technique is taken into account). Establishing a new system for measuring inhaler adherence would only assist the introduction and usage of accurate electronic monitoring systems.

Investigation of relationship between airway obstruction levels and inspiratory inhaler sounds

Future studies are needed to investigate how the acoustic characteristics of inspiratory inhaler sounds are affected by airway narrowing. A number of studies in the literature indicate that the frequency content of breath sounds is influenced by obstructions in the upper airways (Forgacs et al., 1971; Malmberg et al., 1994). In order to explore this effect during inhaler use, airflow could be artificially limited using the drug histamine. Audio recordings obtained during the histamine challenge test may give an indication of how the characteristics of inhaler sounds are affected by airway narrowing. This may prove to be a clinically useful finding as it may assist healthcare professionals in detecting airflow narrowing from a remote monitoring environment.

Prediction of future adverse events

Electronic inhaler monitoring devices, such as the INCA technology, have created the opportunity to record large amounts of data pertaining to inhaler use in real-world settings. The algorithms reported in the studies detailed in this thesis can be used to objectively extract information from this data, such as the time and date of use, technique, PIFR, IC etc. Combining this information with additional sources of quantitative and qualitative data i.e. lung function, quality of life, pollen count, co-morbidities etc. allows one to investigate potential patterns in the data. For patients with asthma and COPD, the main clinical aim is to treat these chronic respiratory diseases in order
to prevent exacerbations and asthma attacks from developing. Future studies could investigate if these adverse events could be predicted before they occur. There are a number of supervised and unsupervised methods in the field of machine learning that may be capable of predicting patterns pertaining to the lead up to an adverse event.

9.6 Final Conclusion

The research questions posed in Chapter 3 have been answered during the course of several studies. Findings from this thesis indicate that acoustic signal processing methods can be employed to objectively assess patients’ adherence to their inhaler therapy. The use of an automated acoustic processing system makes the task of classifying inhaler audio signals more objective and efficient. Another important finding in this thesis was that acoustic features of inspiratory inhaler sounds contain pertinent data relating to physiological changes occurring in the airways. This creates the opportunity for healthcare professionals to longitudinally monitor a crucial aspect of inhaler drug therapy and provide personalised feedback to patients. The conclusions drawn from the experimental results described in this thesis are informative with regards to topics of recent debate in the scientific community on inhaler adherence, agree with and build on recent studies in the area of respiratory acoustic analyses and have a number of clinical implications. Directions for future research are proposed which may extend on the acoustic analysis system described in this thesis.
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Appendices

Appendix A: INCA Microphone Specifications

The SPU0410LR5H-1 is a miniature, high-performance, low power, bottom port silicon microphone. Using Knowles’ proven high performance SiSonic™ MEMS technology, the SPU0410LR5H-1 consists of an acoustic sensor, a low noise input buffer, and an output amplifier. These devices are suitable for applications such as cellphones, smart phones, laptop computers, sensors, digital still cameras, portable music recorders, and other portable electronic devices where excellent wideband audio performance and RF immunity are required.

Features:
- Matched Sensitivity
- Flat Frequency Response
- Low Current
- Small package
- MaxRF protection
- Zero-Height Mic™
- Ultra-Stable Performance
- Standard SMD Reflow
- Omnidirectional
1. **ABSOLUTE MAXIMUM RATINGS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Absolute Maximum Rating</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{DD} ) to Ground</td>
<td>-0.5, +5.0</td>
<td>V</td>
</tr>
<tr>
<td>( \text{OUT} ) to Ground</td>
<td>-0.3, ( V_{DD} ) + 0.3</td>
<td>V</td>
</tr>
<tr>
<td>Input Current to Any Pin</td>
<td>±5</td>
<td>mA</td>
</tr>
<tr>
<td>Temperature Range</td>
<td>-40 to +100</td>
<td>°C</td>
</tr>
</tbody>
</table>

Stresses exceeding these “Absolute Maximum Ratings” may cause permanent damage to the device. These are stress ratings only. Functional operation at these or any other conditions beyond those indicated under “Acoustic & Electrical Specifications” is not implied. Exposure beyond those indicated under “Acoustic & Electrical Specifications” for extended periods may affect device reliability.

2. **ACOUSTIC & ELECTRICAL SPECIFICATIONS**

**TEST CONDITIONS:** 23 ±2°C, 55±20% R.H., \( V_{DD}(\text{min}) < V_{DD} < V_{DD}(\text{max}) \), no load, unless otherwise indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Conditions</th>
<th>Min</th>
<th>Typ</th>
<th>Max</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supply Voltage</td>
<td>( V_{DD} )</td>
<td></td>
<td>1.5</td>
<td>-</td>
<td>3.6</td>
<td>V</td>
</tr>
<tr>
<td>Supply Current</td>
<td>( I_{DD} )</td>
<td></td>
<td>-</td>
<td>120</td>
<td>150</td>
<td>µA</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>( S )</td>
<td>94 dB SPL @ 1 kHz</td>
<td>-39</td>
<td>-38</td>
<td>-37</td>
<td>dB/V/PA</td>
</tr>
<tr>
<td>Signal to Noise Ratio</td>
<td>SNR</td>
<td>94 dB SPL @ 1 kHz, A-weighted</td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>dB(A)</td>
</tr>
<tr>
<td>Total Harmonic Distortion</td>
<td>THD</td>
<td>94 dB SPL @ 1 kHz, ( S = \text{Typ} ) ( R_{LOAD} &gt; 3 \text{kΩ} )</td>
<td>-</td>
<td>0.15</td>
<td>0.2</td>
<td>%</td>
</tr>
<tr>
<td>Acoustic Overload Point</td>
<td>AOP</td>
<td>10% THD @ 1 kHz, ( S = \text{Typ} ), ( V_{DD} = 3.3 \text{V} ), ( R_{LOAD} &gt; 3 \text{kΩ} )</td>
<td>116</td>
<td>118</td>
<td>-</td>
<td>dB SPL</td>
</tr>
<tr>
<td>DC Output</td>
<td>( V_{DD} = 1.5 \text{V} )</td>
<td></td>
<td>-</td>
<td>0.73</td>
<td>-</td>
<td>V</td>
</tr>
<tr>
<td>Output Impedance</td>
<td>( Z_{OUT} )</td>
<td>@ 1 kHz</td>
<td>-</td>
<td>-</td>
<td>400</td>
<td>Ω</td>
</tr>
<tr>
<td>Directivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polarity</td>
<td>Increasing sound pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 100% tested.
2. Maximum specifications are measured at maximum \( V_{DD} \). Typical specifications are measured at \( V_{DD} = 1.8 \text{V} \).
3. FREQUENCY RESPONSE CURVE

Typical Free Field Response
Normalized to 1kHz

Sensitivity (dB)

Frequency (Hz)
4. INTERFACE CIRCUIT

Note: All Ground pins must be connected to ground.

Capacitors near the microphone should not contain Class 2 dielectrics.

Detailed information on acoustic, mechanical, and system integration can be found in the latest SiSonic™ Design Guide application note.
5. MECHANICAL SPECIFICATIONS

<table>
<thead>
<tr>
<th>Item</th>
<th>Dimension</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (L)</td>
<td>3.76</td>
<td>±0.10</td>
</tr>
<tr>
<td>Width (W)</td>
<td>3.00</td>
<td>±0.10</td>
</tr>
<tr>
<td>Height (H)</td>
<td>1.10</td>
<td>±0.10</td>
</tr>
<tr>
<td>Acoustic Port (AP)</td>
<td>Ø0.25</td>
<td>±0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pin #</th>
<th>Pin Name</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OUTPUT</td>
<td>Signal</td>
<td>Output Signal</td>
</tr>
<tr>
<td>2</td>
<td>GROUND</td>
<td>Power</td>
<td>Ground</td>
</tr>
<tr>
<td>3</td>
<td>GROUND</td>
<td>Power</td>
<td>Ground</td>
</tr>
<tr>
<td>4</td>
<td>VDD</td>
<td>Power</td>
<td>Power Supply</td>
</tr>
<tr>
<td>5</td>
<td>GROUND</td>
<td>Power</td>
<td>Ground</td>
</tr>
<tr>
<td>6</td>
<td>GROUND</td>
<td>Power</td>
<td>Ground</td>
</tr>
</tbody>
</table>

Notes: Pick Area only extends to 0.25 mm of any edge or hole unless otherwise specified.
Dimensions are in millimeters unless otherwise specified.
Tolerance is ±0.15mm unless otherwise specified.
6. EXAMPLE LAND PATTERN

```
6.1.2 (2X)

2.103 (3X)

0.634 (2X)

1.015 (2X)

"AP" SEE NOTE
```

7. EXAMPLE SOLDER_STENCIL PATTERN

```
0.966 (2X)

0.723 (2X)

0.612 (2X)

2.103 (3X)

0.610 (2X)

0.562 (2X)

0.150 (2X)

1.015 (2X)
```

Notes: Dimensions are in millimeters unless otherwise specified.
Detailed information on AP size considerations can be found in the latest SiSonic™
Design Guide application note.
Further optimizations based on application should be performed.
8. PACKAGING & MARKING DETAIL

Model Number | Suffix | Reel Diameter | Quantity Per Reel
-----|------|-------------|----------------
SPU0410LR5H-1 | -7 | 13" | 5,700

Alpha Character A:
- "S": Knowles SiSonic™ Production
- "E": Knowles Engineering Samples
- "P": Knowles Prototype Samples
- "JIN NUMBER": Unique Job Identification Number for product traceability

Notes: Dimensions are in millimeters unless otherwise specified.
Vacuum pickup only in the pick area indicated in Mechanical Specifications.
Tape & reel per EIA-481.
Labels applied directly to reel and external package.
9. RECOMMENDED REFLOW PROFILE

<table>
<thead>
<tr>
<th>Profile Feature</th>
<th>Pb-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Ramp-up rate (T_{MAX} to T_P)</td>
<td>3°C/second max.</td>
</tr>
<tr>
<td>Preheat</td>
<td></td>
</tr>
<tr>
<td>• Temperature Min (T_{MIN})</td>
<td>150°C</td>
</tr>
<tr>
<td>• Temperature Max (T_{MAX})</td>
<td>200°C</td>
</tr>
<tr>
<td>• Time (T_{MIN} to T_{MAX}) (t_P)</td>
<td>60-180 seconds</td>
</tr>
<tr>
<td>Time maintained above:</td>
<td></td>
</tr>
<tr>
<td>• Temperature (T_L)</td>
<td>217°C</td>
</tr>
<tr>
<td>• Time (t_L)</td>
<td>60-150 seconds</td>
</tr>
<tr>
<td>Peak Temperature (T_P)</td>
<td>260°C</td>
</tr>
<tr>
<td>Time within 5°C of actual Peak Temperature (t_P)</td>
<td>20-40 seconds</td>
</tr>
<tr>
<td>Ramp-down rate (T_P to T_{MAX})</td>
<td>6°C/second max</td>
</tr>
<tr>
<td>Time 25°C to Peak Temperature</td>
<td>8 minutes max</td>
</tr>
</tbody>
</table>

Notes: Based on IPC/JEDEC J-STD-020 Revision C.

All temperatures refer to topside of the package, measured on the package body surface.
10. ADDITIONAL NOTES

(A) Shelf life: Twelve (12) months when devices are to be stored in factory supplied, unopened ESD moisture sensitive bag under maximum environmental conditions of 30°C, 70% R.H.

(B) MSL (moisture sensitivity level) Class 1.

(C) Maximum of 3 reflow cycles is recommended.

(D) In order to minimize device damage:
   - Do not board wash or clean after the reflow process.
   - Do not brush board with or without solvents after the reflow process.
   - Do not directly expose to ultrasonic processing, welding, or cleaning.
   - Do not insert any object in port hole of device at any time.
   - Do not apply over 30 psi of air pressure into the port hole.
   - Do not pull a vacuum over port hole of the microphone.
   - Do not apply a vacuum when repacking into sealed bags at a rate faster than 0.5 atm/sec.

11. MATERIALS STATEMENT

Meets the requirements of the European RoHS directive 2011/65/EC as amended.


Ozone depleting substances are not used in the product or the processes used to make the product, including compounds listed in Annex A, B, and C of the “Montreal Protocol on Substances That Deplete the Ozone Layer.”
## 12. RELIABILITY SPECIFICATIONS

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal Shock</td>
<td>100 cycles air-to-air thermal shock from -40°C to +125°C with 15 minute soaks. (IEC 68-2-4)</td>
</tr>
<tr>
<td>High Temperature Storage</td>
<td>1,000 hours at +105°C environment (IEC 68-2-2 Test Ba)</td>
</tr>
<tr>
<td>Low Temperature Storage</td>
<td>1,000 hours at -40°C environment (IEC 68-2-2 Test Aa)</td>
</tr>
<tr>
<td>High Temperature Bias</td>
<td>1,000 hours at +105°C under bias (IEC 68-2-2 Test Ba)</td>
</tr>
<tr>
<td>Low Temperature Bias</td>
<td>1,000 hours at -40°C under bias (IEC 68-2-2 Test Aa)</td>
</tr>
<tr>
<td>Temperature / Humidity Bias</td>
<td>1,000 hours at +85°C/85% R.H. under bias. (JESD22-A101A-B)</td>
</tr>
<tr>
<td>Vibration</td>
<td>4 cycles of 20 to 2,000 Hz sinusoidal sweep with 20 G peak acceleration lasting 12 minutes in X, Y, and Z directions. (Mil-Std-883E, method 2007.2 A)</td>
</tr>
<tr>
<td>ESD-HBM</td>
<td>3 discharges of ±2 kV direct contact to I/O pins. (ESD STM5.2)</td>
</tr>
<tr>
<td>ESD-LID/GND</td>
<td>3 discharges of ±8 kV direct contact to lid while unit is grounded. (IEC 61000-4-2)</td>
</tr>
<tr>
<td>ESD-MM</td>
<td>3 discharges of ±2 kV direct contact to I/O pins. (MIL-STD-883E, Method 3015.7)</td>
</tr>
<tr>
<td>Reflow</td>
<td>5 reflow cycles with peak temperature of +260°C</td>
</tr>
<tr>
<td>Mechanical Shock</td>
<td>3 pulses of 10,000 G in the X, Y, and Z direction (IEC 68-2-27, Test Ea)</td>
</tr>
</tbody>
</table>

Note: After reliability tests are performed, the sensitivity of the microphones shall not deviate more than 3 dB from its initial value. After 3 reflow cycles, the sensitivity of the microphone shall not deviate more than 1dB from its initial value.
13. SPECIFICATION REVISIONS

<table>
<thead>
<tr>
<th>Revision</th>
<th>Specification Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Initial Release</td>
<td>9/11/12</td>
</tr>
<tr>
<td>B</td>
<td>New JIN designation; new RoHS statement (C10114438)</td>
<td>12/17/12</td>
</tr>
<tr>
<td>C</td>
<td>Updated humidity conditions, ESD descriptions, AP and Pin 1 designation (C10114466); fixed typos in Reliability Section 12 (C10114690)</td>
<td>3/27/13</td>
</tr>
<tr>
<td>D</td>
<td>Add +/-1 dB tolerance after 3 reflows (C10115609)</td>
<td>1/26/14</td>
</tr>
</tbody>
</table>

Information contained herein is subject to change without notice. It may be used by a party at their own discretion and risk. We do not guarantee any results or assume any liability in connection with its use. This publication is not to be taken as a license to operate under any existing patents.
Appendix B: PIFR Regression Analysis Results

Figure B1: PIFR versus median amplitude for each subject with linear trendline.

Figure B2: PIFR versus MAD Amplitude for each subject with linear trendline.
Figure B3: PIFR versus RMS Amplitude for each subject with linear trendline.

Figure B4. PIFR versus average power in 300-600 Hz frequency band for each subject with linear trendline.
Figure B5: GLS regression results for PIFR vs Median Amplitude.

| PIFR | Coef.  | Std. Err. | z    | P>|z|  | [5% Conf. Interval] |
|------|--------|-----------|------|------|-------------------|
| MA   | 728.662| 31.69965  | 22.99| 0.000| 666.5318, 790.7921|
|     | _cons  | 28.11024  | 1.839411 | 15.28 | 0.000 | 24.50506, 31.71542|

sigma_u = 3.1121892
sigma_e = 0.0150992
rho = 0.1309937 (fraction of variance due to u_i)

Figure B6: GLS regression results for PIFR vs MAD Amplitude.

| PIFR | Coef.  | Std. Err. | z    | P>|z|  | [5% Conf. Interval] |
|------|--------|-----------|------|------|-------------------|
| MAD  | 2879.436| 123.6142 | 23.29| 0.000| 2637.156, 3121.715|
|     | _cons  | 24.45219  | 1.963524 | 12.45 | 0.000 | 20.68375, 28.30062|

sigma_u = 3.2183084
sigma_e = 7.6725414
rho = 0.14962006 (fraction of variance due to u_i)
**Figure B7:** GLS regression results for PIFR vs RMS Amplitude.

| PIFR | Coef. | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|------|-------|-----------|-------|-----|---------------------|
| RMS  | 2243.905 | 99.92989  | 22.45 | 0.000 | 2048.046 - 2439.764 |
| _cons| 16.35855 | 2.273995  | 7.19  | 0.000 | 11.9016 - 20.8155  |

| sigma_u | 2.9476972 |
| sigma_e | 7.9830894 |
| rho     | 0.11990181 (fraction of variance due to u_i) |

**Figure B8:** GLS regression results for PIFR vs $P_{ave}$ in 300-600 Hz frequency band.

| PIFR | Coef. | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|------|-------|-----------|-------|-----|---------------------|
| Power | 4.818139 | 0.154064  | 31.27 | 0.000 | 4.516179 - 5.120399 |
| _cons| 454.2641 | 12.60810  | 35.00 | 0.000 | 429.3957 - 479.1325 |

| sigma_u | 3.0172494 |
| sigma_e | 6.350592  |
| rho     | 0.18358895 (fraction of variance due to u_i) |
Appendix C: IC Regression Analysis Results

Figure C1: Measured IC versus IC calculated from median amplitude (MA) for each subject with linear trendline.

Figure C2: Measured IC versus IC calculated from MAD amplitude for each subject with linear trendline.
**Figure C3:** Measured IC versus IC calculated from RMS Amplitude for each subject with linear trendline.

**Figure C4:** Measured IC versus IC calculated from average power (P_{ave}) in 300-600 Hz frequency band for each subject with linear trendline.
Random-effects GLS regression

Group variable: Subject

Number of obs = 86
Number of groups = 15

R-sq:  
within = 0.9176  
between = 0.8343  
overall = 0.9920

Obs per group:  
min = 3  
avg = 5.7  
max = 8

corr(u_i, X) = θ (assumed)

| FIVC  | Coef. | Std. Err. | z     | P>|z| | 95% Conf. Interval |
|-------|-------|-----------|-------|------|-------------------|
| ICC_MAD_cons | 0.833534 | 0.0305236 | 29.27 | 0.000 | 0.8335282 - 0.8335385 |
| sigma_u | 0.166087 | 0.072242   | 2.30  | 0.022 | 0.1244953 - 0.2076788 |
| sigma_e  | 0.13698415 |
| rho      | 0.23332929 |

(fraction of variance due to u_i)

Figure C5: GLS regression results for IC vs IC calculated from median amplitude.

Random-effects GLS regression

Group variable: Subject

Number of obs = 86
Number of groups = 15

R-sq:  
within = 0.9245  
between = 0.8385  
overall = 0.9947

Obs per group:  
min = 3  
avg = 5.7  
max = 8

corr(u_i, X) = θ (assumed)

| FIVC  | Coef. | Std. Err. | z     | P>|z| | 95% Conf. Interval |
|-------|-------|-----------|-------|------|-------------------|
| ICC_MAD_cons | 0.8817194 | 0.0269933 | 30.41 | 0.000 | 0.8248936 - 0.9385451 |
| sigma_u | 0.1800967 | 0.070627  | 2.56  | 0.010 | 0.1242763 - 0.2319323 |
| sigma_e  | 0.1428549 |
| rho      | 0.26542486 |

(fraction of variance due to u_i)

Figure C6: GLS regression results for IC vs IC calculated from MAD amplitude.
Random-effects GLS regression

<table>
<thead>
<tr>
<th>Number of obs</th>
<th>86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of groups</td>
<td>15</td>
</tr>
</tbody>
</table>

R-sq: within = 0.9172
between = 0.8287
overall = 0.8989

Obs per group: min = 3
avg = 5.7
max = 8

Wald chi2(1) = 842.30
Prob > chi2 = 0.0000

corr(u_i, X) = 0 (assumed)

| FIVC | Coef. | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|------|-------|-----------|-------|------|----------------------|
| ICC  | RMS   |           |       |      |                      |
| _cons|       |           |       |      |                      |
|      | .8864277 | .0305429 | 29.02 | 0.000 | .8256547 .9462907    |
|      | .1727892 | .0730144 | 2.37  | 0.018 | .1296826 .3158339    |

| sigma_u | .14047185 |
| sigma_e | .24887593 |
| rho     | .24186001 (fraction of variance due to u_i) |

**Figure C7:** GLS regression results for IC vs IC calculated from RMS amplitude.

Random-effects GLS regression

<table>
<thead>
<tr>
<th>Number of obs</th>
<th>86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of groups</td>
<td>15</td>
</tr>
</tbody>
</table>

R-sq: within = 0.9365
between = 0.9919
overall = 0.9945

Obs per group: min = 3
avg = 5.7
max = 8

Wald chi2(1) = 1065.09
Prob > chi2 = 0.0000

corr(u_i, X) = 0 (assumed)

| IC | Coef. | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|----|-------|-----------|-------|------|----------------------|
| ICC | RMS   |           |       |      |                      |
| _cons |       |           |       |      |                      |
|      | .6809031 | .0208637 | 32.64 | 0.000 | .640011 .7217952    |
|      | .2055184 | .061300  | 3.36  | 0.001 | .1802001 .3308360   |

| sigma_u | .10041829 |
| sigma_e | .22797453 |
| rho     | .19249512 (fraction of variance due to u_i) |

**Figure C8:** GLS regression results for IC vs IC calculated from \( P_{ave} \) in 300-600 Hz frequency band.
Appendix D: Journal Paper Publications
A method of estimating inspiratory flow rate and volume from an inhaler using acoustic measurements

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Received 22 April 2013, accepted for publication 24 June 2013
Published 26 July 2013
Online at stacks.iop.org/PM/34/903

Abstract

Inhalers are devices employed to deliver medication to the airways in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease. A dry powder inhaler (DPI) is a breath actuated inhaler that delivers medication in dry powder form. When used correctly, DPIs improve patients’ clinical outcomes. However, some patients are unable to reach the peak inspiratory flow rate (PIFR) necessary to fully extract the medication. Presently clinicians have no reliable method of objectively measuring PIFR in inhalers. In this study, we propose a novel method of estimating PIFR and also the inspiratory capacity (IC) of patients’ inhalations from a commonly used DPI, using acoustic measurements. With a recording device, the acoustic signal of 15 healthy subjects using a DPI over a range of varying PIFR and IC values was obtained. Temporal and spectral signal analysis revealed that the inhalation signal contains sufficient information that can be employed to estimate PIFR and IC. It was found that the average power ($P_{ave}$) in the frequency band 300–600 Hz had the strongest correlation with PIFR ($R^2 = 0.9079$), while the power in the same frequency band was also highly correlated with IC ($R^2 = 0.9245$).

This study has several clinical implications as it demonstrates the feasibility of using acoustics to objectively monitor inhaler use.

Keywords: acoustics, asthma, COPD, inhalers, inspiratory flow rate, volume

Online supplementary data available from stacks.iop.org/PM/34/903/mmedia

(Some figures may appear in colour only in the online journal)
1. Introduction

Asthma and chronic obstructive pulmonary disease are two common types of chronic respiratory disease, characterized by airways obstruction. Prevalence of these two respiratory diseases has risen sharply over recent decades, creating a large economic burden due to treatment costs (Mannino 2002, Braman 2006). Obstructive airway diseases are primarily treated by delivering medication to the airways using inhalational devices. Medication efficacy is significantly dependent on the amount of drug reaching the small airways of the lungs. The medication in the inhalers is delivered to the respiratory tract via an inhalational maneuver. The clinical effect of inhaled therapy depends on the lung dose, its particle size distribution, the patient’s inspiratory flow rate, inhaled volume and degree of airways obstruction (Sumby et al 1992). Several studies have highlighted that errors in inhaler technique may be as detrimental as the lack of temporal adherence (Crompton et al 2006, Nikander et al 2011).

The two main types of inhalers used are metered dose inhalers (MDIs) and dry powder inhalers (DPIs). DPIs are considered advantageous over MDIs since they avoid the use of propellants, and are instead actuated during the inhalation (Malmberg et al 2010). The elimination of propellants allows patient coordination issues to be overcome. However, a disadvantage of DPIs is that the particle size distribution of the aerosol generated depends on the inspiratory flow rate through the device (Nielsen et al 1997). This flow rate can vary depending on the resistance of the DPI being used and on a patient’s inspiratory effort and inspiratory capacity (IC). The inspiratory flow rate influences the efficiency of removing particles of the drug formulation from the inhaler and it also affects the efficiency of de-aggregation of the particles and the fine particle dose that gets into the respiratory tract (Vidgren et al 1988). This correlates to an absolute peak inspiratory flow rate (PIFR) above 30 L min\(^{-1}\) and ideally above 60 L min\(^{-1}\) (Pauwels et al 1997).

Previous studies have demonstrated that the primary cause of poor clinical outcomes in inhaler therapy is due to the inability of patients to generate sufficiently high PIFRs through their DPI (Jarvis et al 2007, Wieshammer and Dreyhaupt 2008). Currently, the only methods available to clinicians for assessing inhaler technique are subjective checklist methods and the Clement Clarke In-Check Dial™. Subjective checklist methods give no indication of whether the patient had sufficient inhalational flow effort or IC to achieve adequate drug delivery. The In-Check Dial simulates the resistance of the main types of inhalers to give an estimation of the patient’s PIFR. This method is quite effort dependent and may not correlate well with the in vivo PIFRs developed by the patient while using the actual inhaler device. There is a definite need for a device, which gives real-time feedback of inhalational technique and effort over a prolonged period of time.

This study aims to investigate if a relationship exists between inhaler inhalation sounds and airflow. Inhaler inhalation sounds are a mixture of both respiratory sounds and sounds created from turbulence in the inhaler. It is well known that a relationship exists between airflow and respiratory sounds. Most of the previous research in this area has examined the relationship between respiratory sounds generated at the trachea and on the chest wall to airflow. A relationship between airflow and sound amplitude was established by Shykoff et al (1988). Charbonneau et al (1987) also derived a formula for this relationship using mean amplitude and frequency to predict flow rates from respiratory sounds. Hossain and Moussavi (2004) again established a relationship between amplitude and airflow, but found that the average power in the frequency band 150–450 Hz provided a slightly stronger relationship with flow rate compared to mean amplitude in healthy subjects. Together these studies indicate that a definite relationship exists between airflow and respiratory sounds.
The main objectives of this study were to investigate the relationship between temporal and spectral features of the inhalation signal and inspiratory flow rate and volume measurements in healthy subjects. It was hypothesized that features obtained from the inhalation signal could be used to estimate PIFR and IC. Three measurements of amplitude were used, in addition to the average power at a range of different frequency bands, in order to investigate which acoustic measurement had the best correlation with PIFR and IC. Using the inhalation signal to predict such inspiratory values would establish the feasibility to provide clinicians with new objective measurements on patient inhaler use.

2. Methods

2.1. Participants

Fifteen healthy volunteers between the ages of 18–40 years were recruited. Subjects were excluded if they had any cardiac, respiratory, hepatic, renal dysfunction, recent respiratory tract infection in the last six weeks, a greater than ten pack/year smoking history, a history of drug/alcohol abuse or a known sensitivity to Salmeterol or Fluticasone. Baseline spirometry was performed according to ATS/ERS recommendations (Miller et al 2005) to confirm that subjects had normal lung function.

2.2. Acoustic recording device

The recording device selected to obtain the acoustic signals of inhaler use was the INCA (Inhaler Compliance Assessment) device, manufactured by Vitalograph Ltd. The device (figure 1) primarily consists of a microphone, microcontroller and battery. The microphone is a Knowles Acoustics SPM0204HE5 mini surface mount silicon microphone. The audio files are stored on the INCA device from where they can subsequently be uploaded to a computer via USB connection. The INCA device can be used in conjunction with the common Diskus™ inhaler (known as Accuhaler™ in the United Kingdom). The INCA device starts recording the acoustic signal once the Diskus™ inhaler is opened and switches off once the
Figure 2. Airtight container with the Diskus™ inhaler placed inside and INCA device attached on top.

Diskus™ is closed. The audio signals were recorded as mono WAV files, at a sampling rate of 8000 Hz and a resolution of 8 bits/sample.

2.3. Flow experimental design

A spirometer is a device that is capable of measuring the flow rates and volume of air inspired and expired by the lungs. Several studies have previously employed an airtight container to connect an inhaler to a spirometer in order to obtain flow measurements through an inhaler device (Magnussen et al 2009, Malmberg et al 2010). The airtight container ensures that all inspired air through the mouthpiece of the inhaler comes through the spirometer where it can be measured. In this study a clear PET (Polyethylene Terephthalate) container was used to act as an airtight adaptor between a Diskus™ inhaler and a spirometer. An empty Diskus™ inhaler was placed into the container (figure 2), which had a custom aperture cut for the mouthpiece, the INCA device and the spirometer connector. The mouthpiece was extended out 1 cm in length in order for subjects to get a good seal around the mouthpiece. The aperture for the INCA device was cut so that the position of the INCA device resembled that of real world use i.e. sitting flush on the Diskus™ inhaler; this limited the damping of the acoustic signal. Steinel Hybond 86 adhesive was used to seal any gaps and prevent any unintentional air from going in or out of the container. The container was submerged in a water bath before each test in order to verify that it was airtight. The end result was that air could only enter or exit via the inhaler mouthpiece and through the spirometer connector.

2.4. Spirometer employed

The spirometer used was the Vitalograph Pneumotrac (Model 6800) supplied by Vitalograph Ltd. This spirometer uses a Fleisch pneumotachograph for flow/volume readings. The specifications are presented below:

- Flow detection principle: fleisch type pneumotachograph
- Volume detection: flow integration sampling @ 100 Hz
- Accuracy when in operating range:
2.5. Test procedure

The airtight container described previously was connected to the spirometer. Patients were instructed to exhale gently (to functional residual capacity) and then inhale at a variety of flow rates and volumes. Each patient performed this maneuver six to eight separate times. The airtight container was sterilized after each patient performed the test to ensure that no infections were passed between subjects. A graphical representation of the overall test set up can be seen in figure 3.

2.6. Inhalation signal analysis

The inhalation audio signals were divided into 1024 data samples with 50% overlap between successive segments. A Hanning window was used to analyze each segment, while a fast Fourier transform was used to calculate the power spectral density. Three measures of amplitude were employed in this study: median amplitude (MA), mean absolute deviation (MAD) of the amplitude and root mean square (RMS) of the amplitude. These three measures of amplitude were chosen in order to investigate which had the best correlation with PIFR and IC.

MA was computed using a relative peak detection method. Peaks of the inhalation signal were selected that were greater than their nearest neighbor by a minimum threshold height difference of 200. This method was chosen over calculating the mean value of the inhalation signal in order to reduce the effect of noise in the analysis. MAD is the mean of the absolute
deviations from the central value. This measure addresses the problem of calculating the mean from a sinusoidal measure and was calculated using the following equation (1):

\[ \text{MAD} = \frac{1}{n} \sum_{i=1}^{n} |x_i - \bar{x}|. \]  

(1)

The RMS or quadratic mean is a statistical measure of the effective value of a signal's amplitude, including the mean value. It takes into account sinusoidal waveforms and gives the equivalent non-varying power of a varying waveform. It is the square root of the mean of the squares of the values of either a discrete or continuously varying function. RMS has been used in a previous study, which investigated the volume-dependent changes in regional lung sound amplitudes (Kiyokawa and Pasterkamp 2002). It was calculated using the following equation (2):

\[ \text{RMS} = \left[ \frac{1}{n} \left( x_1^2 + x_2^2 + x_3^2 + \cdots + x_n^2 \right) \right]^{1/2}. \]  

(2)

The average power \( P_{\text{ave}} \) of each inhalation was calculated in the frequency bands: 20–40 Hz, 40–70 Hz, 70–150 Hz, 150–300 Hz, and 300–600 Hz, in addition to 70–300 Hz, 70–450 Hz, 100–300 Hz, 100–450 Hz and 150–450 Hz. These frequency bands were chosen as they were previously used in a study by Hossain and Moussavi (2004) which investigated the best frequency band to estimate flow rate from respiratory sounds obtained from the chest wall.

In spirometry, the area under a PIFR—time curve equates to the volume of an inhalation or IC. Since acoustic measurements were used to predict the PIFR, integration could not be used to determine IC. Instead it was noted that the area under the curve of the inhalational sound waveform (inhalation volume) approximates that of a semi-ellipse, described by the following equation (3):

\[ \text{Inhalation volume} = \frac{1}{2} \pi A B. \]  

(3)

where \( A = \text{PIFR} \) and \( B = \text{duration} \) (see figure 4). Values for MA, MAD, RMS and \( P_{\text{ave}} \) for each inhalation were employed to obtain predicted values for the mean PIFR. These predicted mean PIFR values and the actual duration of the inhalation were used to calculate a predicted IC value (equation (3)). The predicted values for IC were then compared to the actual IC values for each inhalation, as obtained from the spirometer.

2.7. Statistical analysis

Analysis was carried out using the statistical software Stata SE Version 12. This study was designed as a repeated measures study due to the fact that the samples were not independent. A Generalized least squares (GLS) regression model, which accounts for random effects intercept
Table 1. Summary of demographics and baseline lung function data from all subjects \((n=15)\).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.9</td>
<td>4.2</td>
<td>22–35</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>(9/15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.5</td>
<td>6.4</td>
<td>164–185</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.8</td>
<td>9.0</td>
<td>56–91</td>
</tr>
<tr>
<td>BMI(^{a}) (kg m(^{-2}))</td>
<td>23.86</td>
<td>2.21</td>
<td>20.8–29.7</td>
</tr>
<tr>
<td>FEV(_1)(^{b}) (L)</td>
<td>3.98</td>
<td>0.58</td>
<td>2.79–4.85</td>
</tr>
<tr>
<td>FEV(_1)(^{b}) (%) predicted</td>
<td>99.33</td>
<td>5.33</td>
<td>92–110</td>
</tr>
<tr>
<td>FVC(^{c}) (L)</td>
<td>4.90</td>
<td>0.73</td>
<td>3.41–6.24</td>
</tr>
<tr>
<td>FEV(_1)/FVC ratio</td>
<td>0.81</td>
<td>0.06</td>
<td>0.70–0.91</td>
</tr>
<tr>
<td>PEF(_R)(^{d}) (L min(^{-1}))</td>
<td>547.6</td>
<td>103.7</td>
<td>384–744</td>
</tr>
<tr>
<td>FIV(_C)(^{e}) (L)</td>
<td>4.56</td>
<td>0.67</td>
<td>3.34–5.76</td>
</tr>
<tr>
<td>PIF(_R)(^{f}) (L min(^{-1}))</td>
<td>402.1</td>
<td>82.1</td>
<td>276–535</td>
</tr>
</tbody>
</table>

\(^{a}\) BMI—body mass index.

\(^{b}\) FEV\(_1\)—forced expiratory volume in 1 s.

\(^{c}\) FVC—forced vital capacity.

\(^{d}\) PEF—peak expiratory flow rate.

\(^{e}\) FIVC—forced inspiratory vital capacity.

\(^{f}\) PIF—peak inspiratory flow rate.

at the subject level, was used to compare the acoustic parameters of MA, MAD, RMS and \(P_{ave}\) with measured PIFR and IC. The GLS model takes into account the correlation between the observations when calculating the regression model and was thus deemed appropriate for analysis of the data in this study.

3. Results

Table 1 presents the demographics and baseline lung function of the 15 healthy volunteers enrolled in this study. The ethnic origin of subjects was Caucasian for 93.3% (14/15) and Hispanic for the remaining 6.7% (1/15). All subjects had an FEV\(_1\)/FVC ratio >0.7 and a predicted FEV\(_1\) > 89%, confirming normal baseline lung function according to ATS standards.

A total of 120 audio files were obtained from the 15 subjects. 17 audio files were discarded due to an INCA device formatting error. In this study the PIFR range of interest was between 0–100 L min\(^{-1}\) and a subsequent 17 audio files were omitted that had PIFR values greater than 100 L min\(^{-1}\), leaving a total of 86 observations from the 15 subjects. For each inhalation the spirometer provided values for PIFR and IC. PIFR was compared to MA, MAD and RMS of the inhalation signal, while \(P_{ave}\) at several select frequency bands (described earlier) was also compared to PIFR.

It was found that MA, MAD and RMS were all highly correlated with PIFR \((P = 0.0000)\) at a significance level of \(\alpha = 0.05\). The coefficients of determination were found to be \(R^2 = 0.8386\) for MA, \(R^2 = 0.8340\) for MAD and \(R^2 = 0.8320\) for RMS. \(P_{ave}\) for a range of select frequency bands was also calculated. Using a GLS regression model to compare PIFR to \(P_{ave}\) it was found that the relationship was also highly correlated for all of the frequency bands \((P = 0.0000, \alpha = 0.05)\). It is worth noting that at higher powers, the GLS regression model will give PIFRs exceeding the maximum possible flow rate through the inhaler. The \(P_{ave}\) in the frequency band 300–600 Hz had the strongest correlation with PIFR, as the GLS regression model for this frequency band had an \(R^2\) value of 0.9079. A complete analysis of the relationship between \(P_{ave}\) and PIFR for each of the frequency bands analyzed is presented in
Table 2. Correlation scores between $P_{ave}$ and PIFR.

<table>
<thead>
<tr>
<th>Frequency band (Hz)</th>
<th>Coefficient of determination ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40</td>
<td>0.7865</td>
</tr>
<tr>
<td>40–70</td>
<td>0.7018</td>
</tr>
<tr>
<td>70–150</td>
<td>0.8067</td>
</tr>
<tr>
<td>150–300</td>
<td>0.8461</td>
</tr>
<tr>
<td>300–600</td>
<td>0.9079</td>
</tr>
<tr>
<td>70–300</td>
<td>0.8427</td>
</tr>
<tr>
<td>70–450</td>
<td>0.8746</td>
</tr>
<tr>
<td>100–300</td>
<td>0.8431</td>
</tr>
<tr>
<td>100–450</td>
<td>0.7018</td>
</tr>
<tr>
<td>150–450</td>
<td>0.8807</td>
</tr>
</tbody>
</table>

The overall results demonstrating the relationship between MA, MAD, RMS, $P_{ave}$ and PIFR can be seen in figure 5. Individual plots of acoustic parameters versus PIFR for each subject with the associated GLS regression can be found in the online supplementary material (available from stacks.iop.org/PM/34/903/mmedia).

With the analysis of MA, MAD, RMS and $P_{ave}$ it is possible to estimate IC. Figure 5 demonstrates that it is possible to estimate values for PIFR from analysis of the inhalation signal. IC can subsequently be calculated by using equation (3).

GLS regression demonstrated that IC can be estimated using MA, MAD, RMS and $P_{ave}$ ($P = 0.000$, $\alpha = 0.05$). The coefficients of determination ($R^2$) for predicting IC were 0.9020 for MA, 0.9047 for MAD, 0.8989 for RMS and 0.9245 for $P_{ave}$ in the frequency band 300–600 Hz. Figure 6 presents plots of actual IC versus IC estimated from MA (ICma), MAD (ICmad), RMS (ICrms) and $P_{ave}$ (IC$P_{ave}$). GLS Regression outputs for each acoustic parameter and individual plots of calculated versus measured IC for each subject can be found in the online supplementary material (available from stacks.iop.org/PM/34/903/mmedia).

4. Discussion

The aim of this study was to investigate whether acoustic features of inhalations could be used to estimate PIFR and IC in 15 healthy subjects. The main results reveal that MA, MAD and RMS of the amplitude and $P_{ave}$ at a range of different frequency bands all provided a robust method of estimating PIFR and IC. The high level of correlation between PIFR and IC from the acoustic measurements to the ‘gold standard’ method using spirometry is a promising result, suggesting that this approach may be used in future validation studies.

Several previous studies have investigated the relationship between respiratory sounds and airflow. Unlike earlier studies, which have investigated respiratory sounds recorded on the chest wall and trachea, this study focused on sounds generated during inhaler use. Inhaler sounds are a mixture of both respiratory sounds and sounds from the inhaler itself. The microphone was located in the INCA device, which was securely bonded to the inhaler in a location less than 5 cm from the mouth. The results of this study are in accordance with previous research which established that variations in flow are reflected in the intensity and frequency distribution of the sounds generated (Kraman 1984, Gavriely and Cugell 1996). A study by Hossain and Moussavi (2004) indicated that $P_{ave}$ had the strongest correlation with flow rate from respiratory sounds. The results of the present study found that $P_{ave}$ had the strongest correlation with flow rate from inhaler sounds. The same study by Hossain and Moussavi (2004) also reported that the optimum frequency band to calculate $P_{ave}$ was 150–
Figure 5. PIFR versus (a) MA, (b) MAD amplitude, (c) RMS amplitude and (d) average power ($P_{ave}$) in the frequency band 300–600 Hz. The plotted points are calculated PIFRs based on regression equation for each subject. The black line represents overall regression model equation.

Figure 6. Measured IC versus IC calculated from (a) MA, (b) MAD, (c) RMS and (d) $P_{ave}$ in 300–600 Hz frequency band. The plotted points are calculated ICs based on regression equation for each subject. The black line represents overall regression model equation.
450 Hz for healthy subjects, while in the present study we found this optimum frequency band to be 300–600 Hz for inhaler sounds. It is therefore clear to see that the sounds created by the inhaler are different in comparison to normal respiratory sounds. Inhaling through the narrow opening of the Diskus™ inhaler has created a shift in sound intensity towards higher frequencies.

The additional dead space volume of the airtight container adds additional resistance to the overall pathway of the spirometer. This means that a slightly greater patient effort is required in order to obtain PIFR and IC values that would have been reached without the airtight container. This could lead to values of MA, MAD, RMS and $P_{ave}$ obtained being slightly higher than they should be for the corresponding PIFR and IC values. However, for the purposes of this study it was decided that the effects of the containers dead space is small enough to be negligible, given that the ranges studied were quite large (range of 100 L min$^{-1}$ for PIFR and 3.54 L for IC). The additional dead space of the container also met ATS 2005 requirements for spirometry, in that the total dead space of the circuit was less than 350 ml. One point to consider in this study also is that if the sound is generated by the flow through the inhaler, the frequency content of the sound may be proportionally shifted to higher frequencies at higher flows. Further research is required to better interpret this effect on the results of this study and future inhaler based studies.

The current methods of assessing patients’ inhaler technique are limited. At present clinicians make a subjective decision on whether a patient’s inhalation is sufficiently adequate for their medication to reach their airways. However an effective inhalation is dependent on inspiratory flow rate, which cannot be measured subjectively. PIFR can be measured using a Clement Clarke In-Check Dial™ device (Janssens et al. 2008, Amirav et al. 2005), although this device is not widely used and when it is used, it is primarily in clinical environments. Additionally, the effort patients exert in front of the clinician may not correlate to the effort they put into using their inhaler on a day-to-day basis. The method we propose in this paper allows PIFR values from real world patient inhaler use to be acquired, in addition to IC values.

The objective of this study was to demonstrate the feasibility of using acoustic measurements to estimate PIFR/IC from inhalers. The regression models are inherently biased to the dataset used and hence cannot be used to estimate the 95% CI for a population of individuals. Nonetheless, the regression outputs in the online supplementary data (available from stacks.iop.org/PM/34/903/mmedia) show that the 95% CIs for the variables are actually relatively small, proving the potential of carrying out a validation study on a large population. There are numerous potential clinical applications for a system that can accurately predict PIFR and IC from patients’ inhalations during inhaler use. A standard threshold could be put in place to inform clinicians whether a patient performed an effective or ineffective inhalation. PIFR and IC could also be monitored on a day-to-day basis, providing the opportunity to assess patients’ respiratory condition over time. Monitoring PIFR and IC longitudinally may provide the opportunity to predict and prevent exacerbations before they take place. The method of calculating PIFR and IC as described in this study is independent of age and thus has many benefits for monitoring inhaler therapy. Analysis of PIFR may also show when narrowing of the airways occurs, while analysis of IC variations might be used to study dynamic hyperinflation, and monitor the drop in IC associated with exacerbations. Informing patients of their day-to-day PIFR and IC values may also encourage them to take better control of their respiratory disease, as they may come to realize that a greater effort is required on their part, in order to help deliver the medication to their airways. Such active feedback may provide the opportunity to improve the efficacy of the medication, reduce exacerbations and lower the frequency of admittance to hospital emergency departments.
5. Conclusions

In conclusion, it has been shown that acoustics can be employed to estimate the PIFR and IC values of healthy subjects’ inhalations through a DPI device. It was found that $P_{\text{ave}}$ in the frequency band 300–600 Hz provided the best acoustic measurement to predict PIFR, while $P_{\text{ave}}$ in the same frequency band also represented the best method of predicting IC. The ability to use acoustic measurements to estimate PIFR and IC provides clinicians with new objective measurements that reveal the quality of a patient’s inhaler inhalation effort. Such objective measurements may allow clinicians to reach a decision on a patient’s ability to use their inhaler and also to provide feedback to a patient concerning their technique. Quality active feedback may encourage patients to improve their inhaler technique, which in turn may improve the clinical efficacy of inhaler medication, reduce the number of exacerbations, hospital admissions and ultimately prevent an increase in mortality rates.

Acknowledgments

This research was funded by a Higher Education Authority (HEA) Graduate Research Education Program in Engineering (GREP-ENG) scholarship to MSH, a Health Research Board (HRB) grant (number: 2011 219) to RWC and an Enterprise Ireland grant (number: CFTD/05/205) to RBR. The authors of this paper would also like to thank Vitalograph Ltd and GlaxoSmithKline Ltd for generously providing financial support for this study.

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Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices

Terence E. Taylor, MEng,1,2* Martin S. Holmes, BE1,2* Imran Sulaiman, MD,3 Richard W. Costello, MD,3 and Richard B. Reilly, PhD1,2,4

Abstract

Background: The efficacy of drug delivery from inhalers is very much dependent on the user’s peak inspiratory flow rate (PIFR). Current methods to measure PIFR in inhalers are based on subjective checklists. There is a lack of methods currently available to objectively remotely monitor PIFR in pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). In this study, for the first time, non-contact acoustic methods were employed to estimate PIFR through three commonly used inhalers (Diskus™ DPI, Turbuhaler™ DPI, and Evohaler™ pMDI) with the aim of applying these methods to remotely monitor inhaler inhalation technique in future clinical applications.

Methods: Each inhaler was placed inside an airtight container connected to a spirometer to measure PIFR. A high quality microphone was placed 5 cm from the mouthpiece of the inhalers to record inhalation sounds. Over 2000 inhaler inhalation sounds were recorded from 11 healthy participants. A range of temporal and spectral acoustic features from the inhalation sounds were correlated with PIFR. The variation of acoustic features and the repeatability of the inhalation acoustic spectral profile were investigated to further characterize inhaler inhalation sounds and to determine the reliability of acoustics to estimate PIFR.

Results: All acoustic features were significantly correlated with PIFR (p<0.001). The mean power of the inhalation sound generated the most consistent correlation across all inhalers \[ R^2 = 0.77 \text{ (Diskus™)}, R^2 = 0.74 \text{ (Turbuhaler™)}, R^2 = 0.75 \text{ (Evohaler™)} \] . Acoustic features generated low variation and the spectral profile of inhalation sounds was repeatable regardless of flow rate, suggesting that acoustic methods are a reliable method of estimating PIFR.

Conclusions: The methods presented in this study may be employed in a wearable monitoring device in future applications to measure inhaler PIFR. Objective monitoring of PIFR in inhalers may help patients improve their inhaler inhalation technique and therefore may be of significant clinical benefit to both patients and clinicians.

Key Words: acoustics, inhalation, inhaler technique monitoring, peak inspiratory flow rate, signal processing, Diskus, Turbuhaler, Evohaler

Introduction

Poor inhaler inhalation technique can have a detrimental effect on the clinical efficacy of inhalers.1 It has been widely reported that many patients inhale too fast (>90 L/min) when using pressurized metered dose inhalers (pMDIs).2 Other studies have reported that patients with moderate and severe airway obstruction may not reach the recommended flow rate (>30 L/min) when using dry powder inhalers (DPIs).3 Particularly during an exacerbation.2 Although this is beneficial to clinicians, the majority of the devices available do not monitor peak inspiratory flow rate (PIFR) during inhaler use. There is a lack of objective methods to remotely monitor PIFR in both pMDIs and DPIs. It has recently been reported that acoustic methods may be employed to estimate PIFR in healthy participants using

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the Diskus™.(6) Previous acoustic-based studies employed a microelectromechanical systems (MEMS) microphone in an electronic monitoring device (Inhaler Compliance Assessment Device (INCA)) attached to the Diskus™ to detect inhalations automatically(7) and to quantify drug delivery(8) using acoustic analyses. One of the current limitations of the acoustic device employed in these studies is that the INCA device can only be used with the Diskus™. There has recently been a surge in popularity for wearable technologies (i.e., smart watches) and the potential to use non-contact (not attached to the patient’s skin or the inhaler device) acoustic methods to monitor inhaler user technique is a promising opportunity.

Despite previous studies employing acoustic methods to estimate PIFR through the Diskus™, little is known regarding the spectral properties of inhaler inhalation sounds. Spectral properties of normal (i.e., free from adventitious sounds) tracheal and chest wall breath sounds have been reported to be very repeatable at an intra-subject level.(9) Also, the position of peaks and troughs in the acoustic spectral profile from tracheal breath sounds are repeatable regardless of PIFR.(10)

It is hypothesized that these spectral properties also exist in inhaler inhalation sounds. This may be of interest for inhaler acoustic analyses research. The use of tracheal and chest wall contact acoustic sensors may not be practical for monitoring inhaler inhalation technique longitudinally. Therefore, non-contact acoustic sensors near the mouth may be a more suitable approach for analyzing inspiratory inhaler sounds.

The main objective of this study was to use non-contact acoustic methods to estimate PIFR in three commonly used inhalers (Diskus™ DPI, Turbuhaler™ DPI, and Evohaler™ pMDI). The variation of temporal and spectral acoustic features at an intra-subject level was also investigated to determine the reliability of acoustic features in analyzing inhaler inhalation sounds. The repeatability of the acoustic spectral profile was analyzed to determine if the position of the peaks and troughs of the profile remained unchanged within participants across a range of flow rates. This information is intended to provide a baseline for future development of feature extraction methods for inspiratory inhaler acoustic analyses.

Materials and Methods

Participants

Eleven healthy young (age range: 22–31) adult males were recruited. All participants were free from respiratory tract infections and were non-smokers. Baseline spirometry was performed to ATS/ERS recommendations to confirm that all participants had normal lung function.

Inhaler recording setup

Three custom built polyethylene terephthalate (PET) airtight containers were assembled for three commonly used inhalers: Diskus™ (GlaxoSmithKline, London, UK), Turbuhaler™ (AstraZeneca, Södertälje, Sweden), and Evohaler™ (GlaxoSmithKline, London, UK). The airtight containers were connected to a Vitalograph Pneumotrac 6800 (Vitalograph Ltd, Co. Clare, Ireland) spirometer, which was connected to a data acquisition laptop, to obtain peak flow rate measurements. A custom aperture was cut in each airtight container so that participants could seal their lips tightly around the inhaler mouthpiece. Several previous studies have reported using an airtight container as a method to calculate PIFR during inhaler inhalations.(6,11,12) The airtight container design ensured that all air inhaled through each inhaler flowed through the spirometers pneumotachograph from where flow rate can be measured objectively.

An Earthworks TC30 (Earthworks Inc., New Hampshire, USA) omnidirectional microphone was placed 5 cm away from the edge of the inhaler mouthpiece in the airtight container. This setup aimed to simulate a non-contact acoustic recording device to record the sounds associated with inhaler inhalations. The microphone employed has a flat frequency response from 9 Hz to 30 kHz. A Novation nio 2/4 (Novation, Buckinghamshire, UK) was employed as an audio interface and Adobe Audition V6.0 (Adobe System Inc., California, USA) was used to record audio data with a sampling rate of 44.1 kHz and resolution of 32 bits/sample in a data acquisition laptop. Inhaler recording sessions took place in a soundproof recording studio to limit background noise. The complete experimental setup is demonstrated graphically in Figure 1.

Test protocol

Participants were instructed to exhale gently (to functional residual capacity), before inhaling through the inhaler mouthpiece at their PIFR. Participants were asked to inhale at PIFR for 10 recordings. Based on the PIFR achieved, participants were then asked to lower their inspiratory flow rate (IFR) subjectively. For the two DPIs, participants were generally able to inhale with PIFR between 80–90 L/min. Once 10 inhalations were recorded for this IFR band, participants were asked to inhale 10 times at the next lowest IFR band (i.e., 70–80 L/min). This procedure was repeated until 10 inhalations were achieved for each IFR band as low as 20–30 L/min. For each inhalation in all of the IFR bands, the peak flow rate was measured. However, these PIFR measurements were not related to the participants’ maximum effort. Therefore the inspiratory flow measurements are referred to as PIFR simulated in the results section.

For the pMDI, the participants were capable of inhaling with PIFR up to 300 L/min. For this inhaler, participants were asked to inhale 10 times in the IFR band 250–300 L/min. Participants were then asked to lower their IFR subjectively and inhale 10 times for the IFR band 200–250 L/min. This was repeated for all IFR bands greater than 100 L/min. Below 100 L/min, participants were asked to inhale 10 times for IFR bands 75–100 L/min, 50–75 L/min, and 25–50 L/min. All recordings were aurally and visually assessed by an expert reviewer using Adobe Audition.

If participants did not inhale for at least 2 seconds in duration or had coughed, the audio recording was discarded and participants were asked to repeat the inhalation. Each airtight container was disinfected after each recording session to ensure that no infections were passed between participants. The order of inhalers was randomized for each participant to eliminate any fatigue effect on the inspiratory inhaler acoustic features.

Inhalation acoustic analyses

Baseline correction was performed on all inhalation audio recordings by removing any DC offset present in the audio
signal. This was done by subtracting the mean amplitude from each audio recording.

**Acoustic feature extraction**

Each inhalation audio recording was divided into frames of length 1024 with 50% overlap between each frame. A Hanning window was applied to each segment. The Hanning window reduced abrupt discontinuities at the edges of the segments. The Welch power spectral density (PSD) was then estimated, since it could display the power spectrum of the inhalation acoustic signal.

All inhalation sounds were high-pass filtered above 200 Hz to remove low frequency noise. A 5 second sample of background noise was estimated during periods of breath hold for each participant. The PSD was estimated for each participant’s breath hold and then removed from each participant’s audio recordings using spectral subtraction to remove any high frequency noise. This method has been previously employed in breath sound analysis and has been a recommended method for noise removal. The PSD was calculated for all 10 inhalation audio recordings at each IFR band for each participant. The average PSD was then computed over all 10 recordings at each IFR band.

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**FIG. 1.** Inhaler recording setup.

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**FIG. 2.** Averaged PSD estimations of inhaler inhalation sounds from low flow (bottom curve) to high flow (top curve) from one participant from (A) Diskus™, (B) Turbuhaler™, and (C) Evohaler™.
band in order to obtain a sufficient single estimate of the true acoustic spectral profile of each participant at each IFR band. This resulted in one acoustic spectral profile for each IFR band for each participant. Figure 2 shows an example of the inhalation acoustic spectral profiles (where each curve represents the average of 10 inhalations) from one participant for the Diskus™/C212, Turbuhaler™/C212, and Evohaler™/C212.

Acoustic feature selection

Six features were employed to estimate PIFR through each inhaler. The first, second and third quartile frequencies of the acoustic frequency spectrum, which correspond to the frequencies below which 25%, 50%, and 75% of the total spectral power lie (F25, F50 and F75), were employed. Mean power (MP), mean absolute deviation (MAD), and root mean square (RMS) were also employed as features. Acoustic feature analyses was divided into two groups: Group A (F25, F50, and F75) and Group B (MP, MAD, and RMS).

Quartile frequencies (F25, F50, and F75) have been previously employed in breath sound analysis to distinguish physiological differences between healthy individuals and those with asthma and COPD, in particular measuring severity of airway narrowing.(17) Also, it has yet to be reported how frequency content changes with flow rate in inhaler inhalation sounds as mentioned in Holmes et al.(6) Mean power has been previously employed to estimate flow rate from chest wall(18) and tracheal(19) respiratory sounds. Also, mean power, mean absolute deviation, and root mean square have been correlated with PIFR and inspiratory capacity from a Diskus™ inhaler using an INCA device attached to the inhaler.(6)

Statistical analyses of inhaler inhalation sounds

A Generalized Least Squares (GLS) regression model, which accounts for random effects intercept at the subject

### Table 1. Summary Demographics and Baseline Lung Function for Participants (n = 11)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD, {Range}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.36 ± 2.50, {22–31}</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.36 ± 7.86, {167–190}</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.36 ± 8.66, {65–93}</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>23.79 ± 2.77, {21.2–28.7}</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.48 ± 0.47, {3.92–5.18}</td>
</tr>
<tr>
<td>FEV1 predicted (%)</td>
<td>99.27 ± 5.74, {89–112}</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>5.50 ± 0.72, {4.63–6.87}</td>
</tr>
<tr>
<td>FVC/FVC ratio</td>
<td>0.82 ± 0.04, {0.72–0.88}</td>
</tr>
<tr>
<td>PEFR (L/min)</td>
<td>615.09 ± 72.06, {538–640}</td>
</tr>
<tr>
<td>FIVC (L)</td>
<td>5.12 ± 0.59, {4.55–6.13}</td>
</tr>
<tr>
<td>PIFR (L/min)</td>
<td>487.54 ± 46.45, {405–540}</td>
</tr>
</tbody>
</table>

### Table 2. Correlation Scores (Adjusted $R^2$) Between Acoustic Features and PIFRsimulated

<table>
<thead>
<tr>
<th></th>
<th>Diskus™</th>
<th>Turbuhaler™</th>
<th>Evohaler™</th>
</tr>
</thead>
<tbody>
<tr>
<td>F25</td>
<td>0.80</td>
<td>0.64</td>
<td>0.41</td>
</tr>
<tr>
<td>F50</td>
<td>0.85</td>
<td>0.58</td>
<td>0.37</td>
</tr>
<tr>
<td>F75</td>
<td>0.84</td>
<td>0.80</td>
<td>0.18</td>
</tr>
<tr>
<td>MP</td>
<td>0.77</td>
<td>0.70</td>
<td>0.75</td>
</tr>
<tr>
<td>MAD</td>
<td>0.59</td>
<td>0.54</td>
<td>0.60</td>
</tr>
<tr>
<td>RMS</td>
<td>0.55</td>
<td>0.56</td>
<td>0.60</td>
</tr>
</tbody>
</table>

$^a$BMI, body mass index; $^b$FEV1, forced expiratory volume in 1 second; $^c$FVC, forced vital capacity; $^d$PEFR, peak expiratory flow rate; $^e$FIVC, forced inspiratory vital capacity; $^f$PIFR, peak inspiratory flow rate.

FIG. 3. PIFRsimulated versus MP for (A) Diskus™, (B) Turbuhaler™, and (C) Evohaler™. The plotted points are calculated PIFRsimulated values based on the regression equation for each participant. The black line represents the overall regression model equation.
level, was employed using Stata SE Version 12 (StataCorp LP, Texas, USA) to correlate the six selected acoustic features separately with PIFR_{simulated}.

To analyze variation in acoustic features, a Coefficient of Variation (CoV) was calculated for all acoustic features at each IFR band for each participant. The CoV values were then averaged across all participants to compute the average CoV of acoustic features. The CoV was calculated as a percentage ratio of the standard deviation ($\sigma$) to the mean ($\mu$) of acoustic features at each IFR band:

$$\text{CoV} = \frac{\sigma}{\mu} \times 100 \% \quad \text{(Eq. 1)}$$

To determine the repeatability of the acoustic spectral profile across all IFRs, Pearson’s linear correlation coefficient was employed to correlate all spectral profiles for all flow rates. This was repeated for all participants.

**Results**

Table 1 presents demographics and baseline lung function of the 11 participants enrolled in this study. All participants had an FEV1/FVC ratio >0.7 and a predicted FEV1 >89%, confirming normal baseline lung function according to ATS standards.

A total of 2150 inhaler inhalation recordings were obtained in this study consisting of 750 (10 inhalations for each IFR band for each participant) recordings from the Diskus™, 730 recordings from the Turbuhaler™, and 670 recordings from the Evohaler™. One participant’s data was discarded from Evohaler™ acoustic analysis because the data were found to be corrupted.

**Correlation between PIFR_{simulated} and acoustic features**

It was found that all acoustic features employed correlated with PIFR_{simulated} ($p<0.001$) at a significance level of $\alpha=0.05$. Table 2 presents the coefficient of determination ($R^2$) values for each acoustic feature for all three inhalers. It was noted that F50 generated the strongest correlation with PIFR_{simulated} for the Diskus ($R^2=0.85$), F75 for the Turbuhaler ($R^2=0.80$), and MP for the Evohaler ($R^2=0.75$). Figure 3 demonstrates the correlation between MP and PIFR_{simulated} for each inhaler. The MP feature was selected to present in Figure 3 as it was observed to generate the highest consistent $R^2$ values across all inhalers.

**Acoustic feature variation**

The results of the CoV analysis for all acoustic features for each inhaler are shown in Figure 4. It was observed that the average CoV of Group A features remained at approximately 20% in the Diskus™ and Turbuhaler™ across the entire IFR range. This level of variation in respiratory sounds compared favorably to previous literature.

It was found that Group A and Group B CoV values for the Evohaler™ were substantially higher below 100 L/min. This is due to minimal acoustic power generated at inhalations below 100 L/min. The average MAD and RMS CoV values tended to increase with flow rate in the Diskus™ and increase at 40–50 L/min in the Turbuhaler™. Notably, MP generated the least CoV within participants across all inhalers.

**Acoustic spectral profile repeatability**

The $R^2$ values from all participants’ data were divided into flow bands to determine the repeatability of the peaks and troughs of the acoustic spectral profile across different flow rates. Figure 5 displays the distribution of $R^2$ values for all participants relating to how all spectral profiles correlate with each other across all flow rates for each inhaler. All $R^2$ values for the Diskus™, Turbuhaler™, and Evohaler™ were statistically significant ($p<0.001$).

An example of the PSD estimates of 10 inhalations from one participant for each inhaler can be found in the Supplementary Figure S1 (supplementary material is available online at www.liebertpub.com/jamp). which illustrates intra-subject spectral profile repeatability. However, the error bars in Figure 5 indicate that the inspiratory acoustic profile of the Evohaler was not as repeatable across the entire IFR range as it is in the Diskus and Turbuhaler. This was due to limited acoustic power at lower flow rates in the Evohaler.
Discussion

All acoustic features employed were observed to be significantly correlated with PIFR_{simulated} \((p < 0.001)\). Mean power was noted to be the most consistent predictor of PIFR_{simulated} across all inhalers. It was observed that mean power generated minimal variation in each inhaler across all inspiratory flow bands compared to other acoustic features, making it a reliable feature for PIFR estimation through inhalers. The Turbuhaler\textsuperscript{TM} generated the highest acoustic power, within the recommended flow rate ranges, followed by the Diskus\textsuperscript{TM} and Evohaler\textsuperscript{TM}. This behavior can be observed in Figure 2. It also emphasizes how the airflow resistance of inhaler devices affects the turbulent energy generated during inhalations. This has a direct impact on the acoustic power of inhalation sounds.

It was also noted that correlations between acoustic features and PIFR_{simulated} were stronger within participants. This may suggest that acoustic features may vary from person to person even when the effects of sex, age, and height are limited. Personalizing future algorithms for PIFR estimation based on acoustic measurements may be more suitable if these methods are to be translated to a wearable device for inhaler users.

Temporal acoustic features (MAD and RMS) generated higher CoV compared to spectral features (F25, F50, F75, and MP), particularly in the Diskus\textsuperscript{TM} and Turbuhaler\textsuperscript{TM}. DPIs require more inspiratory effort to reach the required inspiratory flow rates. This outcome may lead to instantaneous bursts of noise at the mouthpiece or within the oral cavity at higher flow rates and may skew acoustic features even when averaged over multiple inhalations. Therefore, spectral features may be more suitable for PIFR estimation in DPIs.

There was a noticeable difference between the variation of quartile frequency features (Group A) in the Evohaler\textsuperscript{TM} below 100 L/min and above 100 L/min. This is due to limited turbulent airflow existing in the Evohaler at flow rates below 100 L/min. The inhalation sounds were inaudible at lower flow rates, resulting in poor acoustic measurements. This finding highlights the inability of non-contact acoustic methods to objectively measure PIFR below 100 L/min in the Evohaler\textsuperscript{TM}. This is an important finding considering that the recommended flow rate to obtain maximum therapeutic effect from pMDIs is <90 L/min. Hence, non-contact acoustics may not be a suitable method to monitor inhalation technique in pMDIs.

It was demonstrated that the acoustic spectral profile of inhaler inhalation sounds is repeatable regardless of flow rate. This is an interesting finding as it compares favorably to previous studies that characterized normal breath sounds from the trachea and chest wall.\textsuperscript{(9,10)} This information may assist building future feature extraction methods to analyze inspiratory inhaler sounds.

There are a few limitations to this study. First, the study recruited a small number of healthy participants, which limits the generalization of the results. This number of participants is comparable to previous studies in inhaler inhalation acoustics.\textsuperscript{(6)} Also, over 2000 inhalation recordings were obtained in this study and therefore provided sufficient acoustic estimations to present the efficacy of this

FIG. 5. Boxplot displaying 95% confidence interval notches of the median, the 25\textsuperscript{th} and 75\textsuperscript{th} percentile, and the 95\% population (error bars) of \(R^2\) values demonstrating spectral envelope consistency across all IFR bands within each participant in (A) Diskus\textsuperscript{TM}, (B) Turbuhaler\textsuperscript{TM}, and (C) Evohaler\textsuperscript{TM}.
method. Previous studies also recruited healthy participants to characterize respiratory sounds.\(^{(0,15,20)}\) Second, the inhaler recordings were obtained in a soundproof environment that does not relate to realistic acoustic environments. The soundproof environment allowed for the acquisition of inhaler inhalation sounds with minimal background noise.

The INCA device is currently the only acoustic device available for monitoring technique and temporal adherence for DPIs. At present it is designed for the Diskus only, it must be attached to the inhaler, and is limited to an 8 kHz sampling rate.\(^{(4)}\) In order to gain a greater understanding of the acoustic properties of inhaler inhalation sounds, a greater sampling rate was required. In this study, a non-contact high quality microphone was employed to record inhalation sounds proximal to the mouthpiece of the inhalers. The experimental setup aimed to simulate a wearable non-contact acoustic recording device for inhaler users. In this way, there may be no need to design inhaler-specific monitoring devices in future. Activation of new wearable devices may be through proximity sensors on the inhaler rather than relying on the mechanical function of the inhaler to turn on a recording device.

Monitoring inhaler user technique in patients currently relies heavily on subjective checklists from healthcare professionals, quality of life questionnaires, and self-reports from patients regarding their inhaler use.\(^{(21)}\) The clinical significance of this study lies in developing new novel objective methods to monitor inhaler inhalation technique based on non-contact acoustic measurements. Objective monitoring of inhaler user technique, specifically inhalation technique, may improve the clinical efficacy of inhalers. It may also assist healthcare professionals in selecting an appropriate inhaler for patients depending on their PIFR through an inhaler. This may improve overall quality of life for patients using inhalers.

Conclusions

In this study, it was observed that acoustic features were significantly linearly correlated with PIFR. It was found that mean power generated the highest, most consistent correlation with PIFR in the Diskus™ DPI, Turbuhaler™ DPI, and Evohaler™ pMDI. It was reported that mean power also generated minimal variation compared to other acoustic features. The spectral profile of inhaler inhalation sounds was observed to be repeatable regardless of flow rate. These findings may suggest that non-contact acoustic methods may be employed in a wearable device to monitor inhaler PIFR remotely in future clinical applications.

Acknowledgments

This research was part funded by an Irish Research Council (IRC) Enterprise Partnership Scheme (EPS) scholarship to T.E. Taylor and part funded by Vitalograph Ireland (Ltd.), a Higher Education Authority (HEA) Graduate Research Education Program in Engineering (GREP-ENG) scholarship to M.S. Holmes, and a Health Research Board (HRB) Clinician Scientist Award (CSA) grant (Number: 2012/19) to R.W. Costello.

Author Disclosure Statement

The authors declare that no financial conflicts of interest exist.

References

An Acoustic-Based Method to Detect and Quantify the Effect of Exhalation into a Dry Powder Inhaler

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Abstract

Background: Dry powder inhaler (DPI) users frequently exhale into their inhaler mouthpiece before the inhalation step. This error in technique compromises the integrity of the drug and results in poor bronchodilation. This study investigated the effect of four exhalation factors (exhalation flow rate, distance from mouth to inhaler, exhalation duration, and relative air humidity) on dry powder dose delivery. Given that acoustic energy can be related to the factors associated with exhalation sounds, we then aimed to develop a method of identifying and quantifying this critical inhaler technique error using acoustic based methods.

Methods: An in vitro test rig was developed to simulate this critical error. The effect of the four factors on subsequent drug delivery were investigated using multivariate regression models. In a further study we then used an acoustic monitoring device to unobtrusively record the sounds 22 asthmatic patients made whilst using a Diskus™ DPI. Acoustic energy was employed to automatically detect and analyze exhalation events in the audio files.

Results: All exhalation factors had a statistically significant effect on drug delivery (p < 0.05); distance from the inhaler mouthpiece had the largest effect size. Humid air exhalations were found to reduce the fine particle fraction (FPF) compared to dry air. In a dataset of 110 audio files from 22 asthmatic patients, the acoustic method detected exhalations with an accuracy of 89.1%. We were able to classify exhalations occurring 5 cm or less in the direction of the inhaler mouthpiece or recording device with a sensitivity of 72.2% and specificity of 85.7%.

Conclusions: Exhaling into a DPI has a significant detrimental effect. Acoustic based methods can be employed to objectively detect and analyze exhalations during inhaler use, thus providing a method of remotely monitoring inhaler technique and providing personalized inhaler technique feedback.

Key words: acoustics, diskus, dry powder inhalers, exhalation, humidity, signal processing

Introduction

One frequently observed error for dry powder inhalers (DPIs) is that patients exhale into the inhaler mouthpiece after loading the drug.1–4 Exhaling into a DPI mouthpiece can cause medication to become dispersed, leading to a reduced quantity of drug available for pulmonary administration. Engel et al. (1992) first demonstrated this finding, reporting that inhalations that were preceded by exhalations into the Turbuhaler mouthpiece resulted in poor bronchodilation for patients.5 However, this is the only study in the literature that investigated the effect of this critical inhaler technique error, and little is known on how the dry powder formulation is affected. In addition, there currently exists no method to detect this critical error when it occurs during unsupervised inhaler use.

It has been reported that between 14%–22% of patients exhale into their DPI mouthpiece prior to the inhalation step.3,6 A recent study by our research group reported that in unsupervised environments, 16% of subjects exhaled into the Diskus™ inhaler mouthpiece after loading the drug in more than 20% of cases, despite receiving training.7 Exhaling into a DPI mouthpiece can cause medication to clump and stick to the sides of the mouthpiece (Fig. 1). The inability of many

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patients to use their inhaler device correctly may be a direct consequence of insufficient or poor inhaler technique instruction.\(^\text{4}\) In a study on pharmacists’ knowledge of correct DPI user technique, it was reported that the vast majority were unaware of the requirement to exhale away from the device mouthpiece prior to inhalation.\(^\text{2}\) The outcomes of this error in technique include a lack of improvement in respiratory symptoms. This may cause clinicians to prescribe higher doses of medication to patients, who consequently may then suffer from adverse reactions and incur higher medication costs.

The objective of this study was to quantify the effect of exhaling on drug delivery from the Diskus\textsuperscript{\textregistered} DPI. It was hypothesized that the flow rate of the exhalation, distance between mouth and inhaler mouthpiece, exhalation duration and relative air humidity of the exhalation impact the amount of medication available for delivery. Having shown that exhalations prior to the inhalation step may compromise drug delivery, we then set out to develop a method to detect this critical error. An acoustic approach was taken as the acoustic sound associated with an exhalation may convey important information on the expiratory flow rate, distance from mouth to the inhaler and exhalation duration. It was hypothesized that the energy of exhalation sounds would differentiate this important event from other sounds during inhaler use. Providing objective information to clinicians and patients on the effect that exhaling into a DPI has on drug delivery may encourage patients to modify their inhaler technique and improve their clinical outcomes.

**Materials and Methods**

The Methods Section consists of two main parts. The first part focuses on the simulation of exhalations with the \textit{in vitro} test rig, while the second part focuses on the acoustic signal processing of exhalation sounds.

**Impact of exhalation on delivered dose**

To recreate the effect of an exhalation with dry air, a high capacity airflow pump and critical flow controller (air valve) were connected in series to a glass adaptor (mouthpiece) that mimicked the oropharynx (Fig. 2, Path A). A salmeterol/fluticasone 50\,\mu g/250\,\mu g Diskus\textsuperscript{\textregistered} DPI was tested. Relative air humidity was determined using a Testo 410 Humidity Meter (Testo, Hampshire, UK).

Dry air (relative humidity of 28\%) was blown at the inhaler at flow rates of 30, 60, 90, and 120 L/min, for durations of 2, 4, and 6 seconds and at distances of 0, 5, and 10 cm.

**FIG. 1.** Clumping and attachment of salmeterol and fluticasone drug around the mouthpiece of a Diskus\textsuperscript{\textregistered} DPI obtained from a patient who was exhaling into their inhaler over a one-month period.

**FIG. 2.** Experimental setup used to investigate the impact of exhalations on drug delivery in a dry powder inhaler. Air was propelled at various flow rates and durations through variable flow paths. Path A represents dry air at a relative humidity of 28\%, and Path B included a round bottom flask filled with boiled water to bring the humidity of the air to 80\% relative humidity. Finally the distance between the artificial mouthpiece and the inhaler mouthpiece was also varied.
from the inhaler. Each trial was completed three times for all of the conditions specified (36 variations x 3 runs). After each trial, the inhaler was connected to a dosage unit sampling apparatus (DUSA) [Copley Scientific, Nottingham, UK] and the delivered dose was determined. This corresponds with Path A as shown in Figure 2. For humid air (relative humidity of 80%) air travelled on Path B and the above procedure was repeated. The DUSA apparatus was connected to a high capacity vacuum pump (HCP4, Copley Scientific) and Critical Flow Controller (TPK 2000, Copley Scientific). The Flow Controller was operated at 60 L/min at a pressure drop of 4 kPa for a duration of 4 seconds.

Data analysis
Multivariate regression analysis was performed to investigate what exhalation factors had a significant effect on drug delivery. Eta squared and partial eta squared values were calculated to interpret the individual effect size for the four exhalation factors. Eta squared measures the proportion of the total variance in a dependent variable that is accounted for by variation in the independent variable. It is the ratio of the between groups sum of squares to the total sum of squares. Partial eta squared measures the proportion of variance accounted for by an effect to the proportion of variance accounted for by the same effect plus its associated error variance (i.e., the effects of other independent variables and interactions are partialled out). (8, 9)

Dosage uniformity analysis
To validate our in vitro method of removing drug from the Diskus™ DPI, a DUSA was used to determine the delivered-dose uniformity from a salmeterol/fluticasone 50 µg/250 µg Diskus™ DPI (GlaxoSmithKline, London, UK) (US Pharmacopoeia 601). (10) The Diskus™ DPI was not subject to any exhalations. Ten replications were performed. The target dosage uniformity was 9 of 10 results between 75% and 125% and no more than 1 of 10 results between 65% and 135%. (10)

Particle size distribution of emitted dose
Testing was carried out to investigate the effect of humid air exhalations on the particle size distribution of the total emitted dose (TED) for the Diskus™ DPI. To investigate this, the TED and fine particle fraction (FPF) from a Diskus™ that had previously been subjected to an exhalation were compared to TED and FPF obtained from a Diskus™ that was not subject to an exhalation. This testing was carried out using a Next Generation Impactor (NGI) cascade impactor.

Measurement of salmeterol and fluticasone
High performance liquid chromatography (HPLC) analysis was performed using a Waters Alliance Separations module equipped with a temperature programmable auto-sampler and Waters 2996 Photodiode Array (PDA) detector.

### Table 1. Details of High Performance Liquid Chromatographic (HPLC) Techniques Used for Quantification of Fluticasone Propionate and Salmeterol Xinafoate

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Mobile phase (per 1 L)</th>
<th>Flow rate (mL/min)</th>
<th>Column details</th>
<th>Injection volume</th>
<th>Detection wavelength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone Propionate / Salmeterol Xinafoate</td>
<td>500 mL - 50 mM ammonium phosphate pH 2.4, 1 mL - triethylamine, 250 mL - methanol, 250 mL - acetonitrile</td>
<td>1.2</td>
<td>Varian Pursuit XRs C18 3 µm 4.6 x 150 mm,</td>
<td>200 µL</td>
<td>252 nm</td>
</tr>
</tbody>
</table>

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**FIG. 3.** (A) Inhaler audio signal containing exhalation at 3 sec and inhalation at 6–8 sec; (B) average Filter-Bank Energies (FBE) for channels 1–20 (solid) and channels 8–10 (dashed); (C) difference waveform (FBE<sub>8–10</sub> - FBE<sub>1–20</sub>) and adaptive threshold (dashed line), and (D) inhaler audio signal with automatically detected exhalation colored in gray.
HPLC conditions for fluticasone propionate/salmeterol xinafoate are presented in Table 1. Additional details on the HPLC testing can be found in the Supplementary Material.

**Acoustic method of automatically detecting exhalations**

An acoustic recording device, Inhaler Compliance Assessment (INCA™) device, was employed to investigate the acoustic profiles associated with exhalations during DPI use. The recording device is manufactured by Vitalograph Ltd. (11) and has previously been reported as a method to estimate the peak inspiratory flow rate and inspiratory capacity from the sound profile of inhalation during inhaler use. (12) A training database of inhaler audio files was employed to develop an algorithm to automatically detect exhalation events from non-exhalation events in inhaler audio signals.

Filter-Bank Energies (FBEs) obtained from calculation of the Mel Frequency Cepstral Coefficients (MFCCs) were employed as features to detect exhalations in the audio signals in this study. FBEs are physically meaningful quantities that are known to correlate with human auditory processing. (13) Audio events (exhalation and non-exhalation events) were automatically detected using an adaptive energy threshold in this study. Exhalations were segments with higher energy in certain frequency regions compared to other background noises in the audio signals (Fig. 3). The FBEs are computed using steps described in the Supplementary Material.

The training database consisted of 50 audio files obtained from 10 asthmatic patients using a Diskus™ DPI in uncontrolled real world environments. The training database was employed to calculate which specific FBE channels contained the largest amount of energy for exhalations and in the design of the adaptive energy threshold. The validation dataset comprised of a random cross-section of inhaler audio files obtained from 22 separate asthma patients. Similar to the training database, the audio files were obtained in uncontrolled real world environments. Five audio files were randomly selected from each patient to give a total of 110 audio files in the validation dataset.

Two experienced respiratory clinicians independently classified each audio file in the validation dataset using visual and aural methods. The classification of the audio files by the respiratory clinicians was used as the gold standard method of exhalation detection. Exhalation detection performances of the algorithm were compared to that of the gold standard method and calculated using sensitivity, specificity, and accuracy values.

**Acoustic method of assessing exhalations during inhaler use**

A Diskus™ inhaler with an INCA™ device attached was clamped to a stand. Healthy subjects performed subjectively variable exhalations at distances of 0 cm, 5 cm, and 10 cm from the mouthpiece of the inhaler, in locations above, below, and directly at the mouthpiece of the Diskus™ inhaler. Exhalations were also performed with a mouthseal at subjectively variable flow rates. Forty exhalations from three healthy subjects were analyzed (training dataset) to develop an algorithm for determining the distance of the exhalation from the inhaler mouthpiece and the expiratory flow rate of the exhalation. Mean Absolute Deviation (MAD) and acoustic power in a number of frequency regions were used as features to detect a significant exhalation.

Significant exhalations were defined in this study as any exhalation performed at a distance of 0 cm or 5 cm from the inhaler mouthpiece, directly at the inhaler mouthpiece, or any exhalation performed with a mouthseal. Any exhalation directly at the acoustic recording device was also classified as being significant. The sensitivity and specificity of the method in distinguishing between exhalations performed at 0 cm and exhalations performed at 5 cm was also tested. Further details on the features and equations used to detect

**FIG. 4.** Effect of exhalations on delivered dose as percentage of label claim. (A) Salmeterol delivered dose after exhalation with dry air, (B) salmeterol delivered dose after exhalation with humid air, and (C) interaction plot detailing differences between salmeterol delivered dose for different factors. Results for fluticasone were correspondingly similar.
discrete exponential distribution can be found in the Supplementary Material.

To test the robustness of the algorithm in classifying exhalations, a validation dataset of fifty exhalations from four healthy subjects was acquired. Classification results were compared with documented conditions for the exhalations in the validation dataset to obtain sensitivity and specificity values of the method in determining significantly detrimental exhalations.

**Results**

**Impact of exhalation on delivered dose**

It was found from multivariate regression analysis that all four exhalation factors had a statistically significant effect on both salmeterol and fluticasone drug delivery ($p < 0.05$, significance level $z = 0.05$). From the multivariate regression model, the adjusted R-squared values were 62.67% for salmeterol and 63.4% for fluticasone. Figure 4 details the total percentage of salmeterol delivered as a percentage of the Diskus™ inhaler manufacturer’s claim (nominal dose). A correspondingly similar percentage of fluticasone was also delivered. A scatterplot matrix is also presented to illustrate the difference due to relative air humidity levels.

Exhalations had an overall negative effect on drug delivery. At a distance of 0 cm from the inhaler mouthpiece, less than 50% of drug available is delivered on average for all flow rates using humid air (relative air humidity = 80%). In the worst case scenario, an average of 2.44% of drug is delivered from the Diskus™ DPI when the preceding exhalation is at an expiratory flow rate of 120 L/min and 0 cm from the inhaler mouthpiece (Fig. 4B). Delivered dose was more consistent when dry air was used, but more variable and unpredictable when humid air was used. It was observed that less drug is delivered on average when humid air is used in comparison to dry air (Fig. 4C).

To investigate the effects of each of the four factors on drug delivery, measures of effect size (eta-squared and partial eta-squared) were obtained from the multivariate regression model for each independent variable (Table 2 and Table 3). Results established that distance from the inhaler mouthpiece was the single most influential factor in reducing the percentage of drug delivery from a DPI. Exhalation flow rate and air humidity level were the next most influential factors with similar effect sizes. Although its effect was statistically significant, exhalation duration was the least influential factor in determining drug delivery for the multivariate regression model.

**Dosage uniformity analysis**

The dosage uniformity analysis on the Diskus™ DPI demonstrated that the dose delivered from the Diskus™ was uniform and repeatable. None of the 10 test results fell between 75%–125%, and 1 of the 10 test results was between 65%–135% of the delivered dose label claim, in accordance with US Pharmacopoeial standards. Full results for this testing can be found in the Supplementary Material.

**Particle size distribution of emitted dose**

An NGI cascade impactor was employed to investigate the effect that exhaling into a DPI has on particle distribution. Diskus™ DPIs that had been subject to an exhalation using humid air at a flow rate of 60 L/min, a distance of 5 cm from the mouthpiece and for a duration of 4 seconds, were compared to Diskus™ DPIs that were not subject to exhalations. It was found that there were no differences in the total emitted doses but that the FPF was significantly reduced for inhaler devices subjected to an exhalation. This result demonstrates that exhaled air humidity most probably cause particles to clump together and has a detrimental effect on particle size distribution. Results for this are displayed in Figure 5. Detailed results for particle size distribution can be found in the Supplementary Material.

**Acoustic method of automatically detecting exhalations**

Cohen’s kappa statistic ($K$) was calculated to measure the level of agreement between the two respiratory clinicians who manually classified the presence of exhalation events in each audio file in the validation dataset. $K$ was 1, indicating perfect agreement between the two raters. Using the FBE feature to detect exhalations automatically, performance was evaluated on the 120 audio files from 22 patients in the validation dataset. The overall detection rate (accuracy) on the 22 patients in the validation dataset was found to be 89.1% compared to the gold standard method of classification. Sensitivity (detecting

---

**Table 2. Effect Size for Each of Four Factors on Drug Delivery for Salmeterol**

<table>
<thead>
<tr>
<th>Variable</th>
<th>P &gt;</th>
<th>$\eta^2$</th>
<th>% Change in $\eta^2$</th>
<th>Partial $\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhalation flow rate</td>
<td>0.000</td>
<td>0.1223</td>
<td>18.8898</td>
<td>0.2577</td>
</tr>
<tr>
<td>Distance</td>
<td>0.000</td>
<td>0.3578</td>
<td>55.2553</td>
<td>0.5039</td>
</tr>
<tr>
<td>Duration</td>
<td>0.006</td>
<td>0.0420</td>
<td>6.49827</td>
<td>0.1067</td>
</tr>
<tr>
<td>Air humidity</td>
<td>0.000</td>
<td>0.1253</td>
<td>19.3564</td>
<td>0.2624</td>
</tr>
</tbody>
</table>

---

**Table 3. Effect Size for Each of Four Factors on Drug Delivery for Fluticasone**

<table>
<thead>
<tr>
<th>Variable</th>
<th>P &gt;</th>
<th>$\eta^2$</th>
<th>% Change in $\eta^2$</th>
<th>Partial $\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhalation flow rate</td>
<td>0.000</td>
<td>0.1160</td>
<td>17.7232</td>
<td>0.2514</td>
</tr>
<tr>
<td>Distance</td>
<td>0.000</td>
<td>0.3719</td>
<td>56.8191</td>
<td>0.5185</td>
</tr>
<tr>
<td>Duration</td>
<td>0.006</td>
<td>0.0420</td>
<td>6.4255</td>
<td>0.1085</td>
</tr>
<tr>
<td>Air humidity</td>
<td>0.000</td>
<td>0.1245</td>
<td>19.0320</td>
<td>0.2651</td>
</tr>
</tbody>
</table>
exhalations as exhalations) was 82.2%, and specificity (detecting noise as noise) was 91.6% compared to the gold standard method. \( K \) was also calculated to compare the level of agreement between the proposed algorithm and the gold standard method of classification. Taking the classification of the algorithm as one output and the classification of respiratory clinicians as the gold standard output, \( K \) was 0.6638, indicating substantial agreement between the two classification methods.

**Acoustic method of assessing exhalations during inhaler use**

Exhalations occurring at a distance of 5 cm or less, into the DPI mouthpiece or directly at the INCA \(^\text{TM} \) device were classified as significant. This was chosen because the distance to the inhaler mouthpiece was the single most influential factor in impacting drug delivery from the in vitro testing. It was found that the threshold developed to classify a significant exhalation had a sensitivity of 72.22% and a specificity of 85.71% when tested on the validation dataset. Results for detecting exhalations at 0 cm or a mouthseal and exhalations at 5 cm are presented in Table 4.

**Discussion**

Several commentators have argued that exhaling into a DPI prior to inhalation has a detrimental impact on the dose available for pulmonary delivery.\(^{1-5}\) There are very few studies that have been carried out to clearly delineate and quantify the impact of this effect; nonetheless, exhalation into a DPI has been widely reported as a critical error in the assessment of inhaler technique.

Results showed that exhalation into the Diskus \(^\text{TM} \) DPI had a significant effect on the subsequent delivered dose and that the main determining factors were distance of the exhalation from the DPI mouthpiece, flow rate of exhalation, and humidity of exhaled air. The most important of these was distance of the exhalation from the mouthpiece. The duration of the exhalation had a negligible effect on drug dispersal, even though it was a statistically significant variable in our regression model. On average, more than 50% of salmeterol and fluticasone were dispersed from the DPI after exhalation from a distance of 0 cm using humid air. At 10 cm, less than 25% of drug was found to be lost.

Results demonstrated that the relationship between flow rate, distance, and duration of exhalation using humidified air is less predictable than that using dry air. Drug agglomeration provides a plausible explanation for these results. Particles that have clumped together may either remain inside the DPI or be emitted as a large mass; this accounts for the greater variability in total delivered dose seen with humidified air. To clarify the effect of air humidity, experiments were performed using an NGI. Results from this test indicated that even though the TED may remain constant after an exhalation with humid air, the fine particle fraction is almost halved, meaning that the majority of the TED may be deposited in the upper airways.

In the second part of this study, an acoustic monitoring device was employed to record the audio signals of patients using a Diskus \(^\text{TM} \) DPI. An algorithm was developed to automatically detect exhalations prior to inhalations. The exhalation detection algorithm was successful in detecting exhalations in unsupervised real world inhaler audio signals in comparison to expert raters. Its overall accuracy was demonstrated to be 89.2% in detecting exhalations events from non-exhalation events, while its corresponding sensitivity and specificity values were also

**Table 4. Assessing Significance and Location of Exhalations During Inhaler Use**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant exhalation</td>
<td>72.22</td>
<td>85.71</td>
<td>92.86</td>
<td>54.55</td>
</tr>
<tr>
<td>Exhalation at 0 cm/mouthseal</td>
<td>88.89</td>
<td>70.73</td>
<td>40.00</td>
<td>96.67</td>
</tr>
<tr>
<td>Exhalation at 5 cm</td>
<td>81.25</td>
<td>88.24</td>
<td>76.47</td>
<td>90.91</td>
</tr>
</tbody>
</table>

**FIG. 5.** Analysis of particle size distribution of salmeterol and fluticasone from Diskus \(^\text{TM} \) dry powder inhaler as obtained from a Next Generation Impactor (NGI). (A) Total drug recovered from all sections of the NGI and (B) Fine Particle Fraction (FPF) drug recovered demonstrating a reduction due to exhalations.
high. These results are encouraging if such an algorithm is to be used longitudinally to automatically detect the critical error of exhaling into a DPI.

Furthermore, our calculations based on acoustic power in various frequency bands and MAD of the amplitude was found to be very sensitive and specific for detecting significant exhalations and for differentiation of an exhalation at 0 cm from one at 5 cm. Our in vitro studies clearly showed that distance was the single most important factor accounting for drug dispersal or loss from the DPI. The acoustic based method is therefore a suitable means of not only automatically detecting exhalations but of objectively quantifying the impact of these exhalations on drug delivery.

A shortcoming of this study is that we were limited by the in vitro design. The individual variability in inhaler user technique and the confounding factors of physiological variation, inhalation flow rate, volume, and additional errors mean that the impact of exhalations is difficult to measure accurately in an in vivo clinical study. The acoustic features employed to detect and quantify exhalations during inhaler use were developed using normal breath sounds only. Adventitious breath sounds such as crackles, wheezes, and rhonchi may affect the accuracy of our acoustic based method.

Clearly results indicate that exhaling into a DPI has a negative effect. This critical error needs to be addressed by designers of DPIs as its impact on drug delivery is paramount. Future DPIs need to have a system in place to prevent users from exhaling into the mouthpiece or instructions for inhaler use need to be modified to ensure that inhaler users are told exhale prior to releasing the drug, instead of after as is the current practice.

The current gold standard in assessing inhaler user technique is the checklist method. This method is fraught with limitations; it is very subjective and it cannot be used to monitor patients longitudinally. There is also a significant Hawthorne effect where patients change their behavior because they know they are being assessed. Acoustic analysis of both the inhalation and any critical errors associated with inhaler use, can be used to quantify, in a more objective manner, drug delivery and any critical errors associated with inhaler use, can be detected using normal breath sounds only. Adventitious breath sounds such as crackles, wheezes, and rhonchi may affect the accuracy of our acoustic based method.

The current gold standard in assessing inhaler user technique is the checklist method. This method is fraught with limitations; it is very subjective and it cannot be used to monitor patients longitudinally. There is also a significant Hawthorne effect where patients change their behavior because they know they are being assessed. Acoustic analysis of both the inhalation and any critical errors associated with inhaler use, can be used to quantify, in a more objective manner, drug delivery from dry powder inhalers. Such data can be used to provide clinicians and patients with strong objective evidence on how inhalers are truly being used for the first time.

Acknowledgments

This research was funded by a Higher Education Authority (HEA) Graduate Research Education Program in Engineering (GREP-ENG) scholarship to MSH. A Health Research Board (HRB) grant (number: 2011 219) and a Engineering (GREP-ENG) scholarship to MSH. A Health Authority (HEA) Graduate Research Education Program in research. Human Commun Res. 2002;28:612–625.

References

Acoustic Analysis of Inhaler Sounds from Community-Dwelling Asthmatic Patients for Automatic Assessment of Adherence

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The work of M. S. Holmes was supported by a Higher Education Authority Graduate Research Education Program in Engineering scholarship. The work of R. W. Costello was supported by a Health Research Board under Grant 2011 219. The work of R. B. Reilly was supported by an Enterprise Ireland under Grant CFD/05/205.

ABSTRACT

Inhalers are devices which deliver medication to the airways in the treatment of chronic respiratory diseases. When used correctly inhalers relieve and improve patients’ symptoms. However, adherence to inhaler medication has been demonstrated to be poor, leading to reduced clinical outcomes, wasted medication, and higher healthcare costs. There is a clinical need for a system that can accurately monitor inhaler adherence as currently no method exists to evaluate how patients use their inhalers between clinic visits. This paper presents a method of automatically evaluating inhaler adherence through acoustic analysis of inhaler sounds. An acoustic monitoring device was employed to record the sounds patients produce while using a Diskus dry powder inhaler, in addition to the time and date patients use the inhaler. An algorithm was designed and developed to automatically detect inhaler events from the audio signals and provide feedback regarding patient adherence. The algorithm was evaluated on 407 audio files obtained from 12 community dwelling asthmatic patients. Results of the automatic classification were compared against two expert human raters. For patient data for whom the human raters Cohen’s kappa agreement score was >0.81, results indicated that the algorithm’s accuracy was 83% in determining the correct inhaler technique score compared with the raters. This paper has several clinical implications as it demonstrates the feasibility of using acoustics to objectively monitor patient inhaler adherence and provide real-time personalized medical care for a chronic respiratory illness.

INDEX TERMS

Acoustics, adherence, algorithm, chronic respiratory diseases, inhaler.

I. INTRODUCTION

Respiratory tract diseases are those which affect the airways. Two of the most well-known chronic respiratory diseases are asthma and chronic obstructive pulmonary disease (COPD). Over 235 million people currently suffer from asthma worldwide, and it is the most common chronic disease amongst children [1]. It is estimated that 600 million people suffer some form of COPD, while nearly 3 million people die annually from this disease [2]. Although chronic respiratory diseases such as asthma and COPD are incurable, if treated with the correct medication, they can be controlled [3], [4].

Inhalers are the devices employed to deliver medication to the airways in the treatment of asthma and COPD. They are compact, portable, hand-held devices that contain medication and deliver it in exact doses so that it can be inhaled into the airways. Two types of inhalers commonly employed are metered dose inhalers (MDIs) and dry powder inhalers (DPIs). DPIs are considered advantageous over MDIs since they avoid the use of propellants, and are instead actuated during the inhalation maneuver [5]. The elimination of propellants allows patient coordination issues between the drug release and inhalation to be overcome. When used correctly, inhalers (both MDIs and DPIs) have been shown to greatly...
Nonadherence to inhaler medication is currently a major problem. For inhaled medication, adherence involves both using the inhaler at the correct time of day (temporal adherence) and in the correct manner (technique adherence). Rates of nonadherence among patients suffering from asthma alone range from 30% to 70% [8]. It is estimated that $300 billion is spent annually in the US treating the nonadherence of chronic diseases, with asthma and COPD amongst the diseases with the highest nonadherence rates [9]. Poor inhaler adherence arises from non-use, haphazard use, excessive use or poor inhaler technique. Temporal adherence is rooted in patient perceptions of the disease, belief in the medication, medication cost and access to healthcare [6], [10], while technique adherence is related to errors in dexterity or a lack of instruction [11]. Several studies have highlighted that errors in inhaler technique may be as detrimental as a lack of temporal adherence [12], [13]. Regardless of the causes of poor adherence, the consequences are similar and include poor clinical outcomes, wasted medications, higher healthcare costs, increased morbidity, and higher mortality rates [14]–[17].

Currently there is no method for reliably monitoring patient inhaler adherence outside clinic visits in community dwelling patients. Clinicians have no objective information on how a patient uses their inhaler in-between visits to the clinic. This is a problem that needs to be acknowledged and addressed. To resolve this problem a device that can monitor patients temporal and technique adherence was developed (previously described in [18] and [19]). The inhaler compliance assessment (INCA\textsuperscript{TM}) device can be attached to the side of the widely used Diskus\textsuperscript{TM} DPI, from where it unobtrusively records the audio signal of patients using their inhaler in uncontrolled real life environments. Ambient (non-contact) microphone technology has recently been reported as a method of successfully detecting snore sounds during sleep [20]. With the aid of ambient microphone recordings, the acoustic profile of the different stages required to achieve successful inhaler drug delivery can be identified. An example of the audio signal obtained from the INCA\textsuperscript{TM} device and its corresponding spectrogram for Diskus\textsuperscript{TM} inhaler use are displayed in Fig. 1. In addition to recording the audio signal of inhaler use, the INCA\textsuperscript{TM} device logs the exact time and date that the inhaler was used. This provides a method of analyzing patients’ temporal adherence to their medication. Visual and aural analysis of the audio files can provide information regarding a patient’s inhaler technique and thus their technique adherence. However, manual analysis of the audio files obtained from the INCA\textsuperscript{TM} device is a tedious and time consuming process. It takes an experienced respiratory clinician 30 minutes on average to analyze a patient’s audio files for one month of typical Diskus\textsuperscript{TM} inhaler use (60 audio files corresponding with 60 doses of medication).

This type of labor intensive analysis would not be feasible in a large scale study. The analysis of patients’ inhaler technique from audio signals may also be biased by the subjectivity of clinicians. Therefore an algorithm that could automatically analyze inhaler audio recordings and provide objective feedback on patient inhaler adherence would be of great clinical benefit.

The INCA\textsuperscript{TM} device is capable of detecting important critical inhaler technique errors associated with Diskus\textsuperscript{TM} inhaler use. Critical inhaler errors occur as a result of imperfect patient technique or lack of knowledge on correct usage and significantly impact the delivery of adequate medication [12]. Some of the critical errors associated with Diskus\textsuperscript{TM} inhaler use have been identified as: failure to open the inhaler device until the mouthpiece fully appears, failure to prime/blister drug foil before inhalation, failure to exhale fully before inhalation, exhalation into the inhaler before inhalation and insufficient force behind inhalation maneuver [12], [21]. Given the critical errors observed in Diskus\textsuperscript{TM} DPI use, the main inhaler steps to be identified by an algorithm are breaths (inhalations and exhalations) and the priming/blistering of the drug foil (henceforth referred to as blister).

The primary objective of this study was to design and develop an algorithm that could automatically analyze patient inhaler use, in order to evaluate adherence. A patient’s temporal adherence to their inhaler medication can be analyzed from the time and date stamp of each audio file. Users of the Diskus\textsuperscript{TM} DPI are generally required to take two doses
of medication each day, one dose in the morning, followed by a second dose in a 6–18 hour interval after the preceding dose. It was hypothesized that technique adherence can be analyzed through the detection of the breath and blister events in the audio signal, the number of each event present and the order in which the events take place. The algorithm should be able to detect the critical errors associated with Diskus™ inhaler use and provide a score on patient technique adherence. This information on inhaler use should also be compiled into an easy to understand and accessible format for both the clinician and patient. Such objective data on inhaler use can provide comprehensive information on patient inhaler use in-between clinic visits for clinicians, as well as acting as an educational aid for patients. Detailed constructive feedback from clinicians on inhaler use may encourage patients to take better control of their adherence, which in turn may improve their quality of life, prevent exacerbations and hospitalizations, and ultimately reduce mortality rates associated with chronic respiratory diseases.

II. METHODS

A. ACOUSTIC RECORDING DEVICE

An INCA™ device, manufactured by Vitalograph Ltd. [22], was employed in this study. The INCA™ device enables the acoustics of inhaler use to be recorded for analysis. The INCA™ device contains a microphone, microcontroller and battery. The microphone is a Knowles Acoustics SPM0204HE5 mini surface mount silicon microphone. The audio files are stored on the INCA™ device from where they can be subsequently uploaded to a computer via a USB connection.

The INCA™ device can be used in conjunction with the common Diskus™ inhaler. The INCA™ device can be bonded securely to the side of the Diskus™ inhaler, from where it does not impact on the mechanics of inhaler use. The INCA™ device starts recording once the Diskus™ inhaler is opened and switches off when the Diskus™ is closed. The acoustics of inhaler use are recorded as mono WAV files, at a sampling rate of 8000 Hz and resolution of 8 bits/sample. The INCA™ device has sufficient battery life to record patient inhaler use for a period of one month.

B. STUDY BACKGROUND AND INSTRUMENTATION

To validate the performance of the algorithm data was recorded from 12 community dwelling asthmatic patients (6 female & 6 male). The age range of recruited patients was 20–83 (mean 49 ± 18) years old. All patients had previous experience using the Diskus™ DPI. It was communicated to patients before they began the study that an acoustic recording device that could monitor their temporal and technique adherence would be attached to their Diskus™ inhaler. The Diskus™ used in this study contained the combination drug Seretide™, which is comprised of both salmeterol and fluticasone propionate. In each inhaler there were 60 doses of the Seretide™ drug.

Each patient was given an INCA™ equipped Diskus™ inhaler by their clinician for a period of one month. Patients were instructed to use their inhaler as normal and they were not given any extra advice or special training. After using their INCA™ enabled inhaler for one month the patients returned to their clinic, where the INCA™ device was removed from the inhaler and the audio files were uploaded to a database for analysis.

C. CORRECT DISKUS INHALER USE

The Diskus™ inhaler was originally designed to facilitate easy use and patient acceptability [23]. When patients are given a Diskus™ inhaler they are instructed on how to use the inhaler device correctly by their clinician. In this study patients were instructed to use their inhaler twice daily. As there were 60 doses in each inhaler, this corresponds with 30 days of correct usage. The Diskus™ is opened by sliding a thumbgrip to expose the mouthpiece (see Fig. 2). When this occurs the INCA™ device switches on and begins to record audio. A lever is then pushed back which opens a blister foil containing medication inside in the mouthpiece (blister event). A sharp click noise indicates that the blister foil was pierced and that there is medication available in the mouthpiece for inhalation. The patient is then instructed to exhale gently away from the mouthpiece, taking care not to exhale into the mouthpiece. They should then seal their lips tightly around the mouthpiece, inhale steadily and deeply and hold their breath for 10 seconds. The patient should then exhale slowly after the 10 seconds. Once this is complete the patient should use the thumbgrip again to slide the Diskus™ back to its original position. When the Diskus™ is fully closed the INCA™ device will switch off and save the audio file to its internal memory storage.

D. TECHNIQUE ADHERENCE ALGORITHM DESIGN

The algorithm designed to detect the common inhaler events initially went through a training phase. The 12 patients recruited in this study provided 609 audio files in total. Each of these audio files represented a unique record of inhaler use. There was a great quantity of variation between subjects (inter-subject variability) and also within subjects.

![FIGURE 2. To open a closed Diskus™ DPI (a) slide thumb grip in direction of dashed arrow until mouthpiece is fully exposed as seen in (b). INCA™ device attaches onto Diskus™ inhaler to record audio signal of inhaler use.](image-url)
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Differences in acoustic features (intra-subject variability) in terms of environment and subject technique. 202 (33% of total files available) audio files were randomly selected and employed in the training phase of the algorithm. The inhaler events to be detected specifically from the audio recordings are blisters and breaths (both inhalations and exhalations). To detect the blister events, features such as the mean power at select frequency bands, amplitude and duration are computed. A mel frequency cepstral coefficient (MFCC) approach was employed to detect breaths in this study, due to the fact that breaths have a characteristic MFCC pattern that allows them to be distinguished from other sounds [24]. Extracting MFCCs is a common parameterization method for vocalization, due to the fact that MFCCs model the known variation of the human ears critical bandwidth with frequency. An overview of the steps the algorithm takes to analyze the inhaler recordings is shown in a block diagram in Fig. 3.

**FIGURE 3.** Block diagram of the basic steps the algorithm takes to analyze inhaler recordings.

Several studies have previously described algorithm’s that were developed to detect breaths in speech and song signals [24] and in respiratory volume signals [25]–[27]. Acoustic analysis of breathing has also previously been employed to detect the different phases (inspiration/expiration) of breaths [28]–[31]. This study differs from previous acoustic based studies in that the acoustic signal was obtained in uncontrolled environments. Breath events occurring during inhaler use are also significantly different to those obtained during breathing.

The algorithm was developed to automatically examine each audio file in four stages. The algorithm firstly identifies the piercing of the blister containing the drug (Stage 1), before identifying breath sounds (Stage 2). It then differentiates detected breath sounds as either inhalations or exhalations (Stage 3). Lastly the algorithm calculates a score of user technique (Stage 4) for each individual audio file. A detailed explanation of each stage of the algorithm and how the technique adherence algorithm was designed will now be given.

1) **STAGE 1: BLISTER DETECTION**

The first stage of the algorithm involves detecting the piercing of the blister foil containing the medication. The audio signal is segmented into frames of length 100ms, with an overlap of 10ms. The mean power spectral density (PSD) is calculated for frequencies between 2–3 kHz. For this frequency band it was found from empirical observations in the training dataset that blister sounds had a mean power greater than −65 dB. The reason the power in this frequency band was greater for blisters compared to nonblisters is due to the intrinsic sound associated with the blistering of the drug foil in the Diskus™ inhaler. A fixed threshold (θ₁) was set and any frames greater than the −65 dB threshold are considered as potential blister sounds. The algorithm then examines the proposed blister sounds to remove false positives. Potential blister sounds with maximum normalized amplitude less than 0.7 (θ₂) are removed, in addition to potential blister sounds greater than one second (θ₃) in duration. Finally the mean PSD in the 20Hz–200Hz frequency band is calculated. It was found from the training dataset that blisters had a mean power greater than any false positives in this frequency range, due to the distinctive sound of a blister. Any potential blisters with a power less than −62dB (θ₄) are considered as false positives and removed. The selected thresholds were set as they gave the highest percentage of true positive blister events in the training dataset. A flow chart of the steps employed to detect blister events is displayed in Fig. 4.

2) **STAGE 2: BREATH DETECTION**

Stage 2 of the algorithm involves detecting breath sounds. The audio signal is first filtered to remove high frequency
components above 1400Hz using a low-pass type I 6th order Chebyshev filter. Each signal is separated into frames of length 700ms with an overlap of 20ms. Twelve MFCCs are calculated for each frame, forming a short-time cepstrogram of the signal. Singular value decomposition (SVD) is then employed to obtain a normalized singular vector from the cepstrogram of the signal. Singular vectors have been reported to capture the most important characteristics of breath sounds obtained from MFCC calculations [24]. An adaptive threshold (θb) is set that is 7% higher than the lowest singular vector in the inhaler recording. Singular vectors above this adaptive threshold are marked as potential breath events. This adaptive threshold was found empirically to produce the most accurate detection of breaths in the training dataset. The mean zero crossing rate (ZCR) is then computed to reduce the number of false positive breaths detected by the algorithm.

Breaths were found to have a characteristically high ZCR compared to that of nonbreaths in the training dataset. A fixed threshold (θb) constant of 0.1 was therefore introduced to reflect this fact. In the training dataset, breaths consistently had a ZCR above this threshold value, while false positives were successfully removed. A flow chart of the steps employed to detect breath events can be seen in Fig. 5.

3) STAGE 3: INHALATION/EXHALATION DIFFERENTIATION
Stage 3 involves differentiating breaths into inhalations and exhalations. To do this the mean PSD of identified breaths is calculated for frequencies between 2.52–4 kHz in the original unfiltered signal. It was found from empirical observations in the training dataset that inhalations had a greater power in this specific frequency band compared to exhalations. Based on this fact a fixed threshold (θs) was put in place. Inhalations were found to have a mean power greater than −80dB in the training dataset and exhalations were found to have a mean power below this value. The standard deviation of the ZCR was also found to be higher for inhalations in comparison to exhalations in the training dataset. A fixed threshold (θb) of 0.045 was put in place with inhalations having a value greater than this threshold and exhalations a value below this threshold. A flow chart of the processing steps the algorithm employed to differentiate inhalations and exhalations is displayed in Fig. 6.

4) STAGE 4: USER TECHNIQUE SCORE DECISION
The last stage of the algorithm (Stage 4) is to analyze all of the events which took place in the audio file and make a decision regarding the quality of a patient’s inhaler technique. This information is outputted as a score which can be one of three possibilities; (1) used correctly, (2) technique error or (3) not used. To decide a technique score the algorithm checks to see what events have taken place, the frequency of each type of inhaler event and the order in which these events have taken place (Fig. 7).

The Diskus™ inhaler is deemed to have been used correctly if a patient first blisters the foil and secondly inhales the medication. Exhalations can take place before the blister or after the inhalation, still leading to a ‘used correctly’ score from the algorithm. However, if the patient exhales in the time between the blister and inhalation then they are judged to have committed a ‘technique error’ as they may have exhaled into the mouthpiece of the inhaler and dispersed some of the medication. Such a scenario is viewed as a critical error. Although instructions for Diskus™ inhaler use specify that patients should exhale between the blister and inhalation steps, this should be in a direction away from the mouthpiece.

FIGURE 5. Flow chart of algorithm employed to detect breath events.

FIGURE 6. Flow chart of algorithm employed to differentiate breaths into either inhalations or exhalations.

FIGURE 7. Flow chart demonstrating how algorithm decides inhaler technique score for each audio file.
Such exhalations will not be detected by the algorithm, however, those in the direction of the mouthpiece will be detected and classified as errors in inhaler technique. Any other sequence of inhaler events is deemed to be a technique error. For example: An inhalation event followed by a blister event, a blister event but no inhalation present, exhalation event but no inhalation event etc. If the algorithm detects multiple inhalations or multiple blisters then a technique error will also be judged to have taken place.

E. TECHNIQUE ADHERENCE ALGORITHM VALIDATION

To test the algorithm’s performance 407 new audio files were selected from the 12 asthmatic patients recruited in this study (67% of total audio files obtained). Two human raters, trained by an experienced respiratory clinician to identify correct/incorrect Diskus™ inhaler use, independently classified each of the 407 audio files using the audio tool Audacity®. Each human rater manually examined the audio files using visual and aural methods and scored each individual audio file as one of the three possible outcomes: (1) used correctly, (2) technique error or (3) not used.

F. TEMPORAL ADHERENCE ANALYSIS

As previously mentioned the INCA™ device also provides information regarding the exact time and date that the Diskus™ DPI was employed. Using this data the algorithm automatically computed the number of doses that were taken each day and represented this information in bar chart format. Audio files less than one second in duration are discarded for this analysis due to the fact that this is not a sufficient time period to use the inhaler adequately.

III. RESULTS

The algorithm designed in this study aimed to detect blister, inhalation and exhalation events, analyze the frequency of each event, in addition to the order they took place and output a score on user technique each time the inhaler was employed. The patient user technique score for each inhaler audio file, as computed by the algorithm, was designed to be stored in a text file. However, for the purposes of presenting the specific user technique score to both clinicians and patients, it was decided that a more interpretable output would be needed. Previous research has suggested that people perceive visual cues most accurately from information positioned along a common scale [32]. Based on this information the best method of visualizing data is with the use of scatterplots and bar charts [33]. Bar charts and scatterplot graphs were thus used to display adherence data to clinicians and patients. The algorithm analyzed the time and date stamps from the INCA™ device in order to generate feedback on a patient’s temporal adherence. Fig. 8 presents a bar chart output from the algorithm that can be employed to illustrate patient temporal adherence. In this bar chart graph one can observe if a patient overdoses, underdoses or takes the correct amount of doses of their medication (red dashed line) for each single day that they should be using their inhaler.

Colors are also widely used in data visualization to indicate appropriate levels of risk (i.e. green=safe, red=danger). A traffic light scatterplot was created to display the algorithms score on technique adherence. An example of such a graph is displayed in Fig. 9. This output graph displays information on the time and date the inhaler was used, in addition to how the inhaler was used. The color green indicates that the inhaler was used correctly while the color orange indicates that there was a technique error. This allows clinicians to examine a patient’s adherence to their inhaler medication, while it also provides a method for patients to easily understand when and how they are using their inhaler.

To assess the performance of the algorithm, one month’s data from 12 community dwelling asthma patients using their inhalers in real world environments was analyzed. The validation dataset consisted of 407 audio files in total (mean 34 ± 11 per patient). Each file was scored as either (1) used correctly, (2) technique error or (3) not used, by two trained independent human raters. Cohen’s kappa statistic is a measure of intrarater agreement and takes into account the prior probability of a specific class occurring [34]. The overall kappa agreement (Cohen’s Kappa Statistic) between Rater 1 and Rater 2 was found to be 0.58, indicating moderate agreement between the two human raters. Patients were divided
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into two subgroups based on the kappa agreement scores between the human raters; Group A consisted of patients for whom the raters had almost perfect agreement (kappa > 0.81) and Group B consisted of patients for whom the kappa agreement was below this score (kappa < 0.81). For Group A (n=8), the overall accuracy of the algorithm in deciding the correct user technique score compared to the human raters was found to be 83%. For Group B (n=4), the algorithms accuracy compared to the human raters was found to be 58%. The accuracy of the algorithm in deciding the correct user technique score in comparison to the human raters for each of the eight patients in Group A is displayed in Fig. 10. Table 1 details the classification performances of the algorithm, in comparison to the human raters, for the various types of inhaler technique scores in Group A. Table 2 demonstrates the classification performance of the algorithm in detecting blister, inhalation and exhalation events for Group A in comparison to the human raters. A Cohen’s kappa statistic was calculated to compare the agreement between the algorithm and the expert human raters. For this measure of system performance the algorithm was designated as one rater and one of the expert human raters was randomly selected as the other rater. The user technique score between the two classification approaches was investigated for Group A and it was found that the kappa agreement statistic was 0.49. This indicates moderate agreement between the two classification methods employed in this study.

TABLE 1. Algorithm accuracy compared to human raters in correctly deciding inhaler technique score for each audio file from Group A.

<table>
<thead>
<tr>
<th>Inhaler Technique Score</th>
<th>Files Correctly Classified by Algorithm</th>
<th>Total Number of Audio Files</th>
<th>Algorithm Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used Correctly</td>
<td>124</td>
<td>150</td>
<td>83</td>
</tr>
<tr>
<td>Technique Error</td>
<td>54</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td>Not Used</td>
<td>15</td>
<td>27</td>
<td>56</td>
</tr>
</tbody>
</table>

IV. DISCUSSION

This study presents a method of automatically analyzing patient inhaler adherence through the use of acoustics. This is the first known method of automatically analyzing both the temporal and technique adherence of a patient to their inhaler medication. The algorithm was designed to identify the critical steps associated with Diskus™ inhaler use and the operations that lead to critical errors in user technique. For the patients that the two human raters had almost perfect agreement upon (Kappa > 0.81) the algorithms accuracy was 83% in deciding the correct user technique score. When the algorithm was taken as one rater and the human raters as another rater, the kappa agreement statistic was found to be 0.49, indicating moderate agreement between the two classification techniques. This is an encouraging initial result if this algorithm is to be used in a fully automated system that actively evaluates patient inhaler adherence.

The gold standard used to evaluate the algorithm in this study was the subjective classification of inhaler audio files by two independent human raters. These raters were trained by an experienced respiratory clinician to assess the Diskus™ inhaler audio files and classify user technique. Overall the two raters agreed with each other at a moderate level (Kappa = 0.58). The fact that the agreement between the human raters, who independently classified the dataset, was moderate demonstrates the subjective nature of analyzing patient inhaler user technique. The identification of common Diskus™ inhaler events from acoustic signals, namely blisters, inhalations and exhalations, can be challenging. Often times it can be difficult to distinguish blister events as they can have similar characteristics to other background artifacts in the audio signal. The human raters also found it problematic to differentiate inhalations from exhalations when using visual and aural analysis methods. It was for these reasons that patients were subsequently divided into two subgroups for analysis, Group A (kappa > 0.81) and Group B (kappa < 0.81). For Group A, the algorithm was able to correctly identify blister, inhalation and exhalation events with an accuracy greater than 90%.

Given the level of disagreement between the two human raters, it is clear that a better method of classifying inhaler technique will be needed for future studies. Device specific checklists are currently used as the gold standard to assess inhaler technique in clinical settings, and provide a method of assessing the accuracy of inhaler technique algorithms.
However, such checklist methods are subjective in nature and are limited in that they can only be performed in controlled environments. In addition to this, clinicians have no information on the total emitted dose from the inhaler or drug deposition in the airways. We believe that experiments that provide empirical evidence on inhaler use are required to remove the subjectivity of these checklists. Using acoustic algorithms, such as the one presented in this study, will allow the objective analysis of inhaler technique. Such acoustic algorithms can provide all of the existing information that checklists currently provide and improve them furthermore by being objective. In addition, a number of supplementary objective metrics concerning inhaler use may be obtained such as inspiratory flow rate, inspiratory capacity, total emitted dose and drug deposition in the airways. Recent studies have reported that acoustics may be used to obtain such objective metrics [18], [35].

The accuracy of the algorithm in predicting the user technique score for certain patients in this study was slightly lower than others, for example patients 2, 4 and 7. The primary reason for this was due to these patients consistently fumbling with their inhaler, creating a large number of blister-like sounding events. These patients also had a number of conversations while using their inhaler and their general inhaler technique was poor and erratic. Future developments will focus on the orientation and number of microphones in the INCA™ device, coupled with adaptive noise cancelling. The robustness of the algorithm to a wide variety of real world environmental noises will also be investigated in future studies. Such modifications to the INCA™ device and testing of the algorithm in noisy environments may improve the accuracy of the algorithm in analyzing future patients’ audio files.

One of the major benefits of the algorithm described in this study is that it is able to detect critical errors associated with inhaler use. Analysis of the audio files revealed that many patients unintentionally exhaled into the mouthpiece of the Diskus™ inhaler, dispersing some or even all of the medication. Such detrimental exhalations can only take place after a patient has first carried out the blister step and released medication into the mouthpiece of the inhaler. The algorithm designed in this study is capable of detecting this critical error and will give a ‘technique error’ score if such an exhalation is detected. A previous study demonstrated that acoustics can also be employed to determine if there is a sufficient force behind the inhalation maneuver [18]. Another critical error that was detected during this study was that many patients blister their Diskus™ DPI multiple times or inhale multiple times. The algorithm is capable of automatically detecting these types of critical errors and reporting them to clinicians. As clinicians presently have no method of analyzing patients’ inhaler use in-between clinic visits, the use of acoustics and the algorithm to detect such critical errors would be highly beneficial.

The algorithm designed in this study has many advantages for both inhaler users and clinicians alike. Currently there is no way for clinicians to know how a patient is using their inhaler once they take the inhaler device home with them. Many patients often show no improvement in their respiratory condition despite receiving an appropriate inhaler and medication regime. Clinicians are often left confused as to why these patients show no improvement in their condition. The system described in this study addresses this problem. It provides a record of inhaler use that can be interrogated in order to assess when and how an inhaler was used over a period of days or weeks in uncontrolled environments. For a clinician to manually evaluate a potentially large quantity of audio files would not be very feasible. Thus, an automatic algorithm such as the one described in this study may allow clinicians to efficiently and objectively monitor patients’ inhaler adherence. Such information may be used as an educational tool to provide objective feedback to patients in the hope of them improving their adherence. For patients, improved inhaler adherence may lead to increased levels of medication efficacy. An improvement in adherence rates will lead to a decrease in the number of exacerbations and subsequently hospital admissions.

V. CONCLUSION
In conclusion, an algorithm has been designed and developed that can automatically evaluate patient adherence in a common dry powder inhaler. This algorithm creates the opportunity for clinicians to monitor inhaler users in order to understand if they are consistently using their inhaler device with the correct user adherence technique and at the correct time. Active feedback may encourage patients to improve their adherence and take better control of their disease.

ACKNOWLEDGMENT
The authors would like to thank Vitalograph Ltd. and GlaxoSmithKline Ltd. for generously assisting this study.

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A Method to Assess Adherence in Inhaler Use through Analysis of Acoustic Recordings of Inhaler Events

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Abstract

Rationale: Poor adherence to inhaler use can be due to poor temporal and/or technique adherence. Up until now there has been no way of reliably tracking both these factors in everyday inhaler use.

Objectives: This paper introduces a device developed to create time stamped acoustic recordings of an individual’s inhaler use, in which empirical evidence of temporal and technique adherence in inhaler use can be monitored over time. The correlation between clinical outcomes and adherence, as determined by this device, was compared for temporal adherence alone and combined temporal and technique adherence.

Findings: The technology was validated by showing that the doses taken matched the number of audio recordings \((r^2 = 0.94, p < 0.01)\). To demonstrate that audio analysis of inhaler use gives objective information, in vitro studies were performed. These showed that acoustic profiles of inhalations correlated with the peak inspiratory flow rate \((r^2 = 0.97, p < 0.01)\), and that the acoustic energy of exhalations into the inhaler was related to the amount of drug removed. Despite training, 16% of participants exhaled into the mouthpiece after priming, in >20% of their inhaler events. Repeated training reduced this to 7% of participants \((p = 0.03)\). When time of use was considered, there was no evidence of a relationship between adherence and changes in AQLQ \((r^2 = 0.2)\) or PEFR \((r^2 = 0.2)\). Combining time and technique the rate of adherence was related to changes in AQLQ \((r^2 = 0.53, p = 0.01)\) and PEFR \((r^2 = 0.29, p = 0.01)\).

Conclusions: This study presents a novel method to objectively assess how errors in both time and technique of inhaler use impact on clinical outcomes.

Trial Registration: EudraCT 2011-004149-42


Editor: Anthony Peter Sampson, University of Southampton School of Medicine, United Kingdom

Received November 12, 2013; Accepted April 30, 2014; Published June 6, 2014

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Funding: The work was funded by the Health Research Board in Ireland, www.HRB.ie. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The following authors are named on the patent application for the device described in this paper: RB Reilly, RW Costello, I Killane, MS Holmes and C Hughes. The two authors affiliated with the company Vitalograph are included to acknowledge the contribution they made by providing us with the hardware for our monitoring devices. The patent, PCT/EP2013/067932, was filed on the 29th of August 2013. This does not alter the authors’ adherence to PLOS ONE policies on sharing data and materials.

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Introduction

Inhaled medicines have the advantage of direct application of drug to the lung with less systemic side effects. As with all medicines, failure to achieve a response to a clinically prescribed medicine may be the result of poor adherence. In the case of medication delivered via inhalers poor adherence may arise from non-use, haphazard or excessive use of medicine or poor inhaler technique. Temporal adherence is rooted in patient perceptions of the disease, belief in the medication, medication cost and access to healthcare [1,2], while technique adherence is related to lack of or failure to remember instruction [3]. Several studies have highlighted that errors in inhaler technique may be as detrimental as the failure to use the inhaler [4,5]. Regardless of whether it is from not using their inhaler or using it incorrectly, the consequences are poor clinical outcomes, wasted medications and higher healthcare costs [6–11].

Because there are such important consequences of poor adherence several approaches to assess inhaler adherence have been devised. At present, the most commonly used method in clinical trials is counting doses as read from the inhaler [12]. Other indirect methods include biomarkers such as drug levels and exhaled nitric oxide [13,14]. However, these methods do not give a measure of everyday inhaler use. Electronic devices give a day-to-day measure of inhaler use but they do not assess inhaler technique [15]. Detection of technique errors is traditionally carried out through a face to face process with a clinician [16,17]. However there is no way of assessing technique performance once...
Figure 1. The audio recording device, attached to the Diskus inhaler is shown in (A). In (B) the amplitude of the audio associated with an inhaler being used is shown, in (C) the corresponding audio is shown in the frequency domain. From analysis of the audio the clear differences in the features of each of the steps is shown. After fully opening the device, which starts electronic recording, the first critical step is the lever movement to blister the drug. This step is characterized by a short burst of energy lasting approximately 20–30 ms with a high frequency content (~2 kHz) preceded by a short burst of lower frequency noise (~1 kHz). Prior studies have shown that there is a difference in spectral components in the frequency domain between inhalations and exhalations an exhalation has a sharp increase in amplitude that tapers off with time and the power of exhalation decreases exponentially from 2 kHz to 500 Hz while the spectral power for inhalations are higher and they have a low increase in amplitude compared to that of exhalations.18
doi:10.1371/journal.pone.0098701.g001

Table 1. Comparing Inhaler steps to INCA device Function.

<table>
<thead>
<tr>
<th>Inhaler Checklist</th>
<th>INCA Device Functionality</th>
<th>Impact on Technique Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Use thumb or finger in thumb grip to open device until the mouthpiece appears</td>
<td>INCA device starts recording</td>
<td>Critical</td>
</tr>
<tr>
<td>2 Keeps Diskus horizontal</td>
<td>Experiments reveal that only shaking will remove drug from inhaler</td>
<td>Non-Critical</td>
</tr>
<tr>
<td>3 Slide lever once until it clicks</td>
<td>Blister sound identified from audio signal (“drug priming” in figure 1B)</td>
<td>Critical</td>
</tr>
<tr>
<td>4/5 Breathe out fully When breathing out fully does so away from Diskus</td>
<td>Any exhalations in the direction of the inhaler and be observed in the audio recording. An exhalation after the drug has been blistered is a technique error (Figure 5A)</td>
<td>Critical</td>
</tr>
<tr>
<td>6 Presses lips tightly above &amp; below mouthpiece opening</td>
<td>Inhalation identified from audio signal (“inhalation” in Figure 1B)</td>
<td>Critical</td>
</tr>
<tr>
<td>7 Breaths IN QUICKLY, filling lungs with medicine</td>
<td>Inhalation identified from audio signal (“inhalation” in Figure 1B)</td>
<td>Critical</td>
</tr>
<tr>
<td>8 Holds breath for at least 5 seconds (with or without Diskus in mouth)</td>
<td>This can be detected in the audio signal (“exhalation” in Figure 1B)</td>
<td>Non-Critical</td>
</tr>
<tr>
<td>9 Removes Diskus before breathing normally</td>
<td>Recording ends</td>
<td>Critical</td>
</tr>
<tr>
<td>10 Closes Diskus by placing thumb or finger in the thumb grip &amp; sliding it closed</td>
<td>Recording ends</td>
<td>Critical</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0098701.t001
the patient returns home. Hence, the limitations of all of these methods suggest that there is a need for a technology to longitudinally and objectively monitor both temporal and technique adherence.

The central aim of this work is to validate the hypotheses that technique errors can have an impact on clinical outcomes for users of inhaler medication. This was achieved by employing a device, which for the first time can track a user’s adherence in both the technique and temporal domain over time. Measures of adherence over 12 weeks are determined by processing the audio files, which are created every time the subject uses their inhaler, for evidence of good or poor inhaler use. These values of adherence are then correlated with changes in clinical outcomes to assess the validity of assessing adherence in this manner.

**Methods**

**Adherence Monitoring Device**

The Inhaler Compliance Assessment (INCA) device consists of a microphone, a battery, solid-state memory storage and a microprocessor for recording audio. The prototype device was attached to a Diskus inhaler Figure 1A. Recording is initiated by opening the inhaler and finishes when the inhaler is closed. An electronic real-time clock marks the time the recording is made and this is stored as part of the file’s metadata. The audio is recorded at a sampling rate of 8 kHz with an 8bit sampling resolution, Figure 1B. An initial 49 patients used INCA Version 1. This group of devices had a failure rate of 13%. Additionally, in the last two weeks of the study, in these patients, 6% of device batteries failed, however there was data available for the first two weeks. Modification to the battery and firmware in Version 2 reduced the subsequent device failure rate to 3 of 51 devices (6%).

Each participant was recruited for three consecutive months, at the beginning of Month1 they were given an INCA enabled Diskus inhaler and at the end of that month they returned to the clinic and received a replacement. During their return visit patients had their inhaler technique assessed and corrected if required. The audio files on the INCA device were downloaded and processed for subsequent analysis. The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Protocol in File S1 and CONSORT S1.

**Figure 2.** The amplitude and corresponding spectrogram of an individual with a weak inhalation is shown in (A). In (B) the amplitude and corresponding spectrogram of another individual with a strong inhalation is shown. In (C) the relationship of the amplitude of inhalation to peak inspiratory flow rate is shown, there is a strong relationship between these two variables, $r^2 = 0.97$. In (D) the relationship of amplitude of inhalation to drug removal is shown.

doi:10.1371/journal.pone.0098701.g002
Classification of inhaler events

The package instructions accompanying a Diskus inhaler describe the steps required for its correct use. Table 1 and Figure 1B demonstrate how each of these phases can be identified visually from a display of an acoustic recording created by the INCA device. Visual and audio analysis was carried out using the audio processing software Audacity, (http://audacity.sourceforge.net).

Ethics Statement

This observational study was approved by the Beaumont Hospital Research Ethics Committee 09/58 and the Irish Medicines Board C10026. Written informed consent was obtained for all participants in the study. This study was not registered as a clinical trial as this was considered an observational study of the technology employed.

In vitro testing to acoustically identify the steps involved in inhaler use

Studies showed that there was variability in the amplitude of acoustics when individuals inhaled, Figure 2A and B. We quantified the relationship of the acoustics of inhalation with peak inspiratory flow rates and with drug delivery. The technical details of these experiments are presented in “Objective measures of acoustic profile of inhalation and exhalation” in File S1. The amplitude of inhalation was closely related to the inspiratory flow rate, \( R^2 = 0.97, p < 0.01 \) Figure 2C. The amplitude of inhalation was also related to the weight of drug extracted from the inhaler, Figure 2D. This allowed us to objectively assess if there was a critical error in inhalation, if the median amplitude was less than or equal to 0.016AU (corresponding to a flow rate of 30 L/min) then such an event was classed as an inhalation error.

As many files contained evidence of exhalation, after the lever had moved to prime the inhaler, we performed studies on the effect of exhalation on drug availability. In these it was shown that an effort of exhalation above 1 dB, dispersed more than 50% of the drug. Hence, if an exhalation occurred after the lever had moved then the event was considered to be an error in inhaler technique.

Clinical testing

A salmeterol/fluticasone Diskus inhaler was chosen for clinical studies with the INCA device. The study inclusion and exclusion criteria are shown in Table 2, a consort diagram is shown in Figure 3.

Sixty-nine patients were given an INCA enabled Diskus inhaler. The baseline characteristics of the patients are shown in Table 3. The patient cohort consisted of 30 males (43%) and 39 (57%) females who were prescribed either 50/250 mcg or 50/500 mcg doses of salmeterol/fluticasone to be delivered via a Diskus inhaler. Demographic data such as age, height and weight as well as asthma related measurements such as Asthma Quality of Life Questionnaire (AQLQ) and Peak Expiratory Flow Rate (PEFR) are collected at the initial visit to the clinic. The clinical data relating to the subjects, from month 1 to month 3 of the study, are shown in Table 4.

All participants were recruited from Beaumont hospital and an initial target of 50 participants was set. Initial participant recruitment was from January 2011 until June 2012. Due to device failures a second round of recruitment was required to meet

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**Table 2. Inclusion and exclusion criteria for participant recruitment.**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capable of understanding and willing to provide voluntary informed consent before any protocol specific procedures are performed</td>
<td>Be females of childbearing potential who are pregnant, or intend to become pregnant, or are not using adequate contraceptive methods</td>
</tr>
<tr>
<td>Clinical diagnosis of asthma whose recent clinical condition indicates ongoing need for combination therapy.</td>
<td>Have used any investigational product or device within 3 months of the enrolment visit.</td>
</tr>
<tr>
<td>Age 18 years or older at time of consent.</td>
<td>Have known previous sensitivity to salmeterol/fluticasone.</td>
</tr>
<tr>
<td>Capable of understanding and complying with the requirements of the protocol, including ability to attend for all required visits.</td>
<td>Have a known significant (in the opinion of the investigator) concurrent medical disease.</td>
</tr>
<tr>
<td>Able and willing to take inhaled medication.</td>
<td>In the opinion of the investigator suitable for use of a salmeterol/fluticasone inhaler or already using a salmeterol/fluticasone inhaler.</td>
</tr>
</tbody>
</table>

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![Figure 3. A consort diagram for the 69 patients who participated in the study is shown.](https://example.com/f3.png)

doi:10.1371/journal.pone.0098701.g003
the target number of 50, this was carried out from April 2013 until June 2013. Any participant who experienced more than two device failures over the course of their study period was not included in the analysis. In June 2013 data from 51 participants who had at least 2 months of data from INCA devices was available for analysis.

As this was a validation study the primary endpoint was to demonstrate that the device recordings were equivalent to the dose counter, the current gold standard method. Exploratory secondary aims were to quantify the prevalence of errors in technique and compare the rates of adherence, when assessed in the time domain alone and when technique and time of use were assessed together. Other analysis included a comparison of adherence rates between those subjects who demonstrated clinical improvements in AQLQ and PEFR.

**Statistical methods**

The number of INCA audio recordings, which contained acoustic evidence that the drug was dispensed, was compared to the number of doses taken by the user, quantified by the mechanical counter on the inhaler. The level of agreement between these two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A. A Bland Altman [18] plot is a difference plot used to demonstrate the agreement between two methods of dose counting was investigated using Pearson’s correlation coefficient and a Bland Altman plot, figure 4A.
and E in particular demonstrate the effect technique errors can have on overall adherence. A significant number of technique errors (yellow dots) can be seen in the data for week 1. Although the patient roughly took the recommended number of doses over this period, the technique errors significantly affected adherence rate reducing it from an expected rate of 2 to 0.8. It can then be seen that technique errors improve in subsequent weeks, and adherence rate increase to a more acceptable value, 1.6. In month 1, when considering technique errors the same as missed doses the rate of adherence was 10% lower than when just the temporal adherence was considered alone.

Figure 4. A Bland Altman plot showing the relationship of the doses taken, recorded by the dose counter on the Diskus and the number of audio files logged on the metadata of the INCA device is shown in (A). In (B) the same data is displayed as a correlation of the doses taken to the number of audio recordings.

doi:10.1371/journal.pone.0098701.g004

Relationship of clinical progress to adherence

Among the study participants there was an overall significant increase in AQoLQ ($p<0.001$) over the 12 weeks of study, see Table 4. An exploratory analysis was performed to relate the rate of adherence in those who achieved at least a minimum clinically important improvement in AQoLQ of 0.5 (n = 20) and those who did not (n = 18) [21]. No statistical difference was observed between the two groups for age or baseline PEFR, however there was a statistical difference in the BMI’s and AQoLQ scores for the two groups ($p = 0.04$ and 0.02 respectively). For this analysis temporal adherence only considers whether two doses were taken
in a day. When plotting rate of inhaler use (Figure 7A) no relationship between the rate of adherence and clinical outcomes was observed. When data on time and technique was combined a correlation between the AQLQ-improvers group and this combined adherence rate was observed; with a downward trend in adherence for the non-improving group, (p = 0.017) and an upward trend from improvers (p = 0.02), Figure 7B. The same analysis was carried out comparing those with improvements and no improvements in PEFR, n = 20 and n = 28 respectively. There was no statistical difference in the age, BMI, initial PEFR or AQLQ scores between these two groups. No relationship between adherence, calculated simply by time of use between improvers and decliners, was observed however using a composite rate of adherence showed a distinction in the trend between improvers and non-improvers in terms of their PEFR rate, p = 0.016, (Figure 7 C & 7D).

Discussion

This study reports a novel method to assess the use of an inhaler by an individual. The technology involves an audio recording device and a methodology which provides objective evidence of inhaler use and a novel way to calculate adherence. The clinical significance of this approach is that when both the technique of inhaler use and the time of use are considered together this provides a more objective relationship of the patient’s use of an inhaler to their outcomes.

We undertook this study because there is a need to have a technology that quantifies when and how an inhaler has been used, since clinicians often cannot distinguish if the progression of a condition such as asthma is influenced by adherence to therapy or deterioration in the condition. As a means of assessing inhaler use, audio recordings have several advantages. Electronic recordings are time stamped, so that the time of use can be assessed and the technology involved in audio recording devices has become smaller and more robust. Furthermore, audio can be analysed in
the time and frequency domains, meaning that objective quantifiable features corresponding to each step of the use of the inhaler can be identified and extracted for analysis. We initially used human raters in the assessment of the steps of inhaler use and then devised a method to perform the process automatically. We compared these automated assessments with those made by trained human assessors. The automatic signal processing method has a high sensitivity and specificity [22]. This means that analysis can be performed rapidly so that the information can be presented to an individual in real time.

The traditional methods of assessing adherence with dose counters or electronic recordings reflect when the inhaler was used but they do not assess how it was used. In this study there was no relationship between temporal adherence and clinical outcomes. It was only when errors in inhaler use and time of use were combined that a relationship between changes in adherence and changes in outcomes was identified. This means that it is important to know both when and how an inhaler was used.

Analysis of the audio recordings revealed some important findings that are not easily identified by the traditional method of direct visual assessment. Direct visual assessment simply shows that the individual is competent in using their inhaler but cannot guarantee that the process is followed in the individual’s home environment. In this study all patients were fully trained and judged to be competent in the use of their inhaler at the start of the observation period but nonetheless 17% of patients had more than 20% errors during the initial month. This indicates that errors do persist despite one-to-one education. It has been shown previously

Figure 6. The percentage of all recordings with an error in use is shown in (A). Before participating in the study all patients had demonstrated that they were proficient in inhaler use, nonetheless at the end of month 1, 10% of all inhalations had a critical error. Over the next two months there was a significant reduction in the number of errors made by the patients, (*, p<0.05). In (B) a recording of an individual taking two doses, one after the other is shown. In (C) a recording of an individual moving the lever back twice, effectively wasting a dose. In (D) an example of a recording where the user exhales into the mouthpiece after priming and before inhalation.

doi:10.1371/journal.pone.0098701.g006
that repeated education leads to better inhaler technique [23] and this was also the case in this study. In fact it required three consecutive training sessions, over 3 months, to reduce errors in technique to <5% of all inhaler events. In this observational study eliminating these errors corresponded to the observed improvement in asthma quality of life. The majority of patients who made errors did not do so every time suggesting that these errors reflect carelessness rather than poor proficiency. Despite repeated training three patients did not improve their technique and three actually developed errors in their inhaler technique. Hence, while patients can be seen to be competent in using their inhaler many persist in making mistakes, which have direct clinical impact, when they use their inhaler outside of the training setting. Given that the acoustic algorithm can process the audio data in real-time we can incorporate this information into a tailored training program based on an individual’s own technique errors. By displaying information on rate of use along with information on clinical symptoms and PEFR, as shown in Figure S1, we can provide an individual with a greater insight into the relationship of inhaler use to their own outcomes. A clinical trial is underway to assess if providing such feedback improves clinical outcomes more than generic inhaler training.

In vitro, studies have demonstrated a strong relationship between the acoustics of inhalation and the inspiratory flow rate. Devices such as the peak inspiratory flow rate meter can assess if the patient can achieve a certain flow but they cannot assess the day-to-day flow rate achieved by the patient. Most patients in the study easily achieved an adequate peak inspiratory flow. However other patients, for example those with COPD, may not achieve adequate flow rates, which will limit the effectiveness of their inhaler [24].

The most common error made by patients was an exhalation into the inhaler after the lever had been deployed to activate the drug. This error disperses the medication away from the
mouthpiece and so reduces the quantity of drug available for subsequent inhalation. Another component of this error is the introduction of water vapour to the mouthpiece which can also impact drug delivery (further details on the impact are discussed in the accompanying second manuscript). In this study analysis of the audio files allowed us to objectively identify when this error occurred. For most patients this seemed to occur because they do not recognise the importance of the instruction “exhale fully away from the device”. Having objective evidence from the audio recordings ensures that these errors are identified. Development is currently ongoing to automate the classification of inhaler events. This will result in a very usable system for monitoring patients in a clinical environment. Technique errors are specific to this type of inhaler; however there are many types of inhalers available, each with their individual potential technique errors. For example the orientation of the diskus inhaler is often considered a potential source of technique error. It is recommended that the inhaler is kept horizontal during use. Preliminary experiments demonstrated an inhaler held at 45° or 90° will only loose between 0 and 5% of drug present in the inhaler. It is only with shaking or tapping the inhaler when help at 90° that drug will be dislodged from this inhaler. This study presents a successful framework for identifying technique errors and establishing objective methods of classification of these errors.

There are several limitations to the study. Firstly, the rates of adherence were very high, compared with other studies of adherence in asthma [1,6,8,11,14,15]. The study was performed in the setting of a formal research setting. In other preliminary studies, in general practice, on hospital wards and in their own home following exacerbations of COPD with this device, we have shown much lower levels of adherence [25,26]. In the current study the participants were fully aware of the purpose of the study, which was to assess inhaler use over a period of time. Therefore, the usual limitations of this type of study design apply; including the Hawthorne effect, knowing that adherence was being assessed may well have altered the rates of adherence. The results do indicate that despite high levels of temporal adherence many patients had errors in technique which when they were addressed were associated with improvements in their symptoms. Hence, repeated training in inhaler technique has direct clinical effects.

In summary, we describe the use of audio recordings to provide objective longitudinal evidence of inhaler use. This information can provide an insight into the relationship between inhaler use and an individual’s clinical course over time.

Supporting Information

File S1 This document contains the clinical protocol for data collection, a description of the methods used to relate acoustic properties to peak flow rate, and the supplementary tables, Tables S1 & S2. (DOC)

Figure S1 The figure shows an individual’s inhaler daily use, peak flow recordings and AQLQ over a 90 day period. The patient shows a progressive improvement in PEFR and AQLQ over the time, during which they demonstrate excellent adherence. The figure also shows that having achieved optimal PEFR and AQLQ they show a more variable adherence rate. (TIF)

Figure S2 Experimental setup of equipment used to extract drug from the Diskus DPI is shown. (TIF)

Checklist S1 CONSORT Checklist. (DOC)

Acknowledgments

The authors thank Professors Dermot Kenny (RCSI) and Pat Murray (UCD) as well as Jeremy Towns from the Dublin Clinical Centre for Research. The authors thank Dr. David Leather, Martijn Akveld, and Dr Kate Knobil from GSK for providing the Diskus inhalers for this study and Professor Peter Calverley for advice on an earlier version of this paper. The authors also thank the research nurses in the clinical research centre RCSI and clinical research centre UCD for all their contributions to running this study.

Author Contributions

Conceived and designed the experiments: IK CH MSH TT RWC TA-Z. Performed the experiments: EMH DH RWC. Analyzed the data: SD IS JS JS AJ. Conceived and designed the experiments: IK CH MSH TT RWC TA-Z. Wrote the paper: SD IS RWC RR. Clinical advisors and provided access and clinical protocol for data collection: IK CH MSH TT RWC RA-Z. From medical center for all their contributions to running this study: IK CH MSH TT RWC RA-Z. The authors thank Dr. David Leather, Martijn Akveld, and Dr. Kate Knobil from GSK for providing the Diskus inhalers for this study and Professor Peter Calverley for advice on an earlier version of this paper. The authors also thank the research nurses in the clinical research centre RCSI and clinical research centre UCD for all their contributions to running this study.

References

The Acoustic Features of Inhalation can be Used to Quantify Aerosol Delivery from a Diskus™ Dry Powder Inhaler

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Received: 7 January 2014 / Accepted: 21 March 2014 / Published online: 28 May 2014
© Springer Science+Business Media New York 2014

ABSTRACT
Purpose Some patients are unable to generate the peak inspiratory flow rate (PIFR) necessary to de-agglomerate drug particles from dry powder inhalers (DPIs). In this study we tested the hypothesis that the acoustic parameters of an inhalation are related to the PIFR and hence reflect drug delivery.
Methods A sensitivity analysis of the relationship of the acoustics of inhalation to simultaneously recorded airflow, in a cohort of volunteers (n=92) was performed. The Next Generation Impactor (NGI) was used to assess in vitro drug delivery from salmeterol/fluticasone and salbutamol Diskus™ DPIs. Fine particle fraction, FPF (<5 μm) was measured at 30–90 l/min for 2–6 s and correlated with acoustically determined flow rate (IFRc). In pharmacokinetic studies using a salbutamol (200 μg) Diskus™, volunteers inhaled either at maximal or minimal effort on separate days.
Results PIFRc was correlated with spirometrically determined values (R² = 0.88). In in vitro studies, FPF increased as both flow rate and inhalation duration increased for the salmeterol/fluticasone Diskus™ (Adjusted R² = 0.95) and was proportional

Electronic supplementary material The online version of this article (doi:10.1007/s11095-014-1371-x) contains supplementary material, which is available to authorized users.

Jansen N. Seheult and Peter O’Connell: These authors contributed equally to this work.

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DOI 10.1007/s11095-014-1371-x
to flow rate only for the salbutamol Diskus™ (Adjusted $R^2 = 0.71$). In pharmacokinetic studies, blood salbutamol levels measured at 20 min were significantly lower when PIFRc was less than 60 l/min, $p < 0.0001$.

**Conclusion** Acoustically-determined PIFR is a suitable method for estimating drug delivery and for monitoring inhalation technique over time.

**KEY WORDS** aerosol delivery · asthma · cascade impactor · COPD · inhaler technique

**BACKGROUND**

The best route of administration of drugs in the treatment of COPD and asthma remains inhaled therapy (1). For greatest benefit, the maximum amount of drug needs to reach the site of action, that is, the airways. This depends on the patient’s inspiratory flow, inhaled volume, ramp rate of inhalation and degree of airways obstruction (2,3). Findings from previous studies using the Electronic Lung Model showed that in a large subgroup of patients, only 15–30% of the inhaler dose was deposited in the small airways and alveoli of the lung (4,5).

For patients using a dry powder inhaler (DPI), de-agglomeration of the active drug from its carrier (typically lactose monohydrate) depends on a combination of factors: turbulence, mechanical impaction, particle uptake and mechanical vibration (6,7). One study using a Ventolin Diskhaler™ showed that mechanical impaction was not an effective mechanism for powder de-agglomeration, whereas turbulence was found to have a definite effect (8). Turbulence leads to aerodynamic lift, drag and shear, as well as separation forces. The turbulent energy generated depends on the intrinsic resistance of the inhaler and the flow rate generated by the patient. Some DPIs have high internal resistance, for example the Turbuhaler™, while some have relatively low resistance, like the Diskus™ (9). There is a direct relationship between the intrinsic resistance of a DPI and the peak inspiratory flow rate (PIFR)-dependence for drug delivery. Regardless, it is recommended that optimal drug delivery is achieved with a flow rate of greater than 30 l/min and ideally, greater than 60 l/min (10).

For traditional DPIs, insufficient PIFR can lead to ineffective drug delivery resulting in unintentional non-adherence and poor clinical outcomes. Conversely, some authors have advised that very high inhalation flow rates can lead to increased throat deposition and exhalation of particles that are less than 1 μm in aerodynamic particle size (11,12). While modern, sophistically engineered powders and inhaler devices are less flow-rate dependent, or even flow-rate independent (13), it is our experience that the majority of patients with obstructive airways disease are currently prescribed traditional DPIs like the Seretide Diskus™ or Symbicort Turbuhaler™. Hence, a method of measuring inhaled flow rate, as part of assessing inhaler adherence and technique is required.

Currently, the methods of assessing inhaler technique are limited and problematic. Among these are subjective checklist methods (14). Subjective checklist methods have high inter-operator and intra-operator variability. Apart from this, they do not provide a way to gauge a patient’s inhalational flow or duration, which are vital for effective drug delivery. The Clement-Clarke In-Check Dial™ is a marketed method which simulates the resistance of the main types of inhalers in order to estimate the patient’s PIFR (15). However, this method is likely to have poor correlation with the *in vivo* PIFR generated by the patient while using the actual inhaler device. Given the high healthcare burden of respiratory diseases and the cumulative costs of inhaled medications, there is an urgent need for a real-time system for tracking drug delivery. In this study, we propose a novel method to monitor a critical aspect of inhaler technique, namely PIFR determination using acoustics.

We have devised a monitoring device, the INCA™ device, which records the acoustics of an inhalation while a subject uses the Diskus™ DPI (Figs. 1 and 2) [D’Arcy S, et al. Design and assessment of an adherence monitoring device for inhalers. Trinity Centre for Bioengineering, Trinity College Dublin, Ireland. Unpublished]. The INCA™ device comprises a high fidelity microphone and on-board storage, which logs the date and time the inhaler is used and stores a recording of the inhalation acoustics. This device can be used for at least 60 recordings and hence can give an indication of inhalation technique over a period of a month. We have previously reported on a relationship between inhalation acoustic parameters and PIFR in a group of 15 healthy volunteers (16). One drawback of this study was that it was a repeated measures design in which volunteers subjectively varied their inhalation for up to eight recordings. Also, it is possible that obstructive airways disease might alter the inhalation acoustics while using a DPI.

There is, to date, no universally accepted method of assessing airway drug deposition. Three commonly used methods include *in vitro* particle size and deposition characterisation using Cascade Impactors, pharmacokinetic studies and scintigraphic studies.

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Fig. 1 INCA™ device and functional position on Diskus™ inhaler.
Each of these has been applied to the Diskus™ inhaler and results have consistently shown that while Total Emitted Dose may be flow independent, Fine Particle Dose is significantly dependent on inhalation flow rate. Fuller showed that Fine Particle Mass obtained from a 250 μg fluticasone Diskus™ was almost halved by decreasing the flow rate from 60 to 28 l/min (17). Mahler et al. also concluded that bronchodilator therapy via nebulization should be considered in patients with COPD who have a suboptimal PIFR (<60 l/min) with a Diskus™ DPI (18).

Modern signal processing techniques mean that it is possible to relate the features of sound from inhalations to other measured values such as inspiratory flow rate. Hence, we hypothesized that by analysing the acoustics of inhalation in a group of patients with a variety of respiratory and non-respiratory diseases we could determine the sensitivity and specificity of our method in classifying inhalation flow rate. Furthermore, we hypothesized that we could estimate the Fine Particle Dose emitted from the Diskus™ inhaler into the Next Generation Impactor (NGI) by using calculated values of flow rate and acoustically determined duration. Finally, we hypothesized that this was clinically relevant in vivo by studying the peak concentrations of drug achieved in healthy subjects as a function of PIFR and duration.

METHODS

Study 1: The Relationship Between Acoustics and Physiological Measures of Lung Function

One hundred and ten subjects from a population of patients with asthma, COPD, lung cancer, neuromuscular disease, other respiratory disorders and non-respiratory disorders were recruited by clustered and stratified sampling. All participants were either on inhaled medications as part of their treatment regimens or received training on how to use a Diskus™ inhaler. Patients were recruited from different clinics in Beaumont Hospital in Dublin, Ireland. There were no specific exclusion criteria for this study apart from capacity to comply with instructions. Informed consent was obtained for the study with explanations of the study protocol. Demographics and baseline lung function by spirometry were recorded (Table 1). The study was approved by the local Hospital Ethics Committee (ERC/IRB 13/36).

The construction of the airtight container with the associated Diskus™ inhaler, INCA™ device and spirometer connection used in these studies has been described previously (16). A graphical representation of the overall test set up can be seen in Fig. 3. Patients were instructed to exhale gently to functional residual capacity and then inhale at maximal flow rate and duration. Each patient repeated this manoeuvre until two consecutive PIFR readings were within 20% of each other.

The audio files recorded from the subjects were subsequently analysed using Audacity v2 and MATLAB v9 software packages to determine the value of amplitude and duration of each inhalation. In this case, mean absolute deviation (MAD) amplitude was calculated by applying the equation shown below:

$$\text{MAD Amplitude, } A_{MAD} = \text{mean}(|\text{amplitude, } A| - \text{mean}(\text{amplitude, } A))$$

(1)

PIFRc was calculated using equations derived from our previous dataset of 15 healthy volunteers: (16)

$$\text{PIFRc} = \left(\frac{194.7 * A_{MAD} + 0.1716}{A_{MAD} + 0.02621}\right)$$

(2)

Statistical analysis was done using MATLAB v9 and STATA v13. Creating binary dependent variables using threshold values for measured PIFR, sensitivity and specificity analysis was done comparing acoustically-determined PIFRc with spirometrically-determined PIFRm. Receiver Operating Characteristic Curves were constructed and the value of acoustically-determined PIFRc at which the maximum number of inhalations was correctly classified was determined and presented in tabular form.

Study 2: Correlation of Inhalation Acoustics from a Diskus™ Dry Powder Inhaler with In Vitro Drug Delivery

In vitro deposition and aerodynamic particle size of the delivered dose from the Diskus™ DPI was characterized using the Next Generation Impactor (US Pharmacopoeia 601, Apparatus 5) (19). The NGI was used with a pre-separator and cups 1–8. A high capacity vacuum pump (HCP4, Copley Scientific, UK) and Critical Flow Controller (TPK 2000,
Copley Scientific, UK) were attached to the air intake port. Impaction cups 1–5 were lined with filter papers wetted with 2 mls of a mixture of methanol: acetonitrile: water (25:25:50) and cups 6–8 were coated with 2 mls of solvent only to prevent particle bounce and re-entrainment (20).

Two Diskus™ [GlaxoSmithKline, UK] inhalers were used in this study: salmeterol 50 μg/fluticasone 250 μg and salbutamol 200 μg. An audio recording device was attached to each inhaler so that acoustic recordings of each inhalation were obtained.

The study variables were Flow Rate (IFR) and Duration of Inhalation. The Critical Flow Controller was adjusted to achieve flow rates of 30, 60 and 90 l/min at 2, 4 and 6 s durations. Testing was performed in duplicate at each study condition for both inhalers. For each determination, five individual doses were aerosolized into the induction port via a mouthpiece adaptor. The active ingredients were quantitatively recovered from the induction port (throat), pre-separator, and cups 1–8.

High performance liquid chromatography (HPLC) analysis was performed using a Waters Alliance Separations module equipped with a temperature programmable autosampler and Waters 2996 PDA detector. Chromatographic data was recorded and integrated using Waters Empower chromatography software and quantified using external standards. HPLC conditions for salbutamol sulphate (21), and fluticasone propionate/salmeterol xinafoate are detailed in Table I. Analytical method validation was demonstrated for both methods with regard to accuracy, precision, specificity and linearity as per ICH guidelines (22). The limits of detection for salbutamol, fluticasone and salmeterol peaks were 0.045, 0.032 and 0.014 μg/mL, respectively, while the LOQ values for the same three peaks were 0.136, 0.101 and 0.042 μg/mL, respectively.

The Total Emitted Dose (TED) was determined as the sum of the total drug recovered from the Throat, PS, and cups 1–8. This was averaged for each study condition. The Fine Particle Dose (FPD), i.e. cumulative dose less than particle size 5 μm, was calculated by interpolation on a log-probit plot using pre-specified stage cutpoints at each flow rate. Fine Particle Fraction (FPF) was calculated by expressing the FPD as a percentage of the label claim dose. The Upper Airway Dose (UAD) corresponded to the cumulative dose above an aerodynamic particle size of 5 μm. Flow Rate (IFRc) was calculated from the acoustic parameters using Eq. 1. Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) were also calculated at each study condition for both formulations using published methods (23,24).

Statistical Analysis was performed using STATA v13 and MATLAB v9. Multivariate regression analysis was performed using TED, FPF and UAD as dependent variables and IFR, Duration, IFRc and Acoustic Duration as independent variables. Bar graphs of TED, FPF, and Upper Airway Dose (UAD) for both formulations were generated, grouping by IFR and duration. The regression effect size (η²) was calculated for IFR and duration in each model. Coefficients of Variation (CVs) were determined for IFRc at different levels of measured IFR and for acoustic duration at different levels of preset inhalation duration to analyse our method precision.

Study 3: Pharmacokinetic Study Comparing Inhalation Acoustics with Drug Delivery

This study was approved by the local Hospital Ethics Committee (ERC/IRB 13/53). Ten healthy volunteers were recruited. An INCA™ acoustic recording device was attached

![Apparatus used for Study 1 showing spirometer with PC connection, airtight container and INCA™ Device.](Fig. 3)
to a 200 μg salbutamol Diskus™ with a hot-wire anemometer (FS5, IST, Switzerland) inserted into an air intake port of the Diskus™. The hot-wire anemometer gave a voltage output which was calibrated against flow rate using a vacuum pump.

Blood samples were collected in 7.5 ml serum separator tubes and allowed to coagulate for 20 min. Tubes were then centrifuged at 5,000 g for 15 min and 2–3 ml of serum pipetted into vials for storage at −20°C.

Serum concentration of salbutamol was determined using a competitive Enzyme Linked Immunosorbent Assay [MaxSignal® Salbutamol ELISA Test Kit (Reference 1022-01) from New Market Scientific, UK]. Limit of detection for serum/plasma was 0.25 ng/ml and the assay was linear in the range of 0.05 to 10.0 ng/ml. Total assay imprecision was determined to be 14% with recoveries between 85 and 115%. To account for interference between protein components in the serum and the assay, the baseline sample concentration was subtracted from timed samples.

Preliminary pharmacokinetic profiling showed serum peaks at 20 min and at 2–3 h post-inhalation (Fig. 4). The sampling time of 20 min was used for the comparative study below because this has been reported to represent pulmonary absorption (25).

Due to the wide inter-subject variation in metabolism of salbutamol and other similar compounds, we used each subject as his/her own control to determine the effect of flow rate and duration of inhalation on peak concentration. Each subject was asked to perform a single inhalation at maximal effort [PIFR >60 l/min] and duration from the study apparatus. This was followed by a 10 s breath hold and then a mouth rinse to reduce gastro-intestinal absorption of salbutamol. A previous study has shown this to be an effective method (25). Blood samples were collected at time zero and at 20 min. This was followed by at least a 24 h washout period. The procedure was repeated at a low flow rate [PIFR <60 l/min] and duration (≤50% of maximal duration) after this washout period.

Statistical analysis was done in STATA v13. PIFR and inhalation duration were determined both from the hot-wire anemometer and from the INCA device and correlated for each inhalation. A line graph was done for each subject and an overall regression model was developed using peak concentration as the dependent variable and measured PIFR, duration, calculated PIFR and acoustic duration as independent variables.

RESULTS

Study 1: The Relationship Between Acoustics and Physiological Measures of Lung Function

Eighteen of the 110 patients recruited had corrupted audio recordings. Table II shows the baseline demographics and lung function for the remaining 92 patients. The majority of the patients had obstructive airways disease, either asthma or COPD. Asthmatics, obese patients and patients with non-respiratory conditions had a significantly higher PIFR than the other patient groups.

Figure 5 shows a scatterplot of Test, i.e. Acoustically Determined PIFR versus Reference, i.e. Spirometrically Determined PIFR. Difference and Relative Difference
plots are shown in Fig. 6. Limits for Absolute Difference (+/− 1.96SD) were −11.9 to 19.4. There is a high degree of correlation between the values, with an $R^2$ of 0.881. There is a statistically significant mean bias of 3.78 and mean relative bias of 6.6% from the Reference Method.

$$PIFRc(l/min) = 1.01 \times PIFRm(l/min) + 3.18 \quad (3)$$

The results were partitioned by PIFR values of 45, 90 and 120 l/min. There was a mean bias of 3.4 between 0–45 l/min and 3.8 between 45–90 l/min. The bias above 90 l/min was not significant.

Receiver Operating Characteristic (ROC) Curves for various thresholds of measured PIFR are shown in Fig. 7. AUCs are close to 1 for classification of PIFR ($\eta$) = 0.884. There is a statistically significant mean bias of 3% (Fig. 9).

When regressions through the origin were performed for our data, plots of studentized residuals versus the independent variables highlighted non-horizontal linear trends indicating that a nonzero intercept should be suspected. Hence, all our regression models below included a nonzero intercept, since it is statistically significant.

Fine Particle Fraction (FPF) was directly proportional to inhalation flow rate and duration of inhalation for the salmeterol/fluticasone preparation but FPF was proportional to only IFR for the salbutamol Diskus™. The relationships between FPF, IFRc and duration of inhalation for salmeterol (adjusted $R^2=0.9509$), fluticasone (adjusted $R^2=0.9509$) and salbutamol (adjusted $R^2=0.7104$) are given by the following equations:

**Salmeterol FPF (%)**

$$FPF(p = 0.000, \eta^2 = 0.90115106), \quad Duration(p = 0.029, \eta^2 = 0.05008581)$$

**Fluticasone FPF (%)**

$$FPF(p = 0.000, \eta^2 = 0.90115106), \quad Duration(p = 0.029, \eta^2 = 0.05008581)$$

**Salbutamol FPF (%)**

$$FPF(p = 0.001, \eta^2 = 0.74660896), \quad Duration(p = 0.147 : \text{excluded})$$

While both calculated flow rate and acoustic duration are statistically significant in the regression models for FPF from the salmeterol/fluticasone inhaler, inhalation duration has a minimal effect compared to IFR as estimated by the $\eta^2$. Duration was not a significant variable in the FPF model for salbutamol and all of the models for TED and UAD (S1 and S2 in Online Supplement). The trends for TED were similar to those seen with FPF (Figs. 10 and 11).

A significant proportion of active drug is of a diameter greater than 5 μm and hence, likely to be deposited in the upper airways and throat (Fig. 12). IFRc is only moderately correlated with UAD, with an adjusted $R^2$ of 0.7076 for salmeterol, 0.2951 for fluticasone and 0.5270 for salbutamol. Inhalation duration has no effect on Upper Airway Deposition. Bar graphs of TED, FPF and UAD for both formulations grouped by IFR and duration are displayed in Figs. 10, 11, and 12.

**Study 2: Correlation of Inhalation Acoustics from a Diskus™ Dry Powder Inhaler with In Vitro Drug Delivery**

There was a high correlation between calculated flow rate (IFRc) and the flow rate at which the impactor was operated (IFR); overall imprecision was less than 10% at all three flow rates (Fig. 8). Imprecision of acoustically-determined duration was approximately 3% (Fig. 9).

Study 3: Pharmacokinetic Study Comparing Inhalation Acoustics with Drug Delivery

Baseline demographics for the ten subjects recruited in this study are shown in Table 4 of the Supplementary Appendix. Figure 13 shows that there was a significant difference between peak salbutamol concentration (measured at
Table II: Demographics and Baseline Lung Function Tests for Patients by Disease Category

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Number</th>
<th>Age (years)</th>
<th>Gender (M:F%)</th>
<th>BMI (kg/m²)</th>
<th>FVC (L)</th>
<th>FEV₁ (L)</th>
<th>FPF (L/min)</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Neuro-muscular disease</td>
<td>27</td>
<td>39.1 ± 19.0</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>All Asthma</td>
<td>92</td>
<td>53.1 ± 18.0</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>25</td>
<td>53.1 ± 16.8</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>9</td>
<td>53.1 ± 16.8</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Other respiratory condition</td>
<td>10</td>
<td>52.3 ± 22.3</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Non-respiratory disease condition</td>
<td>14</td>
<td>29.7 ± 14.8</td>
<td>42:58</td>
<td>27.26 ± 6.7</td>
<td>2.49 ± 1.1</td>
<td>187.3 ± 93.6</td>
<td>0.74 ± 0.15</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

In this study we extended our prior observations which showed that analysis of the acoustics of inhalation from a Diskus™ Dry Powder Inhaler could be used to calculate PIFR. Firstly, using a large sample of patients with widely varying PIFR rates, there was a very strong relationship between measured PIFR and calculated PIFR. To confirm that drug delivery to the lungs is dependent on flow rate, and hence can be estimated from the acoustic sounds of inhalation, we performed in vitro and in vivo studies. In vitro, we showed that Fine Particle Dose was dependent on both the inhalation flow rate and the duration of inhalation for salbutamol and fluticasone; duration was not significant for salbutamol FPF. Using the acoustic parameters to determine IFRc and the duration of inhalation, we were able to explain more than 95% of the variance in FPF for salmeterol/fluticasone but only 70% of the variance for salbutamol FPF. In contrast, the Upper Airway Deposition was relatively constant regardless of flow rate and duration. The implications of this is that patients with poor inhalational technique may have all the side effects of thrush and GI absorption with very few beneficial effects of the medication. We also tested the relationship between PIFR and duration of inhalation on drug delivery, in vivo, in ten healthy subjects and showed that there was a significant difference in the serum concentrations of salbutamol when PIFR was low (<60 l/min) compared to when the PIFR was >60 l/min. Together these data suggest that the acoustics of inhalation from a Diskus™ DPI can be used to objectively quantify pulmonary drug delivery.

We undertook this study in order to test the hypothesis that there is a relationship between the acoustic energy an individual generates when they inhale and the resulting peak inspiratory flow rate. Some authors have described the Diskus™ DPI as flow-independent (26). However, on careful review of their results, FPF from the Diskus™ is flow-dependent,
although not to the same degree as that from the Turbuhaler™. There is little published data on the effect of duration or inhaled volume on drug delivery. Our data suggest the effect of inhalation duration to be minimal. However, duration is a significant variable in our regression models for salmeterol and fluticasone FPF and it is likely that at borderline flow rates between 30 and 45 l/min, inspiratory duration plays a more important role in inhaler efficacy. Further studies at inhalation durations less than or equal to 1 s are required to further evaluate any possible relationship.
A number of studies have reported that very high inhalational flow rates through the Diskus™ inhaler may be detrimental to airway drug delivery, arguing that throat deposition is increased and that particles less than 1 μm in size are more likely to be exhaled immediately after inhalation (11,12). In contrast, our study found that even though MMAD decreases as flow rate increases, the lowest MMAD achieved for the salmeterol/fluticasone Diskus™ was 3.47 μm with a GSD of 2.22, which means that a significant proportion of particles would still be in the range of 2–5 μm to be active on the small airways. It is worth mentioning that the MMAD values for salbutamol were lower than the salmeterol/fluticasone formulation. Hence, for the salbutamol formulation, PIFRs >60 l/min may lead to lower pulmonary deposition due to exhalation of particles <1 μm.

We also tested the relationship between PIFR and duration on drug delivery in vivo in ten healthy subjects. We used a salbutamol Diskus™ because salbutamol has the shortest half-life of the drugs studied and it reaches relatively high concentrations in the blood after inhalation with a short time to maximum concentration. It was straightforward to measure serum plasma concentrations using a commercially available ELISA. In preliminary experiments there was an initial peak at 20 min that was distinct from the peak at 2–3 h, which is likely secondary to GI absorption. The initial peak was therefore most likely related to pulmonary absorption and hence, pulmonary deposition and aerodynamic particle size. Our results were concordant with the in vitro studies using the NGI Impactor and confirmed the relationship between PIFR and peak blood concentration. We used each subject as his or her own control since inter-individual drug metabolism is highly variable. We found that each individual achieved a lower Cmax when his or her inhalation flow rate was less than 60 l/min. Furthermore, our equations to estimate PIFR from acoustics were able to correctly classify all of the inhalations as either above or below 60 l/min and acoustically-determined PIFR explained more than 50% of the variance in Cmax. The remainder of the variance is likely due to differences in drug metabolism between individuals. The study was underpowered to detect a relationship between duration of inhalation and peak concentration. The existence of such a relationship is however, questionable since the results of our in vitro studies were inconclusive (even though the results for salmeterol and fluticasone FPF were statistically significant, the magnitude of the effect is minimal).

In Study 1, our acoustic method was also shown to be both sensitive and specific for classifying inhalations according to PIFR, being able to correctly classify upwards of 89% of all

Table III  Table Showing Threshold Values of Acoustic Method for which Most Inhalations are Correctly Classified, with Corresponding Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Reference method (l/min)</th>
<th>Test method (l/min)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Correctly classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
<td>≥33.55</td>
<td>95.12%</td>
<td>90.00%</td>
<td>94.57%</td>
</tr>
<tr>
<td>≥45</td>
<td>≥47.91</td>
<td>91.67%</td>
<td>90.62%</td>
<td>91.30%</td>
</tr>
<tr>
<td>≥60</td>
<td>≥66.27</td>
<td>90.48%</td>
<td>96.00%</td>
<td>93.48%</td>
</tr>
<tr>
<td>≥90</td>
<td>≥90.57</td>
<td>100.00%</td>
<td>91.86%</td>
<td>92.39%</td>
</tr>
</tbody>
</table>

Reference method represents spirometric values and test method represents acoustic method.
inhalations according to preset thresholds of spirometrically-determined PIFR. For these analyses the sensitivities and specificities were greater than 90%. Furthermore, we have shown that the relationship between flow rate and sound amplitude is independent of disease state and is therefore applicable to a large subset of the population.

There are many ways to signal average the inhalation sound; previously, we measured the average power in the frequency band 300–600 Hz, Root Mean Square of Amplitude and Mean Absolute Deviation of the Acoustic Amplitude and found that the first had the best correlation with PIFR (16). In this study, we found that MAD Amplitude had the strongest correlation with PIFR. The most likely explanation for this is that MAD Amplitude is more robust to inter-individual changes and mean power may shift in different frequency bands depending on upper and lower airway anatomy. This is in accordance with previous studies, which showed that the optimum frequency band to calculate average power is different in healthy subjects compared to asthmatics (27).

Furthermore, we found that patients with Neuromuscular Disease and COPD generated lower PIFRs compared to asthmatics, obese patients and those with non-respiratory illnesses. This has important implications in that different sub-populations may be able to use the Diskus™ inhaler with different efficacies. Even though their PIFR may be close to their personal best, they may still not be able to generate sufficient turbulent energy to benefit from the DPI.
Our study does have a number of limitations. The acoustic method is subject to noise interference in everyday life situations. This is likely to affect the calculated values from our models. Noise filtering will allow us to address this problem adequately. We have previously reported the limitations of the apparatus used in Study 1 (16).

One of the limitations of cascade impactor studies is that they require multiple dose actuations in order to enhance detection of very small drug levels in the lower Stages. This increases the chances of particle re-entrainment with each subsequent inhalation and hence, the drug recovered in each stage is likely to be higher than that expected if only one actuation were performed.

There is also limited applicability of our results to new inhaler devices and modern engineered powders, which are not dependent on flow rate for drug delivery. The need to
monitor PIFR during inhaler use may be unnecessary in the future when the use of these more novel products becomes widespread.

Finally, in our pharmacokinetic study we used salbutamol without giving charcoal to the subjects to minimize GI absorption. A consensus statement from the British Association for Lung Research recommends the use of an inhaled drug like fluticasone, which has less than 1% oral bioavailability, in pharmacokinetic studies or another drug in combination with activated charcoal (28). However, we based our method on a previous study, which showed that mouth-rinsing effectively eliminates GI absorption (25). Our data from three volunteers also shows that the peak due to GI absorption happens much later than when we collected our blood samples. It would also have been ideal to use an HPLC or LC-MS/MS assay for detection of salbutamol but our method validation of the ELISA showed that is had an acceptable precision and good recovery.
CONCLUSION

We have shown that our acoustic method for determining drug delivery to the airways is robust and reliable. There is no perfect method of determining pulmonary deposition and our methods are limited to those widely available today. Nonetheless, the INCA™ device provides a novel and more objective way of monitoring a critical aspect of a patient’s inhalation technique over a prolonged period of time.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was primarily funded by an HRB Ireland CSA Research Grant 12/1533. POG and AMH acknowledge funding from Science Foundation Ireland under Grant Nos. 08/CE/I1432, 07/SRC/B1158 and 12/RC/2275. The authors of this paper would also like to thank Vitalograph Ltd and GlaxoSmithKline Ltd for generously providing financial support for this study. We would like to thank the volunteers and patients who participated in the studies and the internal and external staff involved. The patented acoustic device [INCA™] used in this study is manufactured by Vitalograph, Ireland. The first authors of this paper have no affiliation to Vitalograph and are not listed as a holder of the relevant patents. RBR, SD and RWC are listed on the patents.

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