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CHARACTERISATION AND USE OF POROUS ALUMINOSILICATE PELLETS FOR EXTENDED DRUG DELIVERY

Presented by

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DOCTOR OF PHILOSOPHY DEGREE

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Pharmaceutics and Pharmaceutical Technology,
THE SCHOOL OF PHARMACY

March 2004
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Robert Stephen Byrne
To my parents,

Stephen and Nuala
SUMMARY

The initial focus of the research presented in this thesis was on the potential applications of a number of pelletized porous ceramics in drug delivery. These were commercially produced and were marketed for use in the building materials industry and the hydraulic fracturing of oil wells. Characterisation of the porous ceramics showed they were composed of aluminosilicate ceramics, crystalline silica and minor amounts of other materials. Their surfaces were polycationic at low pH's and polyanionic at higher pH's. Each ceramic contained highly interconnected open pores with the open porosity and pore size distribution being dependent on the ceramic.

Drug loading of the ceramics was achieved using a novel modification of a widely used vacuum impregnation technique. The loadings were reproducible and were influenced by the loading solution concentration and the porosity and bulk density of the ceramic. Dissolution testing established that drug release from the ceramics was extended. This was because the drug was entrapped within the porous interior of the ceramic pellets. It was found that the rate of extended drug release was influenced by the pellet size, its porosity, pore size distribution, porous microstructure and by electrostatic interactions between the pellet surfaces and the drug. The solubility of the drug in the dissolution medium and its molecular weight also influenced the release rate. There was, however, an initial burst release of drug from the ceramics. The drug released during this period was primarily located on the external pellet surfaces. Release modifying agents, such as calcium alginate, could be used to reduce or eliminate the burst effect. In addition, these agents further extended drug release.

Following on from the porous ceramic research, a series of porous aluminosilicate pellets were prepared by extrusion-spheronization. These pellets were formulated using kaolin/halloysite, ethylcellulose 100 cps and ethanol. In addition, varying proportions of sucrose were included in the formulations. The extrusion-spheronization products were porous, with the pores having been created by the evaporation of ethanol and the dissolution of sucrose. This meant the pore size distribution of the pellets was bimodal and was dependent on the quantity of sucrose included in the formulation.
The extrusion-spheronization products were drug loaded and dissolution tested. Drug release was characterised by an initial burst followed by extended release. The rate of extended release was dependent on the porosity and pore size distribution of the products. In addition, halloysite containing products gave greater extended drug release than their kaolin based equivalents. This was due to entrapment of the drug within the microtubular structure of halloysite.

Cryopelletization was used to prepare the final group of porous aluminosilicate pellets examined. This is a novel pelletization procedure, which involved freezing aqueous droplets containing varying proportions of kaolin/halloysite and sodium silicate solution. The frozen pellets were freeze dried, which removed ice from the pellets to leave pores behind. It was found that both the proportion of kaolin/halloysite and sodium silicate solution in the formulation influenced the porosity and pore size distribution of the pellets.

As with the porous ceramics and the extrusion-spheronization products, the cryopelletization products could be drug loaded and the release of the loaded drug was extended. The rate of extended release was influenced by the porosity and pore size distribution of the pellets and the average pellet diameter. However, in the case of diltiazem HCl, the microclimate pH of the pellets also had a marked influence on its rate of release. This was because the high pH suppressed the ionisation of diltiazem HCl, thereby reducing its solubility in the dissolution medium.
First and foremost, I wish to thank Professor Patrick Deasy for giving me the opportunity to conduct research in this novel and interesting area of Pharmaceutics. His guidance and constant support over the years and especially in preparing this manuscript are greatly appreciated.

My thanks are extended to the academic and technical staff of Pharmaceutics and Pharmaceutical Technology and in particular, to Dr. Ann-Marie Healy, Brian Canning, Derek Coss and Pat Quinlan, for their assistance during the course of my research. I would like to thank Ingrid Hook for use of the WinSEEDLE v5.1a software (Regent Instruments, Inc., Canada). I also wish to thank Neal Leddy of the Centre for Microscopy and Analysis for his help with SEM and EDX and Oliver Quinn, Risteard Prendergast and Rosemary Heneghan who worked with me on various topics related to the research presented in this thesis.

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      7.2.2.2 Pellet Sphericity
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PRESENTATIONS AND PUBLICATIONS ASSOCIATED WITH THIS THESIS

Oral Presentations


Byrne, R.S., Deasy, P.B., 2004. Use of pelletized porous materials for extended drug delivery. 26th Joint Research Seminar, Queen’s University Belfast, April 2004.

Poster Presentations

Byrne, R.S., Deasy, P.B., 2002. Use of commercial porous ceramics in sustained drug delivery. 24th Joint Research Seminar, Queen’s University Belfast, March 2002.


Publications


ABBREVIATIONS AND SYMBOLS

\( \alpha \)  \quad \text{alpha} \\
\( \beta \)  \quad \text{beta} \\
\( \Delta \rho \)  \quad \text{density difference between continuous and disperse phase} \\
\( \theta \)  \quad \text{theta} \\
\( \mu \text{eq} \)  \quad \text{microequivalents} \\
\( \mu \text{g} \)  \quad \text{micrograms} \\
\( \mu \text{L} \)  \quad \text{microlitres} \\
\( \mu \text{m} \)  \quad \text{micrometres} \\
\( \sigma \)  \quad \text{surface tension} \\
\( ^\circ \)  \quad \text{degrees} \\
\( ^\circ \text{C} \)  \quad \text{degrees centigrade} \\
\( +/- \)  \quad \text{plus or minus} \\
\( \text{A} \)  \quad \text{projected area} \\
\( \text{AIC} \)  \quad \text{Akaike information criterion} \\
\( \text{Al} \)  \quad \text{aluminium} \\
\( \text{ANOVA} \)  \quad \text{analysis of variance} \\
\( \text{Ar} \)  \quad \text{argon} \\
\( \text{C} \)  \quad \text{carbon} \\
\( \text{CD} \)  \quad \text{coefficient of determination} \\
\( \text{Cl} \)  \quad \text{chlorine} \\
\( \text{cm} \)  \quad \text{centimetres} \\
\( \text{cps} \)  \quad \text{centipoise} \\
\( \text{Cs} \)  \quad \text{caesium} \\
\( \text{Cu} \)  \quad \text{copper} \\
\( D_{50} \)  \quad \text{pore diameter below which 50% of the cumulative intraparticulate mercury intrusion occurred} \\
\( d \)  \quad \text{droplet diameter} \\
\( \text{df} \)  \quad \text{degrees of freedom} \\
\( \text{EDX} \)  \quad \text{energy dispersive x-ray} \\
\( E_0 \)  \quad \text{Etövös number} \\
\( \text{F}_b \)  \quad \text{% burst release}
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
<td>iron</td>
</tr>
<tr>
<td>G</td>
<td>gauge</td>
</tr>
<tr>
<td>g</td>
<td>grams (or acceleration due to gravity in Eqn. 7.2a)</td>
</tr>
<tr>
<td>H</td>
<td>hydrogen</td>
</tr>
<tr>
<td>h</td>
<td>hour/hours</td>
</tr>
<tr>
<td>Hg</td>
<td>mercury</td>
</tr>
<tr>
<td>K</td>
<td>potassium</td>
</tr>
<tr>
<td>k</td>
<td>kinetic constant</td>
</tr>
<tr>
<td>k₁</td>
<td>first order release rate constant</td>
</tr>
<tr>
<td>k_H</td>
<td>diffusional release rate constant</td>
</tr>
<tr>
<td>kV</td>
<td>kilovolts</td>
</tr>
<tr>
<td>L</td>
<td>litres (or pellet length in Eqn. 7.2b)</td>
</tr>
<tr>
<td>Li</td>
<td>lithium</td>
</tr>
<tr>
<td>log</td>
<td>logarithm to the base 10</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m</td>
<td>metres</td>
</tr>
<tr>
<td>mA</td>
<td>milliamperes</td>
</tr>
<tr>
<td>mbar</td>
<td>millibars</td>
</tr>
<tr>
<td>Mg</td>
<td>magnesium</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>M_r/M_∞</td>
<td>fraction of drug released</td>
</tr>
<tr>
<td>min</td>
<td>minute/minutes</td>
</tr>
<tr>
<td>ml</td>
<td>millilitres</td>
</tr>
<tr>
<td>mm</td>
<td>millimetres</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>mN</td>
<td>millinewtons</td>
</tr>
<tr>
<td>Mo</td>
<td>molybdenum</td>
</tr>
<tr>
<td>MPa</td>
<td>megapascals</td>
</tr>
<tr>
<td>MSC</td>
<td>model selection criterion</td>
</tr>
<tr>
<td>mtor</td>
<td>millitorr</td>
</tr>
<tr>
<td>mV</td>
<td>millivolts</td>
</tr>
<tr>
<td>N</td>
<td>nitrogen (or normality in the case of solutions)</td>
</tr>
<tr>
<td>n</td>
<td>number of replicates</td>
</tr>
<tr>
<td>Na</td>
<td>sodium</td>
</tr>
</tbody>
</table>
Ni  nickel
nm  nanometres
O   oxygen
PDGF platelet-derived growth factor
pF  picofarads
PFA pore forming agent
pH  minus log of hydrogen ion concentration
pK_a dissociation exponent for a weak acid
P_m perimeter length
p.s.i. pounds per square inch
PVP polyvinylpyrrolidone
Rh  rhodium
rpm revolutions per minute
s   second/seconds
S.D. standard deviation
SEM scanning electron microscopy/micrograph
Si  silicon
SS  total sum of squares
t  time
Ti  titanium
U.C. ultracentrifuge
UV ultraviolet spectroscopy
V   vanadium
v/v  volume per volume
W   pellet width
w/v  weight per volume
w/w  weight per weight
XRD X-ray diffraction
y   actual value
y'  transformed value
Zr  zirconium
INTRODUCTION

1.1 ORIGIN AND SCOPE OF THE WORK

Drugs are rarely administered as the pure substance alone but instead are given as formulated preparations, which are referred to as drug delivery systems. These systems have many important functions. For example, the offensive taste or odour of a drug substance can be concealed using an appropriate system (Ansel et al., 1999). Drug delivery systems can also improve the therapeutic efficacy of a drug by changing its bioavailability (Deasy, 1984), which can be critical to the success of a drug. Thus, novel drug delivery systems, which can modify drug release, are the subject of much research.

Porous ceramics are a class of materials, which have found applications in many areas (Sepulveda and Binner, 1999). These applications include acting as catalyst supports, filters for molten metals and hot gases, refractory linings for furnaces, and porous implants in the area of biomaterials (Uchida et al., 1990; Torniainen et al., 1994; Ishizaki et al., 1998b; Rice, 1998). They may also be suitable for use as modified release drug delivery systems. Recent research on porous ceramics has shown that they can extend drug release (Itokazu et al., 1999; Netz et al., 2001; Paul et al., 2002). However, this research focussed on non-oral drug delivery despite the fact that the oral route is the most commonly used route for drug delivery (York, 2002).

Therefore, the initial focus of this research was to demonstrate that porous ceramic pellets could be effective modified release oral drug delivery systems. A number of pelletized porous ceramics were obtained from commercial sources and their drug delivery potential was assessed. These initial investigations formed the basis for further research on pelletized dosage forms. The aim was to improve the acceptability of porous ceramic pellets in the pharmaceutical industry by using pharmaceutical...
excipients and production processes. The main excipients used in pellet formulations were the aluminosilicate clay minerals, kaolin and halloysite. Kaolin has established pharmaceutical uses (Handbook of Pharmaceutical Excipients, 2000), while halloysite has recently been shown to modify the release of active agents (Price et al., 2001; Levis and Deasy, 2003). Two production processes, extrusion-spheronization and cryopelletization, were investigated. Extrusion-spheronization is a widely used pharmaceutical pelletization process (Ku et al., 1993) that produces porous pellets (O'Connor and Schwartz, 1989). In addition to producing pellets by this technique, the effect of pore forming agents on the pellet structure and on drug loading and release was also examined. The second process, cryopelletization, is a novel pelletization procedure, which involves freezing droplets of aqueous solutions or suspensions of various materials. The resulting frozen pellets are then freeze dried to give a porous pellet (Knoch, 1994). The cryopelletization studies also investigated the effect of changes in formulation parameters on pellet structure, drug loading and release.
1.2 MODIFIED RELEASE DRUG DELIVERY SYSTEMS

This introduction focuses primarily on those topics relevant to this research, which are not commonly encountered in pharmaceutics. Therefore, the discussion of modified release drug delivery systems is brief while the discussion of, for example, porous ceramics is more comprehensive.

1.2.1 Introduction

Modified release systems have found applications in many industries. They are used to change the rate at which a material is released or the environmental conditions, which trigger its release. For example, the material could be released over a period of weeks rather than minutes or when a certain temperature is reached. The industries in which these systems have been most widely applied are the pharmaceutical, agricultural and cosmetic industries. In particular, massive resources have been invested in the development of modified release drug delivery systems (Duncan and Seymour, 1989). This is due to the many benefits, which they offer when compared with conventional drug delivery systems.

1.2.2 Classes of Modified Release Drug Delivery Systems

Many preparations, which provide modified release drug delivery, are commercially available ranging from Nu-Seals® Aspirin to Estraderm TTS®, which contains estradiol (British National Formulary, 2003). Their commercial success relates to the therapeutic benefits they can offer the patient. These benefits are dependent upon the particular modified release drug delivery system employed.

These systems can be divided into a number of classes. Firstly, there are extended release systems, which make the drug available over an extended period of time (United States Pharmacopeia, 2003). Such systems offer a number of benefits to the patient. When a conventional dosage form is taken there are peaks and troughs associated with each dose. These peaks can reach the toxic range leading to adverse effects. This is especially true where there is a build up of drug over time. The troughs can fall into the subtherapeutic range leading to a reduction in therapeutic efficacy of the drug. Extended
release systems can reduce these peaks and troughs by providing a gradual release of drug over time, which maintains plasma levels within the therapeutic range (Fig. 1.2a). Associated with this is a reduction in the frequency of dosing. This can mean the patient misses less doses and hence has improved compliance (Ansel et al., 1999).

Figure 1.2a. Hypothetical plasma levels of a drug following multiple dosing using an immediate release drug delivery system (solid line) and a single dosing from an extended release drug delivery system (dashed line) (Deasy, 1984).

A second class of modified release drug delivery systems is delayed release systems. These do not release drug immediately but rather at a later time. For example, if a drug when given orally irritates the gastric mucosa, its release can be delayed until it reaches the small intestine (United States Pharmacopeia, 2003). This reduces the adverse effects experienced by the patient. A third class of system is a targeted release system, which can concentrate drug at a particular site in the body (Ansel et al., 1999). Such systems have been used in the treatment of inflammatory bowel disease where it is necessary to target drug delivery to the large intestine in order to reduce systemic absorption of the drug. These systems can increase the therapeutic efficacy of a drug and decrease the adverse effects experienced by a patient. The final type of modified release drug delivery system is a repeat action system. This can release a number of doses of drug at different time points. Usually a dose is released soon after administration with further doses being released at later stages. These later doses can be immediate release or
extended release. The principal advantage of such systems is they reduce the dosing frequency leading to improved patient compliance (Ansel et al., 1999; Collett and Moreton, 2002).

1.3 CLAY MINERALS

1.3.1 Introduction

Clay minerals are the most abundant minerals found at the surface of the earth. They are major components of soils, sedimentary rocks and the pelagic oozes blanketing the oceans basins. They are formed by the weathering of minerals such as feldspars and other silicate minerals. The key properties, which define clay minerals, are that they have a grain size less than 2 μm in the largest dimension and a phyllosilicate or sheet structure. For the most part, clay minerals are hydrated aluminosilicates or magnesium silicates with layered structures. The principal groups are smectites such as beidellite and saponite, illite, chlorite, kaolinite and sepiolite-palygorskite. Clay minerals have a variety of uses ranging from long established uses in the production of building materials and ceramic products, to newer applications in catalysis and in the disposal of toxic and radioactive wastes (Velde, 1992a; Moore and Reynolds, 1997a).

1.3.2 Chemical Composition and Structure of Clay Minerals

Clay minerals are composed of silica (SiO₂) with elements such as aluminium, magnesium, iron and potassium also being present depending on the mineral in question. Table 1.3a gives an overview of the clay mineral types and their dominant elements, besides those contained in silica.
Table 1.3a Dominant elements found in the principal clay minerals (Adapted from Velde, 1992b).

<table>
<thead>
<tr>
<th>Clay mineral</th>
<th>Dominant elements</th>
</tr>
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<tbody>
<tr>
<td>Smectites</td>
<td></td>
</tr>
<tr>
<td>Beidellite</td>
<td>Al</td>
</tr>
<tr>
<td>Saponite</td>
<td>Mg, Al</td>
</tr>
<tr>
<td>Illite</td>
<td>K, Al (Fe, Mg minor)</td>
</tr>
<tr>
<td>Chlorite</td>
<td>Mg, Fe, Al</td>
</tr>
<tr>
<td>Kaolinite</td>
<td>Al</td>
</tr>
<tr>
<td>Sepiolite-palygorskite</td>
<td>Mg, Al</td>
</tr>
</tbody>
</table>

While the elemental and chemical composition is an important aspect of the characteristics of clay minerals, their structure is equally important. As already mentioned, the clay minerals have a phyllosilicate structure. This sheet like structure is created from tetrahedral and octahedral molecular units. The tetrahedral unit consists of a silicon atom surrounded by four oxygen atoms (Fig. 1.3a). Although $\text{Si}^{4+}$ is the dominant cation found in the tetrahedral, $\text{Al}^{3+}$ frequently substitutes for it while $\text{Fe}^{3+}$ occasionally substitutes for it.

![Tetrahedral arrangement of silicon and oxygen](Velde, 1992b).

The tetrahedral structures are linked to one another by covalent bonding through sharing of oxygen atoms. The shared oxygen atoms form a plane and are referred to as basal oxygens (Fig. 1.3b). On the opposite side of the linked tetrahedral, apical oxygens are found. The apical oxygen atoms can then link with another series of cations, thereby linking the tetrahedra with another layer of cations.
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Silicon ions

Basal oxygens

Apical oxygens

Figure 1.3b. Linked silica tetrahedral (Velde, 1992b).

In each clay mineral structure there are also octahedral polyhedrons, which are formed by cations coordinated with six oxygens or hydroxyl units (Fig. 1.3c). The cations are usually Al\(^{3+}\), Mg\(^{2+}\), Fe\(^{2+}\) or Fe\(^{3+}\), but other transition elements can also be present. As with the tetrahedral structure, the octahedral structure can be interlinked by shared anions to form a sheet structure.

Figure 1.3c. Octahedrally coordinated cation (Velde, 1992b).

The structure of clay minerals is comprised of linked tetrahedral and octahedral sheets with the apical oxygen in the tetrahedral replacing a hydroxyl ion in the lower plane of the octahedral sheet (Fig. 1.3d). This linkage is repeated along the length of each sheet creating a layer silicate structure. The assembling of one tetrahedral sheet with one octahedral sheet is referred to as a 1:1 layer silicate structure. In a 2:1 layer silicate, there are two tetrahedral sheets to one octahedral sheet (Fig. 1.3e).
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Figure 1.3d. Linkage between tetrahedra and octahedra through a common oxygen atom to form a layer silicate structure (Velde, 1992b).

Stacking of these layer silicate structures creates the final three-dimensional crystal structure. The 1:1 layer silicate structures stack through hydrogen bonding between oxygen ions and hydrogen ions found at the surface of tetrahedral and octahedral sheets, respectively. The 2:1 layer silicate structures stack by bonding through interlayer cations, which are inserted in the basal oxygen array to compensate for charge imbalances in the sheet structure. Two types of ions are found between the layers of basal tetrahedral oxygens. These are tightly fixed ions, which are almost always
potassium and exchangeable ions, which are more varied. They can be either monovalent or divalent and are normally surrounded by water molecules. Calcium is predominant, although sodium and magnesium are also common (Velde, 1992b; Moore and Reynolds, 1997b).

1.3.3 Surface Charge of Clay Minerals

The surface charge of clay minerals has two potential origins, which relate directly to their structure. Firstly, a cation in the mineral structure can be replaced by a cation with one less valence charge. For example, if a Si\(^{4+}\) ion in the tetrahedral sheet is replaced by an Al\(^{3+}\) ion and this is not compensated for in the octahedral sheet a net negative charge results. This type of substitution results in layer charge, which is referred to as permanent charge. The excess negative charge is compensated for by adsorption of cations in layer surfaces, i.e. in the interlayer space. In the presence of water these cations may be exchanged with other cations in solution. The capacity of a clay mineral to exchange cations is referred to as its cation exchange capacity and is an important property of the clay minerals. Secondly, charges occur at the edges of mineral particles where the layer structures end as broken bonds. These bonds are neutralised with hydrogen and hydroxyl ions. The resulting charge is referred to as variable charge as it is a function of the pH of the medium in which the clay mineral is immersed. For example, if there is an excess of hydrogen ions in the medium the mineral will have a net positive charge as these ions attach themselves to the edge surfaces. The differing origin of the surface charges in clay minerals indicates that it is possible for the flat layer surfaces to have a negative charge with the edge surfaces having a positive charge. However, clay minerals tend to have a net negative charge over a wide pH range as the vast majority of charge is due to flat layer charge rather than edge charge (van Olphen, 1963a; Moore and Reynolds, 1997b).

1.3.4 Kaolinites

The kaolinites are a group of clay minerals comprising kaolin, halloysite, dickite and nacrite. They all have a 1:1 layer silicate structure with the main difference between the various group members being in the stacking geometry of the layers. A key feature of this group is they have little substitution in their structure. The tetrahedral layer is
composed principally of Si ions while the octahedral layer is composed almost completely of Al ions. However, small amounts of ferric iron can be present in the octahedral layer depending on the kaolinite in question and its origin (van Olphen 1963a; Velde, 1992b). Kaolin and halloysite are the main focus of the research presented in this thesis and therefore are discussed in more detail.

Kaolin is characteristically a pseudohexagonal structure with straight edges (Fig. 1.3f). It has an empirical formula of $\text{Al}_4\text{Si}_4\text{O}_{10}(\text{OH})_8$ (Bates et al., 1950) and in comparison with other clay minerals, such as sepiolite, kaolin has a relatively low surface area (Murray, 2000). As already mentioned, there is little substitution in the kaolinite group of minerals meaning kaolin has minimal permanent charges and a relatively low cation exchange capacity of 10 μeq/g although this can increase to 100 μeq/g due to the presence of impurities (van Olphen, 1963a; Deer et al., 1992; Velde, 1992). The low substitution in kaolin means it contains relatively low levels of iron, with increasing iron content being associated with increasing structural disorder. Typically, the highest iron content of kaolin is 2% Fe$^{3+}$, which is found in kaolin extracted from tropical soil (Newman and Brown, 1987).

Figure 1.3f. SEM of Czech kaolin from the Pilsen basin area (Pabst et al., 2000).

The traditional use of kaolin is in ceramic production. It is used, in particular, to produce whiteware, sanitaryware, insulators, pottery, and refractories. Its other key use
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is in coating paper where the relatively low viscosity of kaolin suspensions is a beneficial characteristic. In the past, kaolin was widely used as a filler in paper. However, it is largely being replaced by calcium carbonate due to changes in the wood pulp manufacturing process. Kaolin is also used as a functional filler and extender in paint, plastics, rubber and ink. An area in which the use of kaolin has grown rapidly is as a raw material in the production of fiberglass where it supplies both silica and alumina, which are needed in the fiberglass formulation. Kaolin is expected to find increasing uses in dispersing organophilic and hydrophobic systems (Murray, 2000). Kaolin has a number of pharmaceutical applications. Its principal use was as an adsorbent in anti-diarrhoeal preparations. However, this use has declined as it is now recognised that such therapy is of limited value (Sweetman, 2002). Kaolin is still used topically in dusting powders and in poultices (Handbook of Pharmaceutical Excipients, 2000).

Halloysite differs from kaolin and other members of the kaolinite group in a number of ways. Firstly, the hydrated form of halloysite, endellite, possesses water between the 1:1 layer silicate structures. This, in part, contributes to the tubular structure of endellite, which is not observed in other members of the kaolinite group. Other factors, which contribute to this structure are a “misfit” between the silicon-oxygen and aluminium-hydroxyl layers in the 1:1 structural unit and the larger intervening distance between the 1:1 units in endellite as compared with kaolin (Bates et al., 1950). This interlayer water is easily removed near 100 °C to give the dehydrated form of halloysite, known as metahalloysite. The strain caused by the loss of interlayer water contributes to a change in formation with metahalloysite consisting of tubes, which have commonly collapsed or have split and partially or completely unrolled. These changes explain the irreversibility of the dehydration process (Bates et al., 1950). The empirical formula of endellite is $\text{Al}_4\text{Si}_4\text{O}_{10}(\text{OH})_8\cdot 4\text{H}_2\text{O}$, while that of metahalloysite is $\text{Al}_4\text{Si}_4\text{O}_{10}(\text{OH})_8$. Metahalloysite is commonly referred to as halloysite and throughout this thesis this convention is adopted. Fig. 1.3g shows an SEM of the tubular structure of halloysite.
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Figure 1.3g. SEM of halloysite from New Zealand (Levis and Deasy, 2002).

Halloysite contains a relatively high amount of ferric iron (up to 15%) compared to kaolin, with the iron content being dependent on the morphology of the halloysite. The long and short tubular forms contain low levels of iron while higher contents are found in halloysites with spheroidal, “crinkly film” and “crumpled lamellar” morphologies (Newman and Brown, 1987).

Halloysite has a higher surface area and higher cation exchange capacity in comparison to kaolin, although this is the subject of some contradictory observations. The true exchange capacity appears to be about 90-95 μeq/g, with values of 580 μeq/g reported for iron-rich halloysite (Newman and Brown, 1987; Harvey, 1996). The increase in cation exchange capacity relative to kaolin is due to the non-stoichiometric substitution of Al$^{3+}$ by Fe$^{3+}$. This occurs to a greater extent in halloysite than in kaolin.

The principal use of halloysite is in the production of high quality porcelain and bone china. It can be used in similar applications to kaolin, however it is inferior to kaolin in many of these. In addition to these uses, it was one of the earliest clay minerals used as a catalyst and small amounts are still used in this area (Harvey, 1996). Recently, halloysite has shown potential in extended chemical delivery applications. Price et al. (2001) demonstrated it could provide extended delivery of oxytetracycline HCl, khellin and nicotinamide adenine dinucleotide. Levis and Deasy (2003) expanded this work to show halloysite could provide extended delivery of the drugs, diltiazem HCl and propranolol HCl. In a continuation of this research, halloysite based products with dental and agricultural applications have been produced (Kelly, 2002; Salter, 2003).


1.4 POROUS CERAMICS

1.4.1 Definition of a Porous Ceramic

Ceramics are produced by firing clay minerals, such as kaolin, or inorganic, non-metallic materials, such as alumina, at high temperatures. The cellular ceramics are a particular type of ceramic, which are comprised of various arrangements of space-filling polygons. They can be divided into two broad groupings, ceramic honeycombs and porous ceramics. In ceramic honeycombs the cells are in a two-dimensional array, whereas porous ceramics are comprised of a three-dimensional array of hollow polygons. Porous ceramics are usually sub-divided into two further categories, depending on whether or not the individual cells possess solid faces. If the ceramic material is contained only in cell edges, the material is termed open-cell. If the cell faces are present, the porous ceramic is termed closed-cell, as the individual cells are isolated from each other. It is possible that porous ceramics can be partly open or partly closed (Montanaro et al., 1998). Examples of each type of cellular ceramic configuration are shown in Fig. 1.4a.
1.4.2 General Features of Porous Ceramic Production

Porous ceramics have been produced from many materials such as cordierite, mullite, silicon carbide and alumina, and by various processing routes such as capsule-free hot isostatic pressing, gelcasting, the polymeric sponge method, aerogel and sol-gel methods (Montanaro et al., 1998). Each method has the same principal stages with slight variations differentiating the methods.

The first key stage is preparation of a ceramic slurry. In general, the ceramic slurry consists of the ceramic raw material, which is a powder, the dispersion medium and additives (Montanaro et al., 1998). The properties of this powder strongly influence the properties of the resultant porous ceramic. The pore size of the porous ceramic is determined mainly by the particle size of the starting powder while pore shape is governed by particle shape. Both these factors influence the pore size distribution. The surface properties of the ceramic powder influence slurry characteristics, as slurry
properties are governed by the interaction between particles and a liquid matrix (Ishizaki et al., 1998a). It is essential that the slurry is a stable dispersion of the ceramic powder. This is achieved by ensuring the particles are of colloidal size, by adding a deflocculant and by removing a flocculating amount of salt, if present (van Olphen, 1963b). The use of a deflocculant facilitates a high solids loading of the slurry, which is necessary in porous ceramic production. Besides deflocculants other additives can be used in preparing the ceramic slurry. For example, a binder can give strength to the ceramic structure after drying and prevent collapse during volatilisation of the organic portion. Additives can also be used to alter the final sintered porous ceramic properties (Montanaro et al., 1998).

Once prepared, the ceramic slurry is subjected to thermal processing. This is comprised of drying, burning out of the volatile components and sintering of the ceramic portion. This step is essential as it develops a self-supporting ceramic network. Therefore, an important property of a ceramic slurry is that it sinters easily and is able to withstand the thermal processing conditions (Montanaro et al., 1998). The first thermal process, drying, produces a ‘green body’ that is in the desired shape for the final sintered product. This ‘green body’ is porous and usually has an open porosity of 25-70% v/v. Desirable properties of the green body are low density and homogenous packing of particles. The second stage of the thermal cycle is burning out of the volatile components with sintering being the final stage. During sintering particles in a powder compact can be bonded at elevated temperatures below the melting point. As a result the ‘green body’ is densified. The driving force for sintering is the reduction of the surface area associated with pores. This change in surface area causes a reduction in the number of atoms which lack sufficient neighbours and hence, a reduction in surface energy. There are various kinds of fabrication methods for porous materials by sintering. For example, to increase open porosity, sintering is done at lower temperatures or for a shorter period than the conventional sintering process for dense materials. These conditions allow particle bonding without significant densification (Ishizaki et al., 1998a).
1.4.3 Specific Porous Ceramic Production Techniques

There are many techniques by which porous ceramics have been produced. These techniques have the general features discussed above but differ in certain aspects. A widely used production method consists of impregnating a polymeric sponge with a ceramic slurry. The sponge serves as a template for the porous ceramic. Therefore, its characteristics are critically important. Once the optimal sponge is chosen it is immersed in a ceramic slurry, which is compressed while submerged in order to fill all the sponge pores. The sponge is then removed from the slurry and excess material squeezed from the sponge by means of a rolling mill. Following this, drying is carried out in the air or in an oven. After this, thermal processing, which leads to the burning out of the organic portion and the sintering of the ceramic skeleton takes place. The pore size of the resulting porous ceramic is determined by the pore size of the sponge (Montanaro et al., 1998). A flow chart summarising this process is shown in Fig. 1.4b.

In a modification of this method the sponge is produced following the incorporation of the ceramic phase into the sponge precursors. A drawback of this procedure is that the mixing does not provide the high shear stress needed to break up agglomerates into ceramic powders. Therefore, the microstructure can contain agglomerates. A further problem is that the time permitted for mixing is limited by the onset of the sponge forming reaction (Peng et al., 2000).

![Flow chart](Image)

**Figure 1.4b.** Production of a porous ceramic using a polymeric sponge template.
A second widely employed production method is gelcasting. This involves the formation of a gel in an impermeable mould. The gels used in porous ceramic production consist of dense colloidal particles of various shapes, which are linked to each other so as to form a very porous three-dimensional network (Pierre, 1997). Numerous methods have been used to form these gels. One such method uses the polymerisation of organic monomers to form the gel. Commonly used monomers include methyl methacrylate, butyl acrylate, acrylamide and other acrylates. These water soluble monomers are incorporated into the ceramic slurry, which is then foamed either by evolution of a gas or by mechanical frothing. Polymerisation is then brought about by an initiating system. There is usually a period of inactivity between the addition of reagents and the beginning of the polymerisation reaction. This period represents the time available for changes in the bubble structure and is an important determinant of the pore size distribution of the ceramic. For example, when the films surrounding bubbles remain intact until solidification, a closed-cell porous ceramic is formed. Open-celled porous ceramics are produced when the films rupture partially. The length of this period can be controlled, primarily, by altering the concentration of initiator and catalyst. This allows for good control of the final pore size distribution of the ceramic (Sepulveda and Binner, 1999). A flow chart summarising this process is shown in Fig. 1.4c.

![Flowchart](image_url)

Figure 1.4c. Production of a porous ceramic by gelcasting where polymerisation of organic monomers is used to form the gel (Sepulveda and Binner, 1999).
Polysaccharide additives can also be used to form gels. They are particularly attractive as they are safe, easily obtainable and cheap. However, the gels formed often have low strength. While this could be overcome by increasing the amount of polysaccharides in solution, this is undesirable as it increases slip viscosity, causes shrinkage of the formed bodies and creates problems with organic burnout. An alternative solution to the problem of low strength is to use a polysaccharide mixture. For example, mixtures of agar and galactomannan form strong gels, while requiring relatively low amounts of polymers (Olhero et al., 2000). The particular advantage of gelcasting over the use of a polymer sponge is that gelcasting allows for the production of ceramics with small pores. Such porous ceramics cannot be made using polymer sponges (Sepulveda and Binner, 1999).

Porosity can also be created within ceramics using pore forming agents (PFA). These are included in the ceramic slurry and are then evaporated or burned out during sintering. As a result pores are formed. PFA’s can be solid or liquid with the choice depending upon the particular application. Solid PFA’s are suitable for the production of porous materials with relatively large pores and high open porosity, while liquid PFA’s allow for the creation of fine pores in a material. Examples of PFA’s include potato starch, salicylic acid, ammonium tetrachloride, dextrin and liquid paraffin (Ishizaki et al., 1998a). A benefit of using certain PFA’s is that they can also act as a binder. For example, starch can act as both a binder and PFA. This is based on the gelling ability of starch in water. Starch granules undergo a rapid and irreversible swelling by water uptake when heated between 55 and 80 °C. By mixing ceramic powders and starch in a water suspension, pouring it into a mould and heating it to 60-80 °C, the starch particle will swell by water uptake. This swelling removes water from the slip causing the ceramic particles to stick together and consequently consolidate into a solid body (Lyckfeldt and Ferreira, 1998).

A problem with the production methods already discussed is that although they can produce highly porous ceramics, the mechanical strength of these ceramics is often low. A production technique, which can satisfy both these requirements is hot isostatic pressing. It involves pressing the green body under high pressure, e.g. 100 MPa in Ar, at high temperatures, e.g. 1300 °C. This high gas pressure limits densification of the green
body while at the same time enhancing bridging between particles within the green body. It is the enhancement of bridging between particles that increases the mechanical strength of the ceramic (Biasini et al., 1997).

In conclusion, combining the proper ceramic materials and processing method can produce porous ceramics with the desired properties (Montanaro et al., 1998). A key point is that the fabrication method used determines the range of porosity, the pore morphology and pore size distribution.

1.4.4 Production of Porous Ceramic Pellets

A range of techniques have been developed for the production of porous ceramic pellets with an obvious method being to crush sintered porous ceramic blocks to produce granules. This is a conventional fabrication technique for porous ceramic pellets (Liu, 1996) and has been employed to produce porous ceramic pellets for drug delivery applications (Queiroz et al., 2001). However, this method has a disadvantage in that it produces particles with an irregular morphology (Zhang et al., 1989).

Therefore production techniques, which overcome this problem, have been developed. Zhang et al. (1989) described a method whereby hydroxyapatite powder was wetted with water and subjected to vibration and rolling. This gave semi-finished pellets, which were then sintered to give the final product. The final granules were spherical, had diameters in the range 0.5 to 2 mm, porosities of 12% v/v and pores ranging in size from 5 to 50 μm. Paul and Sharma (1999) developed a production technique whereby a hydroxyapatite/chitosan slurry was dispersed in a mixture of light and heavy liquid paraffin. Glutaraldehyde, which is a cross linking agent for chitosan, was added and pellets in the size range 212 μm to 1 mm were formed. The pellets were then sintered, which burnt out the chitosan to give a porous hydroxyapatite pellet. Komlev et al. (2002) used a similar technique based on dispersing a hydroxyapatite/gelatin slurry in vegetable oil. Porous hydroxyapatite beads in the size range <50 μm to 2 mm were formed due to surface tension forces. The exact size range was dependent upon the production parameters employed. Liu (1996) used a drip-casting process to produce porous hydroxyapatite pellets. This involved dripping the ceramic slurry into a prefabricated plaster mould. The slurry was then dried resulting in spherical pellets. The
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Spherical shape was due to surface tension forces and the mould cavity geometry. Following sintering, the final pellets were in the size range 700 μm to 4 mm and had porosities in the range 24-76% v/v. A similar technique based on dripping the ceramic slurry into liquid nitrogen has also been used to produce porous hydroxyapatite pellets (Fabbri et al., 1994). This technique is known as cryopelletization and is a focus of research in this thesis. Therefore, it is discussed in more detail in Section 1.5.2.

1.4.5 Applications of Porous Ceramics

1.4.5.1 Non-Medical Applications of Porous Ceramics

Porous ceramics have many industrial applications from sound insulation (Takahara, 1994) to membrane reactors (Julbe et al., 2001). They have found numerous applications due to the wide range of properties they can have. These depend upon their composition and the method used in their fabrication. Closed cell porous ceramics have few applications relative to open cell ceramics. The former are principally used as lightweight thermal insulating materials with the latter being used as catalyst supports and filters among many other applications (Sepulveda and Binner, 1999).

The oldest application of porous ceramics is in thermal insulation. Their utility as thermal insulators is due to several factors, which combine to give porous ceramics low thermal conductivity. These are the low volume fraction of the solid phase, the small cell size and the low conductivity of gas enclosed within the cells (Gibson and Ashby, 1997b). The oldest examples of porous ceramic thermal insulators are refractory bricks. These are used for kilns and furnaces in many industrial fields. For example, in steel making the blast furnace and converter are constructed from refractory bricks. A wide range of ceramics are used in the manufacture of refractory bricks including alumina, mullite and zirconia (Ishizaki et al., 1998b). Newer thermal insulation applications of porous ceramics include their use as exhaust port liners in cars and complete manifold liners in diesel engines. Porous ceramic coatings on metal components have also been used as thermal insulators in, for example, engines (Rice, 1998).

More recently the sound absorption characteristics of porous ceramics have been recognised. Takahara (1994) found that a particulate aluminosilicate porous ceramic
fabricated by sintering could absorb sound. It was suggested that by controlling the
grain size, bulk density and bulk sample thickness of particulate porous ceramics their
sound absorptivity could be controlled. The ability to easily control the sound
absorptivity would be desirable for any large-scale applications. Aly (2000) reported
that zircon porous ceramics would be valuable sound absorbers for noise emitted from
jet engine exhaust ducts as they have good sound attenuation characteristics over the
audible frequency range. Coupled with this they are lightweight, and thermally and
mechanically stable at the high temperatures, which would be encountered in this
application.

A major industrial application of porous ceramics has been in filtration and separation.
The suitability of porous ceramics for such applications is dependent on their pore size
and pore size distribution. Since they are available with average pore sizes ranging from
nanometres to millimetres and various pore size distributions they have been employed
in numerous applications in this area ranging from gas separation to liquid filtration
(Ishizaki et al., 1998b). Their success relates to the many advantages they have over the
conventionally used materials such as organic membranes. In particular, they are
chemically inert and resistant to organic solvents. However, in addition to this, porous
ceramics are resistant to biological attack and steam sterilization. This is important in
the food and pharmaceutical industries where bacterial contamination must be
prevented (Wu and Lee, 1999).

Porous ceramics have been successfully used in the chemical industry as catalyst
supports and membrane reactors. Their usefulness in this field is associated with their
ability to withstand the high temperatures and chemically harsh conditions required in
some of these processes (Julbe et al., 2001). With regard to their use as catalyst
supports, the availability of porous ceramics with an interconnected highly porous
structure is particularly important. Such ceramics have a low resistance to fluid flow
and their tortuosity generates considerable turbulence. This is advantageous as it
enhances mass and heat transfer (Twigg and Richardson, 2002). There have been
numerous successful applications of porous ceramics as catalyst supports. Torniainen et
al. (1994) investigated the partial oxidation of methane in oxygen to carbon monoxide
and H$_2$ using various metal catalysts supported on an α-alumina porous ceramic. It was
found that using Rh or Ni as the metal catalyst, high and stable yields of H$_2$ were
obtained, demonstrating the suitability of these porous ceramic supported catalysts in this application.

While porous ceramics can act as catalyst supports or as separation membranes, they can also act as membrane reactors, which combine in the same unit the functions of catalysis and separation. This can give improvements in reaction rate, selectivity and yield for a range of reactions. Membrane reactors can be classified in terms of the main membrane functions and the relative placement of the membrane and catalyst. The main membrane functions as a product extractor or a reactant distributor or a contactor, which controls diffusion of reactants to the catalyst. With regard to the placement of the catalyst, it can be located on an inert membrane, dispersed in an inert membrane or the membrane can be inherently catalytic (Julbe et al., 2001). There have been numerous studies reporting the successful application of porous ceramic membrane reactors. For example, the isobutene yield from the dehydrogenation of isobutane was improved using a microporous zeolite membrane with the catalyst located on the membrane. The membrane functioned as a product extractor (Casanave et al., 1995).

An area in which a growing number of applications for porous ceramics are being found is as supports for biological materials. Bioremediation, which is the use of biological agents to remove or neutralize contaminants in soil or water, is a particularly promising area in which these supports have been used. For example, the white rot fungus, Phanerochaete chrysosporium, can degrade chlorinated lignins and low molecular weight chloroorganics, which are a major source of water pollution. However, the commonly used methods to immobilize this fungus are either not amenable to scale-up or are not rigid enough for use in large bioreactors. Porous ceramic spheres are more suitable for immobilization as they are chemically inert in physiological growth media, rigid with good crush strength, porous to facilitate mycelial attachment and reusable after removal of the fungus. It was found that excellent attachment of the fungal mycelium to the pellets occurred. The total lignin peroxidase activities observed in this system were comparable to those in nonimmobilized cultures (Cornwell et al., 1990).

It is also possible to immobilize enzymes on porous ceramic supports. These are then used as catalysts in chemical reactions. For example, the enzyme lipase is used in the preparation of chiral building blocks and enantiomerically pure synthetic and natural
products. Kamori et al. (2000) have immobilized lipase on a particulate porous ceramic support. They found there was increased binding of lipase to the porous ceramic support in comparison to other supports such as microemulsion-based gels or hydrophobic silica gels. The enzyme activity was also higher when immobilized on the porous ceramic support in comparison to free enzyme or when immobilized on other supports.

The non-medical applications of porous ceramics discussed above are by no means a complete list of their applications. The versatility of porous ceramics in terms of composition and structure means they are constantly finding new applications. For example, Reddy and Schmitz (2002) have reported their potential use as superconductors, which allow for the flow of current without resistance at temperatures near absolute zero. Figge et al. (1995) found that porous ceramics applied topically to mine tailings contaminated with high levels of zinc and other heavy metals could stimulate plant growth and germination. This would facilitate reconditioning of contaminated areas and a reduction in pollution of surrounding areas. Another developing application of porous ceramics is as humidity sensors. Their functionality is based on the fact that the electrical conductivity of metal oxides is affected by surrounding water vapour. A number of different porous ceramics have been developed for this purpose (Wu et al., 1991).

1.4.5.2 Medical Applications of Porous Ceramics

Although porous ceramics have many non-medical applications they, for the most part, have found only one medical application, which is in the repair of skeletal defects. These defects can arise from tumours, trauma, disease and birth defects, and make skeletal reconstruction necessary. While a number of techniques are currently used in skeletal reconstruction, each has associated drawbacks. For example, autografts taken from patient donor sites are widely used, but patient donor site morbidity and the limited material supply restricts the utility of this. Allograft bone obtained from tissue donors is also used. However, it is difficult to form into the desired shape, which is important in bone defect repair. There is also the possibility of transferring pathogens from the donor to the patient. Synthetic bone cements are also used, but failure at the bone cement interface and tribological (lubrication) effects can lead to long-term complications (Vail et al., 1999).
Porous ceramics can act as alternative materials for skeletal reconstruction overcoming the problems associated with the more commonly used materials mentioned above. The most widely used ceramics in skeletal reconstruction have been calcium phosphate based ceramics. The main calcium phosphate compounds, which have been used, are beta tricalcium phosphate and hydroxyapatite. The choice of compound depends on the desired properties of the porous ceramic. A combination of compounds can also be used. The main difference in the compounds is in their ability to be reabsorbed in vivo. Beta tricalcium phosphate porous ceramics are reabsorbed over a period of 6-18 months, while hydroxyapatite porous ceramics, on the other hand, are resistant to reabsorption in vivo (Moore et al., 2001). It is therefore possible to achieve controllable rates of reabsorption by using biphasic calcium phosphate ceramics consisting primarily of beta tricalcium phosphate and hydroxyapatite. These exhibit varying degrees of biodegradation depending on the beta tricalcium phosphate content (Liu, 1997).

There have been numerous studies in relation to the use of calcium phosphate based porous ceramics to repair bone defects. In an early study, the suitability of calcium aluminate, hydroxyapatite and beta tricalcium phosphate porous ceramics for bone replacement was assessed. The ceramics were implanted in the skulls of rats and rabbits for up to six months. It was found that no adverse biological response to the ceramics occurred with tissue ingrowth being observed throughout the pores of the ceramics. The particular suitability of calcium phosphate based ceramics for the repair of bone defects was demonstrated as they showed greater tissue ingrowth than the calcium aluminate porous ceramic. New bone growth was also observed within the pores of the ceramics. However, this was mainly in areas in which bone marrow was present indicating its importance in the formation of bone (Uchida et al., 1984). In more recent work, Vail et al. (1999) used selective laser sintering to fabricate porous ceramic implants from calcium phosphate powder microencapsulated with a polymer binder. The ability of these implants to augment alveolar ridge defects in canines was assessed with a view to establishing the safety and efficacy of the implants. The implants showed excellent biocompatibility. It was found that the implants were increasingly infiltrated with new bone over time. Mature mineralised bone was found throughout a significant portion of the implant, especially in macropores. There was also evidence of implant degradation and reabsorption. This is important as it indicates that ultimately the implant will be
entirely degraded and replaced with bone. Uchida et al. (1990) have reported the suitability of hydroxyapatite porous ceramics for the treatment of defects following removal of bone tumours. In this study on 60 patients, no adverse reactions to the ceramic were observed and no local recurrence of the tumour occurred after packing with the ceramic. The functional results were comparable to those of historical controls involving bone grafts other than autografts. Bone regeneration was found both in and around the implanted ceramic, which shows the ceramic aided the regeneration of bone in the defects. Collectively research into the use of calcium phosphate based porous ceramics for bone regeneration has shown they have osteointegrative and osteoconductive properties (Liu, 1997). The factors affecting these properties are the pore size, shape and connectivity as well as the ceramic bioactivity (Jun et al., 2003). Coupled with this, calcium phosphate based porous ceramics have shown excellent biocompatibility with no reports of systemic toxicity or foreign body reactions (Liu, 1997; Moore et al., 2001). As a result calcium phosphate based porous ceramics have been approved for use in humans as bone substitutes (Lasserre and Bajpai, 1998).

While most research has focused on the use of calcium phosphate porous ceramics alone in the healing of bone defects, they can also be used in association with other materials. This approach can overcome the problem of calcium phosphate porous ceramics having a low compressive strength, while at the same time taking advantage of their bioactive properties. Jun et al. (2003) investigated the use of hydroxyapatite porous ceramics reinforced with alumina and found that the compressive strength of porous ceramics containing alumina was significantly improved. At the same time, the coated implants had a similar bioactivity and osteoconductive property to hydroxyapatite porous implants. Fartash et al. (1995) demonstrated that titanium/hydroxyapatite composites were superior to titanium alone in terms of the bonding to bone in drilled holes in rabbit femur. The composites showed higher bond strength at early stages of the treatment. This was attributed to the bioactivity of hydroxyapatite, which contributed to the early bonding strength to bone. Similar bonding strengths were observed at late stages in the treatment. Hence the development of long-term bonding strength was attributed to the high chemical stability of titanium dioxide. Takaoka et al. (1996) investigated the benefit of coating alumina ceramics with porous hydroxyapatite with a view to improving the border between the alumina ceramic and bone. The coated ceramic showed improved osteogenic capacity compared
with the uncoated ceramic. This indicated that the coated ceramic would improve the fixation of alumina ceramics. This would be of benefit in, for example, total joint replacement in which loosening of the replacement joint is a common problem.

Porous ceramics have also been used in a novel application in orthodontics. In orthodontic treatment an arch wire is frequently used to apply a gentle force to teeth causing movement. The wire is placed in slots in brackets, which are bonded to the tooth surface. These brackets can be stainless steel or ceramic. However, ceramic brackets are more acceptable to patients as they are transparent. The principal drawback of ceramic brackets is the high bond strength between the bracket and the tooth. This had led to complications during bracket removal, such as enamel fracture. Arici et al. (1997a) developed an open porous ceramic layer, which was interposed between the bracket and tooth. The pores of the ceramic were filled with adhesive, which held the bracket firmly to the tooth during treatment. During bracket removal the porous ceramic layer was crushed by the action of conventional pliers, which reduced the force required to remove the bracket. In vitro performance testing showed that brackets held using these porous ceramic layers could be bonded to enamel sufficiently strongly for clinical application and could be safely removed without damage to enamel (Arici et al., 1997b). In a second dental application of porous ceramics, Tanaka et al. (1993) used a porous ceramic filled with various resins as a substitute for human and bovine teeth in the pre-clinical cutting training of dental students. Some of the composites prepared were found to well simulate the hardness and cutting behaviour of bovine enamel. Tanaka et al. (1993) speculated that the composites were suitable for use in dental pre-clinical cutting exercises and that they might also have potential uses in the production of machined dental prostheses.

1.4.5.3 Porous Ceramics in Bioactive Agent Delivery

The ability of porous ceramics to act as delivery systems for bioactive agents, such as drugs, has recently become a focus for research. Their usefulness in this area stems from their porosity, which allows for materials to be loaded into the ceramics. The majority of research has focused on loading skeletal implants, as this has been the principal medical application of porous ceramics. A benefit of incorporating bioactive agents in these implants is that it would allow for their targeted release within the bone.
For example, an anticancer agent could be included to prevent the re-growth of cancerous cells following tumour excision. A second advantage of this targeting of release is that effective local concentrations of drugs may be achieved, which otherwise could not be, say by parenteral administration. For example, infected bone has an uncertain blood circulation resulting in antibiotics not reaching the target site (Shinto et al., 1992).

The most commonly employed technique for incorporating bioactive agents within these porous ceramics has been the vacuum impregnation technique. In this method the porous ceramic is placed in the bioactive agent solution and a vacuum is applied. This leads to replacement of the air in the ceramic pores with bioactive agent solution. The ceramic is then removed from the solution and dried leaving the agent deposited within the pores (Itokazu et al., 1999). A less commonly used approach is to place the bioactive agent within a cavity in the porous ceramic. The cavity is then sealed with, for example, a photo resin (Shinto et al., 1992; Netz et al., 2001). In another technique the porous ceramics are left to stand in bioactive agent solution at atmospheric pressure for a time. They are then removed and dried (Queiroz et al., 2001). The final technique, which has been employed to load porous ceramics is to centrifuge the ceramic in the presence of a loading solution containing the bioactive agent (Itokazu et al., 1994).

Using these loading techniques relatively large calcium phosphate porous ceramic bodies intended for implantation have been loaded with anticancer agents such as Adriamycin, cisplatin, methotrexate and 5-fluouracil (Yamamura and Yotsuyanagi, 1992; Itokazu et al., 1999; Landi et al., 2000; Netz et al., 2001). Their potential application is in inhibiting tumour growth following surgical removal of a cancerous region of bone. The antibiotics cefoperazone sodium, cefotiam, flomoxef sodium, gentamicin sulphate and isepamicin sulphate has also been loaded into these blocks with a view to preventing post surgical infections (Shinto et al., 1992; Yamamura et al., 1992; Itokazu et al., 1998). There have been few examples of non-calcium phosphate porous ceramics used in drug delivery. However, Krajewski et al. (2000) demonstrated that a cylindrical alumina porous ceramic, could provide extended delivery of hydrocortisone acetate.
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There have been a number of in vivo studies demonstrating the ability of calcium phosphate porous ceramics to provide extended release of drugs. Thoma et al. (1992) demonstrated that cylindrical beta tricalcium phosphate ceramics could provide sustained release of the antibiotic gentamicin sulphate for 14 days when implanted into bone in rats or rabbits. In a similar study, the ability of hydroxyapatite blocks to provide the extended release of gentamicin sulphate over a period of 90 days when implanted in the proximal tibia of rats was demonstrated by Shinto et al. (1992). Extremely low concentrations of gentamicin sulphate were found in the kidney, liver and plasma in comparison with that in bone. Szymura-Oleksiak et al. (2001) found that porous hydroxyapatite cylinders could provide extended release of the peripheral vasodilator, pentoxifylline, in vivo when implanted in rabbit iliac bones. In a study involving the treatment of patients with bone tuberculosis the effectiveness of rifampicin loaded hydroxyapatite blocks was demonstrated. This treatment was superior to oral treatment, with effective drug concentrations being maintained for 27 weeks. A reduced occurrence of side effects was also seen as drug release was targeted to the infected bone (Sun et al., 1996). Itokazu et al. (1994) showed that antibiotic loaded hydroxyapatite blocks were suitable for the treatment of osteomyelitis. An interesting aspect of this study was that it demonstrated that a number of different pathogens could be treated using these blocks, with the choice of antibiotic loading being made based on the susceptibility of the infecting pathogen.

In addition to acting as drug delivery systems, the ability of porous ceramics to deliver cells and other biological materials has been a focus of research. The principal goal of this research has been to deliver agents, which could improve the healing of bone defects. Caplan et al. (1990) have loaded a porous calcium phosphate ceramic with dispersed whole marrow. This was to act as a source of mesenchymal stem cells, which differentiate into osteoblasts. The porous ceramic was implanted into rat femur, in which a large defect site had been surgically created. This research showed that the ceramic was a suitable delivery vehicle for these cells and that the presence of marrow cells within the ceramic was essential for successful repair of this large defect. Bruder et al. (1998) carried out a similar experiment in a canine model. This further demonstrated the importance of mesenchymal stem cells in promoting bone formation in the defect. In another in vivo study, Ono et al. (1996) found that porous hydroxyapatite blocks loaded with bone morphogenic protein and prostaglandin E1 could promote osteogenic activity.
when implanted beneath the cranial periosteum of a rabbit. Arm et al. (1996) investigated the ability of porous hydroxyapatite rods to deliver platelet-derived growth factor (PDGF). PDGF affects bone growth and fracture healing. The interior surfaces of the ceramic had been coated with albumin/PDGF mixture. Sustained release of PDGF for between 10 and 20 days was seen depending on the implant loading. Denissen et al. (1997) demonstrated the ability of hydroxyapatite blocks to provide the modified release of the biochemical agents, bisphosphonate and alkaline phosphatase. It was envisaged that these blocks would be used as root implants. The purpose of the biochemical agents was to modulate hard and soft tissues to obtain the equivalent of a periodontal ligament around the hydroxyapatite block. This would improve the anchorage of the implant, bringing it closer to that of natural tooth.

In contrast to the relatively large porous ceramics, few researchers have investigated the potential applications of porous ceramic pellets and microspheres as implantable delivery systems. Queiroz et al. (2001) loaded pellets comprised of hydroxyapatite and beta tricalcium phosphate with the antibiotic sodium ampicillin. The pellets were in the size range 250–850 μm and were intended for the treatment of periodontitis. Although the pellets could act as drug carriers, they did not provide any appreciable modification in drug release with most of the antibiotic being released within 14 min. Paul and Sharma (1995) examined the potential of porous hydroxyapatite spheres in the size range 200-400 μm to modify the release of ampicillin trihydrate. They found the release was dependent upon the loading. At the highest drug loading it took 4 h for 100% release to occur. However, at lower levels release was complete within 30 min. It was demonstrated that coating the spheres with either chitosan, phosphatidylcholine or polylactic acid could further modify the rate of drug release. In an extension of this research, they investigated the potential of these spheres coated with polylactic acid to provide sustained in vitro delivery of the protein, human serum albumin. It was found that sustained release of over 60 days occurred although this was dependent on the protein loading with lower loadings showing 100% release in 30 days (Paul and Sharma, 1999). Microspheres have also been prepared using hydroxyapatite and a gelatin binder. The use of a binder made a sintering step unnecessary to prevent the break-up of the microspheres in water. The microspheres had an average diameter of 16 μm and were able to provide extended release of gentamicin for at least 3 days (Sivakumar and Panduranga Rao, 2002).
There have been two reported *in vivo* studies on the release of drugs from porous ceramic pellets. In the first, the release of methylene blue from porous hydroxyapatite microspheres implanted subcutaneously in rats was examined. It was found that extended release of methylene blue occurred over the 128 h study duration. However, these results are only semi-quantitative due to the low number of rats used in the study and therefore must be treated with caution (Komlev *et al*., 2002). In the second study, Paul *et al*.(2002) investigated the potential of polyvinyl acetate coated porous hydroxyapatite microspheres to provide sustained delivery of insulin when implanted in rats. It was found that the microspheres provided extended release of insulin *in vivo*. This was evidenced by decreased serum blood glucose for 48 h post implantation. A drawback of this study was the insulin loading was low and the release relatively rapid when one considers that a desirable insulin delivery system should provide sustained release for 4 to 5 years when implanted in a patient. In addition, the serum glucose level did not determine the rate of insulin release, which would be an essential requirement for an implantable modified release insulin delivery system.

While the majority of research has focused on the use of delivery devices composed entirely of porous ceramics, Shirkhanzadeh *et al*.(1995) developed an extended drug delivery device, which was composed of a surgical alloy coated with micro-porous hydroxyapatite. The coating contained silver ions, which have antimicrobial effects, and provided extended release of these ions over the entire study period of seven days. It was envisaged that this device would facilitate the formation of strong bonds between the implant and bone due the hydroxyapatite coating. At the same time it should prevent post surgical infection.

A novel drug delivery application of porous ceramics has been their use in eluting collars, which are placed behind the electrode of a passively fixed endocardial lead. The drug contained in these collars was dexamethasone sodium phosphate. These collars were envisaged as an alternative to the conventional silicone drug eluting collar, which are used to lower the threshold voltage chronically, and to prevent or reduce the threshold peaking 2 to 3 weeks postimplant. *In vivo* studies in sheep using either ceramic collars or the conventional silicone collars found no significant difference between them in terms of the threshold voltages (Mathivanar *et al*., 1990). In a further study, Anderson *et al*.(1991) demonstrated that a dexamethasone acetate loaded drug
eluting collar significantly reduced short- and long-term thresholds of atrial and ventricular active fixation leads. Collectively, this research into drug delivery from porous ceramics has demonstrated their potential as modified release drug delivery systems.

1.5 PELLETIZATION

Pelletization has been defined as an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units of varying diameter, referred to as pellets. Their diameter is typically 0.5-1.5 mm although a wider range of 0.2-2.0 mm will be considered in this thesis (Ghebre-Sellassie, 1989). Pellets have applications in many areas including in agriculture as, fertilizers or animal feeds, in pharmaceutics as dosage forms and in the ceramic industry (Ghebre-Sellassie, 1989; Vervaet et al., 1995; Lulewicz and Roux, 1998). Many pelletization processes exist, with extrusion-spheronization, solution/suspension layering and powder layering being the most widely used in the pharmaceutical industry (Ghebre-Sellassie, 1989).

The pharmaceutical interest in pelletization is due to a variety of reasons. Firstly, pellets offer therapeutic advantages over single unit dosage forms. Upon administration they disperse freely in the gastrointestinal tract, which maximises drug absorption, reduces peak plasma fluctuations and minimizes potential side effects. In addition, this prevents high local drug concentrations within the gastrointestinal tract, thereby reducing concentration related local side effects. Secondly, pellets provide the formulator with an opportunity to modify the release of a drug either by coating the pellets or modifying the pellet core. In addition, blends of pellets with different release characteristics can be used to obtain the desired release profile. Thirdly, pellets containing different drugs can be blended allowing for the delivery of two or more drugs from the same dosage form (Ghebre-Sellassie, 1989). Pellets also offer technological advantages over other dosage forms such as improved flow properties, reduced friability, uniform packing, ease of coating and narrow particle size distribution (Vervaet et al., 1995).
1.5.1 EXTRUSION-SPHERONIZATION

1.5.1.1 Introduction

The initial step of the extrusion-spheronization process is to mix the formulation components with water or another liquid to form a wet 'plastic' mass. This wet mass is then subjected to extrusion, which is a method of applying pressure to a mass until it flows through an orifice. This produces lengths of material, referred to as the extrudate. The extrudate is placed in a spheronizer, which consists of a vertical hollow cylinder with a horizontal rotating disk located inside. When the disk is spun the extrudate is broken into uniform lengths and gradually transformed into spherical pellets. The spherical pellets are then dried to give the final product. In order to successfully produce pellets by extrusion-spheronization a number of factors must be considered. These include the choice of equipment, processing variables and formulation variables (Hicks and Freese, 1989; Vervaet et al., 1995).

1.5.1.2 Processing Equipment

A range of processing equipment is used during extrusion-spheronization. However, much of this equipment is widely used in other pharmaceutical applications. Therefore, in this Section only the extruder and the spheronizer are discussed, as these are specific to the extrusion-spheronization technique.

There are number of different types of extrusion devices, which can be broadly divided into screw, ram, roll, sieve-type and basket-type extruders. The sieve and basket-type extruders have limited pharmaceutical uses and are not discussed further here.

In a screw extruder the formulation is added through the feed hopper and is forced towards the die plate by the turning of the screw (Fig. 1.5a). This screw generates the pressure required to force the material through the orifices in the die plate, which forms the extrudate. The orifices contained in the die plate are of uniform size and determine the cross sectional geometry of the extrudate. The orifice size strongly influences the final diameter of the pellets. The length of the extrudate is dependent on the physical characteristics of the material being extruded, the extruder used and any post extrusion...
processing it is subjected to (Hicks and Freese, 1989). Screw extruders can be divided into two types, axial and radial, based on the positioning of the die plate relative to the axis of the screw. In axial extrusion the die plate is located at the end of the screw perpendicular to the axis of the screw. In radial extrusion the die plate surrounds the screw with the extrudate discharging perpendicular to the axis of the screw (Vervaet et al., 1995).

![Diagram of an axial-type screw extruder](image)

**Figure 1.5a.** Diagram of an axial-type screw extruder (Hicks and Freese, 1989).

Roll extruders consist of a roller and a ring die. The material to be extruded is fed between the roller and the ring die. This forces the material through the ring die and forms the extrudate. There are a number of variations in the design of roll extruders. In the first, the roller is located inside a cylindrical ring die and the material is forced through the ring die to its outside surface. In the second variation, the roller is located outside the cylindrical ring die and the material is fed between the roller and the die. The extrudate is forced through the ring die into its interior. This arrangement is illustrated in Fig. 1.5b. In the final type the roller is located above a flat, stationary die and the extrudate is produced at the bottom of the die. In each type of extruder knives located at the exit side of the die cut the extrudate into uniform lengths. The factors which determine the extrudate dimensions are the same as for the screw extruder (Hicks and Freese, 1989).
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Figure 1.5b. Diagram of roller extruder with roller external to die (Hicks and Freese, 1989).

Ram extruders contain a piston, which forces the material along a cylinder towards the die plate on each forward stroke. On the return stroke feed material can fall into the cylinder replacing the material, which has been extruded. A diagram of a ram extruder is shown in Fig. 1.5c. The determining factors for the extrudate dimensions are as for the screw and roll extruders. The stroke of the press can also be used to vary the extrudate length (Hicks and Freese, 1989).

Figure 1.5c. Diagram of a ram extruder (Hicks and Freese, 1989).

Once extrusion is complete the damp extrudate is transferred to the spheronizer. This device comprises a vertical hollow cylinder, referred to as a bowl, and a horizontal rotating disc, known as a friction plate. A diagram of a spheronizer is shown in Fig. 1.5d. The extrudate is added to the bowl and when the disc is spun the extrudate is broken into uniform lengths and gradually transformed into spherical pellets.
The friction plate speed and the spheronization time are important considerations in any spheronization process. Both these factors change the number of collisions between particles in the spheronizer thereby changing the final pellet yield and shape. The spheronizer load can also influence the final pellet size and shape (Vervaet et al., 1995). The surface texture of the friction plate also influences the final pellet shape. Patterns in common use include the cross hatch pattern and the radial pattern. For any pattern, the groove size is matched to the desired pellet size. For example, if a 1.0 mm diameter pellet were required a plate with 2.0 mm grooves would be used (Hicks and Freese, 1989).

1.5.1.3 Formulation

A critical aspect of the extrusion-spheronization process is the formulation used. It consists of powders and a granulating solvent or solution, which serves as a binding agent to form the granules as well as a lubricant during the extrusion operation (O'Connor and Schwartz, 1989). The powder phase usually contains the drug and various excipients such as fillers, binders and release modifiers, among others (Gebre-Sellassie and Harris, 1989). The most commonly used granulating solvent is water but water ethanol mixtures have also been used (Millili and Schwartz, 1990; Elbers et al., 1992). The initial wet mass is usually prepared in a granulator, which mixes the powder
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blend and the granulation liquid. The granulation liquid should be homogeneously distributed throughout the granulated mass and evaporation kept to a minimum during mixing (Vervaet et al., 1995). The quantity of granulating liquid used is determined by the behaviour of the wetted mass during the extrusion operation (O'Connor and Schwartz, 1989) and is critical to the success of the process (Elbers et al., 1992). For spheronization the extrudate must have the combined characteristics of cohesiveness, firmness and plasticity (O'Connor and Schwartz, 1989). If too much granulating liquid is used the formulation will adhere to the extruder and individual pellets will agglomerate during spheronization (O'Connor and Schwartz, 1989; Vervaet et al., 1995). If too little is used, a lot of dust is produced during spheronization leading to a large yield of fines (Vervaet et al., 1995).

1.5.1.4 Applications

Direct pharmaceutical applications of extrusion-spheronization were first published in the early 1970s and since then intensive research has been carried out in the area (Ghebre-Sellassie, 1989). Its usefulness lies in the fact that the pelletized product acts as a drug carrier. The drug is commonly incorporated in the pellet matrix during formulation. However, it can also be applied to the pellets after production. In this case, a liquid adhesive is usually used to bind the drug to the pellet surface. Where the drug release from the pellet is unsatisfactory further release modifying techniques are adopted. For example, the pellets can be coated with polymers or lipids to create an extended drug delivery system (Deasy, 1991).

There have been numerous examples of pharmaceutical products prepared using extrusion-spheronization. These products can provide immediate drug release such as some of the propyphenazone products prepared by Schröder and Kleinebudde (1995). However, the principal use of extrusion-spheronization is in the preparation of modified release delivery systems (Chatlapalli and Rohera, 1998). For example, Neau et al. (1996) produced a chlorpheniramine maleate pelletized dosage form using microcrystalline cellulose (Avicel PH 101) and a cross-linked polyacrylic acid (Carbopol® 974P, NF). The drug was dispersed throughout the pellet and it was found that increasing the level of the polyacrylic acid reduced the rate of chlorpheniramine maleate release. A second example demonstrates the use of a rate controlling membrane
to modify drug release from extrusion-spheronization products. Yuen *et al.* (1993) used an ethylcellulose membrane to modify the release of theophylline from microcrystalline cellulose (Avicel PH 101) based pellets. They found that changing the thickness of the membrane could modify the rate of drug release.

While extrusion-spheronization has been widely used in the pharmaceutical industry, it has found few applications in the ceramics industry. The limited use of extrusion-spheronization is surprising as extrusion is widely used to produce a diverse range of ceramic products from furnace tubes to magnets (Janney, 1995). One promising application of extrusion-spheronization is in the production of ceramic pellets for use in nuclear reactors. The pellets are produced from Li₂ZrO₃ and are spherical having a diameter of approximately 1 mm (Lulewicz and Roux, 1998).

### 1.5.1.5 Advantages

Extrusion-spheronization has a number of advantages over conventional pelletization techniques. The process is easily operated and requires less skill on the part of the operator than, for example, the production of drug-loaded non-pareil seeds in a coating pan or similar device (Deasy, 1991). It is a rapid process, which can produce large quantities of pellets in a short time and with low wastage. The pellets have a narrow particle size distribution and low friability assuming the process has been optimised (Gandhi *et al.*, 1999). Coupled with these advantages, the entire process can be run as a batch, semi-batch or continuous operation (Hicks and Freese, 1989).

In terms of drug loading and release, pellets containing more than 90% w/w drug can be produced provided the physicochemical properties of the drug and other formulation constituents are optimum (Ghebre-Sellassie, 1989). Where modified drug release is required, this can often be achieved based on modification of the core properties (Deasy, 1991). If this is not possible, further coating steps can be adopted as the pellets are well suited to this (Gandhi *et al.*, 1999).
1.5.2 CRYOPELLETIZATION

1.5.2.1 Introduction

The production of solid pellets from droplets of solutions or suspensions can be used in the manufacture of pelletized dosage forms (Murata, 1993; Garcia and Ghaly, 1996; Pillay and Fassihi, 1999). The conversion of the liquid to the solid is achieved in a number of ways. One possibility is by chemical reaction. For example, water soluble sodium alginate can be converted into poorly water soluble calcium alginate by reaction with calcium ions (Bodmeier and Paeratakul, 1989; Østberg et al., 1993). A second possibility is to use a temperature dependent solution/gel transformation of polymer solutions, for example, gelatin or agar. A third possibility is to freeze the liquid. This technique is referred to as cryopelletization (Knoch, 1994). It can be defined as a technique in which spherical frozen particles are prepared by introducing a liquid medium, in the form of droplets, to a cooling liquid (Buxton and Peach, 1984). Irrespective of the production method, the pellets are then dried to remove excess water by conventional drying, such as in air or an oven, or by freeze drying (Knoch, 1994). The drying process is relatively quick due to the large surface area of the pellets and their small diameter (Knoch, 1994).

The focus of this Section is cryopelletization, which can produce uniform spherical pellets over a wide size range. Droplet formation is the critical step, which determines both the pellet size and shape. It is influenced by equipment design, processing and formulation variables (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Knoch, 1994). These variables are discussed below.

1.5.2.2 Equipment Design

A number of different equipment designs have been used for cryopelletization (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Jones, 1992; Chatterjee et al., 1994). In its simplest form, this equipment need only consist of a holder for the liquid medium to be frozen, a device for producing droplets of this medium and a holder for the cooling liquid in which the droplets are to be frozen. To illustrate the variety of more complicated designs that can be used, two examples are given below. The key
difference between these designs is the point at which the liquid medium is introduced into the cooling liquid, and the manner in which the droplets are formed.

Buxton and Peach (1984) designed a device in which the liquid droplets are introduced beneath the surface of the cooling liquid. The droplets then float upwards through the cooling liquid, freezing as they rise. The frozen pellets can be collected at or near the surface of the cooling liquid. The key features of this device are a container for the cooling liquid, in this case a vertical column, and an inlet, which produces droplets of the liquid medium to be cryopelletized (Fig. 1.5e). In a modification of this device, a worm mechanism is added, which removes the frozen pellets from the top of the cooling liquid. The pellets are then dropped into a tray, which can be placed in cold storage or brought immediately to a freeze drier (Fig. 1.5f).

**Figure 1.5.** Cryopelletization device designed by Buxton and Peach (1984) in which the liquid medium is introduced at the base of the column and the frozen pellets are (e) collected at the surface of the cooling liquid or (f) extracted by means of a worm mechanism.
Buchmuller and Weyermanns (1989) designed a device in which the liquid medium is added drop-wise to a bath of the cooling liquid, which in this case is liquid nitrogen. Frozen pellets form as the liquid medium falls to the bottom of the bath. These can then be removed continuously by means of a conveyor belt. The key features of this device are a liquid nitrogen bath with the liquid container held above this. This container has at its base two drip plates with bores. The drip plates can be moved in relation to each other, which allows for the flow rate of the liquid medium to be controlled (Fig. 1.5g).

![Diagram of cryopelletization device](image)

**Figure 1.5g.** Section of the cryopelletization device designed by Buchmuller and Weyermanns (1989).

The equipment designed by Buchmuller and Weyermanns (1989) and its operation is based on the assumption that the droplets of liquid medium sink upon hitting the liquid nitrogen. However, this is not always the case, droplets may initially float at the liquid nitrogen surface and then sink. This can lead to problems with droplet agglomeration if the droplets are not completely frozen and meet at the liquid nitrogen surface. To
overcome this, Chatterjee et al. (1994) designed an apparatus whereby the cooling liquid is divided by separators. The cooling liquid container then rotates with one drop falling into each section of the cooling liquid. This ensures that each bead has completely frozen and sunk below the surface of the liquid before the next droplet is added to that section of the cooling liquid.

Having chosen suitable equipment for the cryopelletization process under investigation, the next important consideration is the processing variables. These are discussed in the next Section.

1.5.2.3 Processing Variables

Processing variables have a key role in the cryopelletization process. The choice of variable is dependent upon the equipment design, the formulation being pelletized and the desired properties of the final product.

An initial consideration is the choice of cooling liquid. It should be immiscible and inert with respect to the liquid medium. It should have a density greater than the liquid medium to be frozen if the droplets are to be introduced at its base as in the device shown in Fig. 1.5e/f. This allows for the droplets to float to the surface of the cooling liquid and freeze as they do so. For example, with aqueous based liquid media a cooling liquid with a density in the range 1.05 to 1.40 g/ml is typically used (Buxton and Peach, 1984). Where the droplets are introduced at the surface of the cooling liquid the density of the cooling liquid should be less than that of the liquid medium to be frozen. Suitable liquid coolants include trichloroethane, trichloroethylene, dichloromethane, diethyl ether, fluoroform, dichloroform, and liquid nitrogen (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989). While all these coolants are suitable, liquid nitrogen has a number of advantages over the other liquid coolants. It is inert, extraction of active ingredient does not occur, the final product does not require rinsing, no residual solvents remain and no solvent need be disposed of (Knoch, 1994). A further advantage of liquid nitrogen is that a gas layer forms around the pellets as they enter the liquid nitrogen. This can promote the formation of spherical pellets (Wunderlich et al., 1996). However, the temperature of liquid nitrogen is constant at -196 °C, meaning the rate of freezing of the liquid medium cannot be controlled. In this respect, the use of hydrocarbon liquid
coolants is advantageous as their temperature can be changed. Temperatures of at least 
-50 °C are typically used. Higher temperatures can be used once they are lower than the 
freezing point of the liquid medium (Buxton and Peach, 1984). It should be noted that 
the relative density of the liquid medium and the cooling liquid also influences the final 
pellet size (Buxton and Peach, 1984).

A second important process variable is the height of the cooling liquid. It must be 
sufficient to allow for complete freezing of the droplets before they reach either the 
surface or the bottom of the cooling liquid. Otherwise, pellet agglomeration may occur. 
The height of the cooling liquid can be reduced if the speed with which the droplet 
passes through the liquid medium is reduced. This can be achieved, for example, by 
circulating the cooling liquid in the opposite direction to the movement of the droplets 
(Buxton and Peach, 1984). Where the droplets initially float on the surface of the 
cooling liquid prior to sinking, the height of the cooling liquid is not as important a 
consideration. However, it may be necessary to agitate the cooling liquid to prevent 
particle agglomeration. This can be done by introducing convection currents into the 
cooling liquid using a heater to slightly raise the temperature of a portion of the liquid. 
An alternative approach is to use jets of nitrogen gas to impart velocity to the cooling 
liquid (Chatterjee et al., 1994).

Relating to the problem of droplet agglomeration, is the flow rate of the liquid medium. 
It should be slow enough to allow for individual droplets to be produced (Knoch, 1994). 
However, the flow rate also has economic consequences and must be maintained at a 
rate sufficient to allow for the production of large quantities of pellets in a reasonable 
time. In the case of formulations which float at the cooling liquid surface prior to 
sinking, an additional consideration is that the flow rate must not be so rapid as to allow 
the droplets to agglomerate at the cooling liquid surface. The flow rate can be regulated 
by the filling level of the liquid medium supply container and, in addition, by 
pressurising the container, where necessary (Knoch, 1994).

The length of time the droplets spend in the cooling liquid bath is an important 
processing variable. The dwell time must be sufficient to allow for complete freezing of 
the droplets prior to their removal from the bath. For the equipment shown in Fig. 1.5f, 
the length of time the pellets spend at the cooling liquid surface is determined by the
worm speed. In the equipment shown in Fig. 1.5g, the dwell time is adjusted by varying the speed of the conveyor belt (Buchmuller and Weyermanns, 1989; Knoch, 1994).

In the case of production methods, where the droplets fall prior to hitting the cooling liquid, the height of this fall is important as it influences the sphericity of the final pellets. The droplets should have sufficient time to form a spherical shape prior to entering the cooling liquid, but should not enter at too high a speed as their spherical shape might be impaired. Very viscous liquids require longer falling paths, since they are slower to assume a spherical shape (Buchmuller and Weyermanns, 1989; Knoch, 1994).

The nature of the orifice used to produce the droplets, in particular its size, is a further key processing variable. This strongly influences the droplet size and hence the final pellet size (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989). The diameter of the orifice also influences the flow rate (Knoch, 1994). In the device shown in Fig. 1.5e/f a different orifice size is obtained by changing the diameter of the inlet tubing for the liquid medium. In the device shown in Fig. 1.5g the lower and upper drip plates can be substituted with plates containing different diameter bores. The orifice should also have a shearing edge as this facilitates the discharge of the droplets and contributes to the production of pellets with a narrow size distribution (Buchmuller and Weyermanns, 1989; Knoch, 1994).

1.5.2.4 Formulation Variables

Formulation variables such as viscosity, surface tension and solids content are important with regard to droplet formation. Therefore, choice of the correct formulation components and their levels is essential to produce spherical pellets (Knoch, 1994).

The fundamental requirement of all cryopelletization formulations is that they are liquid. The formulations can be solutions or suspensions with the dispersion medium usually being water, although it may contain a co-solvent, such as ethanol, where necessary (Buxton and Peach, 1984). The solids content of the formulation can vary within a wide range, typically 10-30% w/v in solutions, depending on the formulation. In suspensions an even higher solid materials content is possible. However, the solid
must be dispersed homogeneously and must not settle over the course of production. Otherwise, problems with product content uniformity will occur. In general, a solids content as high as possible is desired in order to maximise the loading of active materials and minimise drying times (Knoch, 1994).

The solids content directly influences another important formulation consideration, which is the viscosity of the formulation. There is both an upper and lower critical viscosity limit for cryopelletization formulations. Above the upper limit, spherical pellets cannot be formed (Knoch, 1994). Below the lower limit, droplets of a defined size cannot be produced (Buchmuller and Weyermanns, 1989). Where problems with high viscosity do exist, methods to promote flow include increasing the liquid medium temperature or pressurising the supply container. Similarly, a sub atmospheric pressure can be applied where the viscosity of the system is too low (Wunderlich et al., 1995a).

A further approach to reduce the viscosity of a formulation is to include a surfactant in the formulation. This reduces the surface tension of the liquid medium. In doing so it aids the flow of the liquid medium and in addition results in the production of smaller size pellets as smaller droplets are produced (Knoch, 1994).

In some cases, the cryopelletization formulation consists primarily of the active ingredient and solvent. However, this is not common, especially in pharmaceutical applications where many other excipients are included. The principal excipient is a carrier material for the active ingredient. Possible carrier materials include hydrolysed gelatin, dextrans and polyvinyl alcohol either alone or mixed with each other (Buxton and Peach, 1984). The carrier material facilitates the formulation of low quantities of active ingredient into either single or multiple unit dosage forms. In addition, it can impart beneficial properties to the product such as improved mechanical properties or release characteristics. To further improve the mechanical properties of pellets, fillers, such as mannitol may also be included. This property is an important consideration as pellets are often processed after drying into, for example, a capsule filling machine. In pharmaceutical applications, excipients which improve the patient acceptability of a product may also be needed. These range from colouring agents, such as carotinoides to flavouring agents such as sugar substitutes. Other excipients, which may be necessary, are preservatives, pH adjusters, emulsifiers and stabilizers (Buxton and Peach, 1984; Wunderlich et al., 1995a). In addition excipients, such as alginates or pectin, which can
modify the release of the active ingredient or enteric materials, such as methacrylic acid derivatives, can be incorporated into the pellets (Wunderlich et al., 1995b).

1.5.2.5 Applications

Cryopelletization has been applied in both pharmaceutical and non-pharmaceutical fields. Buchmuller and Weyermanns (1989) used cryopelletization to produce bacteria containing pellets with diameters from 2–5 mm. They found cryopelletization was superior to other cryopreservation techniques as it allowed for quick and uniform freezing of the suspension. This prevented cold damage to the bacteria, which can reduce bacterial survival rates to unacceptable levels. Wunderlich et al. (1996) produced pellets containing plant extracts using cryopelletization. The products were stable under storage and had unaltered pharmacological and cosmetic characteristics with respect to the native plant extract. Examples of suitable plant extracts are vitamin E from wheatgerm oil, juniper berry oil, Echinacea tincture and Aloe vera juice. Cryopelletization has also been used to produce porous ceramic pellets composed of hydroxyapatite, where their intended use was as a filling material for bone. The pellets had diameters in the region of 3 mm and porosities of approximately 60% (Fabbri et al., 1994).

Cryopelletization has also found a number of pharmaceutical applications. Buxton and Peach (1984) produced oxazepam containing pellets from a suspension containing oxazepam, mannitol and hydrolysed gelatin. The equipment design used was that shown in Fig. 1.5e and the cooling liquid was dichloromethane at –30°C. They were able to produce pellets with diameters in the range 2 to 3 mm. Drugs, such as benzocaine and potassium phenoxyethyl penicillin, have been cryopelletized using the equipment design shown in Fig. 1.5g. In these products, the active agent was dispersed in a solution of hydrophilic macromolecules such as gelatins or collagen hydrolysates. This mixture was then cryopelletized (Wunderlich et al., 1995b). While the majority of pharmaceutical applications have focused on immediate release products, it is also possible to produce extended release products. Alfatec Pharma (Germany) have used cryopelletization to produce a pelletized matrix system based on collagen derivatives. The type of release could be varied by varying the polymer properties. For example, an ibuprofen containing product in which 40% of the drug was released after 2 h and 100%
in 8 h has been produced. In this product, the rate-limiting step in drug release was diffusion of the drug by a Fickian mechanism. A product, which gave zero order release of flurbiprofen, was also produced, with 100% drug release occurring within 5 h (Knoch, 1994).

1.5.2.6 Advantages

The key advantage of cryopelletization over many existing pelletization techniques is it can produce spherical pellets of reproducible, uniform size over a wide size range (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Knoch, 1994). The pellets also have a uniform constitution as the droplets are rapidly frozen. This prevents the formulation being concentrated in a liquid core after the outer regions are frozen. The rapid freezing is due to their small volume and direct heat exchange between the cooling liquid and the drop. In larger bodies, such rapid freezing does not occur (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989). The rapid freezing also makes cryopelletization particularly suitable for freezing materials such as bacterial suspensions, vitamin solutions and vaccines, which are susceptible to cold damage (Buchmuller and Weyermanns, 1989). In addition, as the production technique does not use heat, it would be advantageous in the production of pellets containing thermolabile substances such as peptides (Wunderlich et al., 1995b).

Cryopelletized products, in addition to being suitable carriers for a range of drugs, can deliver these drugs at a variety of rates (Section 1.5.2.5). This does not require an additional coating step, as is common with other multiparticulate modified-release dosage forms, but instead is achieved by formulation changes. This makes cryopelletization a useful single step production technique for modified release dosage forms (Knoch, 1994). Coupled with this, the highly porous nature of cryopelletized products will further influence their release behaviour, as floating dosage forms can provide extended drug delivery due to retention in the gastro-intestinal tract (Kawashima et al., 1991; Wunderlich et al., 1996).

Finally, cryopelletization can be carried out on a laboratory scale, with scale up to industrial levels being easily achieved. For example, Cryopel equipment, which is of the design shown in Fig. 1.5g, is available from Messer Griesheim GmbH (Germany) and
can produce pellet quantities as low as 0.5 kg/h and as high as 120 kg/h. The Cryopel process uses liquid nitrogen as the cooling liquid, thus benefiting from the advantages of liquid nitrogen mentioned in Section 1.5.2.3. Overall, the process is economical with little maintenance and clean up required. In addition, sterility can be achieved where needed (Knoch, 1994; Wunderlich et al., 1995a).

1.6 DILTIAZEM HCl

1.6.1 Introduction

Diltiazem HCl belongs to the benzothiazepine class of compounds. It was first synthesized by Tanabe Seiyaku Co., in Japan and was granted its first patent in 1969 (Mazzo et al., 1994). It is a calcium channel blocking agent and is used in the management of Prinzmetal variant angina, chronic stable angina pectoris, supraventricular tachycardias and hypertension (Drug Information Full Text, 2003).

1.6.2 Molecular Structure

The accepted chemical name of diltiazem HCl is (2S-cis)-3-(acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothiazepin-(5H)-one monohydrochloride. Its molecular formula is C_{22}H_{26}N_{2}O_{4}S.HCl and its molecular weight is 450.98 amu (Mazzo et al., 1994). The chemical structure of diltiazem HCl is given in Fig. 1.6a.

Figure 1.6a. Chemical structure of diltiazem HCl (British Pharmacopoeia, 2002).
1.6.3 Physicochemical Properties

Diltiazem HCl is a white to off-white crystalline powder. It is odourless and has a bitter taste. Diltiazem HCl melts at about 210 °C with decomposition occurring at higher temperatures. In differential scanning calorimetry and thermogravimetric studies, decomposition became apparent above 230 °C (Mazzo et al., 1994).

The solubility of diltiazem HCl in various solvents is given in Table 1.6a. Its relatively high water solubility is reflected in its saturation solubility in aqueous based solutions. For example, Sood and Panchagnula (1998) reported that the saturated solubility of diltiazem HCl in 0.1N HCl was 658.83 +/- 4.40 mg/ml and was 593.20 +/- 3.67 mg/ml in phosphate buffer pH 6.8.

Table 1.6a. Solubility of diltiazem HCl in various solvents at 25 °C (Mazzo et al., 1994). The solubilities are indicated in terms of the United States Pharmacopeia (2003) definitions.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Methanol</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Water</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Dehydrated alcohol</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Benzene</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Ether</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>

The pH of a saturated aqueous solution of diltiazem HCl in water is 3.0, with a 1.0% w/v solution having a pH of 4.7 +/- 0.3 (Mazzo et al., 1994). The pKₐ of diltiazem HCl is 7.7 (Chang and Bodmeier, 1997).
1.6.4 UV Absorption Spectrum

The ultraviolet absorption spectrum of diltiazem HCl in 0.1N HCl is characterised by maxima at approximately 205 nm and 236 nm. The absorbance of a solution containing 10.1 μg/ml in a 1 cm cell is 0.954 at 205 nm and 0.556 at 236 nm (Mazzo et al., 1994).

1.6.5 Stability

Diltiazem HCl is highly stable in the solid state. For example, storage under conditions of room temperature and 33% or 79% relative humidity for 57 days did not cause any physical or chemical degradation. In aqueous buffer solutions (pH 1-7) diltiazem HCl undergoes hydrolysis to desacetyl diltiazem. It is most stable at pH 5 with the shelf life at room temperature being 42 days. This compares with a shelf life of 15.8 days at pH 2. Buffered diltiazem HCl solutions are light sensitive, being degraded more rapidly in the presence of light than if protected from light (Mazzo et al., 1994).

1.6.6 Pharmacology of Diltiazem HCl

The principal physiological action of diltiazem HCl is to inhibit the transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentrations. This inhibits the contractile processes of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries and decreasing myocardial contractility.

In patients with Prinzmetal variant angina, inhibition of spontaneous coronary artery spasm by diltiazem HCl results in increased myocardial oxygen delivery. Dilation of systemic arteries by diltiazem HCl results in a decrease in total peripheral resistance, a decrease in systemic blood pressure, a decrease in the afterload of the heart, and, at high doses, an increase in the cardiac index. The reduction in afterload, seen at rest and with exercise, and the resultant decrease in myocardial oxygen consumption, are thought to be responsible for the effects of diltiazem HCl in patients with chronic stable angina pectoris.
Diltiazem HCl has substantial inhibitory effects on the cardiac conduction system, acting principally at the atrioventricular (AV) node, with some effects at the sinus node. Diltiazem HCl increases AV nodal refractoriness by binding to calcium channels; binding is enhanced during depolarization, and the drug tends to unbind in a time-dependent manner during repolarization. Therefore, when heart rate is increased, calcium channel-bound diltiazem HCl reportedly increases as a result of a greater number of depolarizations and shorter diastolic periods. This allows diltiazem HCl to selectively decrease the heart rate during tachyarrhythmias involving the AV node, while having little or no effect on normal AV nodal conduction at normal heart rates.

In patients with paroxysmal supraventricular tachycardia, the drug's effect at the AV node results in an interruption of conduction along the re-entrant pathway and restoration of normal sinus rhythm. Similarly, diltiazem HCl's effect on the AV node reduces rapid ventricular response rate caused by atrial flutter or atrial fibrillation.

At therapeutic dosing levels, diltiazem HCl is well tolerated. Serious adverse reactions are rare; however, gastrointestinal tract disturbances, skin eruptions, and bradycardia may result in discontinuation of the drug in about 1% of patients (Drug Information Full Text, 2003).

1.7 PROPRANOLOL HCl

1.7.1 Introduction

Propranolol was invented by Sir James Black in the early 1960s and was launched as Inderal® in 1964 by Imperial Chemicals Industries. It was the first commercially available non-selective beta-adrenergic blocking agent and changed the face of cardiovascular medicine (Stapleton, 1997). At present, its principal uses are in the management of hypertension and chronic stable angina pectoris (Drug Information Full Text, 2003).
1.7.2 Molecular Structure

The accepted chemical name of propranolol HCl is (±)-isopropylamino-3-(1-naphthoxy)propan-2-ol monohydrochloride (Pharmaceutical Codex, 1994). Its molecular formula is C\textsubscript{16}H\textsubscript{21}NO\textsubscript{2}.HCl and its molecular weight is 295.8 amu (British Pharmacopoeia, 2002). The chemical structure of propranolol HCl is given in Fig. 1.7a.

![Chemical structure of propranolol HCl](image)

**Figure 1.7a.** Chemical structure of propranolol HCl (British Pharmacopoeia, 2002).

1.7.3 Physicochemical Properties

Propranolol HCl is a white or almost white crystalline powder. It is odourless and has a bitter taste. It melts in the range 163 to 166 °C (Pharmaceutical Codex, 1994; Drug Information Full Text, 2003).

The solubility of propranolol HCl in various solvents is given in Table 1.7a. Coupled with its water solubility, it shows high saturation solubility in aqueous based solutions. For example, Lecomte *et al.* (2003) reported that the saturated solubility of propranolol HCl in phosphate buffer pH 7.4 at 37 °C was 254 mg/ml and in 0.1 N HCl at 37 °C was 220 mg/ml.
Table 1.7a. Solubility of propranolol HCl in various solvents (Sweetman, 2002). The solubilities are indicated in terms of the Extra Pharmacopoeia (Sweetman, 2002) and were measured at temperatures between 15 and 25 °C.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform</td>
<td>Slightly soluble</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Soluble</td>
</tr>
<tr>
<td>Water</td>
<td>Soluble</td>
</tr>
<tr>
<td>Ether</td>
<td>Practically insoluble</td>
</tr>
</tbody>
</table>

Propranolol HCl has a pKₐ of 9.5 and a 1.0% w/v aqueous solution has a pH of between 5.0 and 6.0 (Pharmaceutical Codex, 1994).

1.7.4 UV Absorption Spectrum

The ultraviolet absorption spectrum of propranolol HCl in an aqueous acid solution is characterised by maxima at 288, 305 and 319 nm. The absorptivity in absorbance units for a 1% w/v solution in a 1 cm cell is 222 at 288 nm. There is no shift in these maxima in alkaline solutions (Clarke, 1986).

1.7.5 Stability

In aqueous solutions, propranolol HCl decomposes with oxidation of the isopropylamine side-chain. This is accompanied by a lowered pH and discoloration of the solution. Solutions have maximum stability at pH 3.0 and decompose rapidly at alkaline pH. Propranolol HCl is affected by light and should be protected from light. (Pharmaceutical Codex, 1994; Drug Information Full Text, 2003).

1.7.6 Pharmacology of Propranolol HCl

Propranolol HCl competitively blocks beta-adrenergic receptors within the myocardium and within bronchial and vascular smooth muscle thereby inhibiting responses to adrenergic stimuli (Drug Information Full Text, 2003).
The beta-adrenergic blocking action in the myocardium causes a decrease in heart rate and prevents exercise-induced increases in heart rate. It also decreases myocardial contractility, decreases cardiac output, increases systolic ejection time and increases cardiac volume (Drug Information Full Text, 2003). These factors reduce cardiac work, thereby improving exercise tolerance and relieving symptoms in patients with angina (British National Formulary, 2003).

Propranolol HCl is used in the treatment of hypertension. However, the precise mechanism of its hypotensive effect has not been determined (Drug Information Full Text, 2003). It is known that propranolol HCl reduces cardiac output, alters baroreceptor reflex sensitivity, blocks peripheral adrenoceptors and depresses plasma renin secretion. Some or all of these factors may contribute to its hypotensive effect. In addition, it is possible that a central effect contributes to the reduction in blood pressure (British National Formulary, 2003).

Propranolol HCl acts as an anti-arrhythmic drug by decreasing conduction velocity through the sinoatrial and atrioventricular nodes and decreasing myocardial automaticity (Drug Information Full Text, 2003). It is used also to alleviate some symptoms of anxiety. It has been found that patients with palpitations, tremor and tachycardia respond best. Propranolol HCl can prevent the onset of migraine, although the mechanism of the anti-migraine effect is not known. It may result from inhibition of vasodilation or the inhibition of arteriolar spasms over the cortex (British National Formulary, 2003; Drug Information Full Text, 2003).

At therapeutic dosing levels, propranolol HCl can cause a range of adverse reactions in patients. The most common, serious adverse effects of propranolol HCl are related to its beta-adrenergic blocking activity. Bradycardia is the most common adverse cardiovascular effect of propranolol HCl. Other cardiovascular side effects include heart failure, hypotension, conduction disorders and peripheral vasoconstriction. The beta-adrenergic blocking action of propranolol HCl increases airways resistance and can cause bronchospasm, especially in asthmatics. Propranolol HCl also causes gastrointestinal disturbances, fatigue and sleep disturbances (British National Formulary, 2003; Drug Information Full Text, 2003).
In general, except where otherwise stated, reagent grade chemicals were used. The qualities or grades of materials listed here are those quoted by the manufacturer. Most of these correspond in quality, though not by name, to either the General Purpose Reagent (GPR) or Analar Grade used by BDH Chemicals (UK).

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<th>Description</th>
<th>Lot/Batch Number</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
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<td>Acetic acid, glacial</td>
<td>Lot: K29995416 150</td>
<td>BDH Laboratory Supplies, UK</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>Lot: 60K0107</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>Calcium chloride dihydrate</td>
<td>Lot: 31K1251</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td></td>
<td>Carboceramics, USA</td>
</tr>
<tr>
<td>Carbolite 16/20 (more porous)</td>
<td></td>
<td>Carboceramics, USA</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td></td>
<td>Carboceramics, USA</td>
</tr>
<tr>
<td>Carbon black, calibration standard</td>
<td>Lot: D4</td>
<td>Micromeritics, USA</td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>Lot: AB006N3</td>
<td>The BF Goodrich Co., USA</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Medium molecular weight, Lot: 17813LU</td>
<td>Aldrich Chemicals, USA</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>Lot: 053h20021</td>
<td>Seloc PCAS, France</td>
</tr>
<tr>
<td>Disodium hydrogen phosphate dodecahydrate</td>
<td>A272479 101, A337279 142</td>
<td>Merck KGaA, Germany</td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
<td>Cooley Distillery, Ireland</td>
</tr>
<tr>
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<td>Lot/Batch Number</td>
<td>Supplier</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------</td>
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</tr>
<tr>
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<td>Ethocel Standard 10</td>
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<tr>
<td>Premium, Lot: PL03013T01</td>
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<td></td>
</tr>
<tr>
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<td>Ethocel Standard 100</td>
<td>The Dow Chemical Company, USA</td>
</tr>
<tr>
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</tr>
<tr>
<td>Glycerylmonostearate</td>
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<td>BDH Laboratory Supplies, UK</td>
</tr>
<tr>
<td>Halloysite</td>
<td>Batch No.: 12/98</td>
<td>NZ China Clays Ltd.</td>
</tr>
<tr>
<td>Hydrochloric acid (35.4% w/w; 1.18 g/ml)</td>
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</tr>
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<tr>
<td>N-light N2</td>
<td></td>
<td>Itochu Ceratech Corporation, Japan</td>
</tr>
<tr>
<td>N-light N3</td>
<td></td>
<td>Itochu Ceratech Corporation, Japan</td>
</tr>
<tr>
<td>N-light N4</td>
<td></td>
<td>Itochu Ceratech Corporation, Japan</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>Lot: K25691637 906</td>
<td>BDH Laboratory Supplies, UK</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>Plasdone, K29/32, Batch No.: 4E 386</td>
<td>GAF Great Britain Ltd., UK</td>
</tr>
<tr>
<td>Precirol ATO 5</td>
<td>Lot: 23707</td>
<td>Gattefossé, France</td>
</tr>
<tr>
<td>Propranolol HCl</td>
<td>B/N: 128140</td>
<td>Finechem, England</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Lot: 89H0178</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Lot: 10K0179</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>Sodium dihydrogen phosphate dihydrate</td>
<td>Lot: K91420645 106</td>
<td>Merck KGaA, Germany</td>
</tr>
</tbody>
</table>

55
<table>
<thead>
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<th>Description</th>
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<th>Supplier</th>
</tr>
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<td>Sodium hydroxide pellets</td>
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<td>Sigma Chemical Co, USA</td>
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<tr>
<td>Sodium lauryl sulphate</td>
<td>Lot: 082K 0026</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>Sodium polyphosphate</td>
<td>Lot: JR01112ER</td>
<td>Aldrich Chemicals, USA</td>
</tr>
<tr>
<td>Sodium silicate solution</td>
<td>Lot: 052K 3695</td>
<td>Sigma Chemical Co., USA</td>
</tr>
<tr>
<td>(27% w/v SiO₂ in 14%w/v</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaOH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td></td>
<td>Imerys, UK</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Granulated</td>
<td>Irish Sugar plc, Ireland</td>
</tr>
<tr>
<td>Water</td>
<td>HPLC grade and deionised</td>
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<tr>
<td>Zeta-Potential transfer</td>
<td>Batch No.: 269902</td>
<td>Malvern Instruments Ltd.,</td>
</tr>
<tr>
<td>standard</td>
<td></td>
<td>UK</td>
</tr>
</tbody>
</table>
Chapter 3. Methodology

3.1 CHARACTERISATION OF POROUS PELLETS

3.1.1 Sieve Analysis

Sieve analysis was carried out on the commercially produced porous ceramic pellets. Random 150 g samples of each porous ceramic were obtained by removing three 50 g batches of the porous ceramic from three different points in the bulk material. This was done in order to minimise the effect of sedimentation in the bulk material. Sieve analysis of these samples was performed using a nest of standard sieves, agitated for 10 min on an Endecott sieve shaker (1 MK11, UK) and the retained weight data obtained was used to construct a frequency distribution plot. The size ranges examined for the various porous ceramics are given in Table 3.1a.

Table 3.1a. Sieves used in sieve analysis of the listed porous ceramics.

<table>
<thead>
<tr>
<th>Porous ceramic</th>
<th>Aperture diameters of sieves (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-light N2</td>
<td>2000, 1700, 1400, 1180 and 1000</td>
</tr>
<tr>
<td>N-light N3</td>
<td>1400, 1180, 1000, 850, 710, 600 and 500</td>
</tr>
<tr>
<td>N-light N4</td>
<td>1000, 850, 710, 600, 500, 425, 355, 300 and 250</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td>1400, 1180, 1000, 850, 710, 600 and 500</td>
</tr>
<tr>
<td>Carbolite 16/20 (more porous)</td>
<td>1400, 1180, 1000, 850, 710, 600 and 500</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td>1400, 1180, 1000, 850, 710, 600 and 500</td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td>1400, 1180, 1000, 850, 710, 600, 500, 425, 355, 300 and 250</td>
</tr>
</tbody>
</table>
The size range 850-1000 μm was selected for use in further experiments except in the case of N-light N2 and N-light N4 where the size ranges 1700-2000 μm and 425-500 μm were selected, respectively.

3.1.2 Scanning Electron Microscopy and Energy Dispersive X-ray Microanalysis

Samples of porous pellets were mounted on aluminium stubs using double-sided sticky tape. The pellets were then vacuum coated with a thin film of gold in a sputter coater (Polaron SC500, UK). The coated pellets were examined using a field emission scanning electron microscope (Hitachi S4300, Japan). In a similar manner, cross-sections of the pellets were mounted and examined. To cross-section these pellets, they were cut using a blade in a plane along either their longitudinal or latitudinal axis. Pellets, which crushed during sectioning were not examined. Also, where crushing was evident in a SEM view of a section no further examination of that pellet was made. In the case of Carbolite, cross-sections were prepared by embedding the pellets in an epoxy resin and grinding to give a flat polished surface. This surface was then vacuum coated with gold and examined.

Qualitative EDX microanalysis was carried out using a variable pressure scanning electron microscope (Hitachi S-3500N, Japan) and an X-ray detector (Princeton Gamma Tech). To examine pellet surfaces or cross-sections other than those of Carbolite grades, they were mounted on aluminium stubs using adhesive carbon tape. To examine cross-sections of Carbolite grades, the epoxy resin embedded surface was coated in carbon. In all cases, two random areas on the surface of each of three pellets were analysed.

3.1.3 X-Ray Diffraction Analysis

X-ray diffraction patterns of powdered samples of N-light N3, Starlight SLK1000 and Carbolite 16/20 were obtained using a Siemens D500 X-ray powder diffractometer. A 1.0° dispersion slit, a 1.0° anti-scatter slit and a 0.15° receiving slit were used. The samples were studied by placing a thin layer of the powder in conventional cavity mounts. Measurements were taken from 10.000 - 90.000° on the two θ scale at a step
size of 0.020° per s. The Cu anode X-ray was operated at 40 kV and 30 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays.

3.1.4 Zeta Potential

A 0.001 M potassium chloride solution containing 0.1 mg/ml of either powdered N-light N3, Starlight SLK1000 or Carbolite 16/20 was prepared using HPLC grade deionised water. Using aliquots of this suspension, a series of suspensions with pHs in the range 2-12 were prepared. The pH was adjusted using 0.001, 0.01 and 0.1M hydrochloric acid and sodium hydroxide solutions. The pH was measured using an Orion 520A pH meter (Orion Research Inc., USA). The zeta potential of each suspension was measured using a calibrated Zetasizer 3000 (Malvern Instruments, UK) with associated PCS: Zeta mode vl.51 software. The calibration material used was a calibrated latex solution (zeta potential = -50 +/- 5 mV) supplied by the instrument manufacturer. Prior to each measurement the zeta cell (M3, Malvern Instruments, UK) and associated tubing was washed out three times using propan-2-ol and then three times using double deionised water.

3.1.5 Mercury Porosimetry Studies

The mercury porosimeter used to analyse N-light N2, N3, Carbolite 16/20 and Starlight SLK1000 was the Poresizer 9320 (Micromeritics, U.S.A.), with associated software (Poresizer 9320 software v2.02). The penetrometer used was a 5 cm³ “solid sample” type. Its characteristics are given in Table 3.1b. In order to obtain the penetrometer volume, the penetrometer was calibrated in triplicate. Mercury density was dependent on room temperature. The advancing and receding contact angles for mercury were 130° while its surface tension was 485 dynes/cm. Regarding the contact angle, it is important to note that this was an assumed contact angle as the common method of determining the contact angle between highly porous solids and mercury is inaccurate.
Table 3.1b. Characteristics of the 5 cm³ “solid sample” penetrometer.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrometer constant (μL/pF)</td>
<td>21.63</td>
</tr>
<tr>
<td>Penetrometer weight (g)</td>
<td>69.2287</td>
</tr>
<tr>
<td>Maximum head pressure (p.s.i.)</td>
<td>4.45</td>
</tr>
<tr>
<td>Bulb volume (ml)</td>
<td>5</td>
</tr>
<tr>
<td>Stem volume (ml)</td>
<td>1.131</td>
</tr>
<tr>
<td>Penetrometer volume (ml)</td>
<td>5.894</td>
</tr>
</tbody>
</table>

The sample whose porosity was to be determined was placed in a vacuum oven (Gallenkamp, U.K.) overnight at 50 °C with a vacuum pressure of 600 mbar. The penetrometer was also dried overnight at 50 °C. A mass of sample sufficient to almost fill the penetrometer bulb was accurately weighed. This was placed in the bulb and the bulb sealed with the aid of vacuum grease. The penetrometer was placed in the low pressure port of the mercury porosimeter and slowly evacuated to below 50 μmHg. A manual low pressure analysis (0.5 to ~20 p.s.i.) with automatic reporting was performed followed by an automatic high pressure analysis (~20 p.s.i. to 30,000 p.s.i.). The automatic high pressure analysis was conducted allowing for a 10 s equilibration time. The pressure table used for the automatic high pressure analysis is given in Appendix 3. Each sample was analysed in duplicate.

The remaining samples were analysed using an AutoPore IV 9500 (Micromeritics, U.S.A.) by MCA Services (U.K.). The analysis was conducted in a similar manner to that described above. However, each sample was analysed once and where a number of product batches were available the sample analysed contained an equal amount by weight of each batch.

Mercury porosimetry provided the bulk density of the samples analysed. The bulk density was determined from pellet mass divided by volume. This volume included pellet intraparticulate pores but not interparticulate pores. All references to porosity in this thesis refer to intraparticulate pores and do not account for interparticulate porosity. In addition, a $D_{50}$ value was calculated. This value was the pore diameter below which 50% of the cumulative intraparticulate mercury intrusion occurred.
3.1.6Helium Pycnometry Studies

Helium pycnometry was used to obtain the skeletal density of materials. It was carried out using a calibrated AccuPyc 1330 (Micromeritics, USA). The calibration standard had a volume of 0.718463 cm$^3$ (Micromeritics, USA). Prior to analysis, the samples were dried overnight to a constant weight in a vacuum oven at 50 °C with a vacuum pressure of 600 mbar. Both whole and crushed porous ceramic samples were analysed, with their mass being accurately determined prior to analysis using an MT5 microbalance (Mettler Toledo, Switzerland). Each sample was analysed in duplicate using the run parameters given in Table 3.1c. Following analysis the sample was re-weighed. Where the mass differed from that prior to the run, this mass was used to calculate sample density. This difference can occur if contaminating gases or water were present in the sample prior to analysis. These would be removed by purging during analysis making the post analysis mass a more accurate measure of the sample mass.

Table 3.1c. Run parameters used in helium pycnometry analyses.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of sample cup (cm$^3$)</td>
<td>1</td>
</tr>
<tr>
<td>Number of purges</td>
<td>10</td>
</tr>
<tr>
<td>Purge pressure (p.s.i.)</td>
<td>19.5</td>
</tr>
<tr>
<td>Number of runs</td>
<td>50</td>
</tr>
<tr>
<td>Run fill pressure (p.s.i.)</td>
<td>19.5</td>
</tr>
<tr>
<td>Equilibration rate (p.s.i./min)</td>
<td>0.0050</td>
</tr>
<tr>
<td>Run precision</td>
<td>Yes</td>
</tr>
<tr>
<td>Percent full scale</td>
<td>0.05</td>
</tr>
</tbody>
</table>

3.1.7Surface Area Analysis

Surface area analysis was carried out using a Gemini II 2370 Surface Area Analyser (Micromeritics, USA) with nitrogen as the adsorptive gas. The correct functioning of the instrument was confirmed using carbon black. It had a multipoint surface area of 24.1 +/- 0.6 m$^2$/g and a single point surface area of 23.6 +/- 0.5 m$^2$/g. The saturation pressure of nitrogen was determined at the beginning of each day. Prior to analysis
samples were degassed for 12 h at 50 °C with the exception of porous ceramic samples, which were degassed for 2 h at 200 °C. This was done using the Flow Prep 060 Degasser (Micromeritics, USA). In this apparatus nitrogen gas flows over the sample and removes moisture and other contaminants from the sample. Following degassing the sample mass was determined. The mass used was sufficient to ensure that the surface area available for analysis was greater than 1 m², as this gives greatest accuracy.

Large bulb tubes, one containing the sample and the other containing glass beads of negligible surface area, were used in the analysis of porous ceramic pellets, products prepared by extrusion-spheronization and powder samples. The number of glass beads used was such that approximate volume balance was attained, i.e., the measured free space was between -0.5 and 0.5 cm³. Filler rods were placed in each of the bulbs in order to give a more precise measurement. The filler rods passed through the sample and rested on the base of the bulb. In the case of cryopelletization products, small analysis tubes were used, as a lower mass of material was available. Filler rods were used in both tubes. During each analysis the evacuation rate was 500 mmHg/min, the evacuation time was 1 min and the equilibration time was 10 s. For each porous ceramic sample the volume of nitrogen adsorbed at the relative pressures listed in Table 3.1d was found. In the case of other products and powder samples, the relative pressures 0.05, 0.1, 0.15, 0.2, 0.25 and 0.3 were used. All analyses were repeated once. Using the data obtained, an adsorption isotherm was plotted for porous ceramic pellets. For each sample, the BET multipoint surface area was determined using relative pressures from 0.05 to 0.3. Where it improved the correlation coefficient for the BET plot, the first and/or last points were omitted.

For comparative purposes, the surface area of a non-porous sphere of the same average diameter as the pellet examined was calculated. To do this the number of pellets per gram was counted using an image analysis system (WinSEEDLE v5.1a, Regent Instruments, Inc., Canada). This was then multiplied by the surface area of a single sphere of the same average diameter as the pellet.
Table 3.1d. Relative pressures at which the volume of nitrogen adsorbed on the sample were determined.

<table>
<thead>
<tr>
<th>Point number</th>
<th>Relative pressure</th>
<th>Point number</th>
<th>Relative pressure</th>
<th>Point number</th>
<th>Relative pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0010</td>
<td>10</td>
<td>0.1250</td>
<td>19</td>
<td>0.5000</td>
</tr>
<tr>
<td>2</td>
<td>0.0025</td>
<td>11</td>
<td>0.1500</td>
<td>20</td>
<td>0.5500</td>
</tr>
<tr>
<td>3</td>
<td>0.0050</td>
<td>12</td>
<td>0.1750</td>
<td>21</td>
<td>0.6000</td>
</tr>
<tr>
<td>4</td>
<td>0.0075</td>
<td>13</td>
<td>0.2000</td>
<td>22</td>
<td>0.6500</td>
</tr>
<tr>
<td>5</td>
<td>0.0100</td>
<td>14</td>
<td>0.2500</td>
<td>23</td>
<td>0.7000</td>
</tr>
<tr>
<td>6</td>
<td>0.0250</td>
<td>15</td>
<td>0.3000</td>
<td>24</td>
<td>0.7500</td>
</tr>
<tr>
<td>7</td>
<td>0.0500</td>
<td>16</td>
<td>0.3500</td>
<td>25</td>
<td>0.8000</td>
</tr>
<tr>
<td>8</td>
<td>0.0750</td>
<td>17</td>
<td>0.4000</td>
<td>26</td>
<td>0.8500</td>
</tr>
<tr>
<td>9</td>
<td>0.1000</td>
<td>18</td>
<td>0.4500</td>
<td>27</td>
<td>0.9000</td>
</tr>
</tbody>
</table>

3.2 PRODUCTION OF POROUS ALUMINOSILICATE PELLETS BY EXTRUSION-SPHERONIZATION

3.2.1 Preparation of Excipients

3.2.1.1 Particle Size Reduction of Sucrose

500 g of granulated sucrose was milled in a ball mill (Erweka KM5, Germany) at 30 rpm for 30 min. The size fractions 90-125 µm and 180-250 µm were separated using a nest of sieves and retained. The remaining milled sucrose was then further milled using an ultracentrifuge mill (Retsch ZM100, Germany) fitted with an 8 tooth rotor and a 0.08 mm sieve-ring.

3.2.1.2 Particle Size Analysis of Sucrose by Laser Diffraction

The particle size distribution of the sucrose at various processing stages was determined using a Malvern 2600c (Malvern, USA) laser diffraction particle size analyser. The analyser was fitted with a 300 mm lens. This lens is capable of measuring particles in
the size range 5.8 to 564 μm. Samples of the processed sucrose were placed in the feed tray of a dry powder feeder (PS64, Malvern, USA). The feed rate was controlled in order to distribute the powder into a dispersing air jet, which was sucked across the path of the laser beam by a vacuum. The feed rate was such that the laser obscuration was between 0.15 and 0.4. The resultant scattering from all particles present in the beam gave a measurement of the particle size distribution, which was calculated by the sizer software using Fraunhofer theory. All measurements were repeated 3 times and the results were averaged.

3.2.2 Extrusion-Spheronization Process

3.2.2.1 Mixing

The dry powder excipients were placed in a beaker and thoroughly mixed. The granulating liquid, ethanol, was slowly added to the powders with continuous mixing. Once all the granulating liquid had been added, mixing was continued for 3 min to ensure a uniform mixture was obtained. The beaker was sealed using Parafilm® and the wet mass left at room temperature for at least 12 h to allow the powders and ethanol to equilibrate.

3.2.2.2 Extrusion

The wet mass was extruded using a rotary gravity-fed cylinder-type extruder (Alexanderwerk Type GA65, Germany). This was fitted with a 7.0 cm diameter, 14.8 cm long perforated stainless steel cylinder. The perforations were 1 mm in diameter and the cylinder wall was 4 mm thick. The perforations were spread evenly and centrally over 8.3 cm length of the cylinder wall. The perforated cylinder was located against a solid cylinder in the extruder and rotated at 30 rpm.
3.2.2.3 Spheronization

40 g of the extrudate was spheronized on a 120 mm diameter spheronizer (Caleva Model 120, UK) using a cross-hatch friction plate. The spheronized pellets were collected and dried at room temperature to a constant weight.

3.2.3 Preliminary Extrusion-Spheronization Experiments

For each preliminary experiment 100 g of formulation was prepared. The spheronization speed and time were 1250 rpm and 5 min, respectively.

3.2.3.1 Granulating Liquid and Binder Selection

A series of extrusion formulations were prepared in order to assess the effect of binder inclusion on the resulting spheronized product. Initially formulations containing only kaolin and a granulating liquid were prepared. Following this various binders were included in the formulations. Samples of each spheronized product were placed in 50 ml of water. The pellet integrity was visually assessed after 24 h. Based upon this, a granulating liquid and binder were selected for inclusion in the formulations used in further extrusion-spheronization experiments.

3.2.3.2 Determination of Approximate Granulating Liquid Levels

It was necessary to place constraints on the amounts of granulating liquid, which would be allowed in the extrusion-spheronization experimental design. These constraints were to ensure that the formulations prepared could be extruded and spheronized. A series of formulations containing different levels of sucrose and granulating liquid were prepared. The suitability of these formulations for extrusion and spheronization was visually assessed. Based upon this, constraints for the extrusion-spheronization experimental design were determined.
3.2.4 Extrusion-Spheronization Experimental Design

Using Design Expert v6.0.3 (Stat-Ease Inc., USA), a statistical computer program, an experiment to determine the optimal formulation and process parameters for pellet production was designed. The design was a crossed d-optimal design, which allowed for the assessment of both formulation and process parameters in the one design, while at the same time minimizing the number of design points. The number of design points generated was based on the assumption that the highest order, which modelled the response surface, was quadratic for both the mixture and process components. The design components and their high and low levels are given in Table 3.2a. Table 3.2b shows the constraints of the design. These constraints and the high and low levels of the mixture components were determined based on the preliminary extrusion-spheronization experiments. The binder content was constant at each design point and therefore it was unnecessary to include this in the design generator.

Table 3.2a. Extrusion-spheronization experimental design components.

<table>
<thead>
<tr>
<th>Component</th>
<th>Type</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaolin (g)</td>
<td>Mixture</td>
<td>33</td>
<td>67.5</td>
</tr>
<tr>
<td>Ethanol (g)</td>
<td>Mixture</td>
<td>19.5</td>
<td>30</td>
</tr>
<tr>
<td>Sucrose (g)</td>
<td>Mixture</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Spheronizer speed (rpm)</td>
<td>Numeric</td>
<td>1000</td>
<td>1500</td>
</tr>
<tr>
<td>Spheronization time (min)</td>
<td>Numeric</td>
<td>2.5</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 3.2b. Extrusion-spheronization experimental design constraints.

<table>
<thead>
<tr>
<th>Low Limit</th>
<th>Constraint (g)</th>
<th>High Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3 Kaolin - 6.111 Ethanol + Sucrose</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>3 Kaolin - 7.513 Ethanol + Sucrose</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>Kaolin - 2.1 Ethanol + 0.5 Sucrose</td>
<td>-</td>
</tr>
<tr>
<td>33</td>
<td>Kaolin</td>
<td>67.5</td>
</tr>
<tr>
<td>19.5</td>
<td>Ethanol</td>
<td>30</td>
</tr>
<tr>
<td>0</td>
<td>Sucrose</td>
<td>40</td>
</tr>
<tr>
<td>0</td>
<td>Kaolin + Ethanol + Sucrose</td>
<td>95</td>
</tr>
</tbody>
</table>

Preliminary assessment of the results of the experiment indicated it was necessary to relax the design components and constraints. The relaxed design components and constraints are given in Table 3.2c and 3.2d. An additional 5 design points were generated to explore the relaxed design space. The complete set of design points are given in Appendix 7.

Table 3.2c. Relaxed extrusion-spheronization experimental design components.

<table>
<thead>
<tr>
<th>Component</th>
<th>Type</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaolin (g)</td>
<td>Mixture</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td>Ethanol (g)</td>
<td>Mixture</td>
<td>19.5</td>
<td>30</td>
</tr>
<tr>
<td>Sucrose (g)</td>
<td>Mixture</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Spheronizer speed (rpm)</td>
<td>Numeric</td>
<td>1000</td>
<td>1500</td>
</tr>
<tr>
<td>Spheronization time (min)</td>
<td>Numeric</td>
<td>2.5</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 3.2d. Relaxed extrusion-spheronization experimental design constraints.

<table>
<thead>
<tr>
<th>Low Limit</th>
<th>Constraint (g)</th>
<th>High Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3 Kaolin - 5.54 Ethanol + Sucrose</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>3 Kaolin - 8.14 Ethanol + Sucrose</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>Kaolin - 2.1 Ethanol + 0.5 Sucrose</td>
<td>-</td>
</tr>
<tr>
<td>31</td>
<td>Kaolin</td>
<td>69</td>
</tr>
<tr>
<td>19.5</td>
<td>Ethanol</td>
<td>30</td>
</tr>
<tr>
<td>0</td>
<td>Sucrose</td>
<td>40</td>
</tr>
<tr>
<td>0</td>
<td>Kaolin + Ethanol + Sucrose</td>
<td>95</td>
</tr>
</tbody>
</table>

3.2.5 Spheronized Product Analysis

3.2.5.1 Sieve Analysis

Sieve analysis of the spheronized samples was performed using a nest of standard sieves, agitated for 10 min on an Endecott sieve shaker (1 MK11, UK). The sieve apertures used were 850 and 1400 μm. The mass retained by each sieve and that, which collected on the base plate was found. Each mass was expressed as a percentage of the total mass of sample analysed. In this work, the desirable size range of pellets was between 850 and 1400 μm and any pellets falling in this size range are referred to as “pellets”. Particles above this size are referred to as “large pellets” while those below this size are referred to as “fines”.

3.2.5.2 Sphericity

The sphericity of pellets was determined using pellet parameters measured by an image analysis system (WinSEEDLE v5.1a, Regent Instruments, Inc., Canada). This system analyses a digitised image of the pellets obtained using a flat bed scanner (Visioneer 4400 USB, UK). For each sample, at least 500 randomly chosen pellets were placed on the scanner. The pellets were separated to ensure that each pellet was individually analysed. To accurately analyse the pellets, the system must be able to distinguish between the background and the pellets. In this case the pellets were white against a
black background. However, in the digitised image, there was a gradient from white to grey over the pellet surface. This occurred because the pellets were rounded. The gradient meant that at the default settings, the system could not accurately distinguish between the pellets and the background. To overcome this problem the grey level, which defines what the system considered background, was manually set at 70. This value was found to most accurately distinguish between pellets and the background.

The sphericity of the pellets was calculated using two parameters, the projected perimeter length of the pellet, $P_m$, and the projected area, $A$. It was expressed in terms of Form PE where

$$\text{Form PE} = \frac{4\pi A}{P_m^2} \quad \text{Eqn. 3.2a}$$

The Form PE of a perfect sphere is 1.00 while pellets with a Form PE of 0.833 or less have observable defects or distortions. Form PE is the inverse of a roundness parameter defined by Hileman et al. (1993).

### 3.2.6 Removal of Sucrose from Extrusion-Spheronization Products

Prior to drug loading the extrusion-spheronization products, it was necessary to remove the incorporated sucrose. The pellets were placed in water for 6, 12 or 24 h, then separated using filter paper and dried at 60 °C for 24 h. Complete sugar removal was confirmed by measuring the skeletal density of the pellets using helium pycnometry, as described in Section 3.1.6.

### 3.3 PRODUCTION OF POROUS ALUMINOSILICATE PELLETS BY CRYOPELLETIZATION

#### 3.3.1 Cryopelletization Process

The formulations intended for cryopelletization were prepared by thoroughly mixing the formulation components. The mixtures were then sonicated (Bransonic 220, USA) for 15 min, after which they were continuously stirred. The formulations were then added
Chapter 3. Methodology

3.3.2 Preliminary Cryopelletization Studies

3.3.2.1 Pellet Hardness and Dissolution Studies

A series of aqueous based formulations containing different levels of kaolin (5 – 50 g/100 ml) and sodium silicate solution (0.19 ml – 22.22 ml/100 ml) were prepared. The pellets once prepared were cured at room temperature or 200 °C for 0, 1 or 24 h. The effect of kaolin level, sodium silicate solution level and curing on pellet strength and ability to remain intact in water was investigated.

3.3.2.2 Factorial Studies

A $2^{5-1}$ factorial design was used to investigate the effects of various factors on pellet production. The formulations used are given in Table 3.3a, while the factors investigated are given in Table 3.3b. The complete set of experimental design points are given in Appendix 10.
Table 3.3a. Cryopelletization formulations used in the $2^{5-1}$ factorial study.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Kaolin (g)</th>
<th>Sodium silicate solution (ml)</th>
<th>Water or 2.5% w/v Sodium lauryl sulphate solution (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>7.41</td>
<td>To 100</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>22.22</td>
<td>To 100</td>
</tr>
</tbody>
</table>

Table 3.3b. Design components of the cryopelletization $2^{5-1}$ factorial study.

<table>
<thead>
<tr>
<th>Component</th>
<th>Type</th>
<th>Low level</th>
<th>High level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Categorical</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Sodium lauryl sulphate</td>
<td>Numeric</td>
<td>0</td>
<td>2.5% w/v</td>
</tr>
<tr>
<td>Internal needle diameter</td>
<td>Numeric</td>
<td>0.3 mm (30 G)</td>
<td>0.9 mm (20 G)</td>
</tr>
<tr>
<td>Drop height</td>
<td>Numeric</td>
<td>5 cm</td>
<td>15 cm</td>
</tr>
<tr>
<td>Fall height</td>
<td>Numeric</td>
<td>7.5 cm</td>
<td>15 cm</td>
</tr>
</tbody>
</table>

The defining relation for the design generator was $\text{Fall height} = \text{Formulation} \times \text{Sodium lauryl sulphate} \times \text{Internal needle diameter} \times \text{Drop height}$. The confounding pattern for this design was that the main effects were confounded with four-factor interactions and two-factor interactions were confounded with three-factor interactions. A significance level of 0.01 was chosen.

The sphericity of the pelletized products was found in the same manner as for the products of extrusion-spheronization (Section 3.2.5.2). In this case, the minimum number of pellets per analysis was 100. Using the image analysis system, the diameter of the pellets was also measured. As the pellets were not perfect spheres, their diameter was measured as the longest line that passed through the pellet centre.
The results of this factorial experiment, in conjunction with the results of the pellet hardness and dissolution studies, were used to determine the formulations to be prepared for further investigation and the production parameters to be used.

3.4 DRUG LOADING OF POROUS PELLETS

3.4.1 Solubility Studies

In order to find the saturation solubility of a drug in a particular medium a mass of drug, which exceeded the reference solubility in 5 ml of medium, was weighed out. This was then placed in a 10 ml ampoule. 5 ml of medium were added and the ampoule was flame sealed. It was placed in a shaking water bath (Model 25, Precision Scientific, USA) at the required temperature and shaken at 100 cycles per min for 24 h. Following this, the contents of the ampoule were removed and filtered through a 0.45 μm membrane filter (Gelman Supor-450, USA). Using an appropriate dilution, the absorbance of this solution was found by UV spectroscopy (Spectronic Genesye 5). The quantity of drug in the original 5 ml of medium was calculated. This procedure was repeated with the ampoule being shaken for 48 h. The quantity of drug dissolved at 24 and 48 h was compared. In all studies, there was no significant difference between the two values and the saturation solubility was calculated from the average of these two values. The experiment was repeated once.

3.4.2 Preliminary Drug Loading Studies

Drug loading studies were carried out using N-light N3 and a saturated aqueous diltiazem HCl solution to find which of 3 methods gave the highest drug loading. Each method was carried out in triplicate and crushed samples of the resulting drug loaded porous ceramics were assayed for drug content by UV spectroscopy. Based on these results, a method was selected for other loading experiments. The methods are described below.

Method (i). 3 g of N-light N3 pellets were placed in 33 ml of a 40% w/v diltiazem HCl solution and stirred for 30 min using a magnetic stirrer. The pellets and drug solution
were then allowed to stand for 1 h. Following this, they were separated using filter paper and dried for 24 h at 60 °C.

Method (ii). 3 g of N-light N3 pellets were placed in 33 ml of a 40% w/v diltiazem HCl solution. The mixture was evacuated for 30 min, after which the vacuum was released. The pellets and drug solution were then allowed to stand for 1 h. Following this, they were separated using filter paper and dried for 24 h at 60 °C.

Method (iii). 3 g of N-light N3 pellets were placed in a 10 ml specimen tube, which was capped with a lid containing a single 1 mm hole. The tube was placed in a 50 ml round bottomed flask with the lid to the bottom. A stopcock was attached to the flask. With the stopcock open, the flask was evacuated for 30 min (Fig. 3.4a). 33 ml of a 40% w/v diltiazem HCl solution was introduced to the flask through the stopcock. The pellets and drug solution were allowed to stand for 1 h (Fig. 3.4b). Following this, they were separated using filter paper and dried for 24 h at 60 °C.

Figure 3.4. Representation of drug loading method (iii), (a) prior to introduction of drug solution and (b) following introduction of drug solution and restoration of atmospheric pressure.
3.4.3 Drug Loading Using Optimum Loading Technique

Using method (iii), 1 g of each grade of N-light was mixed and placed in the specimen tube, which was capped with a lid containing a single hole. The following loading solutions were used: 40% w/v aqueous sodium benzoate solution, 40% w/v aqueous diltiazem HCl solution and 30% w/v ethanolic benzoic acid solution. These loading solutions were saturated solutions with the saturation solubility having been determined using the method given in Section 3.4.1. Following drying, the pellets were separated using a nest of sieves. Separation was possible as each grade had a different particle size distribution.

Also using method (iii), 1.5 g of Starlight SLK1000, 9.39 g of each grade of Carbolite, 3 g of the final extrusion-spheronization products and various quantities of the cryopelletized products were loaded with a 40% w/v aqueous diltiazem HCl solution. The cryopelletized products were also loaded with a 20% w/v methanolic propranolol HCl solution. The concentration of this solution was chosen based on previous halloysite G loading studies conducted by Levis and Deasy (2003). Finally, the extrusion-spheronization products referred to as K0 and H0 (Table 6.2k) were loaded with a 12% w/v propranolol HCl aqueous solution, this being a saturated solution.

3.4.4 Assay of Drug Loaded Porous Pellets

A 100 ml volumetric flask was made up to the mark with phosphate buffer pH 6.8, which contained 11.9 g/L of disodium hydrogen phosphate dodecahydrate and 5.2 g/L of sodium dihydrogen phosphate dihydrate. To this a known mass of the sample to be assayed was added. It was necessary to crush Carbolite samples in a ball mill (Retsch MM2, Germany) prior to assay, however all other pellets were crushed by the stirring action of the assay procedure. The medium was stirred for 16 h after which a 5 ml sample was removed and filtered through a 0.45 μm membrane filter. Using appropriate dilutions the absorbance of this solution was found and the quantity of drug in the original sample calculated. The drug loading was expressed either as the percentage drug per mass of drug loaded sample (% w/w) or the percentage drug per volume of drug loaded sample (% w/v).
3.4.5 Calculations

The absorbance of drug solutions was measured at their wavelength of peak absorbance. These wavelengths are given in Appendix 1. The absorbance of the drug solutions was linearly related to their concentration. Linear, least squares regression analysis resulted in a linear calibration curve for each drug. The calibration equations are given in Appendix 1. Using appropriate calibration equations, the concentration of drug solutions was found.

3.5 INVESTIGATIONS INTO THE USE OF RELEASE MODIFYING AGENTS

3.5.1 Polyvinylpyrrolidone, Chitosan and Ethylcellulose 10 cps Loading

Three polymers were loaded into N-light N3 pellets. The method of polymer loading was dependent upon the polymer used. Firstly, for PVP, an aqueous solution containing 10% w/v PVP and 40% w/v diltiazem HCl was prepared. N-light N3 was then loaded with this solution in the manner described in Section 3.4.3. The pellets were then spread over a sieve of mesh size 710 μm and dried overnight at 50 °C. Secondly, for chitosan, N-light N3 was loaded with a 40% w/v aqueous diltiazem HCl solution as described in Section 3.4.3. Following this, the drug loaded pellets were loaded with an aqueous solution, which contained 1% w/v chitosan and 1% v/v glacial acetic acid. The pellets were then spread over a sieve of mesh size 710 μm and dried overnight at 50 °C. Finally, for ethylcellulose 10 cps, the loading method was the same as for chitosan except that a 10% w/v ethanolic ethylcellulose 10 cps loading solution was used. In each case loading was carried out in triplicate.

3.5.2 Calcium Alginate Loading

3 g of N-light N3 was loaded using a 40% w/v aqueous diltiazem HCl solution as described in Section 3.4.3. The pellets were then loaded with an aqueous solution containing 2% w/v sodium alginate and 0.5% w/v sodium polyphosphate again using the method described in Section 3.4.3. However, the loaded material was not dried overnight but instead was dropped immediately into 200 ml of stirred deionised water. After 1 min, 50 ml of a 25% w/v aqueous calcium chloride solution was added. Stirring
was continued for 5 min, after which the mixture was spread over a sieve of mesh size 710 μm and dried overnight at 50 °C.

### 3.5.3 Precirol ATO 5 Coating

3 g of N-light N3 was loaded using a 40% w/v aqueous diltiazem HCl solution as described in Section 3.4.3. 2.5 g of these drug loaded pellets were added to 6.25 g of molten Precirol ATO 5, and stirred. This mixture was added to 100 ml of vigorously stirred boiling water. Following this, 200 ml of cold water was slowly added to the mixture. This mixture was then poured over a sieve of mesh size 710 μm and a further 500 ml of cold water was washed over the pellets to further solidify the Precirol ATO 5. The pellets were left overnight at room temperature to dry.

### 3.6 DISSOLUTION STUDIES ON DRUG LOADED POROUS PELLETS

#### 3.6.1 Dissolution Testing

Dissolution tests were carried out using an Erweka DT6 (Germany) dissolution tester. 900 ml of the dissolution medium, phosphate buffer pH 6.8 (formula given in Section 3.4.4) or 0.1N HCl, was placed in each dissolution vessel. The medium was kept at a temperature of 37 °C throughout the experiment. Samples were contained in baskets, which were rotated at 100 rpm. Each dissolution vessel was covered with a plastic lid throughout the experiment.

5 ml samples were withdrawn at 2.5, 5, 10, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8 and 24 h. Each time 5 ml was withdrawn, it was replaced with 5 ml of fresh dissolution medium maintained at 37 °C. The sample was taken from a zone midway between the surface of the dissolution medium and the top of the rotating basket. This zone was not less than 1 cm from the vessel wall (British Pharmacopeia, 2002).

The samples were filtered through a 0.45 μm membrane filter and analysed using a UV spectrophotometer at an appropriate wavelength. The repeated removal of sample from the dissolution medium was accounted for in the subsequent calculations. Dissolution
tests were carried out in triplicate. Dissolution testing was principally carried out on intact drug loaded porous pellets, but certain crushed drug loaded porous pellets were also tested.

### 3.6.2 Residue Analysis

Following dissolution testing, the sample was crushed and assayed for drug content in the same manner as described for the assay of drug loaded porous pellets in Section 3.4.4.

### 3.6.3 Calculations

Using the appropriate calibration equation, the concentration of drug in each sample was found. The results were presented as percentage drug released. This was found based on the release at 24 h and the drug remaining in the pellets following dissolution testing.

### 3.7 STATISTICAL METHODS

The statistical analyses were carried out using one of two statistical computer programs, Minitab v13.1 (Minitab Inc., USA) and Design Expert v6.0.3 (Stat-Ease Inc., USA).

#### 3.7.1 Two Sample t-Tests

Two sample t-tests were used to compare the means of two independent samples. The test procedure involved defining a null and alternative hypothesis. The null hypothesis was that the sample means were equal, while the alternative hypothesis was that they were not equal. The tests were carried out at a significance level of 0.05. The critical value at this significance level was obtained from a student’s t-distribution with n-1 degrees of freedom. The null hypothesis was rejected when the t-ratio exceeded the critical value. This ratio was calculated using Eqn. 3.7a.
Chapter 3. Methodology

\[
t = \frac{\bar{X}_2 - \bar{X}_1}{S_0}
\]

Eqn. 3.7a

where \( \bar{X}_1 \) is the mean of sample 1, \( \bar{X}_2 \) is the mean of sample 2 and \( S_0 \) is the standard error of the mean difference. In these tests the variances of each sample were not assumed to be equal.

3.7.2 Analysis of Variance

In the previous Section the use of t-tests to compare the means of two independent samples was discussed. ANOVA is an extension of the t-test and was used to compare the means of more than two independent samples. The null hypothesis was that all the means are equal and the alternative was that they are not. ANOVA was carried out by dividing the total sum of squares (SS) and degrees of freedom (df) of the data into components associated with each source of variation in the data. From these values, an adjusted mean square was calculated for each source of variation. The ratio of any two adjusted mean squares gave an F-statistic. Where this exceeded the critical value for the test, the difference between the adjusted mean squares was significant. The critical value was calculated using Tukey's 'Honestly Significant Method' at a family significance level of 0.05. This was more appropriate than using an individual significance level of 0.05, as multiple comparisons of means were being made. However, for the half factorial studies a significance level of 0.1 was used rather than 0.05, as there were a low number of data points available. The results of ANOVA were expressed as p-values. A result was significant if its p-value was less than the significance level.

In all cases, ANOVA was used only if the residuals of the data were normally distributed and had a constant variance, which was not dependent on run order or any one factor. If this were not the case the use of ANOVA to analyse the data would have been invalid. In addition, where model fitting was carried out the adjusted \( R^2 \) value and the predicted \( R^2 \) value of the model had to be in reasonable agreement. If large differences exist this can be due to a problem with the model or the data. The adequate precision value, which measures signal to noise ratio, had to be high enough to indicate
adequate signal. Otherwise the model could not have been used to navigate the design space.

### 3.7.3 Linear Regression Analysis

Linear regression analysis was used to determine if a linear relationship existed between two variables. This linear relationship can be represented by the following equation:

\[
Y = mX + C \quad \text{Eqn. 3.7b}
\]

where \(X\) is the independent variable, \(Y\) is the dependent variable and \(C\) is the value of \(Y\) when \(X = 0\), i.e. the \(Y\)-axis intercept. The equation of the line was fitted to the data using the method of least squares. This method gave the equation of the line, which best fitted the data. The adequacy of the fit was assessed from the \(R^2\) value. The closer this value was to 1 the better the fit.

### 3.7.4 Mathematical Modelling of In Vitro Dissolution Data

The experimental dissolution data was fitted to mathematical models using the non-linear curve fitting program Micromath® Scientist™ for Windows™ Version 1.0 (Micromath® Scientific Software, USA). The goodness of fit and suitability of a model was evaluated using the coefficient of determination (CD) and model selection criterion (MSC).

The CD is a measure of the fraction of the total variance accounted for by the model (Scientist Handbook, 1995). It is calculated using the formula

\[
CD = \frac{\sum_{i=1}^{n} w_i (Y_{obs_i} - \overline{Y}_{obs})^2 - \sum_{i=1}^{n} w_i (Y_{obs_i} - Y_{cal_i})^2}{\sum_{i=1}^{n} w_i (Y_{obs_i} - \overline{Y}_{obs})^2} \quad \text{Eqn. 3.7c}
\]
where \( n \) is the number of points, \( w_i \) is the weight applied to each point and \( Y_{\text{obs}_i}, \bar{Y}_{\text{obs}} \) and \( Y_{\text{cal}_i} \) are the observed data points, the weighted mean of the observed data and the model predicted data points, respectively.

The MSC is a modified Akaike Information Criterion (AIC). The AIC represents the information content of a set of parameter estimates. When comparing two models with different numbers of parameters, it places a burden on the model with more parameters to not only have a better coefficient of determination, but quantifies how much better it must be for the model to be deemed more appropriate. The MSC gives the same rankings between models as the AIC but has been normalized so that it is independent of the scaling of the data points. The MSC is defined by the formula

\[
\text{MSC} = \ln \left( \frac{\sum_{i=1}^{n} w_i (Y_{\text{obs}_i} - \bar{Y}_{\text{obs}})^2}{\sum_{i=1}^{n} w_i (Y_{\text{obs}_i} - Y_{\text{cal}_i})^2} \right) - \frac{2p}{n} \quad \text{Eqn. 3.7d}
\]

where \( p \) is the number of parameters estimated. The most appropriate model will have the largest MSC.
4.1 INTRODUCTION

Porous ceramics, as discussed in Chapter 1, are comprised of a three-dimensional array of hollow polygons, which may be open or closed. Owing to their structure and composition they have proven suitable for many applications ranging from catalyst supports to filters for molten metals and hot gases (Sepulveda and Binner, 1999). More recently, the potential applications of porous ceramics as modified release drug delivery systems have been demonstrated (Itokazu et al., 1999; Netz et al., 2001; Paul et al., 2002). Primarily, these systems were composed of calcium phosphate and designed for use by routes other than the oral route.

The research presented in this thesis aimed to further demonstrate the suitability of porous ceramic pellets as modified release drug delivery systems. In particular, the research focussed on the suitability of porous non-calcium phosphate ceramics as oral drug delivery systems. Owing to their successful application in many industries, porous ceramic products are widely available. Therefore, initial investigations used some commercially available ceramics. The products obtained were Carbolite 16/20, 16/20 (More porous) and 20/40 from Carboceramics, N-light N2, N3 and N4 from Itochu Ceratech Corporation and Starlight SLK1000 from Imerys. The Carbolite ceramics are marketed for use in the hydraulic fracturing of oil and gas wells, while the N-light ceramics and Starlight SLK1000 are marketed for use in the building materials industry.

Prior to testing the suitability of these products as modified release drug delivery systems, it was essential that they were fully characterised. This was necessary as the porous structure and composition of porous ceramics can vary greatly due to the wide
variety of production techniques available. In addition, process and compositional changes can also lead to changes in the porous structure (Montanaro et al., 1998).

4.2 PELLET SIZE DISTRIBUTION

Sieve analysis of each porous ceramic product showed that the Carbolite ceramics had the narrowest pellet size distribution with at least 70% w/w of the pellets located within a single size range (Fig. 4.2a). In the case of Carbolite 16/20 and 16/20 (More porous) this was between 1000 and 1180 μm, while for Carbolite 20/40 it was between 710 and 850 μm. The N-light ceramics and Starlight SLK1000 exhibited a wider pellet size distribution with each grade of N-light having a markedly different pellet size distribution. N-light N2 contained the largest pellets with the majority in the size range 1400-1700 μm, while N-light N4 contained the smallest pellets with the majority in the size range 600-710 μm. Regarding Starlight SLK1000, the majority of pellets were in the size range 710-850 μm, although a large proportion of the fraction analysed was less than 250 μm. This was due to the high proportion of fines present in the Starlight SLK1000 sample. Their presence was attributed to crushing of the Starlight SLK1000 pellets during storage, as they were relatively brittle in comparison to the other porous ceramics.

Based on these results, particular size fractions of each porous ceramic were selected for use in all further experiments. For each Carbolite ceramic, N-light N3 and Starlight SLK1000 the size fraction selected was 850-1000 μm as each of these products contained pellets in this size fraction. The N-light ceramics, N2 and N4, contained only minute quantities of pellets in this size range. Therefore, alternative size ranges for further experimentation were selected. These were 1700-2000 μm for N-light N2 and 425-500 μm for N-light N4. This would allow the influence of pellet size on the properties of N-light to be investigated. A final point regarding the selected sizes is that pellets and minitablets of comparable sizes to the porous ceramics have been loaded into hard gelatin capsules and administered orally (Ansel et al., 1999). Therefore, the porous ceramics under investigation could be orally administered, which was a goal of this research.
Chapter 4. Characterisation of Commercially Produced Porous Ceramic Pellets

4.3 ELEMENTAL AND CERAMIC COMPOSITION OF THE PELLETS

The elemental composition of N-light was determined using EDX microanalysis with N3 being the particular grade investigated. The principal elements in N-light N3 were found to be aluminium and silicon (Fig. 4.3a). This was in agreement with information contained in the material safety data sheet for N-light. In addition to these elements, lower levels of iron and potassium were detected.

Figure 4.2a. Pellet size distribution of each commercially produced porous ceramic.
In order to determine the mineral composition of N-light N3, the results of EDX microanalysis were used in conjunction with XRD. The most intense peak in the XRD pattern at 26.6° 2θ was due to α quartz (Fig. 4.3b). This was confirmed by the presence of less intense peaks due to α quartz at 20.72, 36.46, 39.38 and 50.12° 2θ (Brown, 1980; Moore and Reynolds, 1997c). As silicon and oxygen are the elemental constituents of α quartz, the results of EDX microanalysis supported this identification (Gribble, 1988). In addition, the identification was further confirmed by information in the N-light materials safety data sheet, which states that the mineral composition of N-light is mostly α quartz.

The remaining peaks in the N-light N3 XRD pattern were found at 21.98, 23.74 and 27.7° 2θ, which indicated feldspars were present in N-light N3 (Fig. 4.3b) (Brown, 1980). Feldspars contain aluminium and silicon, which were detected by EDX microanalysis (Gribble, 1988). Feldspars are divided into two groups, the alkali feldspars and the plagioclases. It was not possible to conclusively determine the group present from the XRD pattern, as only three peaks were available for identification purposes. This was because some of the peaks could not be detected above the background noise and also certain α quartz peaks would have coincided with the feldspar peaks (Moore and Reynolds, 1997c). However, EDX microanalysis detected potassium in the N-light N3 sample, which is found in alkali feldspars but not in
plagioclases (Gribble, 1988). This shows that alkali feldspars were present in N-light N3 although plagioclases may also have been present.

![XRD pattern](image)

**Figure 4.3b.** XRD pattern of a powdered sample of N-light N3 (F, feldspar; Q, α quartz).

The mineral composition of N-light N3 can be explained with reference to its original formulation. The manufacturer stated that N-light N3 was produced from pelletized porcelain clay, which was fired at 1350 °C. The porcelain clay consisted of acid-proof stone, weathering granite and Gairome clay. In addition, small quantities of other materials were added, although no information was provided regarding these. While it was not possible to determine what acid-proof stone consists of, granite contains α quartz, alkali feldspars and plagioclases (Clarke, 1992) and Gairome clay contains kaolin associated with minor amounts of tubular halloysite, α quartz and occasionally illite and smectite (Nagasawa, 1978). The presence of granite in the formulation explains the detection of iron by EDX microanalysis, as it is typically found in granite (Clarke, 1992).

During sintering of the pelletized porcelain clay, the α quartz would have inverted to β quartz at 573 °C and remained as such up to 1350 °C. However, upon cooling the α
quartz would have reformed immediately below the inversion temperature (Worrall, 1986). The alkali feldspars melted to form various materials such as leucite but reformed upon cooling (Deer et al., 1992). Finally, the kaolinite minerals would have formed mullite upon sintering (Chen et al., 2004). As this was not detected by XRD, the manufacturer must not have incorporated large amounts of Ga shaping clay in the N-light N3 formulation.

The elemental composition of Starlight SLK1000 was found to be similar to that of N-light N3, with aluminium and silicon being the principal elemental constituents. In addition to these, lower levels of iron, potassium and titanium were also present (Fig. 4.3c).

![EDX microanalysis of Starlight SLK1000](image)

**Figure 4.3c.** EDX microanalysis of Starlight SLK1000.

XRD studies on Starlight SLK1000 showed that it contained α quartz and mullite. The intense peak at 26.54 ° 2θ and the less intense peaks at 20.8 and 50.08 ° 2θ indicated the presence of α quartz (Fig. 4.3d) (Brown, 1980; Moore and Reynolds, 1997c). The remaining eleven peaks were due to mullite (Brown, 1980). This identification was supported by the results of EDX microanalysis, as silicon is an elemental constituent of α quartz and aluminium and silicon are elemental constituents of mullite (Gribble, 1988).
These identifications are also in agreement with information obtained from the manufacturer regarding the composition and production of Starlight SLK1000. The sole formulation constituent used was ball clay, which consists primarily of kaolin and α quartz but also contains varying amounts of mica, feldspars and organic matter (Imerys, 2004). In addition, it can contain minor amounts of other minerals (Reed, 1995). The ball clay was sintered, which caused the kaolin in the ball clay to undergo a structural phase change to mullite (Deer et al., 1992; Schneider et al., 1994; Chen et al., 2004). The α quartz would have reformed from β quartz following sintering (Worrall, 1986). Mica if it were present would have formed potassium feldspar and sillimanite upon sintering (Gribble, 1988). The fact that these minerals or other feldspars were not detected by XRD indicates that mica and feldspars were not present in large quantities in the formulation. However, they may have been present in small quantities as potassium was detected by EDX microanalysis. The low level of iron detected was due to minor amounts of ilmenite (FeTiO₃) and hematite (Fe₂O₃) in the ball clay, while the low level of titanium was due to the presence of rutile (TiO₂) (Reed, 1995).
EDX microanalysis of Carbolite 16/20 found that its elemental composition was similar to that of N-light N3 and Starlight SLK1000. The principal elemental constituents were aluminium and silicon while lower levels of iron and titanium were also detected (Fig. 4.3e).

The XRD pattern of Carbolite 16/20 showed it contained mullite and cristobalite (Fig. 4.3f). The cristobalite peaks occurred at 21.66 and 35.78 ° 2θ with the remaining eighteen peaks being due to mullite (Brown, 1980; Moore and Reynolds, 1997c). These identifications agreed with the composition of Carbolite given in the material safety data sheet and the results of EDX microanalysis, as the elemental constituents of cristobalite are silicon and oxygen, while those of mullite are aluminium, silicon and oxygen (Gribble, 1988).

The manufacturer did not provide the formulation used to produce Carbolite 16/20. However, as both mullite and cristobalite are typically found in ceramics produced by sintering of aluminium containing clay minerals, such as those of the kaolinite group, these were possible constituents (Brown, 1980; Deer et al., 1992). In addition, the sintering temperature must have been greater than 1350 °C as otherwise cristobalite would not have formed (Worrall, 1986; Chen et al., 2004). It was for this reason that cristobalite was not found in Starlight SLK1000 even though its formulation contained kaolin.
Finally, as with Starlight SLK1000 the detection of low levels of iron and titanium in Carbolite 16/20 was due to the presence of impurities in the starting minerals. Iron and titanium are given as constituents of Carbolite 16/20 in its material safety data sheet.

![XRD pattern of a powdered sample of Carbolite 16/20 (C, cristobalite; M, mullite).](image)

**Figure 4.3f.** XRD pattern of a powdered sample of Carbolite 16/20 (C, cristobalite; M, mullite).

### 4.4 SURFACE CHARGE OF THE PELLETS

Zeta potential measurements were used to determine the effect of pH on the surface charge of the porous ceramics. Of the N-light and Carbolite grades, N3 and 16/20 were analysed, respectively. It was found that each porous ceramic had a positive surface charge at low pH, which fell rapidly as the pH increased. It became negative between pH 2 and 3 for Starlight SLK1000 and around pH 4 for the other porous ceramics. With further increases in pH, the surface charge of the ceramics became more negative although the rate of change was slower at high pHs than at low pHs. The surface charge of N-light N3 and Carbolite 16/20 was similar over the complete pH range studied. However, for Starlight SLK1000 it was slightly more negative over this pH range (Fig. 4.4a).
Figure 4.4a. Zeta potential of N-light N3, Carbolite 16/20 and Starlight SLK1000 over a range of pHs.

The influence of pH on the net surface charge of the ceramics can be explained by considering their mineralogical composition (Section 4.3). Cristobalite and α quartz are both forms of crystalline silica and contain surface silicon hydroxyl groups (Si-OH), whose charge is dependent on the pH of the dispersion medium. Under acidic conditions, protonation of the silicon hydroxyl groups is enhanced (Eqn. 4.4a), while deprotonation is promoted in alkaline solutions (Eqn. 4.4b) (van Olphen, 1963c; Tombácz et al., 2004). As silica is an acidic oxide, the reaction shown in Eqn. 4.4b predominates over a wide pH range.

\[
\begin{align*}
\text{Si} - \text{OH} + \text{H}^+ & \Leftrightarrow \text{Si} - \text{O}^+ \text{H}^+ \quad \text{Eqn. 4.4a} \\
\text{Si} - \text{OH} & \Leftrightarrow \text{Si} - \text{O}^- + \text{H}^+ \quad \text{or} \quad \text{Si} - \text{OH} + \text{OH}^- \Leftrightarrow \text{Si} - \text{O}^- + \text{H}_2\text{O} \quad \text{Eqn. 4.4b}
\end{align*}
\]

Mullite and feldspar are aluminosilicate clay minerals in which there are two origins of surface charge. Firstly, substitution of a cation in the mineral structure with a cation that has one less valence charge results in a negative surface charge. This charge is referred to as permanent charge because it is not influenced by the pH of the medium in which
the mineral is dispersed. Secondly, where the tetrahedral and octahedral layers of the mineral end, charges can form on surface hydroxyls (Si-OH, Al-OH). This charge is referred to as variable charge because it is influenced by medium pH (Section 1.3.3). The silicon hydroxyl group behaves in the same manner as in α quartz and cristobalite (Eqn. 4.4a/b). The aluminium hydroxyl groups also become protonated under acidic conditions (Eqn. 4.4c) and deprotonated under alkaline conditions (Eqn 4.4d) (van Olphen, 1963c; Tombácz et al., 2004). However, in contrast to silica, these groups show more amphoteric behaviour (van Olphen, 1987).

\[
\text{Al} - \text{OH} + \text{H}^+ \rightleftharpoons \text{Al} - \text{OH}_2^+ \quad \text{Eqn. 4.4c}
\]

\[
\text{Al} - \text{OH} \rightleftharpoons \text{Al} - \text{O}^- + \text{H}^+ \quad \text{or} \quad \text{Al} - \text{OH} + \text{OH}^- \rightleftharpoons \text{Al} - \text{O}^- + \text{H}_2\text{O} \quad \text{Eqn. 4.4d}
\]

It can be concluded that the net surface charge of the ceramics was dependent on the surface charge of the crystalline silica and the aluminosilicate clay minerals. Under acidic conditions the surface hydroxyl groups in these materials were positively charged, which explains the positive zeta potential observed at low pH. As the dispersion medium became more basic, the surface hydroxyl groups became negatively charged and hence the zeta potential at higher pHs was negative (Fig. 4.4a). Also contributing to the zeta potential was the permanent negative surface charge of the aluminosilicate clay minerals.

The surface charge of the ceramics was important for potential drug delivery applications as binding could modify drug release from the ceramics. The positive surface charge at low pHs indicated that the porous ceramics had good potential to bind anionic drugs like sodium benzoate. Similarly, the negative surface charge at higher pHs indicated good potential to bind cationic drugs like diltiazem HCl.

### 4.5 PELLET APPEARANCE

The general appearance of the porous ceramic pellets is shown in Fig. 4.5a/b. Each grade of N-light consisted of spherical pellets, as did Carbolite 16/20. The other grades of Carbolite, which are not shown, were similar in appearance to Carbolite 16/20.
Chapter 4. Characterisation of Commercially Produced Porous Ceramic Pellets

Starlight SLK1000, in contrast to the other porous ceramics, consisted of pellets with a variety of shapes.

![Figure 4.5a. Photograph of N-light N2, N3 and N4 pellets.](image)

![Figure 4.5b. Photograph of N-light N3, Starlight SLK1000 and Carbolite 16/20 pellets.](image)

SEM was used to examine the microscopic appearance of the porous ceramics. It was found that each grade of N-light had a smooth surface at low magnification. However, at higher magnifications surface pores were evident (Fig. 4.5c/e/f/i). In each grade, the surface pores were distributed over the entire pellet surface and had a range of diameters, which were estimated from the SEM's. For example, the pores highlighted at points A, C, D and H have diameters of 1.43, 2.65, 0.72 and 0.92 μm, respectively (Fig. 4.5c/e/f/i). It was found that the surface pore size distribution was similar for each grade of N-light.

The interior of each N-light grade was highly porous with the pores having a wider size distribution than those seen in surface view (Fig. 4.5d/g/h/j). The presence of relatively large pores not found on the pellet surface was noted. For example, the pores at points B, E, F and I have diameters of 620, 119, 109 and 99 μm, respectively (Fig. 4.5d/g/h/j). Also evident in cross-section were small pores within the larger pores, for example, at point E in Fig. 4.5g and point G in Fig. 4.5h. These small pores created open porosity as they connected the larger pores with each other. However, it is probable that not all pores were interconnected. For example, at point F in Fig. 4.5h, there was no evidence
of openings on the pore surface. Therefore, it is likely that closed pores were also present in the N-light grades.

**Figure 4.5c.** SEM showing the surface of N-light N2 (magnification x 5000).

**Figure 4.5d.** SEM of a cross-section of N-light N2 (magnification x 50).

**Figure 4.5e.** SEM showing the surface of N-light N3 (magnification x 5000).

**Figure 4.5f.** SEM showing the surface pores of N-light N3 (magnification x 20000).

**Figure 4.5g.** SEM of a cross-section of N-light N3 (magnification x 80).

**Figure 4.5h.** SEM of a cross-section of N-light N3 (magnification x 600).
The SEM’s show that each grade of N-light was similar both in terms of internal and surface pore structure, which suggests they were manufactured using the same technique. The overall structure was highly porous, containing both open and closed pores, with the surface pores being smaller than those found in the pellet interior. Access to the larger pores within the pellet interior was through these smaller surface pores. Krajewski et al. (2000) have also noted this for hydroxyapatite and alumina porous ceramics prepared using PFA’s.

The surface of Starlight SLK1000 was highly porous and contained relatively large pores in comparison to the N-light ceramics (Fig. 4.5k). For example, pores with diameters of 84 and 15.6 μm are located at points J and K, respectively. Smaller pores were located on the surface of these larger pores and contributed to the porous interconnected structure of the ceramic. The interior porosity and pore size distribution of Starlight SLK1000 was similar to that of the surface (Fig. 4.5l). For example, the pores at points L and M have diameters of 155 and 68 μm, respectively. These pores also contained smaller pores, which contributed to interconnectivity.
The macroscopic and microscopic appearance of Starlight SLK1000 suggested that it was manufactured using a different technique than for the N-light ceramics. It was probably manufactured as a large block of material, which was then milled to produce the pellets. The similar surface and interior porosities of the pellets, the irregular pellet shape and the high level of fines in the bulk material support this view. This technique is widely used in porous ceramic production (Liu, 1996; Queiroz et al., 2001).

The surface appearance of the Carbolite ceramics was similar to that of the N-light ceramics with small pores being present across their surface (Fig. 4.5m/o/q). For example, the pores highlighted at points N, P and R have diameters of 0.43, 0.90 and 0.78 μm, respectively. This is similar in magnitude to those found on the surface of the N-light ceramics. However, the internal structure of Carbolite was very different to that of N-light, as it was less porous and contained relatively small pores. The typical internal pore diameter of the Carbolite ceramics was 1 μm. Even the largest pores, such as those at points O, Q and S, were relatively small in comparison to those of the N-light ceramics and did not occur frequently (Fig. 4.5n/p/r). The internal pores were interconnected in the same manner as for the grades N-light and Starlight SLK1000. The porous structure of the Carbolite ceramics was sufficiently different to that of the N-light ceramics and Starlight SLK1000 to indicate they were manufactured using a different technique.
Chapter 4. Characterisation of Commercially Produced Porous Ceramic Pellets

Figure 4.5m. SEM showing the surface of Carbolite 16/20 (magnification x 5000).

Figure 4.5n. SEM of a cross-section of Carbolite 16/20 (magnification x 70).

Figure 4.5o. SEM showing the surface of Carbolite 16/20 (More porous) (magnification x 5000).

Figure 4.5p. SEM of a cross-section of Carbolite 16/20 (More porous) (magnification x 60).

Figure 4.5q. SEM showing the surface of Carbolite 20/40 (magnification x 5000).

Figure 4.5r. SEM of a cross-section of Carbolite 20/40 (magnification x 70).

In summary, SEM's in conjunction with visual observations indicated that the N-light ceramics, Starlight SLK1000 and the Carbolite ceramics had been manufactured using different techniques. The porosity of the N-light ceramics and Starlight SLK1000 was
higher than that of the Carbolite ceramics. Their surface pore sizes also differed with those of the N-light and Carbolite ceramics being relatively small in comparison to Starlight SLK1000. The interior pore sizes of the Carbolite ceramics and Starlight SLK1000 were similar to their surface pore sizes. However, in the N-light ceramics relatively large pores were found in the pellet interior.

4.6 MERCURY POROSIMETRY AND HELIUM PYCNOMETRY STUDIES ON THE PELLETS

Mercury porosimetry was used to provide information on the bulk density and porous microstructure of the ceramics. The N-light ceramics and Starlight SLK1000 had bulk densities less than water, while the Carbolite ceramics had bulk densities greater than water (Table 4.6a). This should be of benefit in extended drug delivery, as it has been found that both floating dosage forms and dosage forms with high densities gave increased transit time through the gastrointestinal tract (Bechgaard and Ladefoged, 1978; Kawashima et al., 1991).

Using helium pycnometry, the skeletal densities of the uncrushed and crushed porous ceramics were found (Table 4.6a). The former value reflected both the composition and closed porosity of the porous ceramic, while the latter value reflected only its composition. The crushed skeletal densities of each N-light grade were similar, which indicated that they had similar compositions. The same was true of the Carbolite ceramics. However, the crushed skeletal densities of the Carbolite ceramics, the N-light ceramics and Starlight SLK1000 were different. This was expected, as EDX microanalysis and XRD had shown that their compositions differed (Section 4.3).

The bulk and skeletal densities of the porous ceramics were used to calculate their total, open and closed porosities (Eqn. 4.6a/b/c).

\[
\text{Total Porosity (\% v/v)} = 100 - \left( \frac{\text{Bulk Density} \times 100}{\text{Crushed Skeletal Density}} \right) \quad \text{Eqn. 4.6a}
\]

\[
\text{Open Porosity (\% v/v)} = 100 - \left( \frac{\text{Bulk Density} \times 100}{\text{Uncrushed Skeletal Density}} \right) \quad \text{Eqn. 4.6b}
\]
Closed Porosity (% v/v) = Total Porosity (% v/v) - Open Porosity (% v/v) \textbf{Eqn. 4.6c}

Of the porous ceramics, Starlight SLK1000 had the highest total porosity with the majority of the porosity being due to open pores (Table 4.6a). The N-light ceramics also had high total porosities, although closed pores accounted for a greater proportion of their porosity. The open porosities were similar for N-light N2 and N3, while that of N-light N4 was markedly lower. The Carbolite ceramics had lower total porosities than the other ceramics examined with that of Carbolite 16/20 being particularly low at 10.64 +/- 0.03% v/v. There was a small proportion of closed pores present in Carbolite 16/20, while there were none in Carbolite 16/20 (More porous) and Carbolite 20/40. The negative closed porosity value for Carbolite 20/40 was due to the small but insignificant difference in its uncrushed and crushed skeletal density.

The calculated porosity values were in agreement with the qualitative SEM observations (Section 4.5). These showed that Starlight SLK1000 and the N-light ceramics were more porous than the Carbolite ceramics. The open porosities confirmed that the pores observed in SEM’s were interconnected, although closed pores did exist in Starlight SLK1000, the N-light ceramics and Carbolite 16/20.
Table 4.6a. Densities and porosities of each porous ceramic.

<table>
<thead>
<tr>
<th>Porous ceramic</th>
<th>Bulk density</th>
<th>Uncrushed skeletal density</th>
<th>Crushed skeletal density</th>
<th>Open porosity</th>
<th>Closed porosity</th>
<th>Total porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (g/ml)</td>
<td>S.D.</td>
<td>Average (g/ml)</td>
<td>S.D.</td>
<td>Average (g/ml)</td>
<td>S.D.</td>
</tr>
<tr>
<td>N-light N2</td>
<td>0.6887</td>
<td>0.0278</td>
<td>1.3582</td>
<td>0.0005</td>
<td>2.4045</td>
<td>0.0012</td>
</tr>
<tr>
<td>N-light N3</td>
<td>0.7312</td>
<td>0.0046</td>
<td>1.4095</td>
<td>0.0055</td>
<td>2.4026</td>
<td>0.0003</td>
</tr>
<tr>
<td>N-light N4</td>
<td>0.8477</td>
<td>-</td>
<td>1.3537</td>
<td>0.0038</td>
<td>2.4229</td>
<td>0.0004</td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td>0.3665</td>
<td>0.0072</td>
<td>1.6873</td>
<td>0.0239</td>
<td>2.6010</td>
<td>0.0057</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td>2.5060</td>
<td>0.0059</td>
<td>2.8044</td>
<td>0.0029</td>
<td>2.8334</td>
<td>0.0029</td>
</tr>
<tr>
<td>Carbolite 16/20 (More porous)</td>
<td>2.0061</td>
<td>-</td>
<td>2.8254</td>
<td>0.0007</td>
<td>2.8259</td>
<td>0.0071</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td>1.9435</td>
<td>-</td>
<td>2.8482</td>
<td>0.0002</td>
<td>2.8425</td>
<td>0.0038</td>
</tr>
</tbody>
</table>
Mercury porosimetry was also used to provide information on the pore size distribution of the ceramics. It should be noted that with mercury porosimetry the measured pore sizes primarily reflect surface pore size distributions rather than overall pore size distributions. This is because in order for mercury to access the interior pores it must pass through the surface pores. This means that interior pore sizes are only measured if the surface pores are larger than them. In addition, where larger pores are accessed through smaller pores, their volume is interpreted as being due to that of smaller pores.

For N-light N3, there were two distinct pore size ranges in which intrusion occurred (Fig. 4.6a). The first was around 100 μm and was due to filling of the interparticulate pores formed between the N-light N3 pellets when they were packed into the penetrometer. This was supported by SEM observations, which showed there were no surface pores in this size range in N-light N3 (Section 4.5). Once the interparticulate pores were filled, subsequent intrusion was due to filling of the intraparticulate pores of N-light N3. These pores had diameters less than 1 μm, which was in agreement with SEM observations of the pellet surface. For example, the pore at point D in Fig. 4.5f had a diameter of 0.72 μm. However, in cross-section, pores larger than 1 μm in diameter were observed (Fig. 4.5g/h). For example, at point F in Fig. 4.5h the pore diameter was 109 μm. Pores of this size were not detected by mercury porosimetry as in order for the mercury to access such pores it had to first pass through the smaller surface pores. The presence of pores in the interior of N-light N3 that were larger than its surface pores was confirmed by the presence of a hysteresis in the cumulative mercury intrusion/extrusion curve (Fig. 4.6b). These are usually seen when mercury has been trapped in pores with a narrow neck leading to a large pore interior (Moscou and Lub, 1981). In this case, the hysteresis was due to smaller surface pores connecting to larger interior pores.
Figure 4.6a. Incremental mercury intrusion versus pore diameter for N-light N3.

Figure 4.6b. Cumulative mercury intrusion/extrusion versus pore diameter for the N-light ceramics (Intrusion due to interparticulate pore filling is not shown).

Similar to N-light N3, two distinct pore size ranges were observed for N-light N2 and N4. The larger pores were again interparticulate pores created by packing of the pellets.
in the penetrometer. The volume of these pores differed depending on the grade of N-light, as they had different pellet size distributions and therefore they packed differently in the penetrometer. In order to facilitate comparisons of the intraparticulate porosities of each N-light grade, the intrusion due to interparticulate pore filling is not shown in the cumulative intrusion curves (Fig. 4.6b). From these curves it can be seen that N-light N2 contained larger pores than N-light N3, although its pores were still less than 1 \( \mu m \) in diameter. The \( D_{50} \) for N-light N2 was 0.2063 \( \mu m \), while it was 0.1538 \( \mu m \) for N-light N3. N-light N3 and N4 had similar pore size distributions with the lower cumulative mercury intrusion for N-light N4 reflecting its lower open porosity (Table 4.6a). The \( D_{50} \) for N-light N4 was 0.1257 \( \mu m \), which was less than N-light N3 as there were fewer pores in the size range 0.1 to 1 \( \mu m \). Finally, in each N-light ceramic, pores as small as 0.006 \( \mu m \) were detected, which was the lower limit of detection of the mercury poresizer.

The Carbolite ceramics had a narrower pore size distribution than the N-light ceramics with the majority of pores having diameters in the range 0.05 to 0.2 \( \mu m \), although some larger pores were present (Fig. 4.6c). The surface pores highlighted in SEM's of these ceramics were slightly larger than this (Fig. 4.5m/o/q). However, at higher magnifications pores less than 0.2 \( \mu m \) in diameter were observed. The actual pore size distribution was dependent on the grade of Carbolite with their \( D_{50} \)'s being 0.1015, 0.1257 and 0.1428 \( \mu m \) for Carbolite 16/20, 16/20 (More porous) and 20/40, respectively. The smallest pore diameter detected was 0.0279 \( \mu m \) for 16/20, 0.0357 \( \mu m \) for 16/20 (More porous) and 0.0389 \( \mu m \) for 20/40.
For the N-light and Carbolite ceramics, there was a clear distinction between the interparticulate and intraparticulate pore sizes. However, for Starlight SLK1000 this was not the case as it contained surface pores with diameters similar to those of the interparticulate pores. For example, the pore at point J in Fig. 4.5k had a diameter of 84 µm. Therefore, it was inappropriate to exclude intrusion in the range 10 to 1000 µm from its cumulative mercury intrusion curve (Fig. 4.6d). From this curve it was evident that Starlight SLK1000 had a wide pore size distribution, which was reflected in a relatively high $D_{50}$ of 2.57 µm. This is in agreement with SEM observations that showed relatively large pores were present on the pellet surface. These pores contained smaller pores, which provided access to the porous pellet interior (Fig. 4.5k/l). The lowest pore diameter detected was 0.1 µm.
Figure 4.6d. Cumulative mercury intrusion versus pore diameter for Starlight SLK1000.

4.7 SURFACE AREA ANALYSIS OF THE PELLETS

The surface area of the porous ceramics was calculated using their nitrogen adsorption isotherms, which showed the volume of nitrogen adsorbed per gram of porous ceramic at various pressures. The isotherm for each porous ceramic was a Type II isotherm (Fig. 7.4a), which is the normal form of isotherm obtained with a macroporous (pore width exceeding 50 nm) adsorbent (Sing et al., 1985). It was expected that this type of isotherm would be observed, as SEM’s and mercury porosimetry had shown that macropores were present in each ceramic (Section 4.5/4.6).
The surface areas of the porous ceramics were markedly higher than the calculated surface areas of their non-porous equivalents (Table 4.7a). This confirmed that the ceramics contained a highly interconnected open cell porous structure with the open pores providing a large surface for nitrogen adsorption. These calculations also show that changes in the pellet diameter and hence external surface area had only a small effect on the total pellet surface area.

Since the effects of pellet diameter on surface area were negligible, the differences in the surface area of each ceramic must have been due to changes in their open porosity and overall pore size distribution. As surface area was determined by both these parameters, it was not linearly related to either the open porosity or $D_{50}$ of the ceramics (Section 4.6). In addition, the $D_{50}$ primarily reflected the surface pore size distribution of the ceramics rather than their overall pore size distribution. If these differed substantially, such as in the N-light ceramics, a linear relationship between $D_{50}$ and surface area would not be observed even if the porosity was constant.

For the N-light ceramics, there was no significant difference in the surface areas of N-light N2 and N3, while that of N-light N4 was markedly higher despite its lower open surface.
porosity. Therefore, N-light N4 must have had a smaller overall pore size distribution. Starlight SLK1000 had a higher surface area than N-light N2 and N3. This was due to its increased open porosity, as neither SEM’s nor mercury porosimetry had indicated it had a smaller pore size distribution (Section 4.5/4.6). There was an increase in the surface area of the Carbolite ceramics as their open porosity increased. However, changes in the pore size distribution also occurred, as Carbolite 16/20 (More porous) had a significantly lower surface area than Carbolite 20/40 even though they had similar open porosities.

Table 4.7a. Surface area of each porous ceramic and the calculated surface area of its non-porous equivalent.

<table>
<thead>
<tr>
<th>Porous ceramic</th>
<th>BET multipoint surface area</th>
<th>Surface area of a non-porous equivalent (m²/g)</th>
<th>Ratio of surface areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (m²/g)</td>
<td>S.D.</td>
<td></td>
</tr>
<tr>
<td>N-light N2</td>
<td>0.6784</td>
<td>0.0016</td>
<td>0.004532</td>
</tr>
<tr>
<td>N-light N3</td>
<td>0.6606</td>
<td>0.0142</td>
<td>0.008019</td>
</tr>
<tr>
<td>N-light N4</td>
<td>2.3019</td>
<td>0.1114</td>
<td>0.01530</td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td>1.7513</td>
<td>0.1111</td>
<td>0.01669</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td>0.6449</td>
<td>0.0304</td>
<td>0.001950</td>
</tr>
<tr>
<td>Carbolite 16/20 (More porous)</td>
<td>1.4510</td>
<td>0.0502</td>
<td>0.002020</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td>1.7827</td>
<td>0.0073</td>
<td>0.002982</td>
</tr>
</tbody>
</table>

4.8 CONCLUSION

The commercially produced porous ceramics consisted of spherical pellets with the exception of Starlight SLK1000, which consisted of irregularly shaped pellets. In each case, the ceramics contained pellets with a range of sizes. Starlight SLK1000 had the widest pellet size distribution and contained a high proportion of fines, which was attributed to crushing of the ceramic. The Carbolite ceramics had a narrow size
distribution, while that of the N-light ceramics was wider. For further study, pellets in the size range 850-1000 μm were selected except in the case of N-light N2 and N4, where pellets in the size range 425-500 and 1700-2000 μm were selected, respectively. An important point regarding the pellets is that they were small enough for capsule filling and the possibility of subsequent oral delivery.

Characterisation of the porous ceramics showed their compositions differed. N-light N3 consisted of α quartz and feldspars, Starlight SLK1000 of α quartz and mullite, and Carbolite 16/20 of mullite and cristobalite. However, qualitatively the ceramics had similar elemental compositions with their principal constituents being aluminium and silicon. Depending on the ceramic, lower levels of iron, titanium and potassium were also detected. The ceramics were polycationic at low pH’s and polyanionic at higher pH’s. The influence of pH on their surface charge was due to protonation and deprotonation of surface hydroxyl groups under acidic and increasingly alkaline conditions, respectively. The surface charge should have important consequences for extended drug delivery as it gave the ceramics the potential to bind anionic drugs at low pH and cationic drugs at higher pH.

The N-light ceramics and Starlight SLK1000 had bulk densities less than water, while the Carbolite ceramics had relatively high bulk densities. Each ceramic contained open pores with the open porosity being dependent on the ceramic. This should make it possible to drug load the ceramics and determine the relationship between open porosity and drug loading. The overall pore size distribution depended on the ceramic with the surface pores being smaller than the interior pores in all cases. These interior pores were accessed through the surface pores, which meant the ceramics had a highly interconnected porous microstructure. This was reflected in their relatively high surface area in comparison to their non-porous equivalents. The surface area was dependent on both the open porosity of the ceramic and its overall pore size distribution. Since the pore size distribution of each ceramic varied it should be possible to establish how it affects drug release. The results of drug loading and dissolution testing of the commercially produced porous ceramics are discussed in Chapter 5.
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

Chapter 5

DRUG LOADING AND DISSOLUTION TESTING OF COMMERCIALY PRODUCED POROUS CERAMIC PELLETS

5.1 INTRODUCTION

There have been numerous applications of porous ceramics in many industries. In the pharmaceutical industry, their potential to act as modified release drug delivery systems has received increasing attention over recent years (Section 1.4.5). The aim of the research presented in this Chapter was to investigate potential applications of porous ceramics in oral drug delivery. This application has received little attention despite the oral route being the most widely used delivery route (York, 2002).

Characterisation of the porous ceramics indicated that they should be suitable for use as oral drug delivery systems for two reasons (Chapter 4). Firstly, they consisted of spherical pellets, which were small enough to be filled into a capsule intended for oral administration. Secondly, the ceramics were porous giving them the potential to be drug loaded. Since the porous ceramics differed in terms of their porosities, the effect of this on drug loading could be examined.

It was envisaged that the porous ceramics would act as modified release drug delivery systems due to entrapment of drug within the porous matrix of the pellets and binding of drug to the polyionic surfaces of the ceramic. The porous ceramics differed in terms of their pore size distributions so the influence of pore size on the rate of drug release could be investigated. In addition, as the ceramics had a polycationic surface at low pHs and a polyanionic surface at higher pHs, the influence of surface charge on drug release was examined. Finally, the ability of a number of different polymers and waxes to modify the release of drug from the porous ceramics was determined.
5.2 DRUG LOADING OF POROUS CERAMIC PELLETS

5.2.1 Preliminary Drug Loading Studies

The most widely used porous ceramic drug loading technique involves placing the porous ceramic in a drug solution and applying a vacuum. This facilitates infiltration of the drug solution into the pores of the ceramic. The solvent is then removed by evaporation and the drug is deposited within the pores (Itokazu et al., 1999). The effectiveness of variations upon this technique and other drug loading techniques has not been established. To this end, three techniques were investigated to determine the optimum drug loading technique for the commercially produced porous ceramics. Method (i) did not involve the application of a vacuum. Method (ii) was similar to the loading technique discussed above, while method (iii) was a modification of method (ii).

It was found that there was no significant difference in the loadings obtained using methods (i) and (ii). However method (iii) gave a significantly higher drug loading than the other methods (Fig. 5.2a). Method (iii) proved more effective as it allowed displacement of the air within the pores of the ceramic by drug solution. When drug loading using method (ii), the N-light N3 pellets floated on the drug solution surface and therefore, although air was removed from the pellets by applying a vacuum, it was not replaced with drug solution once atmospheric pressure was restored. If air was replaced by drug solution, the pellets would sink in the loading solution, as N-light N3 has a higher skeletal density than the density of the loading solution. Sinking only occurred using loading method (iii), which is further evidence that this method was the most effective loading technique. These results demonstrate the importance of air displacement in drug loading of porous materials, which is in agreement with other published work (Leong et al., 2001). Based on these results, method (iii) was adopted for all subsequent loadings.
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

Figure 5.2a. Comparison of the loadings obtained when N-light N3 pellets were loaded with diltiazem HCl using three different methods.

Loading method (iii) offers significant advantages over the existing porous ceramic loading techniques, discussed in Section 1.4.5.3. For example, method (i) is similar to methods used by Queiroz et al. (2001) and Sivakumar and Panduranga Rao (2002) in that it does not apply a force, such as reduced pressure, to load drug solution into the porous ceramic. Therefore, this method gave a relatively poor loading in comparison to method (iii) (Fig. 5.2a). In addition, method (i) and similar methods may result in a higher proportion of drug being deposited on the external ceramic surface rather than in the porous ceramic interior, thereby increasing the fraction of drug released as a burst from the porous ceramic (Section 5.3). This change in drug deposition would be most likely to occur when penetration of the loading solution into the porous ceramic interior is impeded due to the ceramic having relatively small surface pores.

Methods similar to method (ii) have been successfully used to drug load porous ceramics, which were denser than the drug loading solution (Paul and Sharma, 1995, 1999; Paul et al., 2002; Itokazu et al., 1998, 1999; Komlev et al., 2002). Successful loading was confirmed by the presence of drug in the porous ceramic interior (Itokazu et al., 1998; Itokazu et al., 1999). However, it has been shown that method (ii) was not
as effective as method (iii) for loading floating porous ceramics (Fig. 5.2a). Therefore, while method (iii) would be an equally effective loading technique for relatively dense porous ceramics, it is superior for floating porous ceramics.

It should be noted that methods (i), (ii) and (iii) incorporate a post loading filtration step, which separates excess drug solution from the pellets, thereby reducing drug deposition on the external pellet surface during drying. While some researchers have used a post loading filtration step (Itokazu et al., 1998, 1999; Komlev et al., 2002) others have not (Paul and Sharma, 1995, 1999; Paul et al., 2002). In the latter case, rather than removing excess loading solution, it was evaporated to dryness under reduced pressure. As a result, higher levels of drug would be deposited on the external ceramic surfaces.

A further advantage of method (iii) is that it could be used to load relatively weak porous ceramics, which is in contrast to methods that load the drug solution into the ceramic using centrifugation. While such methods can effectively incorporate drug into the ceramic interior (Itokazu et al., 1994), it is questionable whether or not a ceramic with a relatively weak structure could withstand the centrifugal forces. Finally, method (iii) can easily be scaled up to an industrial level unlike other methods where the drug is placed in a cavity within the ceramic, which is then sealed (Shinto et al., 1992; Netz et al., 2001).

5.2.2 Drug Loading Using Optimum Loading Technique

Method (iii), was used to drug load each grade of N-light with benzoic acid, sodium benzoate and diltiazem HCl. The highest drug loading achieved was 13.1 +/- 1.5% w/v for sodium benzoate loaded N-light N3 (Table 5.2a). In all cases, the loadings were high enough to indicate that the N-light ceramics could be used for the delivery of both low and high potency drugs.

For N-light N3, the sodium benzoate and diltiazem HCl loadings were not significantly different. However, they were both significantly higher than the benzoic acid loading. The same trend in drug loading occurred for N-light N2 and N4 although the differences in the loadings were not significant. This trend was observed because the benzoic acid
loading solution had a lower concentration than the sodium benzoate and diltiazem HCl solutions. Therefore, the ceramic pores when filled with loading solution contained less drug, which meant they had a lower final drug loading. This indicates that the concentration of the loading solution could be used to control the drug loading of porous ceramics. A similar result was observed by Gren et al. (1996), who used a post production loading technique to drug load porous cellulose matrices.

Table 5.2a. Actual and theoretical loading of each grade of N-light with a number of drugs.

<table>
<thead>
<tr>
<th>Porous ceramic</th>
<th>Drug</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average (% w/v)</td>
<td>S.D.</td>
</tr>
<tr>
<td>N-light N2</td>
<td>Benzoic acid</td>
<td>10.5</td>
<td>1.2</td>
</tr>
<tr>
<td>N-light N2</td>
<td>Sodium benzoate</td>
<td>10.9</td>
<td>1.2</td>
</tr>
<tr>
<td>N-light N2</td>
<td>Diltiazem HCl</td>
<td>13.4</td>
<td>0.9</td>
</tr>
<tr>
<td>N-light N3</td>
<td>Benzoic acid</td>
<td>9.9</td>
<td>0.5</td>
</tr>
<tr>
<td>N-light N3</td>
<td>Sodium benzoate</td>
<td>13.1</td>
<td>1.5</td>
</tr>
<tr>
<td>N-light N3</td>
<td>Diltiazem HCl</td>
<td>12.1</td>
<td>0.4</td>
</tr>
<tr>
<td>N-light N4</td>
<td>Benzoic acid</td>
<td>10.5</td>
<td>0.5</td>
</tr>
<tr>
<td>N-light N4</td>
<td>Sodium benzoate</td>
<td>11.0</td>
<td>0.7</td>
</tr>
<tr>
<td>N-light N4</td>
<td>Diltiazem HCl</td>
<td>11.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Method (iii) was also used to load Starlight SLK1000 and the Carbolite ceramics with diltiazem HCl. In comparing the diltiazem HCl loadings for all the porous ceramics, Starlight SLK1000 had the highest drug loading while Carbolite 16/20 had the lowest (Tables 5.2a/b). This was related to the ceramic porosity with Starlight SLK1000 having the highest open porosity of the ceramics and Carbolite 16/20 having the lowest.

The correlation between open porosity and drug loading is a further indication that loading method (iii) loaded drug into the ceramic pores. There was no correlation between the surface area of the porous ceramic and its drug loading. It can be concluded
that open pore volume rather than open pore surface area was the more important
determinant of drug loading.

Table 5.2b. Actual and theoretical diltiazem HCl loading of Starlight SLK1000 and
each grade of Carbolite.

<table>
<thead>
<tr>
<th>Porous ceramic</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (% w/v)</td>
<td>S.D.</td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td>19.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td>7.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Carbolite 16/20 (More porous)</td>
<td>10.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td>12.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The theoretical maximum drug loadings for each porous ceramic are also given in
Tables 5.2a/b. These values were calculated based on the mass of drug in that volume of
solution, which fills the open pores of each ceramic. Inherent in this calculation is the
assumption that drug was only loaded into the ceramic pores and not onto the pellet
surface. However, for Carbolite 16/20 the drug loading was higher than the theoretical
maximum indicating that drug was deposited on the external pellet surface as well as in
the pores during the loading process. This deposition may also have occurred for the
other porous ceramics, but since their actual drug loadings were not higher than the
theoretical loadings this cannot be ascertained from the loading studies alone.

In comparing the actual and theoretical drug loadings of each porous ceramic, it was
found that the efficiency of loading was related to the bulk density of the porous
ceramic. The Carbolite ceramics, which had a bulk density higher than that of the
loading solution, loaded most efficiently, as during loading the pellets remained beneath
the surface of the loading solution at all times. However, with the N-light ceramics and
Starlight SLK1000, the pellets floated on the surface of the loading solution until the
solution entered the pellet pores making it possible for any air that had entered the
sample tube to enter the pellets in place of the desired loading solution. This explains
the insignificant difference in the loadings of N-light N2, N3 and Carbolite 20/40,
despite the latter having a markedly lower open porosity (Section 4.6).
Overall, these results showed that porous ceramics could be drug loaded. This loading could be controlled by changing the open porosity and bulk density of the ceramic or by changing the concentration of the drug loading solution. The ability to control the loading is important for potential drug delivery applications, as it would allow the dose of drug to be tailored to exact requirements.

5.3 DISSOLUTION TESTING OF DRUG LOADED POROUS CERAMIC PELLETS

5.3.1 Dissolution Rate Modelling Theory

In order to compare the rate of drug release from the porous ceramics, various mathematical models were fitted to the dissolution data. These models are represented by equations containing kinetic parameters, which facilitate quantitative comparison of the dissolution profiles. In addition, they can often be used to elucidate the mechanisms of drug release from dosage forms (Jantzen and Robinson, 1996). The relevant mathematical models, including a brief account of their theoretical basis, are given in this Section.

Ritger and Peppas (1987) described an equation to model the release of drugs from spherical non-eroding, non-swellable polymeric matrices. In these systems, the drug was uniformly dissolved or dispersed throughout the solid polymer. This equation applies where the rate-limiting step in drug release is diffusion of the drug by a Fickian mechanism. The equation takes the form

\[ \frac{M_t}{M_\infty} = k_t t^{0.432} \]  

Eqn. 5.3a

where \( \frac{M_t}{M_\infty} \) is the fraction of drug released at time, \( t \) and \( k_t \) is a kinetic constant characteristic of the system. Lindner and Lippold (1995) extended this equation to include a third constant, \( F_b \), which represents a burst effect or a lag effect. The extended equation for spherical matrices takes the form
In Eqn. 5.3b, where $F_B$ represents a burst effect, it is assumed that the burst effect occurs instantaneously. If this assumption is invalid, Eqn. 5.3b will not adequately fit the release data. Therefore, it becomes necessary to model the burst release of drug. This can be done using a first order equation proposed by Wagner (1969), which describes drug dissolution under sink conditions with a reducing surface area. The equation is

$$\frac{M_t}{M_{\infty}} = F_B (1 - e^{-k_1 t})$$  \hspace{1cm} \text{Eqn. 5.3c}$$

where $k_1$ is a first order release rate constant and $F_B$ is the proportion of drug released by this process, which in this case is the fraction of drug released during the initial burst phase. This first order kinetic model can then be combined with the kinetic model described by Eqn. 5.3b. The combined kinetic model is given by the following equation

$$\frac{M_t}{M_{\infty}} = F_B (1 - e^{-k_1 t}) + k_H t^{0.432}$$  \hspace{1cm} \text{Eqn. 5.3d}$$

It should be noted that where the burst effect is instantaneous (or nearly instantaneous) Eqn. 5.3d would contain a relatively high $k_1$ value and thus reduce to Eqn. 5.3b.

The use of a combination of kinetic models rather than a single kinetic model has been successfully applied by a number of researchers. For example, Gallagher and Corrigan (2000) combined the first order model with a model describing the release of drug based on a polymer degradation mechanism. The first order model was included to account for the burst release of drug, which resulted from rapid dissolution of drug at the surface of the delivery device. In a second example, Griffin and Niebergall (1999) found that an equation combining a first-order and a square root of time kinetic model gave a better representation of the dissolution data than either model alone. This was because initially the release of drug was governed by both a first order and diffusional release
mechanism. However, after a time the first order curve reached a plateau and solely a diffusional process governed the release.

Regarding the proportion of the drug release modelled, it is usual to model the first 60% of drug release when using Eqn. 5.3a (Ritger and Peppas, 1987). However, where a burst release is present higher proportions of drug release can be modelled while still attaining adequate model fits (Dubernet et al., 1990; Leo et al., 2000). More specifically, Lindner and Lippold (1995), using an equation of the same form as Eqn. 5.3b, modelled the first 80% of drug release. In this thesis, Eqn. 5.3b/d were fitted to the first 8 h of the drug release data or the first 80% of drug release if this occurred before 8 h. This convention gave acceptable fits for all systems examined.

5.3.2 Drug Dissolution from N-light N3

N-light N3 was the first commercially produced porous ceramic tested. It was loaded with diltiazem HCl, sodium benzoate and benzoic acid and dissolution tested in both phosphate buffer pH 6.8 and 0.1N HCl. The drugs tested differ in terms of their solubilities in the dissolution media, their ionic character and their molecular weights. Therefore, the influence of these physicochemical properties on drug release could be investigated.

Diltiazem HCl is highly soluble in both phosphate buffer pH 6.8 and 0.1N HCl (Appendix 2). Therefore, the drug alone dissolved rapidly in both media during dissolution testing (Fig. 5.3a). However, by loading diltiazem HCl into N-light N3 its release was extended. The release profiles were characterised by an initial burst release of drug followed by extended release (Fig. 5.3a). This type of drug release is typically observed from porous ceramics (Itokazu et al., 1998, 1999; Landi et al., 2000; Paul and Sharma, 1995; Paul et al., 2002; Queiroz et al., 2001).
In order to quantitatively assess the rate of diltiazem HCl release from N-light N3, Eqn. 5.3b, was fitted to the release data. The equation fitted the release data with the MSC being greater than 4 and the CD greater than 0.98 in each case (Table 5.3a). This indicated the model adequately described the release of diltiazem HCl from N-light N3. This was confirmed by the close agreement between the release predicted by Eqn. 5.3b and the actual release data (Fig. 5.3b). Other commonly used models, such as the zero order model or the first order model did not fit the data (Costa and Lobo, 2001).

The suitability of Eqn. 5.3b for modelling the release of diltiazem HCl from N-light N3 was expected, as the pellets were non-swellable, non-eroding porous matrices. In this way they were similar to the polymeric matrices used by Ritger and Peppas (1987) to develop the model upon which Eqn. 5.3b is based. Additionally, Netz et al. (2001) have found that cisplatin was released from porous hydroxyapatite blocks by a diffusion-based mechanism. One potential difference between the porous ceramic and the polymeric matrices used by Ritger and Peppas (1987) was in the dispersion of the drug. However, since Eqn. 5.3b fits the data, this suggests that the drug was uniformly dispersed throughout the ceramic pellets.
### Table 5.3a. Best fit parameters, when Eqn. 5.3b/d is fitted to the release data for N-light N3.

<table>
<thead>
<tr>
<th>Drug</th>
<th>$F_B$ (%) w/w</th>
<th>$k_1$ (h⁻¹)</th>
<th>$k_H$ (% h⁻⁰.⁴³²)</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average S.D.</td>
<td>Average S.D.</td>
<td>Average S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>27.19 0.74</td>
<td>N/A</td>
<td>N/A</td>
<td>13.81 0.50</td>
<td>4.41 0.9878</td>
</tr>
<tr>
<td>Diltiazem HCl*</td>
<td>40.71 0.93</td>
<td>N/A</td>
<td>N/A</td>
<td>13.72 0.63</td>
<td>4.03 0.9822</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>68.96 2.16</td>
<td>N/A</td>
<td>N/A</td>
<td>14.41 4.33</td>
<td>5.43 0.9956</td>
</tr>
<tr>
<td>Sodium benzoate*</td>
<td>52.68 0.49</td>
<td>N/A</td>
<td>N/A</td>
<td>11.84 0.33</td>
<td>5.27 0.9949</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>74.15 1.09</td>
<td>41.36</td>
<td>2.02 6.93</td>
<td>1.33 7.25</td>
<td>0.9992</td>
</tr>
<tr>
<td>Benzoic acid*</td>
<td>60.39 0.69</td>
<td>27.41</td>
<td>1.26 6.52</td>
<td>0.44 6.68</td>
<td>0.9987</td>
</tr>
</tbody>
</table>

* dissolution medium was 0.1N HCl rather than phosphate buffer pH 6.8
The results of dissolution rate modelling showed that a large fraction of diltiazem HCl was released as a burst in both dissolution media (Table 5.3a). This can be attributed to the release of drug associated with the external surface of the pellets (Point D in Fig. 5.3c) and also to the release of drug, which was poorly entrapped within the pellets. The contribution of both surface associated drug and poorly entrapped drug to burst release from drug delivery devices has been widely noted (El-Raheem El-Helw and El-Said, 1998; Gallagher and Corrigan, 2000).

**Figure 5.3b.** Plot of Eqn. 5.3b fitted to the release data for diltiazem HCl from N-light N3 in phosphate buffer pH 6.8 at 37 °C.
It was found that $F_B$ was significantly higher in 0.1N HCl than in phosphate buffer pH 6.8. Since the solubility and ionic character of diltiazem HCl is similar in both media, it can be concluded that the surface charge of N-light N3 influenced the burst release. N-light N3 was polyanionic at pH 6.8 and therefore could bind the cationic diltiazem HCl molecules. However, at low pH the ceramic surface was polycationic and could no longer bind the diltiazem HCl molecules (Section 4.4) resulting in an increase in $F_B$. This conclusion is supported by the observations of Daniel et al. (1993) who found that $\alpha$ quartz and feldspar, which are the constituents of N-light N3, could bind the cationic dye Janus green B due to charge attraction between the negatively charged surface of $\alpha$ quartz/feldspar and the cationic dye. In addition, Yamamura and Yotsuyanagi (1992) and Queiroz et al. (2001) noted that electrostatic binding influences drug release from porous ceramics. The binding of drugs to the polyionic surfaces of clay minerals is discussed further in Section 6.3. A final point is that in vivo low pHs are encountered in the stomach meaning an enteric coating might be needed to prevent a change in $F_B$ in this area of the gastrointestinal tract.
Following the burst release of diltiazem HCl, there was extended drug release in both media. The extended release can be attributed to the release of diltiazem HCl entrapped within the pores of the ceramic. In contrast to the fraction of drug released as a burst, there was no significant difference between \( k_{H2} \) for both media (Table 5.3a). Therefore, electrostatic binding of diltiazem HCl to the interior ceramic surfaces did not have a significant effect on \( k_{H2} \). This indicated that dissociation of bound diltiazem from the interior ceramic surfaces was not the rate-limiting step in extended release. However, binding of diltiazem HCl to the ceramic was still desirable as the burst release of drug was reduced leaving a greater mass of drug available for extended release. Therefore, at each time point a lower percentage of drug had been released in phosphate buffer pH 6.8 than in 0.1N HCl. The bound drug was slowly released over the course of the dissolution testing with the difference between the percentage drug released at each time point reducing as the dissolution test progressed (Fig. 5.3a). However, this low level of release was not large enough to have a significant effect on \( k_{H2} \). Daniel et al. (1993) also observed the slow release of a bound cationic compound, Janus green B, from the polyanionic surface of \( \alpha \)-quartz.

Since the extended release was proportional to \( t^{0.432} \) (Eqn. 5.3b, Table 5.3a) the rate-limiting step in diltiazem HCl release was diffusion of the drug by a Fickian mechanism (Ritger and Peppas, 1987). The release began with dissolution medium entering the ceramic pores and dissolving the drug entrapped within the pores (Points A, B, C in Fig. 5.3c). The dissolved drug then diffused from the porous ceramic through the dissolution medium filled pores (Higuchi, 1963; Martin, 1993). Diltiazem HCl release decreased with time, as at early times drug dissolved and diffused from regions close to the pellet surface into the bulk dissolution medium. Therefore, the drug had only a short distance to diffuse before reaching the bulk dissolution medium. However, at later times the dissolution medium had moved further into the porous interior. The drug, which dissolved in these inner regions of the pellet then had further to diffuse before reaching the bulk dissolution medium (Langer and Peppas, 1981).

As the extended release observed was due to diffusion of diltiazem HCl through dissolution medium in the pores of the ceramic, the diffusional path length was critically important in determining the rate of release. There were three factors, which contributed to the path length. Firstly, the highly tortuous interior of N-light N3 meant
that the drug had to diffuse further in order to be released, than if the pores were straight. Secondly, the pores did not have a uniform cross-sectional diameter but instead were irregularly shaped (Section 4.5). This increased the diffusional path length of the drug since the distance from the pore entry to exit was increased. The third factor, which contributed to the path length, was the topology of the pores. As the pores were highly interconnected the diffusive transport rate was higher than if the pores were poorly interconnected (Siegel, 1989). This was because the likelihood of the drug finding an exit from a pore and entering another pore was increased.

To confirm that drug entrapment within the ceramic pores was essential for extended drug release, a crushed sample of diltiazem HCl loaded N-light N3 was dissolution tested. It was found that the release of drug from these samples was similar to that of drug alone, which confirmed the importance of the porous ceramic structure in providing extended drug release (Appendix 5). There was some evidence of diltiazem HCl binding causing a delay in the rate of drug release compared to drug alone. Gren et al. (1996) observed a similar effect when drug loaded porous cellulose matrices were crushed.

To further investigate the ability of N-light N3 to act as an extended drug delivery system, the dissolution of sodium benzoate from N-light N3 was examined. Sodium benzoate is highly soluble in phosphate buffer pH 6.8, but has a lower solubility in 0.1N HCl as it can undergo protonization to form benzoic acid, which is slightly soluble in 0.1N HCl (Breitkreutz et al., 2003). Sodium benzoate alone dissolved rapidly in phosphate buffer pH 6.8 during dissolution testing. However, in 0.1N HCl there was extended dissolution of a small percentage of sodium benzoate, which can be attributed to the formation of benzoic acid (Fig. 5.3d). The release of sodium benzoate from N-light N3 was extended in both media with the release profile being characterised by an initial burst release of drug followed by extended release, as was the case with diltiazem HCl release (Fig. 5.3a/d).
It was found that Eqn. 5.3b fitted the release data and, in contrast to diltiazem HCl, the fraction of sodium benzoate released as a burst was significantly higher in phosphate buffer pH 6.8 than in 0.1N HCl (Table 5.3a). The reason for the change in $F_B$ was that in 0.1N HCl the polycationic surface of the ceramic could bind the anionic sodium benzoate molecules. However, at pH 6.8 the surface of the ceramic was polyanionic and sodium benzoate was mainly unionised (Section 4.4). Therefore, binding did not occur, resulting in an increase in $F_B$ for sodium benzoate. This result is further evidence of the importance of electrostatic interactions in determining the burst release of drug from N-light N3.

Following the burst release of sodium benzoate, there was no significant difference in $k_H$ for both media (Table 5.4a). This was unexpected as sodium benzoate is markedly less soluble in 0.1N HCl than in phosphate buffer pH 6.8 due to the formation of benzoic acid. The lower solubility should have resulted in a reduced extended drug release rate (Higuchi, 1963). However, due to the low number of data points available for dissolution rate modelling of sodium benzoate release in 0.1N HCl, the estimate of
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

$k_{11}$ had a relatively high standard deviation. As a result it was difficult to conclusively determine the effect of the solubility change on extended release.

To help further understand the role of solubility in determining drug release from porous ceramic pellets, N-light N3 was loaded with benzoic acid, which is slightly soluble in both phosphate buffer pH 6.8 and 0.1N HCl (Appendix 2). Benzoic acid alone dissolved relatively slowly during dissolution testing compared to sodium benzoate and diltiazem HCl in both phosphate buffer pH 6.8 and 0.1N HCl (Fig. 5.3e). In both media, there was extended dissolution of a small percentage of benzoic acid, which was similar to that observed for sodium benzoate dissolution in 0.1N HCl. Once loaded into N-light N3, the release of benzoic acid was extended with the release being characterised by an initial burst release of drug followed by extended release (Fig. 5.3e).

![Dissolution profiles of benzoic acid alone and when loaded into N-light N3 pellets in 0.1N HCl and phosphate buffer pH 6.8 at 37 °C.](image)

Figure 5.3e. Dissolution profiles of benzoic acid alone and when loaded into N-light N3 pellets in 0.1N HCl and phosphate buffer pH 6.8 at 37 °C.

In contrast to sodium benzoate and diltiazem HCl release from N-light N3, Eqn. 5.3b did not adequately fit the benzoic acid release data (Fig. 5.3f). This was because the assumption that burst release occurs instantaneously was invalid. The reason for this was that benzoic acid had a relatively low solubility in the dissolution media, which led
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

to a relatively low burst release rate (Gallagher and Corrigan, 2000; Appendix 2). Therefore, Eqn. 5.3d, which combines the first order kinetic model proposed by Wagner (1969) and the kinetic model described by Eqn. 5.3b was fitted to the release data. This equation proved suitable for modelling the benzoic acid release data in both media (Table 5.3a). The adequacy of the fit was confirmed by the close agreement between the data predicted by the model and the actual data (Fig. 5.3f). The first order and diffusional component of Eqn. 5.3d are also shown in Fig. 5.3f. It can be seen that the first order release was rapidly completed with the remaining extended release being due to the diffusion of benzoic acid from the ceramic.

![Figure 5.3f](image)

**Figure 5.3f.** Plot of Eqn. 5.3b and 5.3d fitted to the release data for benzoic acid from N-light N3 in phosphate buffer pH 6.8 at 37 °C.

It was found that the fraction of benzoic acid released as a burst from N-light N3 was significantly lower in 0.1N HCl than in phosphate buffer pH 6.8 (Table 5.3a). The same trend was observed for sodium benzoate release and again related to drug binding at the ceramic surface. In addition, k1 was significantly lower in 0.1N HCl due to the reduced solubility of benzoic acid in 0.1N HCl in comparison to phosphate buffer pH 6.8 (Table 5.3a; Appendix 2).
There was no significant difference between $k_{H}$ for 0.1N HCl and phosphate buffer pH 6.8 (Table 5.3a). The same result was observed for diltiazem HCl and sodium benzoate release. However, the lower solubility of benzoic acid in 0.1N HCl should have led to a reduction in $k_{H}$. This suggests that the magnitude of the solubility change was insufficient to cause a significant reduction in $k_{H}$ (Appendix 2).

In comparing $F_{B}$ for each drug in both phosphate buffer pH 6.8 and 0.1N HCl, it can be seen that there were marked differences (Table 5.3a). $F_{B}$ for diltiazem HCl was significantly less than that of sodium benzoate, both where binding occurred and where it did not. The external surface area of the pellets and the drug loading solution concentration were constant, which indicates that a greater proportion of sodium benzoate was poorly entrapped within the porous ceramic interior. A key difference between diltiazem HCl and sodium benzoate is that the latter has a relatively low molecular weight, which suggests that molecular weight has an important role in entrapping drug molecules within the porous ceramic interior.

In comparing $F_{B}$ for sodium benzoate and benzoic acid in both media, it was found that $F_{B}$ for benzoic acid was significantly greater than that of sodium benzoate in 0.1N HCl. However, in phosphate buffer pH 6.8, although $F_{B}$ for benzoic acid was markedly higher than that of sodium benzoate, the difference was not significant. As benzoic acid and sodium benzoate have similar molecular structures, it was expected that they would show similar burst releases. The difference was due to the different solvents used in drug loading. The solvent used during benzoic acid loading was ethanol, which rapidly evaporated during filtration and subsequent drying. This rapid evaporation led to a greater deposition of benzoic acid on the external pellet surfaces and hence a greater $F_{B}$.

Following the burst release of drug, $k_{H}$ differed depending on the drug (Table 5.3a). For benzoic acid, $k_{H}$ was significantly less than for both diltiazem HCl and sodium benzoate in 0.1N HCl and for diltiazem HCl in phosphate buffer pH 6.8. However, although $k_{H}$ for benzoic acid was markedly lower than for sodium benzoate in phosphate buffer pH 6.8, the difference was not significant. This was due to the large standard deviation associated with this estimate $k_{H}$ for sodium benzoate. Overall, the reduced $k_{H}$ value for benzoic acid related to its reduced solubility in both media, as the rate of drug release by a diffusion based mechanism is proportional to its solubility in the dissolution medium.
Other researchers have also observed the influence of drug solubility on release from porous materials. For example, Mathivanar et al. (1990) and Shinto et al. (1992) found that drugs with a higher solubility showed faster release from porous ceramics, while Gren et al. (1996) found that the initial drug release rate from porous cellulose matrices increased with increasing solubility.

With regard to the differences between $R_h$ for sodium benzoate and diltiazem HCl, $R_h$ for sodium benzoate in phosphate buffer pH 6.8 was higher than for diltiazem HCl although this difference was not significant. In contrast, $R_h$ for sodium benzoate in 0.1N HCl was significantly lower than for diltiazem HCl (Table 5.3a). These changes in $R_h$ were due to differing physicochemical properties of the drugs. The higher $R_h$ for sodium benzoate in phosphate buffer pH 6.8 was due to its lower molecular weight than diltiazem HCl. Although solubility is also an important parameter in diffusion based release, the solubilities of both drugs are of a similar magnitude in phosphate buffer pH 6.8 (Appendix 2). However, the reduced $R_h$ in 0.1N HCl was due to a reduction in the solubility of sodium benzoate due to the formation of benzoic acid. This had a greater effect on the release rate than the reduction in its molecular weight relative to diltiazem HCl.

A final point to note regarding the dissolution profiles was that they were smooth indicating regular drug release. This result contradicts observations of Netz et al. (2001), who stated that an irregular porous structure, such as that of N-light N3, leads to irregular drug release.

### 5.3.3 Drug Dissolution from N-light N2

To examine the effect of pellet size on the rate of drug release from porous ceramics, N-light N2, which has a diameter in the range 1700-2000 μm, was loaded with sodium benzoate, benzoic acid and diltiazem HCl. N-light N2 gave extended release of each of the three drugs with the release profile being characterised by an initial burst release of drug followed by extended drug release (Fig. 5.3g). In this respect, the release profiles were similar to those of N-light N3. The release of each drug was modelled in the same manner as N-light N3 with acceptable MSC and CD values being observed (Table 5.3b).
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

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**Figure 5.3g.** Dissolution profiles of sodium benzoate, benzoic acid and diltiazem HCl when loaded into N-light N2 pellets in phosphate buffer pH 6.8 at 37 °C.

**Table 5.3b.** Best fit parameters, when Eqn. 5.3b/d is fitted to the release data for N-light N2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>F&lt;sub&gt;b&lt;/sub&gt; (%) w/w</th>
<th>k&lt;sub&gt;i&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;) Average</th>
<th>S.D.</th>
<th>k&lt;sub&gt;H&lt;/sub&gt; (%) h&lt;sup&gt;-0.432&lt;/sup&gt; Average</th>
<th>S.D.</th>
<th>MSC CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem HCl</td>
<td>23.22</td>
<td>N/A</td>
<td></td>
<td>13.50</td>
<td>0.91</td>
<td>3.98</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>45.98</td>
<td>N/A</td>
<td></td>
<td>24.34</td>
<td>1.44</td>
<td>5.82</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>63.70</td>
<td>36.24</td>
<td>1.86</td>
<td>5.60</td>
<td>0.43</td>
<td>5.82</td>
</tr>
</tbody>
</table>

The fraction of drug released as a burst from N-light N2 followed the same trend as observed for N-light N3 with F<sub>b</sub> for benzoic acid being significantly higher than that of sodium benzoate, which was higher than that of diltiazem HCl. However, there was a significantly lower F<sub>b</sub> for each drug from N-light N2 than from N-light N3 (Tables
5.3a/b). There were two reasons for this reduction in $F_b$. Firstly, the loading of N-light N2 was higher than N-light N3, which meant that a lower fraction of drug was deposited on the external pellet surfaces and hence $F_b$ was reduced. Secondly, N-light N2 had a lower external surface area per unit volume than N-light N3 caused by the increase in pellet diameter. This also decreased deposition of drug on external pellet surfaces during loading and hence reduced $F_b$.

The $k_1$ for benzoic acid release from N-light N2 was significantly lower than that of N-light N3. However, the difference in the rate constants was small and had limited impact on the burst release of benzoic acid. For example, 95% of the burst effect was complete within 5 min for N-light N2 and 4.5 min for N-light N3. The decrease in $k_1$ may have been due to the reduced surface area of drug available for dissolution. However, counteracting this was the decrease in the proportion of drug released as a burst from N-light N2. This would have increased $k_1$ had the surface area of drug available for dissolution remained constant (Gallagher and Corrigan, 2000).

The $k_{II}$ for each drug also followed a similar trend to that of N-light N3, with benzoic acid showing a significantly reduced rate in comparison to both diltiazem HCl and sodium benzoate (Table 5.3b). This result further confirmed the role of drug solubility in determining the rate of release from porous ceramics. However, as already mentioned, other factors such as molecular weight contribute to release from the porous ceramic pellets. Sodium benzoate, despite having a lower solubility in phosphate buffer pH 6.8 than diltiazem HCl, has a significantly higher $k_{II}$ (Table 5.3b, Appendix 2). This indicates that the lower molecular weight of sodium benzoate contributed to an increased diffusion coefficient relative to diltiazem HCl and hence a faster rate of release (Linhardt, 1989). Further evidence of the role of molecular weight in determining the rate of release from porous pellets is presented in Chapter 6.

There were no significant differences in $k_{II}$ for each drug from N-light N2 in comparison with N-light N3 (Tables 5.3a/b). This was unexpected as in delivery systems where drug release is diffusion controlled, the time required for a drug to diffuse a certain distance is proportional to the square of that distance (Siegel, 1989). However, the increased average pore size of N-light N2 relative to N-light N3 would have increased $k_{II}$ thus counteracting the effect of increased pellet size (Section 4.6).
5.3.4 Drug Dissolution from N-light N4

In order to further investigate the influence of pellet diameter on drug release from porous ceramic pellets, N-light N4, which had a pellet diameter in the range 425-500 μm, was also loaded with sodium benzoate, benzoic acid and diltiazem HCl. It gave extended release of each drug with the release again being characterised by an initial burst followed by extended drug release (Fig. 5.3h). However, the initial burst release of each drug was particularly high and the extended release relatively fast in comparison with the other grades of N-light.

![Dissolution profiles of sodium benzoate, benzoic acid and diltiazem HCl when loaded into N-light N4 pellets in phosphate buffer pH 6.8 at 37 °C.](image)

Figure 5.3h. Dissolution profiles of sodium benzoate, benzoic acid and diltiazem HCl when loaded into N-light N4 pellets in phosphate buffer pH 6.8 at 37 °C.

The diltiazem HCl and benzoic acid release data was modelled in the same manner as for N-light N2 and N3. While the model fit was acceptable for benzoic acid release (Table 5.3c), a poor fit was obtained for diltiazem HCl release. However, examination of the diltiazem HCl release predicted by the model showed it was in reasonable agreement with the observed release (Appendix 6). Therefore, the kinetic parameters obtained were suitable for use. With regard to the sodium benzoate release, it was not
possible to fit Eqn. 5.3b to the data as 80% drug release had occurred before the first sampling point.

Table 5.3c. Best fit parameters, when Eqn. 5.3b/d is fitted to the release data for N-light N4.

<table>
<thead>
<tr>
<th>Drug</th>
<th>$F_B$</th>
<th>$k_1$</th>
<th>$k_{II}$</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(% w/w)</td>
<td>(h$^{-1}$)</td>
<td>(% h$^{-0.432}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>51.73</td>
<td>1.30</td>
<td>N/A</td>
<td>17.21</td>
<td>1.19</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>71.54</td>
<td>1.35</td>
<td>62.11</td>
<td>5.60</td>
<td>9.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The kinetic parameters determined by modelling the release data for N-light N4 show that $F_B$ was significantly higher and $k_{II}$ was significantly lower for benzoic acid release in comparison to diltiazem HCl release (Table 5.3c). This same trend was observed for benzoic acid and diltiazem HCl release from N-light N2 and N3.

In comparing drug release from N-light N4 with that of the other grades of N-light, there was a significant increase in $F_B$ for diltiazem HCl in comparison to both N-light N2 and N3. However, for benzoic acid the increase in $F_B$ was only apparent in comparing the N-light N2 with N4 (Tables 5.3a/b/c). These increases remained significant when the differing loadings of the ceramics were accounted for. In addition to the differences in burst release, there was a significant increase in $k_1$ for benzoic acid from N-light N4 in comparison with N-light N2 and N3. The reasons for this have been discussed in Section 5.3.3. Overall, based on these comparisons and those discussed in Section 5.3.3, it can be concluded that as the external surface area of porous ceramic pellets decreases, so too does the fraction of drug released as a burst and the rate at which this release occurs.
The extended release rate constant for diltiazem HCl release from N-light N4 was significantly higher than for N-light N2 and N3. There was no significant difference in $k_{11}$ for benzoic acid although it was higher for N-light N4 than for N2 and N3 (Table 5.3a/b/c). While a definite conclusion regarding the effect of pellet diameter on $k_{11}$ cannot be reached due to the differing porous structures of each grade of N-light, there was a trend of rate increases with decreasing pellet diameter (Section 4.6). Millili and Schwartz (1990) observed the same trend when studying the rate of theophylline release from microcrystalline cellulose pellets, as did Gohel and Amin (1998) when examining the release of diclofenac sodium from calcium alginate microspheres. In other related research, Gren et al. (1996) found that the rate of diffusion controlled release of paracetamol from porous cellulose matrices decreased with increasing particle size.

5.3.5 Drug Dissolution from Starlight SLK1000 and Carbolite Ceramics

In the previous Section, the release of a number of drugs from three grades of N-light was examined. However, as the range of pellet diameters in each grade of N-light differed, it was not possible to conclusively determine the effect of porosity and pore size distribution on drug release. Such investigations were possible using Starlight SLK1000, N-light N3 and the Carbolite ceramics, as they had different porosities and pore size distributions but contained pellets with diameters in the range 850-1000 μm (Chapter 4). Additionally, the pellet surfaces were polyanionic at pH 6.8 meaning surface binding of diltiazem HCl was possible for each ceramic (Section 4.4).

It was found that Starlight SLK1000 and each grade of Carbolite gave extended release of diltiazem HCl (Fig. 5.3i). As with N-light N3, diltiazem HCl release was characterised by an initial burst followed by extended release. Eqn. 5.3b fitted the release data although for Starlight SLK1000, the MSC was less than 4 and the CD was less than 0.98 (Table 5.3d). Examination of the release predicted by the model showed it was in reasonable agreement with the observed release (Appendix 6). Therefore, the kinetic parameters obtained were suitable for use (Table 5.3d).
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Figure 5.3i. Dissolution profiles of diltiazem HCl when loaded into Starlight SLK1000 and each grade of Carbolite in phosphate buffer pH 6.8 at 37 ℃.

Table 5.3d. Best fit parameters, when Eqn. 5.3b is fitted to the diltiazem HCl release data for N-light N3, Starlight SLK1000 and each Carbolite grade.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$F_B$ (% w/w) Average</th>
<th>S.D.</th>
<th>$k_H$ (% h$^{-0.432}$) Average</th>
<th>S.D.</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-light N3</td>
<td>27.19</td>
<td>0.74</td>
<td>13.81</td>
<td>0.50</td>
<td>4.41</td>
<td>0.9878</td>
</tr>
<tr>
<td>Starlight SLK1000</td>
<td>38.17</td>
<td>3.80</td>
<td>80.90</td>
<td>9.12</td>
<td>3.47</td>
<td>0.9690</td>
</tr>
<tr>
<td>Carbolite 16/20</td>
<td>43.31</td>
<td>0.23</td>
<td>14.32</td>
<td>0.16</td>
<td>5.73</td>
<td>0.9967</td>
</tr>
<tr>
<td>Carbolite 16/20 (More porous)</td>
<td>28.98</td>
<td>0.41</td>
<td>37.28</td>
<td>0.49</td>
<td>6.09</td>
<td>0.9977</td>
</tr>
<tr>
<td>Carbolite 20/40</td>
<td>23.62</td>
<td>0.99</td>
<td>66.32</td>
<td>1.71</td>
<td>4.60</td>
<td>0.9899</td>
</tr>
</tbody>
</table>

Quantitative assessment of the diltiazem HCl release data showed that the fraction of drug released as a burst was dependent on the porous ceramic (Table 5.3d). For example, Carbolite 16/20 and Starlight SLK1000 had significantly higher $F_B$ values in comparison to the other porous ceramics. On the other hand, $F_B$ was significantly lower
for Carbolite 20/40. A number of factors contributed to these differences in $F_B$. Firstly, the open porosity of the ceramics influenced the mass of drug loaded into the pellet interior but not the mass deposited on the pellet surface. If the open porosity was relatively low the proportion of the total drug that was deposited on the external pellet surfaces would be higher, giving a higher $F_B$. This is seen in comparing $F_B$ for Carbolite 16/20 with that of the other more porous Carbolite ceramics. Secondly, if the mass of drug loaded into the pellet interior was relatively low in comparison to the theoretical maximum, $F_B$ would also be increased. This is seen in comparing $F_B$ for N-light N3 with that of Carbolite 16/20 (More porous), which had a lower theoretical maximum drug loading (Table 5.2a/b). Thirdly, if relatively large pores were located at the external pellet surfaces, the drug loaded into these pores would not be entrapped within the pores. Instead it would be released rapidly as a burst. Such pores were found only in Starlight SLK1000 and this would have contributed to its relatively high $F_B$ (Section 4.5).

These statements regarding $F_B$ were confirmed by comparing the mass of diltiazem HCl released as a burst per unit volume of the ceramics. There were only small differences in the mass released for N-light N3, Carbolite 16/20, 16/20 (More porous) and 20/40 (Fig. 5.3h). This was expected as the ceramics consisted of pellets in the same size range, which meant the same external surface area was available for drug deposition. However, there was a large increase in the mass released from Starlight SLK1000 even though it consisted of pellets in the same size range as the other ceramics (Fig. 5.3h). This meant there was an increase in the quantity of poorly associated drug in Starlight SLK1000, for the reason given above.
Chapter 5. Drug Loading and Dissolution Testing of Commercially Produced Porous Ceramic Pellets

Figure 5.3h. Burst release of diltiazem HCl from selected porous ceramics (Expressed as mass of drug released per unit volume of ceramic).

The extended release rate of diltiazem HCl was also dependent on the porous microstructure of the ceramics (Table 5.3d; Section 4.5/4.6). This was expected as the drug was released by a diffusion based mechanism. For the Carbolite porous ceramics, \( k_{th} \) increased as the porosity and pore size increased. However, the difference in the porosity of Carbolite 16/20 (More porous) and 20/40 was small, which indicated that their pore size was more important in determining \( k_{th} \). When the \( k_{th} \) values for the Carbolite ceramics were compared with those of the other porous ceramics, it was found that changes in pore size and porosity could not fully explain the changes in \( k_{th} \). For example, \( k_{th} \) for Starlight SLK1000 was not significantly different to that of Carbolite 20/40 despite the latter having a lower porosity and smaller pores. Similarly, there was no significant difference in \( k_{th} \) for Carbolite 16/20 and N-light N3. It was concluded that in addition to porosity and pore size, \( k_{th} \) was also dependent on the porous structure of the ceramic with the tortuosity, pore shape and topology of the pores being important considerations (Section 5.3.2).

Relating to the role of pore structure in extending drug release, the occurrence of interior pores in N-light N3 as large as the surface pores of Starlight SLK1000 was noted in Section 4.5. However, this did not result in comparable \( k_{th} \) values for the two...
ceramics. This can be explained with reference to research conducted by Sheppard et al. (1996). They found that the diffusion of a low molecular weight compound through pores connected by a narrow channel was dependent on the size of the channel with diffusion being slower if the channels were smaller. An analogous situation occurred in N-light N3, as the large pores were connected to its external surface by relatively small pores. The dissolution medium entered the ceramic and the drug diffused out of the ceramic through these small pores. Therefore, the relatively small pores determined the drug release rate, which further demonstrates that factors other than the porosity and the overall pore size distribution of the ceramic influenced the rate of extended drug release.

These conclusions regarding extended drug delivery from porous ceramics are in agreement with published research in this area. The influence of porosity and pore size distribution on drug delivery behaviour as well as the importance of porous walls with pores as fine as possible in order to provide lengthy extended drug release has been noted (Krajewski et al., 2000; Netz et al., 2001).

5.4 INVESTIGATIONS INTO THE USE OF RELEASE MODIFYING AGENTS

Having examined the release of drugs from porous ceramic pellets, the ability of certain materials to modify this release was investigated. The desired modification was a reduction in fraction of drug released as a burst coupled with greater extended drug release from the porous ceramic. The release modifying agents were either incorporated into the porous ceramic interior or coated onto the ceramic surface. In the limited research published in this area, Yamamura et al. (1992) and Thoma et al. (1993) used the former method, while Paul and Sharma (1995, 1999), Landi et al. (2001) and Paul et al. (2002) used the latter.

Materials, which have been successfully used to modify the release of drugs from porous ceramics, include the polymers chitosan, polylactic acid, polyethylene vinyl acetate and polyvinyl alcohol (Paul and Sharma, 1995, 1999; Landi et al., 2001; Paul et al., 2002). Thoma et al. (1993) have used the lipid Precirol ATO 5 to extend the release of gentamicin sulphate from porous ceramic implants, while Yamamura et al. (1992)
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and Paul and Sharma (1995) used egg phosphatidylcholine to extend the release of antibiotics from porous hydroxyapatite ceramics.

The release modifying agents investigated in this research were PVP, chitosan, ethylcellulose 10 cps, calcium alginate and Precirol ATO 5. The results of these experiments are discussed below.

5.4.1 PVP, Chitosan and Ethylcellulose 10 cps

The polymers PVP, chitosan and ethylcellulose have been widely used in pharmaceutical applications (Handbook of Pharmaceutical Excipients, 2000; Chiou et al., 2001). PVP is a non-toxic, high molecular weight polymer, which is readily soluble in water. It can be used as a viscosity enhancing agent and for this reason it was envisaged that it might be able to modify drug release from porous ceramics (Handbook of Pharmaceutical Excipients, 2000).

Chitosan is the deacetylated form of chitin, which is a naturally occurring polysaccharide found in, for example, shrimp and crab shells. It is biocompatible and biodegradable in animal tissue (Paul and Sharma, 1995; Chiou et al., 2001). Chitosan has been used to form water insoluble matrices within pellets or water insoluble films on external pellet surfaces (Tapia et al., 1993; Chiou et al., 2001). This low aqueous solubility means chitosan can act as a barrier delaying the release of drug in aqueous media (Jantzen and Robinson, 1996). For this reason, it was investigated as a potential release modifying agent for porous ceramics.

Ethylcellulose is a non-toxic, high molecular weight polymer produced by reacting alkali cellulose with ethyl chloride. This results in a cellulose molecule in which some of the hydroxyl groups have been replaced with ethoxyl groups (Handbook of Pharmaceutical Excipients, 2000). It has been used in similar applications to chitosan and because of its low aqueous solubility it too can delay the release of drug in aqueous media (Goskonda et al., 1994a; Wesseling and Bodmeier, 1999). Therefore, it was chosen as a potential release modifying agent for porous ceramics.
Prior to investigating the effect of these polymers on drug release from N-light N3, their effect on the diltiazem HCl loading of the pellets was examined. When PVP was incorporated into the pellets, there was a significant reduction in drug loading (Table 5.4a). This was due to the relatively high viscosity of the diltiazem HCl/PVP loading solution, which reduced the level of loading solution that entered the pellet interior. The effect viscosity has on the ability of a liquid to enter porous structures has been noted by Zhu et al. (2001).

Pellets loaded with chitosan, also had a significantly reduced drug loading following chitosan incorporation (Table 5.4a). This was expected as the chitosan loading step involved placing the pellets in an aqueous chitosan/acetic acid solution. Since diltiazem HCl is soluble in aqueous acidic media, some of the pellet drug content was released into this medium thereby reducing the drug loading. Paul and Sharma (1995) observed a similar effect when coating ampicillin trihydrate loaded porous hydroxyapatite microspheres with collagen or chitosan.

In the case of ethylcellulose 10 cps, there was no significant difference between the loading prior to and following incorporation of the polymer (Table 5.4a). This was because diltiazem HCl had a relatively low solubility in the ethanolic ethylcellulose 10 cps loading solution, in contrast to the chitosan loading solution. Therefore, diltiazem HCl was not released into the loading medium.

**Table 5.4a.** Diltiazem HCl loading of N-light N3 pellets prior to and following incorporation of/coating with release modifying agents.

<table>
<thead>
<tr>
<th>Release modifying agent</th>
<th>Average loading (% w/w)</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14.2</td>
<td>0.4</td>
</tr>
<tr>
<td>PVP</td>
<td>11.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Chitosan</td>
<td>12.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Ethylcellulose 10 cps</td>
<td>14.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcium alginate</td>
<td>9.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Precirol ATO 5</td>
<td>5.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Release of diltiazem HCl from N-light N3 both prior to and following PVP, chitosan or ethylcellulose 10 cps incorporation was characterised by an initial burst release of drug followed by extended release (Fig. 5.4a). The release data fitted Eqn. 5.3b, although for PVP and ethylcellulose 10 cps, the MSC’s were less than 4 and the CD’s were less than 0.98 (Table 5.4b). However, the predicted release was in close agreement with the actual release, indicating Eqn. 5.3b adequately described the observed drug release (Appendix 6).

**Figure 5.4a.** Dissolution profile of diltiazem HCl, when loaded into N-light N3 prior to and following incorporation of selected polymers, in phosphate buffer pH 6.8 at 37 °C.
Table 5.4b. Best fit parameters, when Eqn. 5.3b is fitted to the diltiazem HCl release data for N-light N3 prior to and following incorporation of coating with release modifying agents.

<table>
<thead>
<tr>
<th>Release modifying agent</th>
<th>F_B (% w/w)</th>
<th>k_H (% h^-0.432)</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
</tr>
<tr>
<td>None</td>
<td>27.18</td>
<td>0.74</td>
<td>13.81</td>
<td>0.50</td>
</tr>
<tr>
<td>PVP</td>
<td>52.27</td>
<td>0.60</td>
<td>12.36</td>
<td>0.41</td>
</tr>
<tr>
<td>Chitosan</td>
<td>22.21</td>
<td>0.21</td>
<td>11.29</td>
<td>0.14</td>
</tr>
<tr>
<td>Ethylcellulose 10 cps</td>
<td>26.89</td>
<td>0.67</td>
<td>12.42</td>
<td>0.46</td>
</tr>
<tr>
<td>Calcium alginate</td>
<td>4.58</td>
<td>0.07</td>
<td>1.16</td>
<td>0.05</td>
</tr>
<tr>
<td>Precirol ATO 5</td>
<td>0.00</td>
<td>0.21</td>
<td>5.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Incorporation of PVP into N-light N3 significantly increased the fraction of diltiazem HCl released from the pellets as a burst (Table 5.4b). This was due to the reduction in the penetration of the loading solution into the porous ceramic interior, which meant that a higher proportion of the loaded drug was located on the external pellet surfaces. There was also a significant increase in $k_H$ for diltiazem HCl release from the pellets (Table 5.4b). This was also related to reduced penetration of the loading solution into the inner regions of the ceramic. As a result, the drug had a shorter distance to diffuse before reaching the bulk dissolution medium. In related research, Levis (2000) found that PVP did not extend the release of diltiazem HCl from halloysite, while Paul and Sharma (1995) found that coating porous hydroxyapatite pellets with collagen, which like PVP swells rapidly in aqueous media, did not extend the release of ampicillin trihydrate from the pellets.

Incorporation of chitosan into N-light N3 significantly reduced the fraction of diltiazem HCl released as a burst (Table 5.4b). This was due to removal of some of the poorly associated drug from the ceramic during chitosan loading. However, a large burst release still occurred as the chitosan loading solution, which remained on the ceramic surface after filtering contained a high concentration of diltiazem HCl. The drug was then deposited on the external pellet surfaces during subsequent drying. In contrast,
there was no significant change in $F_B$ following ethylcellulose 10 cps incorporation (Table 5.4b). This was because poorly associated drug was not released into the polymer solution during loading, as discussed above.

The incorporation of chitosan or ethylcellulose 10 cps led to a significant reduction in $k_{H}$ (Table 5.4b). However, the reduction was relatively small, which was unexpected, as both chitosan and ethylcellulose have been widely used to produce marked decreases in drug release rates (Tapia et al., 1993; Goskonda et al., 1994a; Paul and Sharma, 1995). The small changes were due to the fact that the polymers used had a relatively low molecular weight and in addition, the solution concentrations were relatively low. This was necessary to facilitate incorporation of the polymer solutions into the ceramic interior. However, as a result the polymer matrix formed within the pellet interior had a high porosity and low tortuosity and therefore had a limited impact on the release of diltiazem HCl.

An alternative approach would be to coat the external surfaces of the pellets with the polymers, rather than incorporating them into the pellet interior. This would allow for greater flexibility in the molecular weight of the polymers and the concentration of the polymer solutions used. Additionally, the level of coating applied could be tailored to give the required drug release rate.

### 5.4.2 Calcium Alginate

Sodium alginate is the sodium salt of alginic acid, which is a hydrophilic carbohydrate colloid occurring in the cell walls and intercellular spaces of various species of brown seaweed. It is non-toxic and is widely used in pharmaceutical preparations. It is soluble in water and forms viscous colloidal solutions (Handbook of Pharmaceutical Excipients, 2000). In solution, sodium alginate can react with calcium to form calcium alginate, which is water insoluble but water permeable. It has been used both as a matrix to form drug delivery systems and also as a coating material for drug delivery systems (Bhagat et al., 1994; Türkoglu et al., 1997). In these products, the calcium alginate hydrates to form a gel through which the drug must diffuse in order to be released into the bulk dissolution medium. This leads to a reduction in the rate of drug release from the dosage form (Bhagat et al., 1994).
The potential of calcium alginate to extend the release of diltiazem HCl from N-light N3 was assessed in this research. Incorporation of calcium alginate into diltiazem HCl loaded N-light N3 significantly reduced the drug loading of the pellets (Table 5.4a). This was due to release of diltiazem HCl into the aqueous sodium alginate and calcium chloride solutions used during loading. The reduction in drug loading was significantly greater than that observed during chitosan incorporation. This was because the calcium chloride solution was of a relatively high volume (250 ml), meaning its diltiazem HCl concentration was relatively low. Therefore, a relatively low mass of diltiazem HCl was deposited on the external pellet surfaces during subsequent drying.

The diltiazem HCl release profile observed following calcium alginate incorporation was markedly different to those previously observed (Fig. 5.4b). There was a very low burst release of drug followed by extended drug release. It was found that Eqn. 5.3b fitted the release data, indicating diffusion of drug from the ceramic interior was the rate-limiting step in drug release (Table 5.4b). This has been observed for the release of other low molecular weight drugs from calcium alginate matrices (Türkoglu et al., 1997; Kikuchi et al., 1999).

![Graph](image)

**Figure 5.4b.** Dissolution profile of diltiazem HCl when loaded into N-light N3 prior to and following incorporation of calcium alginate in phosphate buffer pH 6.8 at 37 °C.
Calcium alginate incorporation led to a significant reduction in the fraction of diltiazem HCl released as a burst from N-light N3 (Table 5.4b). This was due to the removal of poorly associated drug from the ceramic during the loading step, as discussed above. In addition, there was a significant reduction in $k_{H}$ (Table 5.4b). The reduction in $k_{H}$ was due to the creation of a calcium alginate matrix throughout the porous structure of the pellets, as well as on the external pellet surfaces. This matrix made the pellet interior less porous and the diffusional path more tortuous, thereby decreasing the rate of diltiazem HCl diffusion into the bulk dissolution medium (Higuchi, 1963).

This result demonstrated the suitability of calcium alginate incorporation for extending the release of drugs from porous ceramic pellets. An interesting way in which this might be applied is by incorporating calcium into the porous ceramic during production. Therefore, upon introduction of sodium alginate solution the formation of the insoluble calcium alginate would take place rapidly. This would form both within the porous ceramic interior and on the external pellet surface providing a uniform coating.

5.4.3 Precirol ATO 5

Lipid coating has been widely used to modify the release of water-soluble drugs from pellets. For example, Bayomi et al. (1994) found that by coating mebeverine HCl containing pellets with beeswax the release of mebeverine HCl from the pellets was extended. In this research, the lipid used to coat N-light N3 was Precirol ATO 5, which is a palmito-stearyl glyceride. It is used pharmaceutically as a lubricant, binder, taste masking agent and controlled release agent (Gattefosse, 2003).

The method used to coat N-light N3 with Precirol ATO 5 can be described as a melted dispersion cooling process (Watanabe and Hayashi, 1976). It utilises the thermal behaviour of Precirol ATO 5, which has a melting point in the range 53-57 °C (Gattefosse, 2003). The N-light N3 pellets were dispersed in the molten lipid and the resulting mixture was poured into water at a lower temperature than the melting point of Precirol ATO 5. This caused the lipid to solidify and form a layer over the pellet surface.
There was a significant reduction in the diltiazem HCl loading of N-light N3 following coating with Precirol ATO 5 (Table 5.4a). This was again due to dissolution of poorly associated diltiazem HCl, which is lipid soluble, into the surrounding melted Precirol ATO 5 during coating (Cassidy et al., 1988). However, the reduction in loading, which was expressed as percentage weight per weight, was particularly high. This was also associated with the marked increase in pellet weight following Precirol ATO 5 coating rather than dissolution of diltiazem HCl into the lipid medium during the coating process. Such large increases in pellet mass were not observed during the other polymer incorporation techniques.

The release of diltiazem HCl from the Precirol ATO 5 coated N-light N3 was markedly different to the release prior to lipid coating (Fig. 5.4c). The profile was characterised by extended diltiazem HCl release without a burst release of drug. As with uncoated N-light N3, Eqn. 5.3b fitted the release data indicating that diltiazem HCl diffusion was the rate-limiting step in drug release (Table 5.4b).

![Graph of dissolution profile of diltiazem HCl](image)

**Figure 5.4c.** Dissolution profile of diltiazem HCl when loaded into N-light N3 prior to and following Precirol ATO 5 coating in phosphate buffer pH 6.8 at 37 °C.
Precirol ATO 5 coating eliminated the burst release of diltiazem HCl from N-light N3 and significantly reduced $k_{h1}$ (Table 5.4b). These changes were due to the formation of a lipid coat on the external pellet surfaces. In order for drug to be released into the bulk dissolution medium it either had to diffuse through the coating material or pass through aqueous channels in the coating (Griffin and Niebergall, 1999). If drug release involved diffusion through the lipid coating, a zero order equation would have described the release profile. Since Eqn. 5.3b fitted the release data, drug release must have occurred by diffusion through aqueous channels in the lipid. As a result, the diffusional path length of the drug increased explaining the observed reduction in $k_{h1}$.

A further benefit of Precirol ATO 5 coating was that it could be used to change the floating properties of porous ceramic pellets. For pellets whose density is greater than water, such as Carbolite 16/20, lipid coating would reduce the bulk density of the pellets thereby creating a floating dosage form. This would be of benefit in extended drug delivery (Kawashima et al., 1991).

With reference to the coating technique used, a particular advantage of it was that it did not require organic solvents, which due to regulatory constraints have reduced acceptability in coating processes (Achanta et al., 1997). Coupled with this, the process is suitable for coating water soluble, thermally stable drugs and drug carriers, which can be challenging candidates for coating (Watanabe and Hayashi, 1976). However, a drawback of this technique was that a high level of pellet agglomeration occurred during coating. In addition, it may not be possible to use this technique for large-scale production of lipid coated pellets. However, this research did demonstrate the feasibility of lipid coating to modify drug release from porous ceramics and where necessary lipid coating techniques, such as hot-melt fluid bed coating could be used. This method can produce large quantities of coated pellets, while overcoming the problem of pellet agglomeration during coating (Jozwiakowski et al., 1990).
5.5 CONCLUSION

The research presented in this Chapter focussed initially on developing a drug loading technique for the commercially produced porous ceramic pellets. It was found that a novel modification of the standard vacuum loading method could be used to obtain reproducible drug loadings. This method was designed to load floating porous ceramic pellets and was significantly more effective than loading using the standard methods. In addition, it proved suitable for loading porous ceramics with relatively high bulk densities. The drug loadings were influenced by the loading solution concentration and the porosity and bulk density of the porous ceramic. Therefore, by changing these parameters it should be possible to tailor drug loading to exact requirements. Overall, the drug loadings achieved indicated that porous ceramic pellets should be suitable for the delivery of both low and high potency drugs.

Reproducible, extended release of drugs from the porous ceramic pellets occurred with the release taking the form of an initial burst followed by extended drug release. The proportion of drug released during the initial burst was influenced by the pellet size and electrostatic interactions between the drug and pellet surfaces. The rate at which this drug was released was dependent on its solubility in the dissolution medium. The rate-determining step in extended drug release was diffusion of the drug from the porous pellet interior into the bulk dissolution medium. This rate was influenced by the pellet size, its porosity, pore size distribution, porous microstructure and by electrostatic interactions between the pellet surfaces and the drug. The solubility of the drug in the dissolution medium and its molecular weight also influenced the release rate. The presence of the porous microstructure was found to be essential in providing this extended release.

Where the release of drug from the porous ceramic pellets alone did not meet requirements, it was possible to either load or coat the pellets with release modifying agents to further delay drug release. It was found that incorporation of calcium alginate into the pellet interior or coating the external pellet surfaces with Precirol ATO 5 led to a marked reduction in the burst release and a decrease in the release rate of diltiazem HCl from N-light N3.
Although only in vitro studies were conducted in this research, the ability of dissolution testing to indicate the in vivo release pattern of drugs from porous ceramics has been demonstrated (Mathivanar et al., 1990; Shinto et al., 1992). Therefore, it can be concluded that the porous ceramics would be suitable for the extended delivery of drugs given orally. Release of such drugs should occur throughout the GIT, with the porous ceramic material remaining unabsorbed. This is expected, as similar materials, such as kaolin and bentonite, are not absorbed from the GIT. A particular advantage that porous ceramics offer over existing drug delivery systems is that drug is incorporated into them post-production. Therefore, stability problems with, for example, thermo-sensitive drugs, can be avoided. In addition, each porous ceramic could be used to deliver a range of different drugs giving them potential applications in treating numerous conditions. For example, Itokazu et al. (1994) demonstrated the suitability of porous hydroxyapatite ceramics as drug carriers in the treatment of osteomyelitis. The ceramics were loaded with different antibiotics depending on the susceptibility of the infecting pathogen.
Chapter 6. Production of Porous Aluminosilicate Pellets by Extrusion-Spheronization

6.1 INTRODUCTION

This Chapter focuses on the production of pellets from the aluminosilicate clay minerals, kaolin and halloysite. The aim was to produce pellets, which could modify drug release according to requirements. The production technique adopted was extrusion-spheronization, as it can produce pellets with a structure similar to the commercial porous ceramics already investigated (Chapters 4/5). In addition, it has been found that changing the pellet core composition can modify the release of incorporated drugs (O'Connor and Schwartz, 1989). For example, Varshosaz et al. (1997) found that by increasing the percentage of Eudragit L100-55 in the pellet core, the release of the drug phenylbutazone was extended.

The production of kaolin and halloysite based pellets by extrusion-spheronization was particularly challenging for three reasons. Firstly, the majority of published extrusion-spheronization research relates to formulations which contain high concentrations of microcrystalline cellulose and/or lactose (Deasy, 1991). There have been no published reports on the use of kaolin or halloysite as principal formulation excipients, although Liu and Chou (2000) have successfully extruded a kaolin/alumina based formulation using water as the granulating solvent. Secondly, extrusion-spheronization is seldom used in the ceramic industry with one of its few applications being in the production of breeder materials for nuclear reactors (Lulewicz and Roux, 1998). Thirdly, a high temperature sintering step could not be used to prevent pellet break-up in aqueous solutions, as this would destroy the microtubular structure of halloysite (Salter, 2003).

In addition to producing kaolin and halloysite based pellets by extrusion-spheronization, the pellets had to be capable of modifying drug release according to requirements. It has
been shown that drug release can be extended using release modifying agents such as calcium alginate (Section 5.4). However, if the release were already too slow it would be necessary to increase the rate of release. To this end, the effect of PFA’s on pellet structure, drug loading and release was investigated.

6.2 PRODUCTION OF POROUS ALUMINOSILICATE PELLETS BY EXTRUSION-SPHERONIZATION

6.2.1 Preliminary Formulation Investigations

Initial investigations focussed on determining the formulation components necessary to successfully extrude and spheronize mixtures containing high levels of the aluminosilicate, kaolin. The granulating solvents selected were water and ethanol, and it was found that the wet mass produced, using either solvent, could be extruded and spheronized. However, the pellets did not remain intact after 24 h in water (Table 6.2a). This made them unsuitable for extended drug delivery, as they would rapidly release the incorporated drug upon pellet break-up (Section 5.3.2).

As already mentioned, a sintering step, although commonly used in porous ceramic production could not be used in this case to prevent pellet break-up. An alternative approach was to include a binder in the formulation (Sivakumar and Panduranga Rao, 2002). The binders and the binder concentrations investigated are listed in Table 6.2a. Of these, PVP, methylcellulose and ethylcellulose have been used in ceramic extrusion (Janney, 1995). It was found that only pellets containing the non-aqueous binder ethylcellulose 100 cps at a concentration of greater than 5% w/w remained intact with acceptable strength after 24 h in water (Table 6.2a). Based on this, the components selected for use in further formulations were ethanol, as a granulating solvent, and 5% w/w ethylcellulose 100 cps, as a binder.

The choice of ethanol as a granulating solvent was unusual as aqueous based systems are the most widely used granulating solvents in extrusion-spheronization (Deasy, 1991). Lindberg et al. (1987) did produce an extrudate containing anhydrous citric acid and sodium bicarbonate using ethanol as a granulating liquid. However, they did not spheronize the extrudate. Millili and Schwartz (1990) found that poor quality products
were obtained when a microcrystalline cellulose based formulation was extruded and spheronized using ethanol as the granulating solvent. Where ethanol has been successfully used, it was as a component of an ethanol/water granulating solvent rather than alone (Millili and Schwartz, 1990; Elbers, 1992).

Table 6.2a. Integrity of a series of extrusion-spheronization products after 24 h in water.

<table>
<thead>
<tr>
<th>Formulation components</th>
<th>Pellet integrity after 24 h in water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaolin: Water</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Ethanol</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: PVP (2% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: PVP (5% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: PVP (10% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: Carbopol 974P (2% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: Carbopol 974P (10% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: Glycerylmonostearate (10% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: Methylcellulose (2% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Water: Methylcellulose (10% w/w)</td>
<td>Not intact</td>
</tr>
<tr>
<td>Kaolin: Ethanol: Ethylcellulose 100 cps (1% w/w)</td>
<td>Partially intact</td>
</tr>
<tr>
<td>Kaolin: Ethanol: Ethylcellulose 100 cps (2.5% w/w)</td>
<td>Intact but low strength</td>
</tr>
<tr>
<td>Kaolin: Ethanol: Ethylcellulose 100 cps (5% w/w)</td>
<td>Intact</td>
</tr>
<tr>
<td>Kaolin: Ethanol: Ethylcellulose 100 cps (10% w/w)</td>
<td>Intact</td>
</tr>
</tbody>
</table>

Preliminary formulation investigations also focussed on establishing a method to control the porosity and pore size distribution of the resultant pellets. It was decided that this would be best achieved through inclusion of a PFA in the formulation. It was essential that the PFA could be easily removed from the pellets, as this would generate porosity. The most widely used method to remove PFA’s from porous ceramics has been to burn them out during sintering of the ceramic. However, the microtubular structure of halloysite, which was also to be pelletized, is destroyed at high temperatures making this method unsuitable (Salter, 2003). Removal of the PFA by dissolution was
identified as an alternative. Since the pellet formulation contained ethanol, as a granulating solvent, a suitable PFA would have low ethanol solubility but high solubility in another solvent. Sucrose met these requirements having an ethanol solubility of 0.25% w/v and a water solubility of 200% w/v (Handbook of Pharmaceutical Excipients, 2000). In addition, sucrose is already used in extrusion-spheronization to improve the ease of spheronization and also to adjust pellet drug loading (Deasy, 1991).

A second desirable property of the PFA was availability in a range of different particle size distributions to allow for the production of pellets with varying pore size distributions. The particle size distribution of granulated sucrose was examined initially. It was found that although granulated sucrose contained particles in a wide size range, the majority of particles were larger than 500 μm (Fig. 6.2a.). Since the desired pellet size range was between 850 and 1400 μm, the sucrose would be similar in size to the pellets making this grade unsuitable for use.

![Particle size distribution of granulated sucrose.](image)

**Figure 6.2a.** Particle size distribution of granulated sucrose.

In order to obtain sucrose particles of a size suitable for inclusion in the pellet formulation, the granulated sucrose was milled. This proved a suitable method for
particle size reduction with the resulting size distribution being dependent on the mill used (Fig. 6.2b/c). When the ultracentrifuge mill was used, the resulting particles were all less than 79.3 µm in size (Fig. 6.2c). This was expected as the mill was fitted with an 80 µm sieve, which ensured that only particles less than 80 µm in size were produced. Sucrose, which has been processed using the ultracentrifuge mill, is referred to as U.C. sucrose throughout the text. Based on these results, it was concluded that sucrose with a range of particle sizes could be obtained and thus was a suitable PFA for use in the pellet formulations.

Figure 6.2 Particle size distributions of sucrose after (b) 30 min ball milling and (c) 30 min ball milling followed by ultracentrifuge milling.
The final aim of preliminary formulation studies was to assess the suitability of various formulations for extrusion-spheronization. In order to produce acceptable products by extrusion-spheronization, a balance between plasticity and brittleness must be achieved in the formulation (Pinto et al., 1992). Therefore, a formulation was deemed suitable if it could be extruded and if the bind in the extrudate was sufficient to allow it to be spheronized to some extent. However, the bind should not be so great as to prevent a spheronized product in the approximate size range 850-1400 µm being obtained.

It was found that the quantity of ethanol required to produce a wet mass suitable for extrusion-spheronization was dependent on the proportion of kaolin and sucrose in the formulation (Table 6.2b). As the proportion of sucrose increased the level of ethanol required decreased indicating that the wettability of the formulation had decreased. Other researchers have also observed changes in the wettability of formulations when the components were changed (Jaiyeoba and Spring, 1980; Eerikäinen, 1991; Elbers et al., 1992). In this case, the change was due to the low capacity of sucrose to absorb ethanol in comparison to kaolin, which is an important factor in granulation processes (Kristensen and Schaefer, 1987).

The results of these preliminary investigations into formulation wettability were used to define the linear constraints for the experimental design given in Section 3.2.4.
Table 6.2b. Assessment of the suitability of a range of formulations for extrusion-spheronization.

<table>
<thead>
<tr>
<th>Kaolin (g)</th>
<th>Sucrose (g)</th>
<th>Ethanol (g)</th>
<th>Ethylcellulose 100 cps (g)</th>
<th>Suitability for extrusion-spheronization</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.5</td>
<td>0</td>
<td>32.5</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>65</td>
<td>0</td>
<td>30</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>67.5</td>
<td>0</td>
<td>27.5</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>70</td>
<td>0</td>
<td>25</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>30</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>57.5</td>
<td>10</td>
<td>27.5</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>55</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>45</td>
<td>20</td>
<td>30</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>47.5</td>
<td>20</td>
<td>27.5</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>25</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>27.5</td>
<td>40</td>
<td>27.5</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
<td>25</td>
<td>5</td>
<td>Not suitable</td>
</tr>
<tr>
<td>33</td>
<td>40</td>
<td>22</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>34</td>
<td>40</td>
<td>21</td>
<td>5</td>
<td>Suitable</td>
</tr>
<tr>
<td>35</td>
<td>40</td>
<td>20</td>
<td>5</td>
<td>Suitable</td>
</tr>
</tbody>
</table>

6.2.2 Determination of Optimum Production Parameters

6.2.2.1 Experimental Design

The experimental design used to determine the optimum formulation and process parameters for pellet production has been discussed in Section 3.2.4. Regarding this design, although spheronizer load and extruder speed can influence the final product, they were not investigated due to the large number of parameters already under investigation (Newton et al., 1995; Vervaet et al., 1995; Law, 1996). The levels at which these parameters were fixed was based on work carried out by Law (1996) and Salter (2003) using the same extrusion-spheronization equipment. The range of spheronizer speeds and times investigated were based on commonly reported literature.
values (Vervaet et al., 1995; Law, 1996; El-Mahdi, 1998; Salter, 2003). In addition, preliminary experiments established that the ranges used were appropriate for the spheronization of kaolin based formulations.

The formulation parameters and formulations investigated were based on the results of preliminary formulation investigations (Section 6.2.1). Linear constraints were used to exclude formulations from the experimental design, which were deemed unsuitable for extrusion-spheronization in the preliminary formulation studies (Table 6.2b). They were created by specifying formulations allowed in the design and determining constraints based on this. The suitable formulations and their compatibility with the initial linear constraints (Table 3.2b) are given in Table 6.2c. Using these constraints a design space from which formulations were selected for investigation was created (Fig. 6.2d). Preliminary assessment of experimental results indicated it was necessary to relax the design constraints somewhat in order to investigate formulations outside of the initial design space. The compatibility of these formulations with the relaxed linear constraints (Table 3.2d) is given in Table 6.2c, while the design space is shown in Fig. 6.2e.

**Figure 6.2d.** Ternary phase diagram showing, in the highlighted region, the initial experimental design space.  
**Figure 6.2e.** Ternary phase diagram showing, in the highlighted region, the relaxed experimental design space.
Table 6.2c. Suitable formulations for extrusion-spheronization and the expressions used to place linear constraints on the experimental design (Underlined formulations were not allowed in the initial design space but were allowed in the relaxed design space).

<table>
<thead>
<tr>
<th>Formulation components</th>
<th>Initial linear constraints</th>
<th>Relaxed linear constraints</th>
<th>Common constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Kaolin – 6.111 Ethanol</td>
<td>3 Kaolin – 7.513 Ethanol</td>
<td>Kaolin – 2.1</td>
</tr>
<tr>
<td></td>
<td>+ Sucrose &gt; 0</td>
<td>+ Sucrose &lt; 0</td>
<td>Ethanol + 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sucreose &gt; 0</td>
</tr>
<tr>
<td>Kaolin (g)</td>
<td>Ethanol (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.5</td>
<td>0</td>
<td>35.5</td>
<td>0.45</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>29</td>
<td>5.10</td>
</tr>
<tr>
<td>67.5</td>
<td>0</td>
<td>27.5</td>
<td>9.75</td>
</tr>
<tr>
<td>69</td>
<td>0</td>
<td>26</td>
<td>14.40</td>
</tr>
<tr>
<td>56</td>
<td>10</td>
<td>29</td>
<td>7.50</td>
</tr>
<tr>
<td>57.5</td>
<td>10</td>
<td>27.5</td>
<td>2.85</td>
</tr>
<tr>
<td>59</td>
<td>10</td>
<td>26</td>
<td>9.40</td>
</tr>
<tr>
<td>48.5</td>
<td>20</td>
<td>26.5</td>
<td>4.75</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>25</td>
<td>7.50</td>
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<tr>
<td>51.5</td>
<td>20</td>
<td>23.5</td>
<td>12.15</td>
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<tr>
<td>53</td>
<td>20</td>
<td>22</td>
<td>16.80</td>
</tr>
<tr>
<td>31</td>
<td>40</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>35.5</td>
<td>40</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>40</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>32.5</td>
<td>40</td>
<td>22.5</td>
<td></td>
</tr>
</tbody>
</table>
6.2.2.2 Fines Yield

The fines yield, large pellet yield, pellet yield and sphericity for each experimental design point are given in Appendix 7. In order to analyse this data, it was necessary to mathematically transform the data. The appropriate transformation for the fines yield, large pellet yield and pellet yield results was

\[
y' = \sin^{-1} \sqrt{y}
\]

Analysis of the transformed fines yield data showed the appropriate model for the data was a crossed linear by two-factor interaction model (Appendix 8). The model had an F-value of 27.41 (Table 6.2d), which shows the model terms had a significant effect on the response, which was fines yield. The lack of fit of the model, which showed the variation between replicate points and the model points, was insignificant (p> 0.05). This indicates the model could predict points within the design space other than the design points. The R^2 value, which was a measure of the amount of variation around the mean explained by the model, was 0.8392. This was deemed acceptable for this model. There was variation between the observed fines yield and those predicted by the model (Appendix 9). However, a linear trend was evident, indicating the model was suitable.
Table 6.2d. ANOVA of a crossed linear by two-factor interaction model fitted to the transformed fines yield data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>1.1736</td>
<td>8</td>
<td>0.1467</td>
<td>27.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Linear Mixture</td>
<td>0.3248</td>
<td>2</td>
<td>0.1624</td>
<td>30.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronizer Speed</td>
<td>0.2918</td>
<td>1</td>
<td>0.2918</td>
<td>54.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronization time</td>
<td>0.1238</td>
<td>1</td>
<td>0.1238</td>
<td>23.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sucrose x Spheronizer Speed</td>
<td>0.0940</td>
<td>1</td>
<td>0.0940</td>
<td>17.57</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sucrose x Spheronization time</td>
<td>0.0723</td>
<td>1</td>
<td>0.0723</td>
<td>13.51</td>
<td>0.0007</td>
</tr>
<tr>
<td>Ethanol x Spheronizer Speed x Spheronizer</td>
<td>0.0422</td>
<td>1</td>
<td>0.0422</td>
<td>7.89</td>
<td>0.0075</td>
</tr>
<tr>
<td>Spheronization time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose x Spheronizer Speed x Spheronization time</td>
<td>0.0266</td>
<td>1</td>
<td>0.0266</td>
<td>4.97</td>
<td>0.0313</td>
</tr>
<tr>
<td>Residual Error</td>
<td>0.2248</td>
<td>42</td>
<td>0.0054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Fit</td>
<td>0.2178</td>
<td>37</td>
<td>0.0059</td>
<td>4.19</td>
<td>0.0571</td>
</tr>
<tr>
<td>Pure Error</td>
<td>0.0070</td>
<td>5</td>
<td>0.0014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>1.3984</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As the model was suitable for predicting the fines yield, the effect of changes in the formulation or process parameters on the fines yield could be investigated. The formulation components had a significant effect on the fines yield. In addition, ethanol and sucrose were involved in significant interactions with the process parameters (Table 6.2d). Ternary phase diagrams were used to represent the effect of formulation changes on fines yield at particular process parameter levels (Fig. 6.2f). The contour plots show the predicted fines yield. At low spheronomizer speeds and also at high speeds and low spheronization times increasing the proportion of solid components in the formulation increased the level of fines produced (Fig. 6.2f (i)/(ii)/(iii)). This occurred as there was...
insufficient bind within the extrudate, which led to the break up of the extrudate upon spheronation (Deasy, 1991). However, at a spheronomizer speed of 1500 rpm and a time of 10 min there was a small decrease in the fines yield as the proportion of solids in the formulation increased (Fig. 6.2f (iv)). For example, there was a 2% w/w decrease when the ethanol content was decreased from 29% w/w to 26% w/w in formulations containing no sucrose. This decrease was unexpected and occurred because the ethanol and sucrose content of the formulation significantly interacted with spheronomizer speed and time. These interactions were detected, as there was a small increase in the level of dust expelled from the spheronomizer at high spheronomizer speeds and times due to a reduced bind in the product, which related to increased evaporation of the volatile granulating solvent. This meant that there was a reduction in the mass of material less than 850 μm in size and therefore a reduction in the fines yield. Deasy and Gouldson (1996) observed a similar effect as spheronation time was increased when using a non-aqueous granulating solvent.

The fines yield at a constant ethanol level was also dependent on the ratio of kaolin to sucrose in the formulation. At low spheronomizer speeds and also at high speeds and low spheronation times, increases in the kaolin level and decreases in the sucrose level led to an increase in the fines yield (Fig. 6.2f (i)/(ii)/(iii)). This was because formulations containing higher levels of kaolin require a higher proportion of ethanol to create a wet mass with similar bind and consistency to formulations containing higher levels of sucrose (Section 6.2.2.1). However, at a spheronomizer speed of 1500 rpm and a time of 10 min the fines yield decreased as the proportion of kaolin increased (Fig. 6.2f (iv)). This again related to the increased level of dust expelled from the spheronomizer.
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Figure 6.2f. Ternary phase diagrams showing the predicted contour plots for fines yield (expressed as a fraction) at various spheronizer speeds and times: (i) 1000 rpm for 2.5 min (ii) 1000 rpm for 10 min (iii) 1500 rpm for 2.5 min (iv) 1500 rpm for 10 min.

The effect of increasing spheronizer speed was to increase the fines yield. Similarly, increasing the spheronization time increased the fines yield (Fig. 6.2f). This was due to an increase in the number of collisions between particles leading to a reduction in the particle size and increased particle break-up. This was in agreement with the observations of Bianchini et al. (1992), who found that an increase in spheronizer speed led to an increase in the production of smaller pellets and those of Deasy and Gouldson (1996) who found that the fines yield increased as spheronization time increased.
Finally, the fines level was relatively high at high spheronizer speeds and times. This may have been partly due to a milling effect at the edge of the friction plate, which increased the fines yield. An approach to reduce this would be to use a spheronizer with a swept up edge on the friction plate (Vervaet et al., 1995).

6.2.2.3 Large Pellet Yield

Analysis of the transformed large pellet yield data showed the appropriate model for the data was a crossed linear by two factor interaction model (Appendix 8). The model terms had a significant effect on the response and the model had an insignificant lack of fit (Table 6.2e). The $R^2$ value for the model was 0.8155, which was acceptable. There was a linear trend between the observed large pellet yields and those predicted by the model, indicating the model was suitable (Appendix 9).
Table 6.2e. ANOVA of a crossed linear by two-factor interaction model fitted to the transformed large pellet yield data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>4.7294</td>
<td>7</td>
<td>0.6756</td>
<td>27.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Linear Mixture</td>
<td>3.4717</td>
<td>2</td>
<td>1.7359</td>
<td>69.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronizer Speed</td>
<td>0.8027</td>
<td>1</td>
<td>0.8027</td>
<td>32.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronization time</td>
<td>0.1201</td>
<td>1</td>
<td>0.1201</td>
<td>4.82</td>
<td>0.0335</td>
</tr>
<tr>
<td>Sucrose x Spheronizer Speed</td>
<td>0.0299</td>
<td>1</td>
<td>0.0299</td>
<td>1.20</td>
<td>0.2792</td>
</tr>
<tr>
<td>Sucrose x Spheronization time</td>
<td>1.133 x 10^-7</td>
<td>1</td>
<td>1.133 x 10^-7</td>
<td>4.5552 x 10^-6</td>
<td>0.9983</td>
</tr>
<tr>
<td>Sucrose x Spheronizer Speed x Spheronization time</td>
<td>0.1190</td>
<td>1</td>
<td>0.1190</td>
<td>4.78</td>
<td>0.0342</td>
</tr>
</tbody>
</table>

Residual Error                         | 1.0702| 43 | 0.0249 |

Lack of Fit                            | 1.0116| 38 | 0.0266 | 2.27   | 0.1825 |

Pure Error                             | 0.0586| 5  | 0.0117 |

Cor Total                              | 5.7996| 50 |

As in the case of fines yield, the formulation components had a significant effect on the large pellet yield, and ethanol and sucrose were involved in significant interactions with the process parameters (Table 6.2e). The ternary phase diagrams show that at all spheronizer speeds and times the effect of changes in the formulation components were the same. However, the magnitude of the changes differed because of the significant interactions already mentioned (Fig. 6.2g). An increase in the proportion of solids in the formulation decreased the large pellet yield. This was because the bind within the extrudate was reduced and therefore less particle agglomeration occurred during spheronization, leading to a lower large pellet yield. Bianchini et al. (1992) and Wan et al. (1993) observed similar effects when the proportion of solids in their formulations changed.
At constant ethanol levels, increases in the proportion of kaolin relative to the proportion of sucrose decreased the large pellet yield. This was because the formulation was drier for reasons discussed in Section 6.2.2.2. The effect of increasing spheronizer speed or time was to decrease the large pellet yield (Fig. 6.2g). As with the fines yield, this was due to an increase in the number of collisions between particles leading to a reduction in particle size.

Figure 6.2g. Ternary phase diagrams showing the predicted contour plots for large pellet yield (expressed as a fraction) at various spheronizer speeds and times: (i) 1000 rpm for 2.5 min (ii) 1000 rpm for 10 min (iii) 1500 rpm for 2.5 min (iv) 1500 rpm for 10 min.
6.2.2.4 Pellet Yield

Analysis of the transformed pellet yield data showed the appropriate model for the data was a crossed linear by two factor interaction model (Appendix 8). The model terms had a significant effect on the response and the model had an insignificant lack of fit (Table 6.2f). The $R^2$ value for the model was 0.708, which was acceptable. There was a linear trend between the observed pellet yields and those predicted by the model, indicating the model was suitable (Appendix 9).

Table 6.2f. ANOVA of a crossed linear by two-factor interaction model fitted to the transformed pellet yield data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>2.2918</td>
<td>6</td>
<td>0.3820</td>
<td>17.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Linear Mixture</td>
<td>1.7220</td>
<td>2</td>
<td>0.8610</td>
<td>40.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronizer Speed</td>
<td>0.1992</td>
<td>1</td>
<td>0.1992</td>
<td>9.27</td>
<td>0.0039</td>
</tr>
<tr>
<td>Ethanol x Spheronization time</td>
<td>0.0105</td>
<td>1</td>
<td>0.0105</td>
<td>0.49</td>
<td>0.4887</td>
</tr>
<tr>
<td>Sucrose x Spheronization time</td>
<td>0.1598</td>
<td>1</td>
<td>0.1598</td>
<td>7.44</td>
<td>0.0091</td>
</tr>
<tr>
<td>Ethanol x Spheronizer Speed x Spheronization time</td>
<td>0.2004</td>
<td>1</td>
<td>0.2004</td>
<td>9.33</td>
<td>0.0038</td>
</tr>
<tr>
<td>Residual Error</td>
<td>0.9454</td>
<td>44</td>
<td>0.0215</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Fit</td>
<td>0.8797</td>
<td>39</td>
<td>0.0226</td>
<td>1.72</td>
<td>0.2869</td>
</tr>
<tr>
<td>Pure Error</td>
<td>0.0657</td>
<td>5</td>
<td>0.0131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>3.2372</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA of the transformed pellet yield data found that the formulation components had a significant effect on the pellet yield. In addition, ethanol and sucrose were involved in significant interactions with the process parameters (Table 6.2f). This was expected, as these effects were also significant for both fines yield and large pellet
yield. From the ternary phase diagrams it can be seen that the pellet yield was higher for those mixtures containing a lower proportion of ethanol at all process parameter settings (Fig. 6.2h). This reflected the fact that the decrease in the large pellet yield was greater than the increase in fines yield at low spheronizer speeds and at high speeds and short spheronization times (Fig. 6.2h (i)/(ii)/(iii)). However, at a spheronizer speed of 1500 rpm and a time of 10 min, the pellet yield increase reflected a decrease in both the large pellet yield and the fines yield (Fig. 6.2h (iv)). The reasons for these changes have already been discussed in Sections 6.2.2.2 and 6.2.2.3. The importance of the proportion of granulating liquid in determining pellet yield has been widely noted (Bianchini et al., 1992; Ku et al., 1993; Newton et al., 1995).

The ternary phase diagrams also show that the effect of changing the sucrose level was dependent upon the spheronization time. When the spheronization time was short there was a greater pellet yield for formulations containing a high level of sucrose at all spheronizer speeds (Fig. 6.2h (i)/(iii)). This was not the case for longer spheronization times, when equivalent pellet yields could be obtained for all mixtures (Fig. 6.2h (ii)/(iv)). This can be explained by the significant interaction between sucrose and spheronization time (Table 6.2f). This interaction caused a greater decrease in pellet yield for high sucrose levels than for low sucrose levels as spheronization time increased, which reduced the difference in pellet yield between mixtures containing high and low sucrose levels. This interaction was related to the insolubility of sucrose in ethanol, which meant that extrudate bind decreased as the sucrose level increased. The decreased bind caused greater particle break up upon spheronization, which was further increased as the spheronization time increased.
Figure 6.2h. Ternary phase diagrams showing the predicted contour plots for pellet yield (expressed as a fraction) at various spheronizer speeds and times: (i) 1000 rpm for 2.5 min (ii) 1000 rpm for 10 min (iii) 1500 rpm for 2.5 min (iv) 1500 rpm for 10 min.

A final point regarding the ternary phase diagrams was that for short spheronization times, higher pellet yields were obtained when the spheronizer speed was increased (Fig. 6.2h (i)/(iii)). This was not the case for long spheronization times, as the yields remained approximately equal despite spheronizer speed increases (Fig. 6.2h (ii)/(iv)). This can be explained by considering the significant interactions between ethanol and spheronizer speed and between ethanol and spheronizer speed and time (Table 6.2f). The first interaction meant the pellet yield increased as spheronizer speed or the
proportion of ethanol in the formulation increased. The second interaction meant pellet yield decreased as the level of any of the interacting factors increased. The effect of this interaction was less important for short spheronization times, meaning the interaction between ethanol and spheronizer speed predominated, leading to an increase in the pellet yield. However, for longer spheronization times the interactions tended to cancel each other out, meaning there was little change in pellet yield when the spheronizer speed was increased. These interactions were again associated with the bind in the formulation. Other researchers have also found spheronizer speed and time have an important role in determining pellet yield (Bianchini et al., 1992; Ku et al., 1993; Newton et al., 1995). Overall, these results demonstrate the importance of choosing the correct formulation and process parameters to maximise pellet yield, which is in agreement with the findings of O'Connor and Schwartz (1989).

6.2.2.5 Pellet Sphericity

While the pellet yield is an important parameter in determining optimum production conditions, it cannot be considered without also considering the pellet sphericity if the pellets do not have a uniform width (Lindner and Kleinebudde, 1994). This is because the pellet shape has an influence on the results of sieve analysis. For example, if pellets are longitudinally elongated, their width rather than their length will be measured by sieve analysis. A situation may exist where a high pellet yield is obtained but because the pellets are not spherical they would not be acceptable. Therefore, in this research pellet sphericity was also determined.

In order to analyse the pellet sphericity data, it was necessary to mathematically transform the data. The appropriate transformation was

\[ y' = \ln \left( \frac{y - \text{lower limit}}{\text{upper limit} - y} \right) \]

**Eqn. 6.2b**

where the upper limit was 1 and the lower limit was 0.

Analysis of the transformed sphericity data showed the appropriate model for the data was a crossed linear by linear model (Appendix 8). The model terms had a significant
effect on the response and the model had an insignificant lack of fit (Table 6.2g). The R² value for the model was 0.7077, which was acceptable. There was a linear trend between the observed sphericity data and those predicted by the model, indicating the model was suitable (Appendix 9).

Table 6.2g. ANOVA of a crossed linear by linear model fitted to the transformed sphericity data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>6.7646</td>
<td>5</td>
<td>1.3529</td>
<td>21.79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Linear Mixture</td>
<td>3.9968</td>
<td>2</td>
<td>1.9984</td>
<td>32.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethanol x Spheronization time</td>
<td>0.6412</td>
<td>1</td>
<td>0.6412</td>
<td>10.33</td>
<td>0.0024</td>
</tr>
<tr>
<td>Sucrose x Spheronizer Speed</td>
<td>1.1040</td>
<td>1</td>
<td>1.1040</td>
<td>17.78</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sucrose x Spheronization time</td>
<td>1.0226</td>
<td>1</td>
<td>1.0226</td>
<td>16.47</td>
<td>0.0002</td>
</tr>
<tr>
<td>Residual Error</td>
<td>2.7935</td>
<td>45</td>
<td>0.0621</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Fit</td>
<td>2.4635</td>
<td>40</td>
<td>0.0616</td>
<td>0.93</td>
<td>0.6095</td>
</tr>
<tr>
<td>Pure Error</td>
<td>0.3300</td>
<td>5</td>
<td>0.0660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>9.5581</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As the model was suitable for predicting Form PE values, which indicate pellet sphericity, the effects of changes in the formulation or process parameters on sphericity could be investigated. The formulation components had a significant effect on the pellet sphericity, while there were also significant interactions between formulation components and process parameters (Table 6.2g). Ternary phase diagrams show there was an increase in pellet sphericity as the proportion of ethanol in the formulation increased (Fig. 6.2i). This was due to increased plasticity in the extrudate, which allowed it to become rounder during spheronization (Lindner and Kleinebudde, 1994). However, this effect was less apparent at shorter spheronization times (Fig. 6.2i (i)/(iii)) due to the significant interaction between ethanol and spheronization time (Table 6.2g).
This interaction meant that the increase in the sphericity of formulations containing higher proportions of ethanol was greater than for those with lower proportions when spheronization time increased. This interaction related to the evaporation of ethanol over the course of spheronization. Formulations containing higher proportions of ethanol took longer to reach the same dryness and hence plasticity as those which contained lower proportions of ethanol. Therefore, as spheronization time lengthened the formulations with a higher proportion of ethanol remained sufficiently plastic to spheronize for longer and thus showed a greater increase in sphericity.

The sphericity of the pellets was also dependent on the relative proportions of kaolin and sucrose in the formulations. As the proportion of sucrose in the formulation increased and the kaolin proportion decreased, there was a decrease in pellet sphericity (Fig. 6.2i). The reason this occurred was that sucrose, unlike kaolin, does not absorb ethanol and thus the bind between the powder components of the extrudate was reduced. The bind is important for adequate spheronization. However, the effect of sucrose level on sphericity was less apparent as either spheronizer speed or spheronization time increased due to significant interactions between these factors (Table 6.2g). These interactions led to a greater increase in sphericity at higher sucrose levels than at lower levels when either spheronizer speed or time increased.

Overall, the effect of increasing the spheronizer speed was to increase the pellet sphericity because at low spheronizer speeds the necessary particle interactions, which cause rounding, happen to a lesser extent than at high speeds (Fig. 6.2i; Newton et al., 1995). The same effect has been widely observed by other researchers (Hileman et al., 1993; Wan et al., 1993; Newton et al., 1995). Similarly, the effect of increasing spheronization time was to increase pellet sphericity. This occurred, as there was an increase in particle interactions when the length of the spheronization process increased. As with spheronizer speed, the effect of spheronization time on pellet sphericity has been widely noted (Bianchini et al., 1992; Hileman et al., 1993; Wan et al., 1993).
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Figure 6.2i. Ternary phase diagrams showing the predicted contour plots for pellet sphericity at various spheronizer speeds and times: (i) 1000 rpm for 2.5 min (ii) 1000 rpm for 10 min (iii) 1500 rpm for 2.5 min (iv) 1500 rpm for 10 min.

6.2.2.6 Optimum Production Parameters

Models describing the fines, large pellet and pellet yield and also the pellet sphericity over a range of spheronizer speeds and times were discussed above. Of these, pellet yield and pellet sphericity were the key results, which could be used to determine if a production process was acceptable. Therefore, their models were used to determine the optimum formulation and process parameters for pellet production at various sucrose...
levels. In addition, they were used to predict the resulting pellet yield and sphericity at these sucrose levels.

A complication with regard to the predictions was that as pellet yield increased, pellet sphericity decreased. This was due to the fact that the maximum pellet yield occurred at lower proportions of ethanol than the maximum sphericity. The reason this occurred was that at lower ethanol contents, the extrudate was more brittle and hence fractured more frequently along its length, meaning a higher yield of pellets was obtained. However, as extrudate brittleness increased the pellet sphericity decreased. To ensure acceptable products were produced, a minimum pellet yield of 60% w/w and Form PE of 0.87 were specified. It was found that formulations could contain up to 35% w/w sucrose and still meet these minimum specifications. Based on this, formulations containing 0, 17.5 and 35% w/w sucrose were selected for investigation. The optimum formulation and process parameters at each of these sucrose levels are given in Table 6.2h. It can be seen that although the spheronization time was 10 min in each case, the spheronizer speed varied.

Table 6.2h. Optimum formulations for the production of kaolin based products.

<table>
<thead>
<tr>
<th>Sucrose (% w/w)</th>
<th>Kaolin (% w/w)</th>
<th>Ethanol (% w/w)</th>
<th>Ethylcellulose 100 cps</th>
<th>Ethylcellulose 1000 cps</th>
<th>Spheronizer speed (rpm)</th>
<th>Spheronization time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>67.36</td>
<td>27.64</td>
<td>5</td>
<td>1000</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>17.5</td>
<td>52.62</td>
<td>24.88</td>
<td>5</td>
<td>1500</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>37.66</td>
<td>22.34</td>
<td>5</td>
<td>1500</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

It has been found that changes in spheronizer speed and time can affect the porosity of pellets made by extrusion-spheronization (Bataille et al., 1993; Juppo et al., 1997). Since the porosity and pore size distribution were important properties under investigation, it was decided that each product should be produced using the same process parameters. Therefore, the spheronizer speed and time for the product containing 0% w/w sucrose were fixed at 1500 rpm and 10 min, respectively. The final formulations used in kaolin pellet production are given in Table 6.2i, while the pellet
yield and Form PE prediction for each formulation are given in Table 6.2j. The confidence intervals for these predictions were wide due to the complexity of the design under investigation and the low number of design points. However, this was acceptable as the principal goal of these experiments was to investigate drug loading and drug release from aluminosilicate pellets, with the investigation of their production being a secondary goal.

Table 6.2i. Final formulations used for the production of kaolin based products.

<table>
<thead>
<tr>
<th>Sucrose (% w/w)</th>
<th>Kaolin (% w/w)</th>
<th>Ethanol (% w/w)</th>
<th>Ethylcellulose 100 cps</th>
<th>Spheronizer speed (rpm)</th>
<th>Spheronization time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>67.58</td>
<td>27.42</td>
<td>5</td>
<td>1500</td>
<td>10</td>
</tr>
<tr>
<td>17.5</td>
<td>52.62</td>
<td>24.88</td>
<td>5</td>
<td>1500</td>
<td>10</td>
</tr>
<tr>
<td>35</td>
<td>37.66</td>
<td>22.34</td>
<td>5</td>
<td>1500</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 6.2j. Prediction of the pellet yield and sphericity for each kaolin based product.

<table>
<thead>
<tr>
<th>Sucrose (% w/w)</th>
<th>Prediction</th>
<th>95% confidence interval</th>
<th>99% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Pellet yield (% w/w)</td>
<td>59.98</td>
<td>47.38 - 71.95</td>
</tr>
<tr>
<td>0</td>
<td>Form PE</td>
<td>0.883</td>
<td>0.865 - 0.899</td>
</tr>
<tr>
<td>17.5</td>
<td>Pellet yield (% w/w)</td>
<td>59.99</td>
<td>51.18 - 68.50</td>
</tr>
<tr>
<td>17.5</td>
<td>Form PE</td>
<td>0.877</td>
<td>0.863 - 0.890</td>
</tr>
<tr>
<td>35</td>
<td>Pellet yield (% w/w)</td>
<td>60.00</td>
<td>50.31 - 69.32</td>
</tr>
<tr>
<td>35</td>
<td>Form PE</td>
<td>0.871</td>
<td>0.848 - 0.891</td>
</tr>
</tbody>
</table>

6.2.3 Production of Final Products

6.2.3.1 Pellet Yield and Sphericity

The final products intended for drug loading and dissolution testing were produced using the optimised formulation and process parameters discussed in the previous
Section. In determining these parameters, kaolin based formulations containing U.C. sucrose were used. However, these parameters were extended to the production of products containing different sucrose size fractions and to products containing a different aluminosilicate, halloysite. In extending the use of these production parameters, it was accepted that they might no longer be optimal for these products. However, by maintaining constant production parameters, comparisons of drug loading and release between products were facilitated, as at each sucrose level only the sucrose particle size or the aluminosilicate used will have changed.

The pellet yield and Form PE for each product are given in Table 6.2k. There were variations between the predicted pellet yield and sphericity and the actual values. However, the products still had acceptable pellet yields and sphericity for the purposes of this research. The highest pellet yields, obtained for the halloysite based products and for K0, were not significantly different (Fig. 6.2k). At over 70% w/w, these were high yields and indicate the suitability of the process for pellet production. The kaolin based products containing 17.5 and 35% w/w sucrose gave significantly lower pellet yields (Fig. 6.2k). These yields were low and the process would require further optimisation if it were to be used on a production scale.

The sphericity of each of the kaolin based products was high ranging from 0.895 for K35a to 0.902 for K17.5c. There was no significant difference between the sphericities of the kaolin based products. However, each of the halloysite based products had a significantly lower sphericity than the kaolin based products (Fig. 6.2l). This could explain the higher pellet yields for the sucrose containing halloysite based products, as in determining the optimum production parameters for kaolin based products, higher pellet yields were obtained when the pellets were less spherical (Section 6.2.2.6). The lower sphericity of the halloysite based products indicated that either the formulation or
process parameters used were not the optimum parameters for the production of halloysite based products. Therefore, it can be concluded that although kaolin and halloysite are both aluminosilicate clay minerals, they do not exhibit the same extrusion-spheronization behaviour. This may be due to the higher surface area of halloysite in comparison to kaolin (Section 6.2.3.6). It has been reported that the number of liquid bridges formed between powder particles is a function of the particle size and therefore the surface area. This means that because of its higher surface area, halloysite containing formulations had an increased granulating solvent requirement (Kristensen and Schaefer, 1987).

<table>
<thead>
<tr>
<th>H17.5</th>
<th>H35</th>
<th>H0</th>
<th>K35a</th>
<th>K17.5a</th>
<th>K35b</th>
<th>K35c</th>
<th>K17.5b</th>
<th>K0</th>
<th>K17.5c</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.845</td>
<td>0.849</td>
<td>0.864</td>
<td>0.895</td>
<td>0.897</td>
<td>0.898</td>
<td>0.899</td>
<td>0.899</td>
<td>0.900</td>
<td>0.902</td>
</tr>
</tbody>
</table>

**Figure 6.21.** Comparison of the Form PE for each product (There is no statistically significant difference between products joined by a black line).
Table 6.2k. Pellet yield and sphericity of final aluminosilicate based products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Aluminosilicate</th>
<th>Sucrose level (% w/w)</th>
<th>Sucrose size distribution</th>
<th>Pellet yield Average (% w/w)</th>
<th>S.D.</th>
<th>Form PE Average</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>K0</td>
<td>Kaolin</td>
<td>0</td>
<td>N/A</td>
<td>75.67</td>
<td>0.67</td>
<td>0.900</td>
<td>0.021</td>
</tr>
<tr>
<td>K17.5a</td>
<td>Kaolin</td>
<td>17.5</td>
<td>U.C.</td>
<td>56.70</td>
<td>6.81</td>
<td>0.897</td>
<td>0.022</td>
</tr>
<tr>
<td>K17.5b</td>
<td>Kaolin</td>
<td>17.5</td>
<td>90-125 μm</td>
<td>54.66</td>
<td>7.13</td>
<td>0.899</td>
<td>0.021</td>
</tr>
<tr>
<td>K17.5c</td>
<td>Kaolin</td>
<td>17.5</td>
<td>180-250 μm</td>
<td>51.37</td>
<td>8.46</td>
<td>0.902</td>
<td>0.023</td>
</tr>
<tr>
<td>K35a</td>
<td>Kaolin</td>
<td>35</td>
<td>U.C.</td>
<td>59.38</td>
<td>5.76</td>
<td>0.895</td>
<td>0.023</td>
</tr>
<tr>
<td>K35b</td>
<td>Kaolin</td>
<td>35</td>
<td>90-125 μm</td>
<td>53.07</td>
<td>2.66</td>
<td>0.898</td>
<td>0.022</td>
</tr>
<tr>
<td>K35c</td>
<td>Kaolin</td>
<td>35</td>
<td>180-250 μm</td>
<td>52.94</td>
<td>4.47</td>
<td>0.899</td>
<td>0.022</td>
</tr>
<tr>
<td>H0</td>
<td>Halloysite</td>
<td>0</td>
<td>N/A</td>
<td>79.44</td>
<td>2.55</td>
<td>0.864</td>
<td>0.034</td>
</tr>
<tr>
<td>H17.5</td>
<td>Halloysite</td>
<td>17.5</td>
<td>U.C.</td>
<td>80.54</td>
<td>3.45</td>
<td>0.845</td>
<td>0.040</td>
</tr>
<tr>
<td>H35</td>
<td>Halloysite</td>
<td>35</td>
<td>U.C.</td>
<td>73.03</td>
<td>3.64</td>
<td>0.849</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Note: References to K17.5 and K35 in the text indicate the average result from the grades a, b and c has been used.
6.2.3.2 SEM Prior to PFA Removal

The surface and internal structure of each product was examined using SEM. Surface pores, created by the evaporation of ethanol from the pellets, were evident in each product. Examples of such pores are seen at points A and B in Fig. 6.2m and 6.2n. These pores were relatively small, with those at points A and B having diameters of 0.16 and 0.83 μm, respectively. The surface porous structure was repeated in the interior of the pellets. Examples of interior pores are seen at points D and E in Fig. 6.2o and 6.2p. These pores have diameters of 0.85 and 1.51 μm, respectively. The plate-like structure of kaolin and the microtubular structure of halloysite were also evident in the SEM's.

Figure 6.2m. SEM showing the surface of K0 (magnification x 20000).

Figure 6.2n. SEM showing the surface of H17.5 (magnification x 20000).

Figure 6.2o. SEM of a cross-section of K0 (magnification x 25000).

Figure 6.2p. SEM of a cross-section of H17.5 (magnification x 20000).
SEM’s of products, which contained sucrose in their formulation, showed they contained some large surface defects (Point F in Fig. 6.2q). This was in contrast to products containing no sucrose, which had smooth surfaces free from large defects. The surface defects were found to occur at points where large areas of the sucrose particles were exposed. These defects were present because sucrose absorbed low amounts of the granulating solvent, ethanol, and hence there was less bind at these regions. The number of defects per pellet was low in comparison to the number of sucrose particles in the pellet, which indicated that the majority of particles had only a small part of their surface exposed on the pellet surface. In the pellet interior, numerous sucrose particles were evident and the particle size range used in the formulation could easily be determined. For example, in comparing the sucrose particles at point C in Fig. 6.2n and at point G in Fig. 6.2r, the difference in particle size is clear. The pellet shown in Fig. 6.2n was formulated using U.C. sucrose while the pellet shown in Fig. 6.2r was formulated using sucrose in the size range 180-250 μm.

![Figure 6.2q. SEM showing the surface of K35c (magnification x 50).](image1)

![Figure 6.2r. SEM of a cross-section of K35c (magnification x 50).](image2)

6.2.3.3 Removal of PFA

Prior to drug loading and dissolution testing, sucrose had to be removed from the products in order to maximise their porosity. It was envisaged that because sucrose is very soluble in water, it would be possible to remove it from the pellets by placing them in water. This could be confirmed using skeletal density measurements as sucrose had a lower skeletal density than the other principal product constituent, the aluminosilicate.
Consequently, sucrose removal would lead to an increase in the skeletal density of the product.

The skeletal density of the kaolin based products after 0, 12 and 24 h in water are shown in Fig. 6.2s. Using ANOVA, it was found that there were no statistically significant differences between the skeletal density of K0 at each time point. This was expected, as K0 did not contain sucrose. For the other products, sucrose dissolution was confirmed by a significant difference between their skeletal densities at 0 h and 12 h. With the exception of K35a, complete sucrose dissolution had occurred at 12 h, as there was no significant increase in their skeletal densities after 24 h in water. In the case of K35a, the 95% confidence interval for the increase from 12 to 24 h was between 0.05 and 2% of its skeletal density. As this increase was deemed too small to be of experimental significance, it was concluded that 12 h was sufficient to give maximal dissolution of sucrose.

To further confirm that sucrose removal was complete, the skeletal density of each product prior to and following sucrose removal was calculated from the skeletal densities of their solid constituents (Fig. 6.2s). The calculated skeletal densities were in close agreement with the observed skeletal densities, which provided further evidence that sucrose removal was complete after 12 h in water. The small differences which did exist between the actual and predicted values may have been due to changes in the skeletal densities of the powders caused by the extrusion-spheronization process. Based on these results, all products were placed in water for 12 h prior to drug loading.
6.2.3.4 SEM Following PFA Removal

The dried products were examined after sucrose dissolution using SEM. There was no change in the appearance of products, which had not contained sucrose. In contrast, products formulated with sucrose showed an increase in their surface porosity, demonstrating that sucrose had acted as a PFA. The increase in porosity was related to the quantity of sucrose in the formulation (Fig. 6.2t/v). Ishizaki et al. (1998a) have noted the same relationship between solid PFA quantity and the resultant product porosity.

Interestingly, many surface pores in each product were of a similar size. For example, in Fig. 6.2u and w, the pores at points H and J have diameters of 11.7 and 12.2 μm, respectively. This was despite the fact that the former product had contained U.C. sucrose while the latter had contained sucrose in the size range 180-250 μm. This result can be explained by considering that the many sucrose particles will only have a small contact area with the spherical pellet surface. Therefore, despite the products having contained sucrose with different particle sizes, surface pores of a similar size will be
observed. However, in some cases, relatively large surface pores were formed when a large area of a sucrose particle was exposed at the surface (Point I in Fig. 6.2v).

Overall, the pores created by sucrose dissolution were larger than those created by ethanol evaporation (Fig. 6.2 m/n/u/w). This was expected as solid PFA’s typically create larger pores than liquid PFA’s (Ishizaki et al., 1998a). As a result, products that had contained sucrose had a larger average pore size and a bimodal pore size distribution. Krajewski et al. (2000) observed similar effects upon inclusion of solid PFA’s in alumina and hydroxyapatite porous ceramics.

**Figure 6.2t.** SEM showing the surface of K35a after sucrose dissolution (magnification x 60).

**Figure 6.2u.** SEM showing the surface of K35a after sucrose dissolution (magnification x 1000).

**Figure 6.2v.** SEM showing the surface of K35c after sucrose dissolution (magnification x 60).

**Figure 6.2w.** SEM showing the surface of K35c after sucrose dissolution (magnification x 500).
Cross-sections of the products after sucrose dissolution were also examined using SEM. There was no change in products that had not contained sucrose. Those products, which had contained sucrose showed an increase in their internal porosity (Fig. 6.2 x/y). The increase in porosity was greatest for those products containing 35% w/w sucrose. Unlike the surface porosity, there was a clear relationship between the interior pore size and the sucrose particle size used in the product formulation. Examples of this can be seen in Fig. 6.2x and 6.2y at points K and L, which have diameters of 57 and 198 \( \mu \text{m} \), respectively. These diameters are contained within the sucrose particle size range used in the product formulation (Fig. 6.2c). Overall, the interior pore sizes were markedly higher than the surface pores sizes. This is in agreement with the findings of Fabbri et al. (1994) and Liu (1996), who observed that the average surface pore size of porous ceramics created using PFA’s was less than their average interior pore size.

A final point regarded the SEM’s is that some pores larger than the sucrose particle size used were seen. This occurred when two sucrose particles were in contact with each other within the pellet. Therefore, when removed they left a relatively large pore. In some cases, the observation of larger pores may have been an artefact of sectioning. This would have occurred when a pore was sectioned through an oblique plane resulting in its diameter appearing larger in SEM’s than it actually was.

**Figure 6.2x.** SEM of a cross-section of K35a (magnification x 50).

**Figure 6.2y.** SEM of a cross-section of K35c (magnification x 50).

In summary, SEM’s have shown that each product contained both surface and internal pores due to the evaporation of ethanol. Those products, which had contained sucrose showed an increase in their porosity after removal of the sucrose. The pores created
were relatively large compared with the pores created by ethanol evaporation. Changing the particle size of the sucrose did change the surface pore size distribution of the products, although many surface pores of similar sizes were still observed. However, with regard to the internal pore size distribution, pores of similar sizes were not observed. In comparing the kaolin and halloysite based pellets, the only difference was in the aluminosilicate structure. Kaolin had a plate like structure while halloysite had a microtubular structure.

6.2.3.5 Mercury Porosimetry and Helium Pycnometry Studies Following PFA Removal

Mercury porosimetry and helium pycnometry studies were used to quantitatively assess the differences in porosity and pore size distribution of the extrusion-spheronization products. The bulk density and pore size distribution for each product was obtained using mercury porosimetry, while the skeletal density was obtained using helium pycnometry (Table 6.21). However, bulk density values for the products K17.5b, K17.5c and K35b were unavailable, as they had not been analysed by mercury porosimetry. Therefore, two alternative methods for bulk density determination were investigated. In the first method, the bulk density was calculated from the volume occupied by a known mass of pellets in a measuring cylinder. This gave bulk densities that were higher than those measured by mercury porosimetry, as the measured volume included the volume occupied by interparticulate pores. The second method determined the volume of a known mass of pellets from the volume of water they displaced. This method gave bulk densities, which were lower than those obtained using mercury porosimetry. This was due to filling of some pellet pores with water as evidenced by the liberation of gas bubbles from the pellets. Therefore, it was decided for the products K17.5b and K17.5c that the bulk density of K17.5a obtained using mercury porosimetry would be used as an estimate. This estimate should be valid, as the products had the same formulation and although the size distribution of the sucrose differed, the volume of sucrose in each product was the same. This meant that the bulk density of the products would be the same both prior to and following sucrose removal. Similarly for K35b, the average bulk density of K35a and K35c was used to estimate its bulk density.
The bulk density of each product was less than 1.5 g/ml and was dependent on the proportion of sucrose included in the initial formulation (Table 6.21). Products, which had contained 35% w/w sucrose had bulk densities less than 1 g/ml and thus would act as floating drug delivery systems. The relatively low bulk densities of the products reflected their open porosities. The open porosity was lowest in the case of products formulated without sucrose. By incorporating sucrose in the formulation, the open porosity of the products was increased as the sucrose acted as a PFA, which was removed by dissolution in water. As expected, the porosity increase was dependent on the level of sucrose included in the initial formulation. These results are in agreement with the qualitative SEM observations, discussed in Section 6.2.3.4.

The open porosities of the halloysite and kaolin based products were similar despite the fact that the microtubular structure of halloysite created additional porosity in the products (Table 6.21). This indicates that the volume of these pores was relatively low in comparison to the volume of pores created by the PFA’s. As a result, the effect of the microtubular structure of halloysite on the total open porosity of the pellets was relatively small.

To determine if closed pores were present in the products, the skeletal densities of uncrushed samples of each product were compared with those of crushed samples. There was no significant difference between these values, which indicated there was no closed porosity in the products. This was expected as the pores in each product were created by evaporation of ethanol and dissolution of sucrose. These processes could not occur if a connection did not exist with the surface of the pellets either directly or through other pores. Therefore, the pores created must have been open pores.
Chapter 6. Production of Porous Aluminosilicate Pellets by Extrusion-Spheronization

Table 6.21. Bulk density, skeletal density and open porosity of each extrusion-spheronization product.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Bulk density</th>
<th>Skeletal density</th>
<th>Open porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (g/ml)</td>
<td>S.D.</td>
<td>Average (g/ml)</td>
</tr>
<tr>
<td>K0</td>
<td>1.4269</td>
<td>-</td>
<td>2.3519</td>
</tr>
<tr>
<td>K17.5a</td>
<td>1.0877</td>
<td>-</td>
<td>2.2931</td>
</tr>
<tr>
<td>K17.5b</td>
<td>1.0877^e</td>
<td>-</td>
<td>2.2977</td>
</tr>
<tr>
<td>K17.5c</td>
<td>1.0877^e</td>
<td>-</td>
<td>2.2948</td>
</tr>
<tr>
<td>K35a</td>
<td>0.8735</td>
<td>-</td>
<td>2.1662</td>
</tr>
<tr>
<td>K35b</td>
<td>0.8369^e</td>
<td>-</td>
<td>2.1575</td>
</tr>
<tr>
<td>K35c</td>
<td>0.8003</td>
<td>-</td>
<td>2.1514</td>
</tr>
<tr>
<td>H0</td>
<td>1.3461</td>
<td>-</td>
<td>2.2898</td>
</tr>
<tr>
<td>H17.5</td>
<td>1.0482</td>
<td>-</td>
<td>2.2316</td>
</tr>
<tr>
<td>H35</td>
<td>0.7963</td>
<td>-</td>
<td>2.1379</td>
</tr>
</tbody>
</table>

^e indicates estimated result

The cumulative mercury intrusion curve for K0 shows that it contained relatively small pores, which were created by the evaporation of ethanol from the pellets (Fig. 6.2z). The majority of these pores had diameters in the size range 0.02 to 0.17 μm, although larger pores were also present. This is in agreement with qualitative SEM observations of the K0 pellets (Fig. 6.2m/o). Pores in these size ranges were also present in K17.5a and K35a (Fig. 6.2z). However, the pore size distributions of these products were markedly different in comparison to each other and to K0. There was an increase in the proportion of relatively large pores in the pellets as the proportion of sucrose in the initial formulation increased. This was reflected in the D50 values for each product, which were 0.0852, 0.1447 and 0.6538 μm for K0, K17.5a and K35a, respectively. The increase was due to the creation of larger pores in the pellets by the dissolution of sucrose. Such pores were evident in SEM micrographs (Fig. 6.2t/u/x). The cumulative mercury intrusion curves confirm that K17.5a and K35a contained two types of pore, relatively small pores created by ethanol evaporation and larger pores created by sucrose dissolution.
Chapter 6. Production of Porous Aluminosilicate Pellets by Extrusion-Spheronization

Figure 6.2z. Cumulative mercury intrusion versus pore diameter for selected kaolin based products.

The particle size of the sucrose incorporated in the formulation also influenced the pore size distribution of the product. This is seen in comparing the cumulative pore size distributions of K35a and K35c (Fig. 6.2z). The actual change in the pore sizes present in the pellets can be more easily seen in comparing the incremental mercury intrusion curves for these products (Fig. 6.2aa). For K35c, there was an increase in the proportion of pores with diameters in the range 10 to 100 μm, while there was a decrease in the proportion less than 1.5 μm. The presence of a greater number of relatively large pores in K35c in comparison to K35a was evident in SEM micrographs (Fig. 6.2t/v/x/y). These pores were primarily found in the pellet interior rather than on the pellet surface and therefore their increased diameter should not have greatly influenced the porosimetry results. However, because there were some relatively large pores on the surface of K35c, its interior pores were intruded with mercury at lower pressures than those of K35a. This caused a large increase in the average pore size of K35c compared with K35a, which was not reflective of the small change in the average surface pore size.
The cumulative mercury intrusion curves for the halloysite based products show that the inclusion of sucrose in the initial formulation had the same effect on their pore size distribution as for the kaolin based products (Fig. 6.2ab). This was reflected in the $D_{50}$ values of 0.0252, 0.5115 and 1.5773 μm for H0, H17.5 and H35, respectively. However, differences existed in the cumulative mercury intrusion curves for the kaolin and halloysite based products (Fig. 6.2z/ab). For the kaolin based products the curve plateaus at approximately 0.05 μm. No such plateau was observed for the halloysite based products as the mercury was filling the microtubules of halloysite. Therefore, in addition to the porosity created by sucrose dissolution and/or ethanol evaporation, the microtubular structure of halloysite influenced the pellet pore size distribution.
Chapter 6. Production of Porous Aluminosilicate Pellets by Extrusion-Spheronization

Figure 6.2ab. Cumulative mercury intrusion versus pore diameter for halloysite based products.

6.2.3.6 Surface Area Analysis Following PFA Removal

Surface area analysis of the extrusion-spheronization products was carried out following removal of sucrose. Each product had a relatively high surface area in comparison its non-porous equivalent (Table 6.2m). This has also been found for the commercial porous ceramics already examined (Section 4.7) and as with the porous ceramics, this reflected the high open porosity of the extrusion-spheronization products (Table 6.2l). However, despite in some cases having similar open porosities, the extrusion-spheronization products had significantly higher surface areas than the porous ceramics. This was because the porous ceramics were sintered during production. When clay minerals are sintered, the driving force for sintering is a reduction in the surface area associated with pores in the material. Therefore, a marked reduction in surface area occurs (Ishizaki et al., 1998c). The greater surface area of the extrusion-spheronization products meant they had a greater cation exchange capacity and hence a greater ability to adsorb cationic drugs. This has been shown to be beneficial in providing extended cationic drug delivery (Section 5.3).
In comparing the kaolin and halloysite based products, it was found that the latter had a significantly higher surface area (Table 6.2m). This was because the microtubular structure of halloysite gave these products a high surface area relative to the kaolin based products (Harvey, 1996). Surface area analysis of the raw powders confirmed this. Kaolin had a surface area of 16.06 +/- 0.07 m^2/g in comparison to a surface area of 57.28 m^2/g for halloysite, as reported by Levis (2000).

In the halloysite based products, an increase in the proportion of sucrose in the initial formulation led to a significant decrease in the specific surface area of the pellets following sucrose removal (Table 6.2m). Principally this was due to the increase in the average pore size of the pellets, which accompanied increases in the proportion of sucrose in the initial formulation (Fig. 6.2ab). These larger pores had a reduced surface area in comparison to the smaller pores. A second factor was that as the proportion of sucrose in the formulation increased, the ratio of ethylcellulose 100 cps to halloysite increased. Ethylcellulose 100 cps had a surface area of 0.8062 +/- 0.0001 m^2/g. This was markedly lower than that of halloysite and would have also contributed to a reduction in the specific surface area of the products.

For the kaolin based products, the same trend in surface area was apparent, although the differences were not significant (Table 6.2m). Additionally, there was no significant difference between the surface areas of kaolin based products, which had contained sucrose with different size distributions. This was not expected as SEM showed that larger sucrose particles created larger pores within the pellets. Therefore, these pellets should have a lower surface area. However, the magnitude of this change would be relatively small in comparison to the experimental error and hence was not detected.
Table 6.2m. Surface area of each extrusion-spheronization product and the calculated surface area of its non-porous equivalent.

<table>
<thead>
<tr>
<th>Extrusion-spheronization product</th>
<th>BET multipoint surface area</th>
<th>Surface area of a non-porous equivalent (m²/g)</th>
<th>Ratio of surface areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K0</td>
<td>11.3034 0.1489</td>
<td>0.002582</td>
<td>4378.49</td>
</tr>
<tr>
<td>K17.5a</td>
<td>10.5763 1.8073</td>
<td>0.003264</td>
<td>3240.27</td>
</tr>
<tr>
<td>K17.5b</td>
<td>9.9605 0.9010</td>
<td>0.002896</td>
<td>3439.09</td>
</tr>
<tr>
<td>K17.5c</td>
<td>9.3903 0.8317</td>
<td>0.003430</td>
<td>2737.59</td>
</tr>
<tr>
<td>K35a</td>
<td>6.6908 2.3009</td>
<td>0.003970</td>
<td>1685.28</td>
</tr>
<tr>
<td>K35b</td>
<td>6.7755 0.2968</td>
<td>0.004291</td>
<td>1579.08</td>
</tr>
<tr>
<td>K35c</td>
<td>7.2448 1.4497</td>
<td>0.004361</td>
<td>1661.39</td>
</tr>
<tr>
<td>H0</td>
<td>54.9007 0.6650</td>
<td>0.002235</td>
<td>24567.84</td>
</tr>
<tr>
<td>H17.5</td>
<td>48.5091 2.2020</td>
<td>0.002708</td>
<td>17910.36</td>
</tr>
<tr>
<td>H35</td>
<td>37.1539 3.5100</td>
<td>0.003881</td>
<td>9572.74</td>
</tr>
</tbody>
</table>

6.3 DRUG LOADING AND DISSOLUTION TESTING OF POROUS ALUMINOSILICATE PELLETS

6.3.1 Loading Studies

Each extrusion-spheronization product was drug loaded in triplicate using loading technique (iii) (Section 3.3.2). As discussed in Section 5.2.1, this was found to be the optimum loading technique of the three procedures examined. It was possible to load each product with a high level of diltiazem HCl, with the highest loading obtained being 37.5 +/- 2.4% w/v for K35a (Table 6.3a).

It was found that the drug loading of the extrusion-spheronization products was dependent on a number of factors. Firstly, there were significant increases in the drug
loading of both the kaolin and halloysite based products as the initial proportion of sucrose in their formulations was increased (Table 6.3a). These increases were due to an increase in their open porosity as has been observed for commercial porous ceramics (Table 6.21; Section 5.2.2). Secondly, the halloysite based products had a significantly reduced drug loading in comparison to the corresponding kaolin based products. It may have been that the narrow halloysite microtubules reduced penetration of the loading solution into the pellets.

Additionally, the particle size distribution of the sucrose used in the formulation significantly affected the drug loading obtained in comparing K35a and K35c. This difference in loading was unexpected, as the pore volume of the pellets should primarily influence drug loading where the pores are relatively large. For all other products in which the particle size distribution of the sucrose differed, the pore volume of the pellets was the primary determinant of drug loading.

Finally, the actual drug loadings were higher than the theoretical maximum drug loadings indicating that in addition to drug deposition within the pellet pores, there was also drug deposited on the external pellet surfaces (Section 5.2.2). Evidence for the localisation of drug on the external surfaces of commercial porous ceramics was presented in Section 5.3.2.
Table 6.3a. Actual and theoretical diltiazem HCl loading of each extrusion-spheronization product.

<table>
<thead>
<tr>
<th>Extrusion-spheronization product</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (% w/v)</td>
<td>S.D.</td>
</tr>
<tr>
<td>K0</td>
<td>21.8 1.1</td>
<td>15.7 &lt;0.1</td>
</tr>
<tr>
<td>K17.5a</td>
<td>29.0 2.8</td>
<td>21.0 0.1</td>
</tr>
<tr>
<td>K17.5b</td>
<td>27.4 0.9</td>
<td>21.1 &lt;0.1</td>
</tr>
<tr>
<td>K17.5c</td>
<td>28.2 1.1</td>
<td>21.0 0.1</td>
</tr>
<tr>
<td>K35a</td>
<td>37.5 2.4</td>
<td>23.9 0.1</td>
</tr>
<tr>
<td>K35b</td>
<td>33.3 2.3</td>
<td>24.5 0.1</td>
</tr>
<tr>
<td>K35c</td>
<td>30.7 1.7</td>
<td>25.1 0.1</td>
</tr>
<tr>
<td>H0</td>
<td>17.8 1.5</td>
<td>16.5 &lt;0.1</td>
</tr>
<tr>
<td>H17.5</td>
<td>24.3 1.3</td>
<td>21.2 0.1</td>
</tr>
<tr>
<td>H35</td>
<td>29.4 2.8</td>
<td>25.1 0.2</td>
</tr>
</tbody>
</table>

In addition to loading the extrusion-spheronization products with diltiazem HCl, selected products were loaded with propranolol HCl. The loadings obtained were significantly less than the corresponding diltiazem HCl loadings due to the lower concentration of the propranolol HCl loading solution (Table 6.3b; Section 5.2.2). In comparing the actual propranolol HCl loadings, that of H0 was higher although the difference was only weakly significant (p= 0.066). This was in contrast to the diltiazem HCl loadings and the difference was due to the reduced viscosity of the propranolol HCl loading solution. The change in viscosity meant that penetration of the loading solution into the halloysite microtubules was no longer restricted, as was the case with the diltiazem HCl solution. The actual propranolol HCl loadings were higher than the theoretical maximum loadings due to drug deposition on the external pellet surfaces.
Table 6.3b. Actual and theoretical propranolol HCl loading of selected extrusion-spheronization products.

<table>
<thead>
<tr>
<th>Extrusion-spheronization product</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (w/v) S.D.</td>
<td>Average (w/v) S.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K0</td>
<td>7.4 0.2</td>
<td>4.7 &lt;0.1</td>
</tr>
<tr>
<td>H0</td>
<td>9.2 0.8</td>
<td>5.0 &lt;0.1</td>
</tr>
</tbody>
</table>

6.3.2 Dissolution Testing

The release of diltiazem HCl from each of the kaolin based extrusion-spheronization products was assessed using dissolution testing (Fig. 6.3a). In order to quantitatively assess the rate of diltiazem HCl release from each product, the models, discussed in Section 5.3, were fitted to the release data. It was found that Eqn. 5.3d best fitted the release data with the MSC being greater than 4 and the CD greater than 0.98 in all cases (Table 6.3c).

Figure 6.3a. Dissolution profiles of diltiazem HCl when loaded into kaolin based pellets in phosphate buffer pH 6.8 at 37 °C.
Table 6.3c. Best fit parameters, when Eqn. 5.3d is fitted to the diltiazem HCl release data for kaolin based extrusion-spheronization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>( F_B )(^{% , \text{w/w}} )</th>
<th>( k_1 )( (h^{-1}) )</th>
<th>( k_H )( (% , h^{-0.432}) )</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
</tr>
<tr>
<td>K0</td>
<td>35.54</td>
<td>2.87</td>
<td>23.37</td>
<td>4.24</td>
<td>34.18</td>
</tr>
<tr>
<td>K17.5a</td>
<td>40.99</td>
<td>7.04</td>
<td>31.72</td>
<td>8.13</td>
<td>52.73</td>
</tr>
<tr>
<td>K17.5b</td>
<td>40.24</td>
<td>1.87</td>
<td>35.57</td>
<td>2.81</td>
<td>53.78</td>
</tr>
<tr>
<td>K17.5c</td>
<td>48.32</td>
<td>4.96</td>
<td>42.78</td>
<td>9.22</td>
<td>47.07</td>
</tr>
<tr>
<td>K17.5</td>
<td>42.52</td>
<td>3.48</td>
<td>35.76</td>
<td>4.92</td>
<td>51.74</td>
</tr>
<tr>
<td>K35a</td>
<td>34.88</td>
<td>12.68</td>
<td>47.51</td>
<td>28.25</td>
<td>81.38</td>
</tr>
<tr>
<td>K35b</td>
<td>40.07</td>
<td>2.41</td>
<td>38.17</td>
<td>2.79</td>
<td>75.76</td>
</tr>
<tr>
<td>K35c</td>
<td>47.33</td>
<td>7.68</td>
<td>35.32</td>
<td>6.30</td>
<td>64.23</td>
</tr>
<tr>
<td>K35</td>
<td>40.56</td>
<td>5.61</td>
<td>39.41</td>
<td>7.02</td>
<td>74.17</td>
</tr>
</tbody>
</table>

An example of the release predicted by Eqn. 5.3d using the best fit parameters for K0 (Table 6.3c) is shown in Fig. 6.3b. The predicted release is in close agreement with the actual experimental data points. Fig. 6.3b also shows the contribution of the first order component and the diffusional component of Eqn. 5.3d to the overall predicted release. It can be seen that the early release was accounted for by a combination of both components. However, the later release was accounted for solely by the diffusional component, as the first order release was complete.
The release profiles for diltiazem HCl from the kaolin based products were similar to those of the commercial porous ceramics previously examined (Section 5.3). There was a rapid initial burst release of diltiazem HCl followed by extended drug release. This was expected as SEM’s and mercury porosimetry had shown that the kaolin based pellets had a similar structure to the porous ceramics.

The initial burst release was, as with the porous ceramics, attributed to the release of poorly associated drug from the pellets. This drug would be found, in particular, on the external pellet surfaces. Binding of diltiazem HCl to these surfaces was probable as kaolin has a polyanionic surface at pH 6.8 (van Olphen, 1963c). This is supported by literature reports that alkaloids such as atropine, oral hypoglycaemics such as tolbutamide and antibiotics such as ampicillin can bind to kaolin (Evcim and Barr, 1955; Barr and Arnista, 1957; Said and Al-Shora, 1980; Khalil et al., 1984). Therefore, it can be concluded that, as with the porous ceramics, binding of diltiazem HCl to the external pellet surfaces contributed to a reduction in the burst release of drug from the kaolin based products (Section 5.3). However, in contrast to the porous ceramics, the burst release of diltiazem HCl from the kaolin based products was relatively slow.
(Table 6.3c). This may have been due to the higher external pellet surface area of the kaolin based pellets (Table 4.6b/6.2m). This would have allowed for greater binding of diltiazem HCl causing a decrease in the first order release rate constant.

The creation of pores in the pellets using sucrose as a PFA had no significant effect on the fraction of diltiazem HCl released during the initial burst phase (Table 6.3c). However, if the different loadings of the kaolin based pellets are accounted for, the actual mass of drug released per unit volume of pellets increased with increasing proportions of PFA. This indicates there was an increase in the mass of poorly entrapped drug in the products, as the external surface area of the products was constant. The poorly entrapped drug was located in relatively large pores, close to the pellet surface, which were created by sucrose dissolution. This drug was then released by a first order mechanism rather than a diffusion based mechanism. In addition to changes in the burst release, there were also significant differences in the rate at which the burst release occurred, with the rate being significantly slower for K0 than for K17.5 and K35. However, these differing rates had a limited effect on the overall release profile. For example, for K0, it took approximately 7.5 min to release 95% of the burst component of diltiazem HCl, while this took 5 min for K17.5 and 4.5 min for K35.

The extended release of diltiazem HCl from the kaolin based products was, as with the porous ceramics, attributed to entrapment of diltiazem HCl within the pellet pores (Section 5.3). The rate of extended diltiazem HCl release from the kaolin based pellets was dependent on the quantity of sucrose included in the initial formulation, with the rate being significantly higher for products formulated with sucrose (Table 6.3c). In addition, when the sucrose level was increased from 17.5 to 35% w/w there was a weakly significant increase in the rate of extended release (p= 0.06). These increases in $k_{H}$ were due to increases in the porosity and average pore size of the products (Sections 6.2.3.4/6.2.3.5). Firstly, the increasing porosity led to greater pore interconnectivity with other pores and with the pellet surface. This shortened the diffusional path length of the drug thereby increasing $k_{H}$. Secondly, larger pores were present within the pellets and at the pellet surface. Since the drug diffused at a faster rate through these pores in comparison to the smaller pores created by the evaporation of ethanol, this also increased $k_{H}$. These findings are in agreement with the results of Section 5.3, where the
importance of porosity and pore size distribution in providing extended release of drugs from porous ceramics was demonstrated.

The effect of the particle size distribution of the sucrose used in the kaolin based formulations was also investigated. It was found that the rate of drug release was not dependent on the particle size distribution of the sucrose used in their formulation (Fig. 6.3c/d; Table 6.3c). This was because despite large differences in the internal pore size distribution of the products, there were only small differences in their surface pore size distributions. This indicates that the surface pore size distribution was of greater importance in determining drug release from these products. This was also observed for drug release from the porous ceramics already examined (Section 5.3). In addition, Krajewski et al. (2000) observed a similar phenomenon, stating that the larger internal pores can be thought as an internal reservoir that can only be accessed through surface pores.

![Dissolution profiles of diltiazem HCl loaded into kaolin based pellets formulated with 17.5% w/w sucrose in phosphate buffer pH 6.8 at 37 °C.](image)

**Figure 6.3c.** Dissolution profiles of diltiazem HCl loaded into kaolin based pellets formulated with 17.5% w/w sucrose in phosphate buffer pH 6.8 at 37 °C.
Figure 6.3d. Dissolution profiles of diltiazem HCl loaded into kaolin based pellets formulated with 35% w/w sucrose in phosphate buffer pH 6.8 at 37 °C.

Halloysite based products were produced according to the same formulation and process parameters as the kaolin based products. As with the kaolin based products, these products gave extended release of diltiazem HCl, with the release profiles being characterised by an initial burst release of diltiazem HCl followed by extended drug release (Fig. 6.3e). Eqn. 5.3d was found to best fit the release data for each product (Table 6.3d). Such similarities were expected as SEM’s showed that the halloysite based products had a similar structure to the kaolin based products. As well as this, halloysite, like kaolin, has a polyanionic surface at pH 6.8 and can therefore bind certain drugs (Levis and Deasy, 2003). For example, Evcim and Barr (1955) and Barr and Arnista (1957) found that halloysite could bind the alkaloids strychnine, atropine and quinine, while Levis and Deasy (2003) found that halloysite could bind diltiazem HCl. However, Evcim and Barr (1955) and Barr and Arnista (1957) did find that halloysite had superior binding properties to kaolin, which may contribute to differences in drug release between the kaolin and halloysite based products.
Figure 6.3e. Dissolution profiles of diltiazem HCl when loaded into halloysite based pellets in phosphate buffer pH 6.8 at 37 °C.

Table 6.3d. Best fit parameters, when Eqn. 5.3d is fitted to the diltiazem HCl release data for halloysite based extrusion-spheronization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$F_B$ (%) w/w</th>
<th>$k_I$ (h$^{-1}$)</th>
<th>$k_H$ (% h$^{-0.432}$)</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
<td>S.D.</td>
</tr>
<tr>
<td>H0</td>
<td>24.99</td>
<td>1.60</td>
<td>2.28</td>
<td>0.19</td>
<td>19.16</td>
</tr>
<tr>
<td>H17.5</td>
<td>39.67</td>
<td>2.02</td>
<td>10.54</td>
<td>1.02</td>
<td>21.31</td>
</tr>
<tr>
<td>H35</td>
<td>52.09</td>
<td>2.64</td>
<td>21.59</td>
<td>1.75</td>
<td>29.42</td>
</tr>
</tbody>
</table>

For the halloysite based products, there were significant increases in $F_B$ as the proportion of PFA in the formulation increased (Table 6.3d). These differences remained when the initial drug loading of each product was accounted for. As with the kaolin based products, they were due to increases in the proportion of poorly entrapped drug in the pellets. However, in contrast to the kaolin based products, there were relatively large differences in the rates at which this fraction of drug was released from the halloysite based products. This was because halloysite has a markedly higher
surface area than kaolin (Section 6.2.3.6). Therefore, in the halloysite based products, when the level of sucrose in the formulation increased, there was a greater reduction in the external surface area available for drug binding. This led to larger changes in $k_1$ in comparison to the kaolin based products. For example, for H0, it took 79 min for 95% of the burst component of diltiazem HCl to be released, while this took 17 min for H17.5 and 8 min for H35.

Overall, the amount of drug released as a burst from the halloysite based products was significantly lower than from the corresponding kaolin based products, with the exception of products containing 35% w/w sucrose in their formulation. In addition, the rate at which this drug was released was significantly slower for the halloysite based products. These differences are further evidence that the microtubular structure of halloysite and the associated increase in surface area significantly affects the initial burst release of drug.

With regard to the extended release of diltiazem HCl from the halloysite based products, $k_{1H}$ increased with increasing levels of sucrose in the initial formulation. This was due to increases in the porosity and average pore size of the products (Section 6.2.3.5). In comparison to the kaolin based products, $k_{1H}$ was significantly lower for each of the corresponding halloysite based products. This was due to the microtubular morphology of halloysite, which has been shown to contribute to the extended release of materials (Price et al., 2001; Levis and Deasy, 2003). In effect, it reduced the pore size of the products (Section 6.2.3.5) and created a more tortuous matrix within the pellets. Both these factors extended the release of diltiazem HCl.

In an extension of this research, the release of propranolol HCl from K0 and H0 was examined. Propranolol HCl is highly soluble in phosphate buffer pH 6.8 and like diltiazem HCl dissolved rapidly during dissolution testing. However, by loading the drug into either K0 or H0, its release was extended (Fig. 6.3g). As with diltiazem HCl, Eqn. 5.3d fitted the release data (Table 6.3e).
Quantitative comparison of the propranolol HCl release profiles showed $F_B$ and $k_1$ were significantly lower for H0 than for K0 (Table 6.3e). This trend was observed also for diltiazem HCl release. With regard to propranolol HCl extended release, $k_{1H}$ was higher for K0, although the difference was only weakly significant ($p = 0.0917$). This result is in contrast to the marked differences in $k_{1H}$ for diltiazem HCl release from K0 and H0. This indicates that the ability of the microtubular structure of halloysite to extend the release of drugs is influenced by the molecular weight of the drug, as propranolol HCl
has a lower molecular weight than diltiazem HCl. Evidence that molecular weight influences the rate of drug release from porous materials was also found in comparing the release of sodium benzoate and diltiazem HCl from N-light N2 (Section 5.3.3).

For both K0 and H0 the fraction of propranolol HCl released during the initial burst phase was significantly reduced in comparison to diltiazem HCl, although in the case of H0 the reduction was weakly significant (p=0.0571). The reduction may have been due to the decreased viscosity of the loading solution, which facilitated superior incorporation of solution into the pellet interior. The effect of loading solution viscosity on \( F_B \) has already been noted for N-light N3 (Section 5.4). With regard to the rate at which this fraction of drug was released, there was no significant difference for K0 and a small but significant increase for H0. However, this increase had a limited impact on the release profile with 95% of the burst fraction of diltiazem HCl released within 79 min, while it took 63 min for 95% of the propranolol HCl to be released.

With regard to the extended release, the rate of propranolol HCl release from H0 was significantly higher than for diltiazem HCl release. In the case of K0, while there were no significant differences in \( k_{11} \) for the two drugs, a significantly greater proportion of propranolol HCl was released after 24 h (98.1 +/- 0.1% versus 93.5 +/- 0.3%). The increased release of propranolol HCl was despite its lower solubility in phosphate buffer pH 6.8 in comparison to diltiazem HCl (Appendix 2). This result is a further indication of the importance of molecular weight in the determining the rate of drug release from porous materials.

6.4 CONCLUSION

The aluminosilicate clay minerals, kaolin and halloysite were pelletized by extrusion-spheronization. In addition to a clay mineral, the formulations also contained a binder, ethylcellulose 100 cps, a PFA, sucrose, and ethanol as the granulating solvent. With the exception of halloysite, all the formulation components have established pharmaceutical acceptability (Handbook of Pharmaceutical Excipients, 2000). It is expected that halloysite will also prove pharmaceutically acceptable as it is in the same mineral group as kaolin and, like kaolin, should pass through the GIT unabsorbed. The formulations used were quite different from those conventionally used in extrusion-spheronization
Chapter 6. Production of Porous Aluminosilicate Pellets by Extrusion-Spheronization

for two reasons. Firstly, the main constituent was an aluminosilicate clay mineral, rather than a cellulose based compound, such as microcrystalline cellulose. Secondly, non-aqueous granulating solvents have had limited applications in extrusion-spheronization (Deasy, 1991). Additionally, unlike most clay mineral pellets, these pellets remained intact in water without the need for subsequent sintering. This was advantageous as high temperature sintering would have reduced the surface area of the pellets (Ishizaki et al., 1998c) and destroyed the microtubular structure of halloysite (Salter, 2003).

Investigations into the influence of formulation and process parameters on pellet production were conducted to determine the optimum production conditions. It was found that the proportion of ethanol, kaolin and sucrose in the formulation, as well as the spheronizer speed and time significantly affected pellet production. Based on the results of these investigations, final formulations containing 0-35% w/w sucrose were successfully pelletized. This should promote the use of extrusion-spheronization in clay mineral pelletization where to-date it has found few uses.

Characterisation of the extrusion-spheronization products showed they had a similar structure to the commercial porous ceramics already examined. The pores found within the pellets were created either by evaporation of the granulating solvent, ethanol, or by dissolving the PFA, sucrose. This led to the creation of a bimodal pore size distribution within the pellets, with the overall porosity and pore size distribution being related to the quantity of PFA included in the initial formulation. Interestingly, while there was a clear relationship between interior pore size distribution and the size of the PFA included in the formulation, this was less apparent for the surface pore size distribution. With regard to the surface area of the products, it was significantly higher than that of the porous ceramics already examined despite their similar structures. This was because a sintering step had not been used during production and additionally in the case of halloysite its microtubular structure contributed to a particularly high surface area.

Drug loading of the extrusion-spheronization products was carried out using the modified vacuum loading technique discussed in Section 5.2.1. It was found that, as with the commercial porous ceramics, the extrusion-spheronization products could be reproducibly drug loaded with either diltiazem HCl or propranolol HCl. The loading
was dependent on the concentration of the loading solution used and the porosity of the pellets.

The extrusion-spheronization products gave reproducible extended release of both diltiazem HCl and propranolol HCl. The release was characterised by an initial burst release of drug followed by extended release due to diffusion of the drug from the porous pellet interior. The mass of drug released as a burst was dependent on the quantity of PFA included in the formulation. For all products, the rate at which this burst release occurred was significantly slower than for the commercially produced porous ceramics and was dependent on the aluminosilicate contained in the pellets and the quantity of PFA included in the formulation.

The rate of extended drug release was also dependent on the aluminosilicate in the pellets. The halloysite based products gave greater extended drug release than the kaolin based products, due to entrapment of the drug within the microtubular structure of halloysite. However, this effect was less significant for propranolol HCl release than for diltiazem HCl release probably due to the lower molecular weight of propranolol HCl. For both the kaolin and halloysite based products, the extended release rate constant increased as the quantity of PFA in the formulation increased. This was due to an increase in the porosity and average pore size of the pellets. However, the use of a PFA with a different size distribution had no effect on the extended release observed. This was because the surface pore sizes were similar even though the interior pore sizes were markedly different. This further demonstrates the importance of surface pore size distribution in determining the rate of extended drug release.

Overall, these products could provide extended drug release without the need for subsequent coating. The rate of drug release could be tailored to individual requirements by changing aluminosilicate or the quantity of PFA in the formulation. However, if the burst release of drug was unacceptable or the extended release was still too rapid, subsequent coating steps could be used (Section 5.4).
Chapter 7

PRODUCTION OF POROUS ALUMINOSILICATE PELLETS BY CRYOPELLETIZATION

7.1 INTRODUCTION

This Chapter focuses on the use of cryopelletization to produce porous aluminosilicate pellets intended for drug delivery applications. Cryopelletization is a technique where frozen pellets are prepared by introducing a liquid medium, in the form of droplets, to a cooling liquid (Buxton and Peach, 1984). The pellets are then dried, by conventional drying or by freeze drying, to remove excess water (Knoch, 1994). Cryopelletization products are typically spherical and have a narrow size distribution, which is dependent on formulation and process parameters (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Knoch, 1994).

Cryopelletization’s main application has been in the production of drug delivery systems (Buxton and Peach, 1984; Wunderlich et al., 1995a). The principal formulation components of these systems were the drug, which was usually incorporated during pellet production, and a carrier material such as gelatin or dextran. In most cases the pellets broke up rapidly upon addition to water and therefore acted as immediate release drug delivery systems (Buxton and Peach, 1984; Wunderlich et al., 1995b). However, Wunderlich et al. (1995b) noted that cryopelletization could also be used to produce modified release drug delivery systems. For example, by incorporating enteric materials, such as methacrylic acid derivatives, a delayed release system could be prepared. In addition to its pharmaceutical uses, cryopelletization has also been used to produce porous hydroxyapatite pellets intended for use in bone reconstruction (Fabbri et al., 1994).

The existing applications of cryopelletization indicated that the technique might be suitable for the production of porous aluminosilicate pellets. Investigations into this
potential application began by examining the effect of changes in formulation and processing variables on pellet characteristics. Following this, the ability of these pellets to act as drug delivery systems was assessed. In particular, the effect of changes in pellet characteristics on drug loading and subsequent drug release was examined.

7.2 PRODUCTION OF POROUS ALUMINOSILICATE PELLETS BY CRYOPELLETIZATION

7.2.1 Preliminary Investigations

Cryopelletization studies carried out by Prendergast et al. (2002) investigated the suitability of three cooling liquids, ethyl acetate, hexane, and liquid nitrogen, for the cryopelletization of an aqueous kaolin suspension. Of these, liquid nitrogen proved most suitable, as its temperature was relatively low in comparison to the other cooling liquids. In addition, liquid nitrogen was immiscible and inert with respect to the kaolin suspension, this being a requirement for cryopelletization (Buxton and Peach, 1984). Based on these results, liquid nitrogen was the cooling liquid used in the research presented in this Chapter.

The relative densities of the cooling liquid and the liquid medium determine the point at which the liquid medium is introduced into the cooling liquid (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989). Since liquid nitrogen was less dense than the aqueous aluminosilicate suspensions under investigation, the droplets were added at the surface of the liquid nitrogen. However, rather than immediately sinking, the droplets floated on the surface of the liquid nitrogen and then sunk. This was attributed to the generation of nitrogen gas around the droplets as they froze. The initial floating of droplets necessitated controlling the rate of droplet production, as when it was too high droplet agglomeration occurred. The rate used was such that each droplet had sunk prior to the addition of the next droplet. In doing so, the rate of pellet production was greatly reduced. At an industrial level, this rate would be too low to make the technique commercially viable for pelletization. However, this problem could be overcome using an apparatus designed by Chatterjee et al. (1994), which allows for a high rate of production even where droplets float on the liquid nitrogen surface prior to sinking. The
apparatus has been successfully used to cryopelletize liquid reagents needed for the analysis of biological samples.

It should be noted that in these cryopelletization experiments the droplets were produced using a needle. This was ideal because its pointed tip facilitated the discharge of the droplets and contributed to the production of pellets with a narrow size distribution (Buchmuller and Weyermanns, 1989; Knoch, 1994).

Having established the initial processing conditions, preliminary investigations focussed on determining the formulation components necessary to produce aluminosilicate pellets, which did not break up in water and had sufficient strength to withstand subsequent processing. It was found that spherical frozen pellets could be produced from kaolin suspensions. However, if the kaolin concentration was less than 30% w/v, the pellets did not retain their integrity upon subsequent freeze drying. In addition, the pellets broke up almost immediately upon addition to water. Heating the pellets to 200 °C for either 1 h or 24 h had no effect on this. Therefore, it was necessary to include a binder in the pellet formulation.

In the cryopelletization studies carried out by Prendergast et al. (2002), inclusion of the binder ethylcellulose 100 cps did not prevent pellet break up in water. A literature review indicated that a hydrosol of a metal oxide might prove a more suitable binder for porous aluminosilicate pellets produced by cryopelletization. Such hydrosols, when frozen, undergo an irreversible sol-gel transformation due to the removal of solvent water caused by the formation of ice. This causes an increase in the concentration of the sol, which leads to the formation of an aggregated particle network. The ice formed during freezing can then be removed to leave a porous gel structure. This phenomenon is referred to as freeze gelation and has recently attracted considerable attention as a method for the manufacture of porous ceramics (Mukai et al., 2003; Soltmann et al., 2003).

The hydrosol investigated was sodium silicate solution, which is an alkali-silicate binder containing amorphous silica and sodium hydroxide in water. It has traditional uses in detergent and paper-adhesive manufacture and as a dispersant and deflocculant in the ceramics industry (Brook and Cahn, 1990). However, Mukai et al. (2003) have
shown that it is also a suitable hydrosol for freeze gelation. To establish the suitability of sodium silicate solution for cryopelletization, pellets were initially prepared using a range of dilutions of the solution. These pellets broke up immediately in water if they were not heat-treated. However, following heat treatment at 200 °C for either 1 or 24 h break up was prevented. This was also the case when mixtures of kaolin and sodium silicate solution were pelletized. Therefore, in these studies all pellets were heat treated at 200 °C for 1 h following freeze drying.

Having selected the formulation components, it was necessary to determine the levels of kaolin and sodium silicate solution needed to produce pellets, which had sufficient strength to withstand further processing. It was found that formulations containing both kaolin and sodium silicate solution had increased strength over formulations containing either component alone. In addition, increasing the level of either kaolin or sodium silicate solution in the formulation increased the pellet strength. Knoch (1994) also found that increasing the concentration of the formulation components increased the pellet strength. Heat-treating the pellets at 200 °C for 1 or 24 h had no effect on their strength. Based on these studies it was decided that a minimum level of 10% w/v kaolin and 7.41% v/v sodium silicate solution was needed to obtain pellets with the minimum desired strength.

It was also necessary to determine maximum levels of the formulation components with the limiting factor for these levels being the apparent viscosity of the formulation. If it were too high, the formulation would not be suitable for syringing. The apparent viscosity of the formulations increased with increasing kaolin and/or sodium silicate solution levels. This meant that using a needle with an internal diameter of 0.3 mm (30 G) the system containing 30% w/v kaolin and 22.22% v/v sodium silicate solution was the most concentrated formulation that could be syringed. Therefore, these levels were selected as the maximum levels for each formulation component.

An important point regarding the pellet formulation selected during these preliminary investigations is that it should prove pharmaceutically acceptable. As already discussed, kaolin has long established pharmaceutical uses (Handbook of Pharmaceutical Excipients, 2000), while halloysite should also prove pharmaceutically acceptable because it is in the same mineral group as kaolin. Sodium silicate solution contains
amorphous silica, which is used pharmaceutically as a suspending and thickening agent. It is also used as an anticaking agent in the food industry. The other component of this solution is sodium hydroxide, which is widely used pharmaceutically (Sweetman, 2002). Finally, the use of liquid nitrogen instead of organic solvents as a cooling liquid meant there was no residual adverse solvent in the pellets, which could have represented a health hazard (Knoch, 1994). Although the formulation chosen for investigation was rather simple, if it were intended to market these products additional excipients could be added. For example, colouring agents, such as carotinoides, or flavouring agents, such as sugar substitutes, might be needed to improve patient acceptability. Excipients, which improve the stability of the dosage form, such as preservatives, pH adjusters and stabilizers, could also be included (Buxton and Peach, 1984; Wunderlich et al., 1995a).

7.2.2 Determination of Optimum Production Parameters

Following the preliminary investigations, further research focussed on determining the effects of various formulation and process parameters on pellet diameter and sphericity. In particular the effect of a surfactant, sodium lauryl sulphate, on these pellet characteristics was examined. The results of these studies are discussed in this Section.

7.2.2.1 Pellet Diameter

The factors affecting pellet diameter were investigated using a $2^{5-1}$ half factorial study (Appendix 10). A half normal probability plot was used to identify significant main effects and interactions. In such plots, effects that are null behave like a random sample from a single Normal distribution, i.e., they lie along a straight line apart from chance variation. Therefore, large deviations from a line suggest the presence of non-null effects. The half normal probability plot for the pellet diameter data showed the non-null main effects were formulation, sodium lauryl sulphate, internal needle diameter and drop height. The non-null interactions were sodium lauryl sulphate by internal needle diameter and sodium lauryl sulphate by drop height (Fig. 7.2a).
Figure 7.2a. Half normal probability plot for the pellet diameter data. The significant effects and interactions are indicated (DH = Drop height, F = Formulation, IND = Internal needle diameter, SLS = Sodium lauryl sulphate).

Having identified the non-null main effects and interactions, these were modelled using ANOVA. The model equations are given in Appendix 11. The model terms had a significant effect on the response (Table 7.2a) with the R² value for the model being 0.9709, which was acceptable. There was a linear trend between the observed pellet diameters and those predicted by the model, indicating the model was suitable (Appendix 12).
Table 7.2a. ANOVA of a two-factor interaction model fitted to the pellet diameter data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>2.7297</td>
<td>6</td>
<td>0.4550</td>
<td>50.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Formulation</td>
<td>0.1788</td>
<td>1</td>
<td>0.1788</td>
<td>19.69</td>
<td>0.0016</td>
</tr>
<tr>
<td>Sodium lauryl sulphate</td>
<td>0.3928</td>
<td>1</td>
<td>0.3928</td>
<td>43.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>Internal needle diameter</td>
<td>1.9670</td>
<td>1</td>
<td>1.9670</td>
<td>216.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drop height</td>
<td>0.0702</td>
<td>1</td>
<td>0.0702</td>
<td>7.73</td>
<td>0.0214</td>
</tr>
<tr>
<td>Sodium lauryl sulphate x Internal</td>
<td>0.0827</td>
<td>1</td>
<td>0.0827</td>
<td>9.11</td>
<td>0.0145</td>
</tr>
<tr>
<td>needle diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium lauryl sulphate x Drop</td>
<td>0.0378</td>
<td>1</td>
<td>0.0378</td>
<td>4.16</td>
<td>0.0717</td>
</tr>
<tr>
<td>height</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual Error</td>
<td>0.0817</td>
<td>9</td>
<td>0.0091</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>2.8115</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The factorial study showed that formulation B, which contained a higher level of both kaolin and sodium silicate solution (Table 3.3a), formed significantly larger pellets than formulation A (Table 7.2a; Appendix 11). The change in pellet diameter was due to an increase in the apparent viscosity of the formulation as the proportion of kaolin increased (Knoch, 1994; Sweetman, 2002). This resulted in larger droplets forming at the needle and therefore larger pellets were produced. Other researchers noted similar effects on droplet/pellet size when the apparent viscosity of the liquid formulation was changed (Bodmeier and Paeratakul, 1989; Buchmuller and Weyermanns, 1989; Østberg et al., 1993; Knoch, 1994; Garcia and Ghaly, 1996; Cerdeira et al., 1998).

The importance of surface tension in determining droplet size was demonstrated by the fact that including sodium lauryl sulphate significantly reduced the pellet diameter (Table 7.2a; Appendix 11). Since sodium lauryl sulphate is a surfactant, it reduced the surface tension of the formulation. This meant that the droplets formed at the needle...
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were smaller and as a result so too were the pellets. Knoch (1994) noted a similar effect upon inclusion of a surfactant in a formulation intended for cryopelletization. The effect of sodium lauryl sulphate on pellet diameter was dependent on the internal needle diameter with the reduction being greatest for the larger needle size (Table 7.2a; Appendix 11). This interaction occurred because the droplets detached from the needle when the buoyancy force equalled the force due to interfacial tension (Kumar and Kuloor, 1970). The buoyancy force was dependent on the droplet weight, which was determined by the orifice size. The interfacial tension was dependent on the surface tension of the formulation, which was reduced by sodium lauryl sulphate.

The internal needle diameter, when changed from 0.9 mm to 0.3 mm, significantly reduced the pellet diameter (Table 7.2a; Appendix 11). This was expected, as needles with a smaller internal diameter produce smaller droplets. The droplet size is an important determinant of the final pellet size. Other researchers have found that changing the orifice size had similar effects on pellet diameter (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Chong-Kook and Eun-Jin, 1992).

In addition to the factors already discussed, when the height the droplets fell prior to hitting the liquid nitrogen was increased from 5 to 15 cm there was a significant reduction in the pellet diameter (Table 7.2a; Appendix 11). This was because with a drop height of 15 cm, the droplets had more time to form a spherical shape prior to entering the liquid nitrogen. Since the pellet diameter was measured as the longest line, which passed through the centre of the pellet, the formation of more spherical pellets meant the pellet diameter was reduced. Other researchers have observed similar drop height effects (Buchmuller and Weyermanns, 1989; Knoch, 1994). The changing sphericity also explains the significant interaction between drop height and sodium lauryl sulphate (Table 7.2a; Appendix 11). Because sodium lauryl sulphate reduced the surface tension of the formulation, the droplets were less spherical at a given drop height (Clift, 1978; Chhabra, 1993). However, when the drop height was 15 cm, the pellets had more time to become spherical. This meant the reduction in sphericity and hence diameter of the droplets was less.

Finally, of the factors examined, only the fall height in the liquid nitrogen did not have a significant effect on the pellet diameter. This was expected, as the droplets had partially
frozen prior to sinking in the liquid nitrogen and thus the pellet diameter was already fixed. As a result, changes in the fall height did not affect the pellet diameter.

7.2.2.2 Pellet Sphericity

The factors affecting pellet sphericity were also investigated using a $2^{5-1}$ half factorial (Appendix 10). Prior to analysis, the sphericity data was transformed using Eqn. 6.2b. The half normal probability plot showed the non-null main effect was internal needle diameter. Whether or not kaolin by sodium lauryl sulphate was a non-null interaction was unclear (Fig. 7.2b). However, as discussed below, ANOVA indicated this was the case (Table 7.2b).

![Half normal probability plot for sphericity data. The significant effects and interactions are indicated (F = Formulation, IND = Internal needle diameter, SLS = Sodium lauryl sulphate).](image)

**Figure 7.2b** Half normal probability plot for sphericity data. The significant effects and interactions are indicated (F = Formulation, IND = Internal needle diameter, SLS = Sodium lauryl sulphate).

The non-null main effects and interactions indicated by the half normal probability plot were modelled using ANOVA. The model equation is given in Appendix 11. It was found that the model terms had a significant effect on the response (Table 7.2b) with the $R^2$ value for the model being 0.7657, which was acceptable. There was a linear trend
between the observed pellet sphericities and those predicted by the model, indicating the model was suitable (Appendix 12).

Table 7.2b. ANOVA of a two-factor interaction model fitted to the transformed pellet sphericity data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>0.4011</td>
<td>4</td>
<td>0.1003</td>
<td>8.99</td>
<td>0.0019</td>
</tr>
<tr>
<td>Formulation</td>
<td>0.0033</td>
<td>1</td>
<td>0.0033</td>
<td>0.30</td>
<td>0.5976</td>
</tr>
<tr>
<td>Sodium lauryl sulphate</td>
<td>0.0243</td>
<td>1</td>
<td>0.0243</td>
<td>2.18</td>
<td>0.1679</td>
</tr>
<tr>
<td>Internal needle diameter</td>
<td>0.3328</td>
<td>1</td>
<td>0.3328</td>
<td>29.83</td>
<td>0.0002</td>
</tr>
<tr>
<td>Formulation x Sodium lauryl sulphate</td>
<td>0.0407</td>
<td>1</td>
<td>0.0407</td>
<td>3.65</td>
<td>0.0825</td>
</tr>
<tr>
<td>Residual Error</td>
<td>0.1227</td>
<td>11</td>
<td>0.0112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>0.5238</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The internal needle diameter significantly affected the sphericity of the pellets with the sphericity increasing when the internal needle diameter decreased (Table 7.2b; Appendix 11). This can be explained with reference to a dimensionless parameter known as the Etővös number (Eo), which is given by Eqn. 7.2a.

\[
Eo = \frac{\Delta \rho g d^2}{\sigma} \quad \text{Eqn. 7.2a}
\]

It has been observed that as Eo decreases, droplets become more spherical (Clift, 1978; Chhabra, 1993). Eo is proportional to the square of the droplet diameter \((d^2)\), which in this case was dependent on the internal needle diameter. Therefore, when the internal needle diameter decreased, so too did Eo. This gave more spherical cryopelletization products.
The formulation by sodium lauryl sulphate interaction was also significant (Table 7.2b). Therefore, the effect of both factors on pellet sphericity must be considered together. Firstly, for formulation A, the sphericity of the pellets was increased by inclusion of sodium lauryl sulphate. However, the inclusion of sodium lauryl sulphate in formulation B had no significant effect on the pellet sphericity. In comparing the pellets made from formulation A with those from formulation B, the sphericity of the latter was higher when the formulation did not contain sodium lauryl sulphate. However, when sodium lauryl sulphate was included in the formulation, the sphericity of pellets made using formulation B was lower. This interaction occurred as $E_0$ is proportional to the droplet density ($\Delta \rho$), the square of the droplet diameter and inversely proportional to the surface tension of the droplet ($\sigma$) (Eqn. 7.2a) (Clift, 1978; Chhabra, 1993). These parameters were dependent on the proportion of kaolin, sodium silicate solution and sodium lauryl sulphate in the formulation. Therefore, an interaction between formulation and sodium lauryl sulphate could be expected.

Although drop height and the drop height by sodium lauryl sulphate interaction did not significantly affect the Form PE value for the pellets, their effect on pellet sphericity was indirectly detected through significant changes in the pellet diameter (Section 7.2.2.1). This reflected the increased sensitivity of the experiment to changes in pellet diameter, as it was a direct measurement. In contrast, pellet sphericity was a parameter calculated from two measurements (Eqn. 3.2a). It is expected that had drop height been studied over a wider range, significant changes in Form PE would have been detected, as the magnitude of the change in pellet sphericity would have been greater.

Finally, as with pellet diameter, fall height had no significant effect on the pellet sphericity, as the droplets had partially frozen prior to sinking in the cooling liquid.
7.2.2.3 Optimum Production Parameters

The model equations obtained from the factorial study related the formulation and process parameters to the resulting pellet diameter and sphericity. Therefore, these equations could be used to determine the conditions, which produce the smallest and most spherical pellets for each formulation. These conditions are given in Table 7.2c, while the predicted pellet diameters and sphericities are given in Table 7.2d. Regarding fall height, the factorial study found that it had no significant effect on either pellet diameter or sphericity; therefore, a fall height of 15 cm was arbitrarily chosen.

Table 7.2c. Optimum cryopelletization production conditions determined from the $2^{5-1}$ factorial study.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Formulation A</th>
<th>Formulation B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium lauryl sulphate</td>
<td>2.5% w/v</td>
<td>2.5% w/v</td>
</tr>
<tr>
<td>Internal needle diameter</td>
<td>0.3 mm (30 G)</td>
<td>0.3 mm (30 G)</td>
</tr>
<tr>
<td>Drop height</td>
<td>15 cm</td>
<td>15 cm</td>
</tr>
</tbody>
</table>

Table 7.2d. Prediction of pellet diameters and sphericities using the optimum production conditions given in Table 7.2c.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Prediction</th>
<th>95% confidence interval</th>
<th>99% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Diameter (mm)</td>
<td>1.56</td>
<td>1.41 - 1.70</td>
<td>1.35 - 1.76</td>
</tr>
<tr>
<td>A Form PE</td>
<td>0.905</td>
<td>0.893 - 0.915</td>
<td>0.888 - 0.919</td>
</tr>
<tr>
<td>B Diameter (mm)</td>
<td>1.77</td>
<td>1.62 - 1.91</td>
<td>1.56 - 1.97</td>
</tr>
<tr>
<td>B Form PE</td>
<td>0.893</td>
<td>0.880 - 0.905</td>
<td>0.874 - 0.909</td>
</tr>
</tbody>
</table>

7.2.3 Production of Final Products

Using the optimum production parameters, given in Section 7.2.2.3, a series of cryopelletization products were produced. The formulations used are given in Table
Chapter 7. Production of Porous Aluminosilicate Pellets by Cryopelletization

7.2e and represent a $3^2$ factorial design with kaolin at three levels (0, 10 and 30% w/v) and sodium silicate solution at three levels (7.41, 14.82 and 22.22% v/v).

**Table 7.2e.** Final formulations used for kaolin based pellet production by cryopelletization.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Kaolin (% w/v)</th>
<th>Sodium silicate solution (% v/v)</th>
<th>2.5% w/v Sodium lauryl sulphate solution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS7.41</td>
<td>0</td>
<td>7.41</td>
<td>To 100</td>
</tr>
<tr>
<td>SS14.82</td>
<td>0</td>
<td>14.82</td>
<td>To 100</td>
</tr>
<tr>
<td>SS22.22</td>
<td>0</td>
<td>22.22</td>
<td>To 100</td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>10</td>
<td>7.41</td>
<td>To 100</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>10</td>
<td>14.82</td>
<td>To 100</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>10</td>
<td>22.22</td>
<td>To 100</td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>30</td>
<td>7.41</td>
<td>To 100</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>30</td>
<td>14.82</td>
<td>To 100</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>30</td>
<td>22.22</td>
<td>To 100</td>
</tr>
</tbody>
</table>

In addition to the kaolin based products, a halloysite based product, referred to as H30 SS22.22, was also produced. H30 SS22.22 had the same formulation as K30 SS22.22, except that it contained halloysite rather than kaolin. It was necessary to use a needle with an internal diameter of 0.5 mm (25 G) to produce this product, as the formulation rapidly blocked the needle with an internal diameter of 0.3 mm (30 G). This was because the halloysite raw material contained relatively large aggregates of halloysite particles in addition to individual tubules (Salter, 2003), which increased the likelihood of needle blockage in comparison to kaolin based formulations.

**7.2.3.1 Pellet Diameter**

The average pellet diameter and sphericity of the final cryopelletization products are given in Table 7.2f. The pellet diameter and Form PE values of K10 SS7.41 and K30 SS22.22 are contained within the 95% confidence intervals of the predicted values.
Chapter 7. Production of Porous Aluminosilicate Pellets by Cryopelletization

(Table 7.2d), which further demonstrates the predictive ability of the model equations obtained from the $2^{5-1}$ factorial study (Appendix 11).

**Table 7.2f.** Average pellet diameter and sphericity of the final cryopelletization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Pellet diameter</th>
<th>Form PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (mm)</td>
<td>S.D.</td>
</tr>
<tr>
<td>SS7.41</td>
<td>1.45</td>
<td>0.06</td>
</tr>
<tr>
<td>SS14.82</td>
<td>1.34</td>
<td>0.03</td>
</tr>
<tr>
<td>SS22.22</td>
<td>1.27</td>
<td>0.03</td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>1.57</td>
<td>0.04</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>1.48</td>
<td>0.04</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>1.56</td>
<td>0.04</td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>1.93</td>
<td>0.10</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>1.86</td>
<td>0.09</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>1.83</td>
<td>0.12</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>1.80</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Overall, the pellet diameters of the aluminosilicate containing cryopelletization products were relatively large in comparison to the commercial porous ceramics and the extrusion-spheronization products already examined (Chapters 4/6). Ideally pellets in the size range 850-1000 or 850-1400 $\mu$m should have been prepared for comparative purposes. However, the apparent viscosity of the clay mineral suspensions and the presence of suspended particles precluded the production of pellets in these size ranges (Zaniboni et al., 1995). The diameters of the cryopelletization products were typical of pellets produced by dropping techniques. For example, Chong-Kook and Eun-Jin (1992) prepared pellets using droplet sizes of 2 and 4 mm, while Zaniboni et al. (1995) produced pellets in the size range 1.5 to 3 mm.

A particular advantage of cryopelletization over other pelletization techniques was the low variability in pellet diameter (Table 7.2f). This narrow size distribution is typical of
pellets produced by dropping techniques (Bodmeier and Paeratakul, 1989; Chong-Kook and Eun-Jin, 1992; Zaniboni et al., 1995; Cerdeira et al., 1998). Where the size uniformity was not sufficient, additional uniformity could have been achieved by sieving out a certain fraction of the pellets (Wunderlich et al., 1996).

The pellet diameter data for the kaolin based pellets was analysed as a $3^2$ factorial using ANOVA. The model equation is given in Appendix 13. It was found that the model terms had a significant effect on the response (Table 7.2g) with the $R^2$ value for the model being 0.9764, which was acceptable. There was a linear trend between the observed pellet diameters and those predicted by the model, indicating the model was suitable (Appendix 14).

**Table 7.2g.** ANOVA of a two-factor interaction model fitted to the pellet diameter data.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>1.3331</td>
<td>8</td>
<td>0.1666</td>
<td>88.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kaolin</td>
<td>1.2225</td>
<td>2</td>
<td>0.6112</td>
<td>323.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium silicate solution</td>
<td>0.0486</td>
<td>2</td>
<td>0.0243</td>
<td>12.85</td>
<td>0.0004</td>
</tr>
<tr>
<td>Kaolin x Sodium silicate solution</td>
<td>0.0317</td>
<td>4</td>
<td>0.0079</td>
<td>4.20</td>
<td>0.0153</td>
</tr>
<tr>
<td>Pure Error</td>
<td>0.0322</td>
<td>17</td>
<td>0.0019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>1.3652</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using the $3^2$ factorial analysis, it was found that the pellet diameter was dependent on both the level of kaolin and sodium silicate solution in the formulation (Table 7.2g). Formulations containing a higher concentration of kaolin produced larger pellets due to their increased apparent viscosity (Fig. 7.2c). However, formulations containing a higher level of sodium silicate solution typically produced smaller pellets, despite their increased apparent viscosity. This was because of an accompanying decrease in surface tension, which had a greater effect on droplet size (Glassven, 2004). For example, the
formulations used to produce SS7.41 and SS22.22 had surface tensions of 35.2 +/- 0.1 and 31.3 +/- 0.1 mN m\(^{-1}\), respectively. It should be noted that in some cases there was no change in pellet diameter, as there was a significant interaction between the level of kaolin and sodium silicate solution in the formulation (Table 7.2g). The interaction reflected the role of both formulation apparent viscosity and surface tension in determining pellet diameter, as had already been noted (Section 7.2.2.1).

![Figure 7.2c. Interaction plot showing the pellet diameter at different kaolin and sodium silicate solution levels.](image)

Finally, the pellet diameter of the halloysite based formulation, H30 SS22.22, was not significantly different to that of the equivalent kaolin based formulation, K30 SS22.22. This was unexpected as H30 SS22.22 was made using a needle with an internal diameter of 0.5 mm (25 G), which should have produced larger pellets (Section 7.2.2.1). From this, it can be concluded that the behaviour of a cryopelletization formulation was dependent on the aluminosilicate.

### 7.2.3.2 Pellet Sphericity

The pellet sphericity data for the final products showed they were spherical with the Form PE values being approximately 0.9 for each product (Table 7.2f). This is typical
of pellets produced using dropping techniques (Buxton and Peach, 1984; Bodmeier and Paeratakul, 1989; Buchmuller and Weyermanns, 1989; Chong-Kook and Eun-Jin, 1992; Knoch, 1994; Zaniboni et al., 1995; Cerdeira et al., 1998). As with pellet diameter, the variability in pellet sphericity for each product was low, indicating the shape of pellets produced by cryopelletization was consistent.

The pellet sphericity data for the kaolin based pellets was analysed as a $3^2$ factorial using ANOVA. The model equation is given in Appendix 13. It was found that the model terms had a significant effect on the response (Table 7.2h) with the $R^2$ value for the model being 0.8723, which was acceptable. There was a linear trend between the observed pellet sphericities and those predicted by the model, indicating the model was suitable (Appendix 14).

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>0.1640</td>
<td>8</td>
<td>0.0205</td>
<td>14.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kaolin</td>
<td>0.1372</td>
<td>2</td>
<td>0.0686</td>
<td>48.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium silicate solution</td>
<td>10.0061</td>
<td>2</td>
<td>0.0031</td>
<td>2.16</td>
<td>0.1455</td>
</tr>
<tr>
<td>Kaolin x Sodium silicate solution</td>
<td>0.0166</td>
<td>4</td>
<td>0.0042</td>
<td>2.95</td>
<td>0.0510</td>
</tr>
<tr>
<td>Pure Error</td>
<td>0.0240</td>
<td>17</td>
<td>0.0014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor Total</td>
<td>0.1881</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The factorial study showed that as the proportion of kaolin in the formulation increased there was a significant decrease in pellet sphericity (Table 7.2h; Fig. 7.2d). This was due to the increased density and diameter of the droplets, which led to the formation of less spherical droplets and hence less spherical pellets at a given drop height (Eqn. 7.2a) (Clift, 1978; Chhabra, 1993). The change in pellet sphericity with increasing kaolin
content was dependent on the level of sodium silicate solution in the formulation. However, the sodium silicate solution level itself did not significantly affect pellet sphericity (Table 7.2h; Fig. 7.2d). This interaction reflects the complex interplay of droplet density, diameter and surface tension in determining droplet sphericity, as has already been discussed (Section 7.2.2.2).

![Interaction plot showing the Form PE value for pellets at different kaolin and sodium silicate solution levels.](image)

**Figure 7.2d.** Interaction plot showing the Form PE value for pellets at different kaolin and sodium silicate solution levels.

Finally, there was no significant difference in the sphericity of H30 SS22.22 and K30 SS22.22, even though internal needle diameter was found to significantly affect pellet sphericity (Section 7.2.2.2). This further demonstrates that the behaviour of the cryopelletization formulations was not only dependent on their aluminosilicate content but also on the nature of the aluminosilicate.

### 7.2.3.3 SEM

SEM’s were used to examine the surface and interior structure of the final cryopelletization products, with particular attention being paid to their porosity and pore size distribution. Initially, pellets produced from sodium silicate solution alone were
examined. These pellets were spherical with rough surfaces composed of areas of low porosity and areas of relatively high porosity (Fig. 7.2e/g). In the areas of low porosity the pore diameter was typically 1 \( \mu \text{m} \). However, in the areas of high porosity, larger pores were present. For example, the pores shown at points A and B in Fig. 7.2f and h have diameters of 6.3 and 12.5 \( \mu \text{m} \), respectively. The pores in these pellets were created by the sublimation of ice during the freeze drying stage of pellet production. The pores therefore had the shape of the former ice crystals (Knoch, 1994; Soltmann et al., 2003). The ice crystals were relatively small due to the rapid freezing rate achieved by dropping the formulation into the intensely cold liquid nitrogen (Harris et al., 1998).

After freeze drying the solid component that remained consisted of aggregated silica particles and associated sodium hydroxide (Mukai et al., 2003). It was this solid material that built the network of fine channels and pores present in the cryopelletized product (Wunderlich et al., 1995a).

**Figure 7.2e.** SEM showing the surface of SS7.41 (magnification x 70).

**Figure 7.2f.** SEM showing the surface of SS7.41 (magnification x 2000).

**Figure 7.2g.** SEM showing the surface of SS22.22 (magnification x 60).

**Figure 7.2h.** SEM showing the surface of SS22.22 (magnification x 2000).
SEM’s of cross-sections of pellets produced from sodium silicate solution alone showed they had highly porous interiors (Fig. 7.2i/k), which is typical of cryopelletization products (Knoch, 1994; Wunderlich et al., 1996). The porosity of the products decreased with increasing levels of sodium silicate solution. This was expected, as the proportion of water and hence PFA in the formulation had decreased. The same relationship has been observed in the production of porous ceramics by freeze-casting, which is a process similar to cryopelletization (Schmedders et al., 2001). At higher magnifications the highly interconnected porous network of the cryopelletization products was evident (Fig. 7.2j/l). This network extended throughout the pellets and was linked with the pellet surface. For example, at point B in Fig. 7.2h, four smaller pores are linked to the surface through one larger pore.

**Figure 7.2i.** SEM of a cross-section of SS7.41 (magnification x 60).

**Figure 7.2j.** SEM of a cross-section of SS7.41 (magnification x 2000).

**Figure 7.2k.** SEM of a cross-section of SS22.22 (magnification x 60).

**Figure 7.2l.** SEM of a cross-section of SS22.22 (magnification x 5000).
Having examined the cryopelletization products, formulated with sodium silicate solution alone, kaolin containing pellets were examined. These pellets were also spherical but, unlike products formulated with sodium silicate alone, they had a smooth surface at low magnification (Fig. 7.2m/o). At higher magnifications, the porous nature of the pellets was apparent (Fig. 7.2n/p). For example, pores with diameters of 3.86 and 1.31 \( \mu \text{m} \) can be seen at points C and D in Fig. 7.2n and 7.2p, respectively. The porosity and pore size distribution of the surface was dependent on the proportion of kaolin and sodium silicate solution in the formulation. When the level of either component increased, the surface porosity and pore size decreased due to the reduction in the PFA content of the formulation.

As with the pellets produced from sodium silicate solution alone, SEM's of cross-sections of the kaolin based products showed they were highly porous with pores
extending throughout the pellet interior (Fig. 7.2q/s). The majority of interior pore sizes were less than 3 μm, with these pores being evident at higher magnifications (Fig. 7.2r/t). However, in products that contained high proportions of kaolin relatively large pores were also found in the pellet interior. For example, the pore shown at point E in Fig. 7.2s has a diameter of 160 μm. These large pores were interconnected with the rest of the porous structure by smaller pores located on their surface (Fig. 7.2t). This has been observed also for the N-light ceramics (Section 4.5).

The large pores in these cryopelletization products were produced when the formulation droplets contained air bubbles, which had become entrained in the suspension during stirring. They were found only in pellets containing a high proportion of solids because these formulations had a high apparent viscosity, which delayed the escape of the air bubbles from the formulation. Bodmeier and Paeratakul (1989) observed the same phenomenon when they produced chitosan and calcium alginate pellets by a dropping technique. The creation of porosity in ceramics by foaming clay mixtures is a commonly employed technique (Sepulveda and Binner, 1999) and was used by Fabbri et al. (1994) to generate porosity in hydroxyapatite pellets prepared by cryopelletization.

In SEM’s there was no evidence of kaolin aggregates in the pellets, which showed the kaolin was evenly dispersed throughout the pellets. This was expected as the rapid freezing of the droplets fixed the system instantaneously, meaning sedimentation of the suspended kaolin particles did not occur (Wunderlich et al., 1995a). Compositional uniformity is a typical feature of products prepared by cryopelletization and other dropping procedures (Buxton and Peach, 1984; Buchmuller and Weyermanns, 1989; Knoch, 1994; Zaniboni et al., 1995).

Finally, regarding the effect of changes in the level of each formulation component on the internal porosity of the pellets, it was not possible to visually assess this. However, it is expected that the effects were similar to those observed in surface views of these products and in surface and cross-sectional views of products formulated with sodium silicate solution alone.
SEM's of H30 SS22.22 showed that its surface contained pores that were typically 1-5 μm in diameter (Fig. 7.2u/v). Large aggregates of halloysite were observed at the surface of the pellets (Points F and G in Fig. 7.2v). These aggregates were also found in the halloysite raw material, which indicates that the cryopelletization production process did not break them up. Their presence contributed to the larger surface pores of H30 SS22.22 in comparison to K30 SS22.22, as the halloysite was not as evenly dispersed in the pellets as kaolin.

SEM's of cross-sections of H30 SS22.22 showed that the pellet interior contained a highly interconnected porous network (Fig. 7.2w/x). The halloysite aggregates seen at the pellet surfaces were also present in the pellet interior (Point H in Fig. 7.2x). It was not possible to determine if there were differences in the internal pore size of H30...
SS22.22 and K30 SS22.22. However, it was expected that differences similar to those observed at the surface existed.

**Figure 7.2u.** SEM showing the surface of H30 SS22.22 (magnification x 45).

**Figure 7.2v.** SEM showing the surface of H30 SS22.22 (magnification x 1000).

**Figure 7.2w.** SEM of a cross-section of H30 SS22.22 (magnification x 50).

**Figure 7.2x.** SEM of a cross-section of H30 SS22.22 (magnification x 1000).

In conclusion, the cryopelletization products were spherical and had smooth surfaces when an aluminosilicate was included in the formulation. The surface was highly porous with the porosity and pore size distribution depending on the proportion of water, which acted as a PFA, in the formulation. In addition, the type of aluminosilicate included in the formulation influenced the pore size distribution due to the presence of large aggregates in the halloysite raw material. The interior of the cryopelletization products was also highly porous with the porous structure being highly interconnected.
7.2.3.4 Mercury Porosimetry and Helium Pycnometry Studies

Mercury porosimetry data was available for only four of the ten cryopelletization products. Therefore, an alternative method was used to determine their bulk density. Image analysis of the pellets had measured the pellet length \( (L) \) and width \( (W) \), which could be used to determine the pellet volume (Eqn. 7.2b).

\[
\text{Pellet volume} = \frac{L \pi W^2}{6} \quad \text{Eqn. 7.2b}
\]

The total pellet volume was then used to calculate the bulk density of the sample, as a known mass of pellets had been analysed in each case.

The bulk densities of each of the cryopelletization products were less than water due to their relatively high open porosities. Therefore, each product was a floating drug delivery system, which should be of benefit in extended drug delivery (Section 4.6). The open porosity was dependent on the proportion of kaolin and sodium silicate solution in the formulation, as was observed in SEM's (Section 7.2.3.3). This change in porosity occurred because the amount of PFA in the formulation decreased when the level of either component increased (Table 7.2i).

The skeletal density of each product was dependent on the level of kaolin and sodium silicate solution in the formulation (Table 7.2i). In products formulated with sodium silicate solution alone, their skeletal density increased as its level increased. This was because the silica particles, which formed the silica aggregates in the final product, were more densely packed. The skeletal density was also dependent on the level of kaolin in the product, as kaolin had a higher skeletal density than the constituents of sodium silicate solution. Therefore, increasing the proportion of kaolin in the product increased its skeletal density.

The skeletal densities of uncrushed samples of each product were compared with those of crushed samples. There was no significant difference between these values, which indicated that the samples did not contain closed pores. This was expected as the porosity of the products had primarily been created by sublimation of water during the...
freeze drying process (Section 7.2.3.3). Therefore, the created pores must be connected with the surface of the pellets either directly or through other pores and thus must be open pores.

Finally, the porosity of K30 SS22.22 and H30 SS22.22 were not significantly different, which was expected because each formulation contained the same proportion of PFA. However, the skeletal density of H30 SS22.22 was significantly lower than that of K30 SS22.22 (Table 7.2i). This was due to the lower skeletal density of halloysite in comparison to kaolin. As with the kaolin based products, there were no closed pores in H30 SS22.22.

**Table 7.2i.** Bulk density, skeletal density and open porosity of each cryopelletization product.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Bulk density</th>
<th>Skeletal density</th>
<th>Open porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
</tr>
<tr>
<td></td>
<td>(g/ml)</td>
<td></td>
<td>(g/ml)</td>
</tr>
<tr>
<td>SS7.41</td>
<td>0.1046</td>
<td>0.0073</td>
<td>1.5812</td>
</tr>
<tr>
<td>SS14.82</td>
<td>0.2177</td>
<td>0.0122</td>
<td>1.8206</td>
</tr>
<tr>
<td>SS22.22</td>
<td>0.3777</td>
<td>0.0366</td>
<td>1.8913</td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>0.1905</td>
<td>0.0175</td>
<td>1.9854</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>0.2970</td>
<td>0.0163</td>
<td>2.0849</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>0.4120</td>
<td>0.0129</td>
<td>2.1212</td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>0.3227</td>
<td>0.0325</td>
<td>2.2371</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>0.4741</td>
<td>0.0595</td>
<td>2.3023</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>0.5766</td>
<td>0.0128</td>
<td>2.3242</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>0.5947</td>
<td>0.0152</td>
<td>2.2835</td>
</tr>
</tbody>
</table>

Selected cryopelletization products were analysed using mercury porosimetry (Fig. 7.2y). This showed that the majority of pores in each product were in the size range 1 to 10 \( \mu m \). The pore size decreased as the proportion of kaolin or sodium silicate solution in the product formulation increased. This was reflected in the \( D_{50} \) of each product. K30 SS22.22 had a \( D_{50} \) of 1.4721 \( \mu m \), while those of K10 SS22.22 and K30 SS7.41 were
2.5017 μm and 2.5483 μm, respectively. It should be noted that although K30 SS7.41 had a larger $D_{50}$ than K30 SS22.22, it contained more pores in the size range 0.006 to 0.5 μm. This was due to the reduced packing density of the silica particles in K30 SS7.41.

SEM’s had shown that relatively large pores were present in the interior of K30 SS22.22 (Fig. 7.2s/t). These were not detected using mercury porosimetry, as it primarily measures surface pore size distributions rather than overall pore size distributions (Section 4.6). However, K30 SS22.22 contained more pores in the size range 10 to 25 μm than the other products. Such pores were created when the relatively large interior pores partially opened at the pellet surface. Pores in this size range were observed in SEM’s, although they occurred infrequently.

The halloysite based product, H30 SS22.22, had a larger pore size distribution than its kaolin based equivalent, which was reflected in its $D_{50}$ value of 2.0049 μm (Fig. 7.2y). This was due to the presence of halloysite aggregates, which were not evenly dispersed throughout the product (Section 7.2.3.3). H30 SS22.22 also contained relatively small pores, which were not found in K30 SS22.22. This indicated that the microtubular structure of halloysite had contributed to the pore size distribution of the products, as has been observed for halloysite based extrusion-spheronization products (Section 6.2.3.5). Overall, the results of mercury porosimetry analysis of the products were in agreement with SEM observations (Section 7.2.3.3).
7.2.3.5 Surface Area Analysis

Surface area analysis of the cryopelletization products demonstrated that each product had a relatively high surface area compared to their non-porous equivalents (Table 7.2j). This was expected, as the products were highly porous and had a small average pore size (Sections 7.2.3.3/7.2.3.4). The surface area of each product was influenced by its porous structure and composition. For example, in products containing the same proportion of kaolin, the surface area decreased as the proportion of sodium silicate solution in the formulation increased. This was due to the accompanying decrease in the porosity of the products, as well as the increase in the packing density of the silica particles (Section 7.2.3.3/7.2.3.4). The effect of porosity and pellet composition on surface area was also apparent when comparing products formulated without kaolin with those of kaolin containing products. Inclusion of kaolin in the formulation decreased the porosity of the products, while the kaolin particles themselves provided an increased surface area for nitrogen adsorption. Therefore, the effect of kaolin inclusion on surface area was dependent on the level of sodium silicate solution in the formulation. For example, products formulated with 7.41% v/v sodium silicate solution
had a decreased surface area following kaolin incorporation, while those formulated with 22.22% v/v had an increased surface area.

H30 SS22.22 had a significantly higher surface area than K30 SS22.22 due to the microtubular structure of halloysite. This was also noted for the extrusion-spheronization products and further demonstrates the role of pellet composition in determining surface area (Section 6.2.3.6).

Table 7.2j. Surface area of each cryopelletization product and the calculated surface area of its non-porous equivalent.

<table>
<thead>
<tr>
<th>Cryopelletization product</th>
<th>BET multipoint surface area</th>
<th>Surface area of a non-porous equivalent</th>
<th>Ratio of surface areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (m²/g)</td>
<td>S.D.</td>
<td>(m²/g)</td>
</tr>
<tr>
<td>SS7.41</td>
<td>10.3787</td>
<td>3.1138</td>
<td>0.042371</td>
</tr>
<tr>
<td>SS14.82</td>
<td>6.6654</td>
<td>2.2580</td>
<td>0.022433</td>
</tr>
<tr>
<td>SS22.22</td>
<td>0.7918</td>
<td>0.0503</td>
<td>0.013501</td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>5.7369</td>
<td>0.2813</td>
<td>0.021533</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>3.8994</td>
<td>1.3640</td>
<td>0.014898</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>2.4932</td>
<td>0.3276</td>
<td>0.011103</td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>6.0570</td>
<td>0.9177</td>
<td>0.011181</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>3.2517</td>
<td>0.2627</td>
<td>0.009172</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>2.3291</td>
<td>0.2015</td>
<td>0.005482</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>9.5717</td>
<td>0.5132</td>
<td>0.007272</td>
</tr>
</tbody>
</table>

The surface areas of the cryopelletization products were the same or higher than the surface areas of the commercial porous ceramics (Section 4.7). The differences were dependent on their relative porosities and pore sizes, as well as their composition. However, an exact relationship could not be established, as the sintering step used in the production of the porous ceramics would have reduced the surface area of their
constituents in comparison to those of the cryopelletization products (Ishizaki et al., 1998c).

7.3 DRUG LOADING AND DISSOLUTION TESTING OF CRYOPELLETIZATION PRODUCTS

7.3.1 Loading Studies

The cryopelletization products were loaded with diltiazem HCl using loading method (iii) (Section 3.3.2). This gave relatively high loadings, with the highest loading being 37.1 +/- 2.8% w/v for K10 SS14.82 (Table 7.3a). In most cases, the diltiazem HCl loading increased as the porosity of the products increased. Similar relationships were observed for commercial porous ceramics and extrusion-spheronization products (Sections 5.2.2/6.3.1). However, in some cases despite differences in their open porosities, the drug loadings of the products were not significantly different. This occurred because drug loading was also dependent on the external surface area of the pellets and their bulk density (Section 5.2.2). For example, SS14.82 had a higher bulk density and external surface area per unit volume than SS7.41. These factors gave it a relatively high drug loading, given its open porosity.

The diltiazem HCl loading of H30 SS22.22 was significantly lower than that of K30 SS22.22 (Table 7.3a). In comparing kaolin and halloysite based extrusion-spheronization products, the same trend was observed (Section 6.3.1). As already discussed, this may have been because the narrow halloysite microtubules reduced penetration of the loading solution into the pellets.
Table 7.3a. Actual and theoretical diltiazem HCl loading of each cryopelletization product.

<table>
<thead>
<tr>
<th>Cryopelletization product</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (%) w/v</td>
<td>S.D.</td>
</tr>
<tr>
<td>SS7.41</td>
<td>33.4</td>
<td>0.4</td>
</tr>
<tr>
<td>SS14.82</td>
<td>35.3</td>
<td>1.7</td>
</tr>
<tr>
<td>SS22.22</td>
<td>27.2</td>
<td>0.8</td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>37.1</td>
<td>2.8</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>32.7</td>
<td>3.0</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>28.6</td>
<td>1.5</td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>31.8</td>
<td>1.6</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>30.3</td>
<td>3.8</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>30.4</td>
<td>0.9</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>26.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Selected cryopelletization products were also loaded with propranolol HCl. The loadings were lower in comparison to the diltiazem HCl loadings due to the lower concentration of the propranolol HCl loading solution (Table 7.3b). This further demonstrates the importance of loading solution concentration in determining the final drug loading of porous pellets (Sections 5.2.2/6.3.1).

Table 7.3b. Actual and theoretical propranolol HCl loading of selected cryopelletization products.

<table>
<thead>
<tr>
<th>Cryopelletization product</th>
<th>Actual drug loading</th>
<th>Theoretical drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (%) w/v</td>
<td>S.D.</td>
</tr>
<tr>
<td>SS22.22</td>
<td>17.8</td>
<td>0.2</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>16.9</td>
<td>0.4</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>15.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>
For both the diltiazem HCl and propranolol HCl loaded products, the actual drug loadings were close to the theoretical maximum loadings (Tables 7.3a/b). The differences between these values depended on the product because, as already discussed, drug loading was not solely determined by open porosity.

### 7.3.2 Dissolution Testing

The release of diltiazem HCl from each of the cryopelletization products was assessed using dissolution testing. Initially, products formulated with 7.41% v/v sodium silicate solution were examined. Each product gave extended release of diltiazem HCl (Fig. 7.3a), which was attributed to entrapment of the drug within the porous structure of the pellets and binding of the drug to kaolin and/or silica. Diltiazem HCl binding was probable as both kaolin and silica have a polyanionic surface at pH 6.8 (van Olphen, 1963c; Schmedders et al., 2001). The ability of both materials to bind cationic compounds has already been discussed (Sections 5.3/6.3.2).

![Figure 7.3a.](image)

**Figure 7.3a.** Dissolution profiles of diltiazem HCl when loaded into cryopelletization products containing 7.41% v/v sodium silicate solution in their formulation in phosphate buffer pH 6.8 at 37 °C.
The diltiazem HCl release data for these products was fitted to the mathematical models discussed in Section 5.3.1. It was found that, although Eqn. 5.3b and 5.3d fitted the release data, the kinetic parameters of the equations did not adequately describe the visually observed trends in the release. This problem arose because there were relatively few data points available for model fitting. For example, 80% of the loaded diltiazem HCl was released from SS7.41 within 15 min, which meant that only four data points could be used for model fitting.

Since model fitting was unsuitable, the diltiazem HCl release was compared based on the percentage drug released after 2.5 min \( (100M_{2.5}/M_{\infty}) \) and 15 min \( (100M_{15}/M_{\infty}) \). At both time points, a significantly lower percentage of diltiazem HCl was released from K30 SS7.41 than from the other products and, in comparing K10 SS7.41 and SS7.41, significant differences existed at 2.5 min (Table 7.3c). These differences in diltiazem HCl release were due to changes in both the burst and extended release of drug from the products. Firstly, inclusion of kaolin in the products increased the number of available binding sites for diltiazem HCl on the external pellet surfaces, which lowered the burst release of drug (Section 5.3.2). Secondly, the pellet diameter increased with increasing kaolin levels. As a result the pellets had a lower external surface area per unit volume, which also reduced the burst release (Table 7.2f). Thirdly, inclusion of kaolin in the products reduced their porosity and pore size (Sections 7.2.3.3/7.2.3.4). This, along with the increased pellet diameter, extended the release of diltiazem HCl (Sections 5.3/6.3.2).

Overall, the ability of these products to extend diltiazem HCl release was poor. For example, in the case of K30 SS7.41, 80% of the incorporated diltiazem HCl was released within 30 min. Such products would not be suitable for use as extended diltiazem HCl delivery systems.
Table 7.3c. Percentage drug released from products containing 7.41% v/v sodium silicate solution in their formulation after 2.5 and 15 min in phosphate buffer pH 6.8 at 37 °C.

<table>
<thead>
<tr>
<th>Sample</th>
<th>100M_{2.5}/M_{\infty} (% w/w)</th>
<th>Average</th>
<th>S.D.</th>
<th>100M_{15}/M_{\infty} (% w/w)</th>
<th>Average</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS7.41</td>
<td>61.0</td>
<td>6.9</td>
<td></td>
<td>79.4</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>K10 SS7.41</td>
<td>44.6</td>
<td>1.7</td>
<td></td>
<td>77.2</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>K30 SS7.41</td>
<td>33.9</td>
<td>5.4</td>
<td></td>
<td>61.2</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Having examined the release of diltiazem HCl from products formulated with 7.41% v/v sodium silicate solution, the effect of increasing this to 14.82% v/v was investigated. It was found that this caused a marked extension in the duration of diltiazem HCl release from the products (Fig. 7.3a/b).

Figure 7.3b. Dissolution profiles of diltiazem HCl when loaded into cryopelletization products containing 14.82% v/v sodium silicate solution in their formulation in phosphate buffer pH 6.8 at 37 °C.
The extension of diltiazem HCl release was partly due to decreases in the porosity and pore size of the products (Sections 7.2.3.3/7.2.3.4). However, the investigations into drug release from commercial porous ceramics and extrusion-spheronization products indicated that given the porosity and pore size of the cryopelletization products, the diltiazem HCl release should have been faster. Additionally, the change in diltiazem HCl release should have been smaller when the proportion of sodium silicate solution was increased (Sections 5.3/6.3.2). Therefore, a factor not encountered during these previous investigations must have affected drug release. This factor was the increase in the microclimate pH of the pellets with increasing proportions of sodium silicate solution, which is a basic solution. The increased pH suppressed diltiazem HCl ionisation (pKₐ 7.7), thereby reducing its solubility in the diffusion medium and extending its release from the pellets (Higuchi, 1963). Goskonda et al. (1994b) have also shown that changes in the microclimate pH of pellets can modify the rate of release of an ionisable drug.

Dissolution rate modelling showed that Eqn. 5.3b fitted the diltiazem HCl release data for these products, which indicated that the release of diltiazem HCl was diffusion controlled (Table 7.3d; Section 5.3.1). An example of the release predicted by Eqn. 5.3b using the best fit parameters for K30 SS14.82 is shown in Fig. 7.3c. The predicted release is in close agreement with the actual experimental data points.

Table 7.3d. Best fit parameters, when Eqn. 5.3b is fitted to the diltiazem HCl release data for various cryopelletization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>F_B (% w/w)</th>
<th>k_H (% h⁻⁰.⁴³²)</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td>Average</td>
<td>S.D.</td>
</tr>
<tr>
<td>SS14.82</td>
<td>10.92</td>
<td>1.92</td>
<td>40.53</td>
<td>1.92</td>
</tr>
<tr>
<td>K10 SS14.82</td>
<td>14.13</td>
<td>2.18</td>
<td>37.21</td>
<td>1.99</td>
</tr>
<tr>
<td>K30 SS14.82</td>
<td>16.33</td>
<td>1.80</td>
<td>29.95</td>
<td>1.52</td>
</tr>
</tbody>
</table>
Quantitative assessment of the diltiazem HCl release showed there was a significantly lower fraction of drug released as a burst from SS14.82 in comparison to K30 SS14.82 (Table 7.3d). However, accounting for the different loadings of these products, the mass of drug released as a burst per unit volume of pellets was not significantly different. Therefore, although each product consisted of different size pellets, the differences were not large enough to significantly affect the burst release of drug (Table 7.2f; Section 5.3). It has already been noted that increasing the level of kaolin in the products increased the number of anionic binding sites on the external pellet surface. However, this did not influence the burst release of diltiazem HCl from these products, as its ionisation was suppressed.

The extended release rate constant of K30 SS14.82 was significantly lower than that of K10 SS14.82 and SS14.82 (Table 7.3d). This was due to the reduction in the porosity and pore size of the pellets, as well as the increase in pellet diameter (Sections 7.2.3.3/7.2.3.4). These factors have been shown to influence \( k_1 \) for commercial porous ceramics and extrusion-spheronization products (Sections 5.3/6.3.2).
The final group of products examined were formulated using 22.22% v/v sodium silicate solution. In contrast to products formulated with 7.41% v/v sodium silicate solution, these products markedly extended the release of diltiazem HCl (Fig. 7.3a/d). This was again associated with suppression of diltiazem HCl ionisation by the increased microclimate pH of the pellets.

![Dissolution profile graph](image)

**Figure 7.3d.** Dissolution profiles of diltiazem HCl when loaded into cryopelletization products containing 22.22% v/v sodium silicate solution in their formulation in phosphate buffer pH 6.8 at 37 °C.

Dissolution rate modelling showed that Eqn. 5.3b fitted the diltiazem HCl release data for these products. However, the parameter F_b did not significantly improve the model fit. It was therefore eliminated from the model to give Eqn. 5.3a, which fitted the release data (Table 7.3e).
Table 7.3e. Best fit parameters, when Eqn. 5.3a is fitted to the diltiazem HCl release data for various cryopelletization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$k_H$ (%) Average</th>
<th>S.D.</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS22.22</td>
<td>46.50</td>
<td>0.44</td>
<td>5.52</td>
<td>0.9960</td>
</tr>
<tr>
<td>K10 SS22.22</td>
<td>37.30</td>
<td>0.38</td>
<td>6.55</td>
<td>0.9986</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>25.96</td>
<td>0.31</td>
<td>8.02</td>
<td>0.9997</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>37.02</td>
<td>0.35</td>
<td>6.61</td>
<td>0.9987</td>
</tr>
</tbody>
</table>

The rate of extended diltiazem HCl release from these products was dependent on the proportion of aluminosilicate in the formulation. As the proportion increased, there were significant reductions in $k_H$ (Table 7.3e). This was due to decreases in the porosity and pore size of the pellets, as well as the increase in pellet diameter (Table 7.2f; Sections 7.2.3.3/7.2.3.4).

The extended release rate constant was also dependent on the aluminosilicate contained in the product (Table 7.3e). In contrast to the extrusion-spheronization products (Section 6.3.2), the halloysite based cryopelletization product, H30 SS22.22, gave a significantly faster release of diltiazem HCl than the corresponding kaolin based product, K30 SS22.22. This occurred because H30 SS22.22 had a larger average pore size than K30 SS22.22. With the exception of the small volume of pores created by the halloysite microtubules, H30 SS22.22 had a similar pore size distribution to K10 SS22.22 (Sections 7.2.3.3/7.2.3.4). As a result, the $k_H$ values for these products were not significantly different, which further demonstrates the importance of pore size distribution in extended drug delivery.

Increasing the level of sodium silicate solution in the formulations from 14.82 to 22.22% v/v had limited effects on $k_H$. The actual change in $k_H$ was dependent on the proportion of kaolin in the product. For example, $k_H$ for SS22.22 was significantly higher than that of SS14.82, although the 95% confidence interval for the minimum difference between these two values was only 1.25% $h^{-0.432}$ (Tables 7.3d/e).
increase in the release rate occurred despite a decrease in the porosity and pore size distribution of the product (Sections 7.2.3.3/7.2.3.4). This was because SS22.22 had a smaller pellet diameter than SS14.82 (Table 7.2f). For products formulated using 30% w/v kaolin, the opposite effect occurred. K30 SS22.22 had a lower $k_{11}$ due to its decreased porosity and pore size, as there was no significant difference in their pellet diameters (Sections 7.2.3.3/7.2.3.4; Table 7.2f). Overall, the changes in the extended release were small in comparison to those observed when the level of sodium silicate solution was increased from 7.41% v/v to 14.82% v/v. Therefore, it can be concluded the level of sodium silicate solution in the formulation primarily affected diltiazem HCl ionisation. This was more important for extended release than the accompanying changes in porosity and pore size distribution.

To further investigate the role of microclimate pH in extending the release of ionisable drugs from these cryopelletization products, the release of propranolol HCl was examined. This drug has a higher $pK_a$ than diltiazem HCl, with the $pK_a$'s being 9.5 and 7.7, respectively. Dissolution testing showed that products formulated using 22.22% v/v sodium silicate solution extended the release of propranolol HCl, although the release was faster than that of diltiazem HCl (Fig. 7.3d/e).

There was limited data available for dissolution rate modelling of propranolol HCl release, as it was rapidly released from the cryopelletization products. This meant it was not possible to conclusively determine which of the equations, discussed in Section 5.3.1, most appropriately modelled the release data. To facilitate quantitative comparisons between the release of diltiazem HCl and propranolol HCl, Eqn. 5.3a was fitted to the release data (Table 7.3f). This equation adequately described the propranolol HCl release, which was in part due to the low number of data points modelled. However, diffusion of propranolol HCl from the porous interior of the pellets was probably the rate determining step in drug release, as this was the case with diltiazem HCl. Whether or not a burst release of drug from the external pellet surfaces occurred could not be determined.
Figure 7.3e. Dissolution profiles of propranolol HCl when loaded into cryopelletization products containing 22.22% v/v sodium silicate solution in their formulation in phosphate buffer pH 6.8 at 37 °C.

Table 7.3f. Best fit parameters, when Eqn. 5.3a is fitted to the propranolol HCl release data for various cryopelletization products.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$k_H$ ( % h^{-0.432} )</th>
<th>MSC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>S.D.</td>
<td></td>
</tr>
<tr>
<td>SS22.22</td>
<td>210.79</td>
<td>5.13</td>
<td>7.95</td>
</tr>
<tr>
<td>K30 SS22.22</td>
<td>121.00</td>
<td>2.61</td>
<td>3.72</td>
</tr>
<tr>
<td>H30 SS22.22</td>
<td>144.53</td>
<td>3.51</td>
<td>4.07</td>
</tr>
</tbody>
</table>

Quantitative assessment of the propranolol HCl release data showed that inclusion of an aluminosilicate clay mineral in the formulation significantly reduced the rate of propranolol HCl release from the pellets (Table 7.3f). In addition, the release of propranolol HCl from H30 SS22.22 was significantly faster than from K30 SS22.22. These same trends were observed for diltiazem HCl release from these products.
For each cryopelletization product, the rate of propranolol HCl release was significantly faster than that of diltiazem HCl (Tables 7.3e/f). Based on the investigations into drug release from extrusion-spheronization products, these large changes in $k_{t1}$ cannot be accounted for by the lower molecular weight of propranolol HCl in comparison to diltiazem HCl (Section 6.3.2). In fact, the large increase in the release rate is further evidence that microclimate pH is an important factor with regard to the release of ionisable drugs from these cryopelletization products. Propranolol HCl has a higher $pK_a$ than diltiazem HCl. Therefore, although the microclimate pH of pellets formulated using 22.22% v/v sodium silicate solution was sufficient to suppress ionisation of diltiazem HCl, it did not suppress ionisation of propranolol HCl to the same extent. This meant its effective solubility in phosphate buffer pH 6.8 was higher than that of diltiazem HCl. Hence, $k_{t1}$ for propranolol HCl was significantly higher. In related research, Chang and Bodmeier (1997) also found that diltiazem HCl release from monoglyceride based drug delivery systems was slower than that of propranolol HCl at pH 7.4. This was because only 50% of the diltiazem HCl molecules were ionised in comparison to 100% for propranolol HCl.

7.4 CONCLUSION

Cryopelletization was used to produce pharmaceutically acceptable pellets whose principal constituents were kaolin or halloysite, which are aluminosilicate clay minerals, and sodium silicate solution, which is an alkali-silicate binder. The latter constituent was needed to increase the pellet strength and prevent them breaking up in water. Factorial studies demonstrated that both process and formulation parameters significantly influenced the resultant pellet size and shape. The formulation apparent viscosity and surface tension as well as the internal needle diameter used to produce the formulation droplets were particularly important. These parameters could be used to control the resulting pellet diameter, which would be essential for industrial applications. Overall, the pellets produced were spherical and had a narrow size distribution.

Each cryopelletization product had a relatively high open porosity, which was dependent on the proportion of water in its formulation. This was because the water acted as a PFA, with the pores being created by the sublimation of ice during freeze
drying. Since the products had high open porosities, their bulk densities were less than water, which meant they were floating drug delivery systems. Their open porosities also gave the products a relatively high surface area in comparison to their non-porous equivalents.

SEM’s showed that pellets formulated using sodium silicate solution alone had rough surfaces containing areas of low and high porosity. The surface pore size was dependent on the porosity of the area, with larger pores being present in the more porous areas. Inclusion of kaolin in the formulation gave pellets with smooth surfaces and regular surface porosities and pore sizes. In comparison to products formulated using sodium silicate solution alone, these products had a lower surface porosity and smaller pore size. Their surface pore size decreased as the level of either kaolin or sodium silicate solution in the formulation increased. The interior of the pellets consisted of a highly porous interconnected structure, with the interior pore diameter being typically less than 3 μm. However, in pellets produced from viscous formulations relatively large pores were also present. Air bubbles in the formulation had created these pores. Finally, the halloysite based product differed from its kaolin based equivalent, as it contained relatively large halloysite aggregates. This increased its D₅₀, although smaller pores created by the halloysite microtubules were still present.

Each cryopelletization product could be loaded with a high level of drug. The drug loading was dependent on the porosity of the product, its bulk density, the concentration of the drug loading solution and the aluminosilicate contained in the formulation. Overall, the actual drug loadings were close to the theoretical maximum loadings with the exact differences being product dependent.

The cryopelletization products gave extended release of diltiazem HCl with the rate-determining step in release being diffusion of the drug from the porous interior of the pellets. A number of factors influenced drug release, with the proportion of sodium silicate solution in the formulation being particularly important, as it influenced the microclimate pH of the pellets. When the proportion of sodium silicate solution was 14.82 or 22.22% v/v the ionisation of diltiazem HCl was suppressed, thereby reducing its solubility in the dissolution medium and delaying its release. Other factors, which influenced drug release, were the porosity and pore size distribution of the pellets and
the average pellet diameter. The cryopelletization products also gave extended release of propranolol HCl. However, its release rate was significantly higher than that of diltiazem HCl, as the microclimate pH of the pellets was not high enough to suppress propranolol HCl ionisation to the same extent as for diltiazem HCl. Overall, the results demonstrated that cryopelletization is a suitable technique for the production of extended release drug delivery systems.
GENERAL DISCUSSION

The research presented in this thesis focussed on the potential applications of porous aluminosilicate pellets in extended drug delivery. Initially, porous ceramics were examined, as these materials can extend drug delivery both in vivo and in vitro (Itokazu et al., 1999; Netz et al., 2001; Paul et al., 2002). However, existing research in this area has been on non-oral drug delivery, despite the fact that the oral route is the most commonly used route for drug administration (York, 2002). Therefore, porous ceramic pellets were investigated, as it is well established that pellets can be orally administered (Ghebre-Sellassie, 1989).

Since porous ceramics have numerous industrial applications, it was possible to obtain seven different pelletized porous aluminosilicate ceramics from commercial sources. The N-light ceramics were obtained from Itochu Ceratech Corporation, Starlight SLK1000 from Imerys and the Carbolite ceramics from Carboceramics. They are marketed for use in the building materials industry and in the hydraulic fracturing of oil wells. The ceramics were cheap and available in large quantities, which would be essential for any future applications in the pharmaceutical industry. In all cases, the pellets were small enough to be filled into a capsule, which was important, as it would allow them to be administered by the oral route.

The porosity of the ceramics meant it was possible to load them with drugs. In the published literature in this area, the most commonly employed drug loading technique has been a vacuum impregnation technique (Paul and Sharma, 1995, 1999; Paul et al., 2002; Itokazu et al., 1998, 1999; Komlev et al., 2002). However, this technique was not particularly effective for drug loading the N-light N3 pellets, as they floated on the loading solution. Therefore, a novel modification of the existing vacuum impregnation technique was developed. This proved effective for loading floating porous ceramics as well as those which had bulk densities greater than the loading solutions.
Since drugs are most commonly incorporated into the dosage form during the formulation stage, the loading method adopted in this research was unusual. However, there were a number of advantages associated with loading the porous ceramics after their manufacture. Firstly, the pellets could be loaded with a range of different drugs or combinations of drugs (Itokazu et al., 1994). Secondly, the drug loading could be easily adjusted to meet dosing requirements, as it was dependent on factors such as the porosity of the pellets and the concentration of the drug loading solution. Thirdly, stability problems that can occur when drugs are included in the pellet formulation can be avoided. For example, drugs that are prone to hydrolysis would be broken down in most pellets, as they typically contain residual water. When the pellets are loaded after their manufacture, a non-aqueous loading solution can be used thereby preventing hydrolysis. Given that porous ceramics can be loaded with a variety of drugs at different doses, irrespective of their stability, they represent an extremely versatile, novel drug carrier system.

If porous ceramics are to be widely used as drug carrier systems, large quantities of the drug loaded product would have to be relatively easy to manufacture. This should be possible, as the vacuum impregnation technique used in this research was relatively simple and can be scaled up. In addition, it is a rapid process that takes less than 24 h to produce the final drug loaded product. Future research should focus on scaling up the loading process and shortening production times. This would allow large quantities of drug loaded product to be rapidly produced.

Having established that porous ceramics could act as drug carriers, the manner in which these drugs were released was examined. In all cases, there was an initial burst release of poorly entrapped drug from the pellets. This drug was located on the external pellet surface or in relatively large pores at or near the surface. The mass of drug released during this period was influenced by the pellet size and by electrostatic interactions between the drug and pellet surfaces. These interactions occurred because the ceramics had polycationic surfaces at low pHs and polyanionic surfaces at high pHs, which facilitated the binding of anionic and cationic drugs, respectively. The rate at which the burst release occurred was influenced by the solubility of the drug in the dissolution medium.
The initial burst release of drug was followed by extended release of the remaining drug. Extended release occurred because the drug was entrapped within the pellet and had to diffuse through its porous interior in order to reach the bulk dissolution medium. The rate at which this occurred was influenced by the pellet size, its porous microstructure and by electrostatic interactions between the pellet surfaces and the drug. The solubility of the drug in the dissolution medium and its molecular weight also influenced the release rate. In vivo the release of drugs would be further extended by delayed transit of the pellets through the GIT (Bechgaard and Ladefoged, 1978; Kawashima et al., 1991).

In contrast to many existing pelletized drug delivery systems, the porous ceramics could extend drug release without the need for subsequent coating. However, a burst effect did occur, which would be unacceptable in certain applications. In such cases, a release modifying agent, such as calcium alginate or Precirol ATO 5, could be used to reduce or eliminate this burst effect and further extend drug release. Since numerous release modifying agents are used pharmaceutically, there is the potential for further research in this area. The aim of that research should be to establish the extent to which a particular agent modifies drug release from the porous ceramics. This would allow the most suitable release modifying agent to be selected for a given application.

These investigations demonstrated that commercially available porous ceramics could be used as extended release drug delivery systems. However, their future applications in this area might be limited because they are manufactured using methods not typically encountered in the pharmaceutical industry. In addition, their pharmaceutical acceptability has yet to be established.

Therefore extrusion-spheronization, which is a commonly employed pharmaceutical pelletization technique (Ghebre-Sellassie, 1989), was used to produce porous aluminosilicate pellets. An important feature of this technique is that large quantities of pellets can be manufactured, which would be essential for commercial applications (Hicks and Freese, 1989). In this research, the formulations used contained kaolin or halloysite, ethanol, ethylcellulose 100 cps and sucrose. With the exception of halloysite, these materials have established pharmaceutical acceptability (Handbook of Pharmaceutical Excipients, 2000). However, it is expected that halloysite will prove
pharmaceutically acceptable, as it is in the same mineral group as kaolin and, like kaolin, should pass through the GIT unabsorbed.

Initial formulation/process investigations found that the proportion of ethanol, kaolin and sucrose in the formulation, as well as the spheronizer speed and time significantly affected pellet production. Based on these initial investigations, a series of products containing different quantities of sucrose were produced. The formulation and process parameters used were based on mathematical models developed from the initial investigations. The models had good predictive ability given the large number of variables under investigation. At an industrial level, these models could be used to provide a starting point for the development of a specific product with further formulation/process optimisation then being carried out. For example, the sucrose containing kaolin based extrusion-spheronization products gave pellet yields that were too low to be industrially acceptable. However, with some further experimentation it is expected that the process would reach industrial standards.

The extrusion-spheronization products did not need to be sintered to prevent their break-up in water. This was in contrast to the commercial porous ceramics and was advantageous for three reasons. Firstly, high temperature sintering would have reduced the surface area of the pellets, thereby reducing the potential for drug binding (Ishizaki et al., 1998c). Secondly, it would have destroyed the microtubular structure of halloysite (Salter, 2003), which has been shown to contribute to the extended release of materials (Price et al., 2001; Levis and Deasy, 2003). Thirdly, high temperature sintering is an expensive process and would therefore have increased the production costs.

The structure of the extrusion-spheronization products was similar to that of the commercial porous ceramics. Porosity was created by evaporation of ethanol from the pellets but could be further increased by including sucrose in the pellets and then removing it by dissolution in water. The porosity of the products allowed them to be drug loaded and given that the porosity could be changed, the drug loading could be tailored to meet dosing requirements.
In loading the pellets after production, only pellets in the required size range were used. This meant that drug was not wasted since it was not present in the fines or large pellets, which were discarded. This overcomes a problem typically encountered when drug is incorporated at the formulation stage of extrusion-spheronization. However, if required the drug could be included at the formulation stage. This might be done where the manufacturer does not wish to use the vacuum impregnation loading technique. However, in doing so a certain amount of product versatility would be lost. Heneghan et al. (2003) demonstrated that this application was feasible by preparing drug loaded kaolin based pellets from formulations similar to those used in this thesis. This research established that kaolin could act as a pelletization aid for extrusion-spheronization. Further research in this area should be carried out, as pelletization excipients that can be granulated using organic liquids are desired (Chatlapalli and Rohera, 1998). Such excipients would be of particular value when the drug under investigation is prone to hydrolysis.

The extrusion-spheronization products that were drug loaded after pelletization were dissolution tested to assess their potential applications as extended release drug delivery systems. It was found that the loaded drug was released in a similar manner to that observed for the commercial porous ceramics. This was expected as the products had similar structures. With regard to the burst effect, the mass of drug released during this period and the rate at which it was released were dependent on the aluminosilicate and the proportion of PFA included in the formulation. This meant the burst release of drug could be changed if required. This would be beneficial where it is necessary to deliver a specific loading dose to a patient prior to a maintenance dose.

In addition to the burst effect, there was also extended release of drug from the pellets. As with the burst effect, the rate of extended release was dependent on the proportion of PFA in the formulation and the aluminosilicate in the formulation. This further demonstrated the importance of the porous microstructure in extending drug release and provided a means to tailor the rate of drug release to meet clinical requirements. The differing behaviour of pellets formulated with kaolin and halloysite was due to differences in the structure of these clay minerals. The microtubular structure of halloysite entrapped the drug and extended its release, unlike the plate-like structure of kaolin. This was in agreement with the observations of a number of other researchers.
Having demonstrated that extrusion-spheronization could be used to produce porous aluminosilicate pellets, a second pelletization technique, cryopelletization, was investigated. This is a novel technique that should find widespread uses in the pharmaceutical industry for two reasons. Firstly, it is a relatively simple technique that can rapidly produce large quantities of pellets. Secondly, equipment that can manufacture pellet quantities ranging from 0.5 to 250 kg/h is commercially available (Knoch, 1994). This would allow product development to begin on a small scale in research facilities before it is increased to production scale.

Preliminary cryopelletization studies were carried out to determine the excipients needed to produce pharmaceutically acceptable pellets. It was found that although aqueous slurries of kaolin could be cryopelletized, the resulting pellets were relatively weak and broke up rapidly in water. Therefore, sodium silicate solution was included in the formulation. Having established the necessary formulation components, the effects of process and formulation parameters on pellet size and shape were investigated. The formulation apparent viscosity and surface tension, as well as the internal needle diameter used to produce the formulation droplets, were particularly important. These parameters could be used to control the pellet diameter, which would be essential for industrial applications.

Based on the results of these initial investigations, a series of products containing different proportions of kaolin/halloysite and sodium silicate solution were prepared. These products were highly porous with the pores being created by the sublimation of ice during freeze-drying. The porosity facilitated drug loading of the products, meaning they could act as drug carrier systems. Although loading was carried out after pelletization, the drug could also have been incorporated at the formulation stage (Buxton and Peach, 1984; Wunderlich et al., 1995b). This is an area in which research could be carried out in the future.
As with the commercial porous ceramics and the extrusion-spherization products, the cryopelletization products extended the release of incorporated drugs. This was due to entrapment of the drug within the porous interior of the pellets. It was found that the porous microstructure of the pellets influenced the rate of drug release. Since the proportion of aluminosilicate and sodium silicate solution in the formulation affected the porous microstructure, the release could be modified to clinical requirements. In the case of diltiazem HCl, the microclimate pH of the pellets also had a marked influence on its rate of release. This was because it suppressed the ionisation of diltiazem HCl, thereby reducing its solubility in the dissolution medium. As the microclimate pH was dependent on the proportion of sodium silicate solution in the formulation, it could be used to change the rate of diltiazem HCl release.

In summary, each of the porous products examined could act as an extended release drug delivery system. The drug loading and release were reproducible and could be modified to meet clinical requirements, which made the products particularly versatile. In addition, even where an individual product did not meet these requirements, a mixture of products with different porous microstructures could be used to obtain the desired drug loading or release. A point regarding these conclusions is that they are based on the results of in vitro dissolution testing. However, it is expected that in vivo testing will confirm that the porous products can act as extended release drug delivery systems. This is because the ability of dissolution testing to indicate the in vivo release pattern of drugs from porous ceramics has been demonstrated (Mathivanar et al., 1990; Shinto et al., 1992). To confirm this is the case, in vivo testing of the porous products should be carried out in the future.

In addition to demonstrating that porous aluminosilicate pellets could act as extended release drug delivery systems, the mechanisms governing drug release were investigated. The burst effect was modelled using a first order equation, which described drug dissolution under sink conditions with a reducing surface area (Wagner, 1969). However, where the rate of drug release during this period was relatively high, this equation reduced to a single parameter. The extended drug release was modelled using an equation proposed by Ritger and Peppas (1987), which indicated that the rate-limiting step in drug release was diffusion of the drug by a Fickian mechanism. By establishing the mechanisms of drug release from the porous products, this expanded on
the limited research that has been carried out in this area. With further research, it should be possible to establish exact relationships between drug physicochemical properties and rates of release from different porous products. This would allow for accurate prediction of the pellet characteristics required for a particular drug delivery application without the need for extensive preliminary dissolution testing.

The research presented in this thesis focussed on pelletized dosage forms containing aluminosilicate clay minerals. In particular, the applications of kaolin and halloysite were investigated. However, these are only two of many clay minerals that have potential pharmaceutical applications. For example, Evcim and Barr (1955) examined the adsorptive capacity of attapulgite for selected alkaloids and found it was superior to that of either kaolin or halloysite. In related research, Khalil et al. (1984) demonstrated that veegum and attapulgite adsorbed greater levels of ampicillin than kaolin. Further research should be carried out to determine whether these and other clay minerals are suitable for pelletization. The ability of the resulting pellets to act as extended release drug delivery systems could then be assessed. To this end, Barry and Deasy (2004) are currently investigating the potential applications of sepiolite in extended drug delivery. Sepiolite is a magnesium silicate clay mineral, which occurs as large bundles of crystalline fibres with channels of molecular dimensions running along the longitudinal direction of the fibres (Molina-Sabio et al., 2001). It is envisaged that these channels may entrap low molecular weight drugs in the same manner as the halloysite microtubules thereby extending drug release.

In addition to drug delivery applications, the products examined in this thesis have many potential non-pharmaceutical applications. Given their ability to extend drug release, the products could also be used to extend chemical delivery. Examples of potential applications in this area include the delivery of agrochemicals in pest control, reactants in chemical reactions and nutrients in biological media. In addition, if the extrusion-spheronization and cryopelletization products were sintered at high temperatures, they would be able to withstand the high temperatures and chemically harsh conditions encountered in certain chemical processes (Julbe et al., 2001). The resulting products could then be used as catalyst supports and membrane reactors. However, the effects that high temperature sintering had on the products would need to be determined.
Finally, extrusion-spheronization and cryopelletization have not been widely applied in the production of porous clay/ceramic pellets. Therefore, they represent new production methods for the ceramics industry. It is expected that they will find widespread applications in this industry, as the resulting products have relatively small pores in comparison to those produced using methods such as polymer sponge replication (Sepulveda and Binner, 1999). In addition, the porous microstructure can be modified to meet the requirements of a particular application. For example, in the extrusion-spheronization products the porous microstructure would be influenced by the quantities and sizes of the liquid and solid PFA’s in the formulation.

In conclusion, the porous products examined represent a novel class of extended release drug delivery systems. It is expected that the research presented in this thesis will act as a stimulus for further research in this area, as a wide variety of clay minerals have potential pharmaceutical uses. Apart from these high value applications, the pelletization techniques and porous products investigated should find uses in the ceramic and chemical industries.
REFERENCES

Achanta, A.S., Adusumilli, P.S., James, K.W., Rhodes, C.T., (1997),
Development of hot melt coating methods,

Aly, M.E., (2000),
Effect of bulk-reacting liners on sound wave propagation in annular variable area ducts,

Active fixation leads – long-term threshold reduction using a drug-infused ceramic collar,
*PACE*, **14**, 1767-1771.

Ansel, H.C., Allen, L.V., Popovich, N.G., (1999),
Modified release dosage forms and drug delivery systems,

Arici, S., Minors, C.J., Messer, P.F., (1997a),
Porous ceramic lamellae for orthodontic ceramic brackets. 1. Fabrication and characterization,
Arici, S., Minors, C.J., Messer, P.F., (1997b),
Porous ceramic lamellae for orthodontic ceramic brackets. 2. *In vitro* performance testing,

Effect of controlled release of platelet-derived growth factor from a porous hydroxyapatite implant on bone ingrowth,
*Biomaterials*, 17, 703-709.

Barr, M., Arnista, E.S., (1957),
Adsorption studies on clays. I. The adsorption of two alkaloids by activated attapulgite, halloysite and kaolin,

Barry, A., Deasy, P.B., (2004),
Development of advanced drug delivery systems based on macroporous carrier particles,
*Unpublished*.

Study on the influence of spheronization and drying conditions on the physico-mechanical properties of neutral spheroids containing Avicel PH101 and lactose,

Morphology and structure of endellite and halloysite,

Preparation and dissolution characteristics of prolonged release mebeverine-HCl beads,
References

Bechgaard, H., Ladefoged, K., (1978),
Distribution of pellets in the gastrointestinal tract. The influence of transit time exerted by the density or diameter of pellets,

Bhagat, H.R., Mendes, R.W., Mathiowitz, E., Bhargava, H.N., (1991),
A novel, self-correcting membrane coating technique,

Bianchini, R., Bruni, G., Gazzaniga, A., Vecchio, C., (1992),
Influence of extrusion-spheronization processing on the physical properties of d-ibuprofen pellets containing pH adjusters,

Biasini, V., Parasporo, M., Bellosi, A., (1997),
Fabrication and characterisation of Al₂O₃ porous bodies by hot isostatic pressing,
*Thin Solid Films*, 297, 207-211.

Bodmeier, R., Paeratakul, O., (1989),
Spherical agglomerates of water-insoluble drugs,
*J. Pharm. Sci.*, 78, 964-967.

Breitkreutz, J., Bornhöft, M., Wöll, F., Kleinebudde, P., (2003),
Pediatric drug formulations of sodium benzoate: I. Coated granules with a hydrophilic binder,

British National Formulary, (2003),

258
References

British Pharmacopoeia, (2002),  

Brook, R., Cahn, R.W., (1990),  
Silicates,  

Brown, G., (1980),  
Associated minerals,  

Bruder, S.P., Kraus, K.H., Goldberg, V.M., Kadiyala, S., (1998),  
The effects of implants loaded with autologous mesenchymal stem cells on the healing of canine segmental bone defects,  

Buchmuller, J., Weyermanns, G., (1989),  
Device for the controlled freezing of viscous liquids,  
U.S. Patent 4, 829, 783.

Buxton, I.R., Peach, J.M., (1984),  
Process and apparatus for freezing a liquid medium,  

Caplan, A.I., (1990),  
Cell delivery and tissue regeneration,  
Control of transport properties with a microporous membrane reactor to enhance
yields in dehydrogenation reactions,

Lipid solubility of a series of drugs and its relevance to fatal poisoning,

Hydroxypropyl methylcellulose phthalate beads containing a model non-steroid
anti-inflammatory drug,

Chang, C.-M., Bodmeier, R., (1997),
Binding of drugs to monoglyceride-based drug delivery systems,
_Int. J. Pharm., 147_, 135-142.

Chatlapalli, R., Rohera, B.D., (1998),
Physical characterization of HPMC and HEC and investigation of their use as
pelletization aids,

Chatterjee, B.K., Buhl, S.N., Yu, C.-S., Tang, T.N., Smith, G.L., Bhayani, B., Alvarado,
A., Wong, S., (1994),
Cryogenic apparatus,
U.S. Patent 5, 275, 016.

Chen, Y.F., Wang, M.C., Hon, M.H., (2004),
Phase transformation and growth of mullite in kaolin ceramics,
Chhabra, R.P., (1993),
Fluid particles in non-Newtonian media,

Chiou, S.-H., Wu, W.-T., Huang, Y.-Y., Chung, T.-W., (2001),
Effects of the characteristics of chitosan on controlling drug release of chitosan coated PLLA microspheres,
*J. Microencap.*, 18, 613-625.

Chong-Kook, K., Eun-Jin, I., (1992),
The controlled release of blue dextran from alginate beads,

Clarke, D.B., (1992),
Classification and occurrence of granitoid rock,

Clarke, E.G.C., (1986),

Ellipsoidal fluid particles,

Collett, J., Moreton, C., (2002),
Modified-release peroral dosage forms,
Cornwell, K.L., Tinland-Butez, M.F., Tardone, P.J., Cabasso, I., Hammel, K.E., (1990), Lignin degradation and lignin peroxidase production in cultures of Phanerochaete chrysosporium immobilized on porous ceramic supports, Enzyme Microb. Technol., 12, 916-920.


References

Denissen, H., van Beek, E., Martinetti, R., Klein, C., van der Zee, E., Ravaglioli, A., (1997),
Net-shaped hydroxyapatite implants for the release of agents modulating periodontal-like tissues,

Drug Information Full Text, (2003),
*Drug Information Full Text*, American Society of Hospital Pharmacists, Maryland, USA.

Dubernet, C., Benoit, J.P., Peppas, N.A., Puisieux, F., (1990),
Ibuprofen-loaded ethylcellulose microspheres: release studies and analysis of the matrix structure through the Higuchi model,
*J. Microencap.*, 7, 555-565.

Duncan, R., Seymour, L.W., (1989),
Introduction and terminology,

Eerikäinen, S., (1991),
Effects of spheronization on some properties of uncoated and coated granules containing different kinds of fillers,
*Int. J. Pharm.*, 77, 89-106.

Elbers, J.A.C., Bakkenes, H.W., Fokkens, J.G., (1992),
Effect of amount and composition of granulating liquid on mixing, extrusion and spheronization,

El-Mahdi, I.M., (1998),
Peroral targeting of ketoprofen to the colon,
*PhD. Thesis*, Trinity College Dublin, University of Dublin.
References

Preparation and characterization of agar beads containing phenobarbitone sodium,
*J. Microencap.*, **5**, 159-163.

Evcim, N., Barr, M., (1955),
Adsorption of some alkaloids by different clays,

Fabbri, M., Celotti, G.C., Ravaglioli, A., (1994),
Granulates based on calcium phosphate with controlled morphology and porosity for medical applications: physico-chemical parameters and production technique,

Long-term evaluation of titania-based ceramics compared with commercially pure titanium *in vivo*,

Role of expanded clay and porous ceramic amendments on plant establishment in minespoils,

Gallagher, K.M., Corrigan, O.I., (2000),
Mechanistic aspects of the release of levamisole hydrochloride from biodegradable polymers,

Gandhi, R., Kaul, C.L., Panchagnula, R., (1999),
Extrusion and spheronization in the development of oral controlled-release dosage forms,
Garcia, A.M., Ghaly, E.S., (1996),

Preliminary spherical agglomerates of water soluble drug using natural polymer and cross-linking technique,


Gattefosse, (2003),

Precirol ATO 5 product information,


Ghebre-Sellassie, I., (1989),

Pellets: A general overview,


Gibson, L.J., Ashby, M.F., (1997a),

Introduction,


Gibson, L.J., Ashby, M.F., (1997b),

Thermal, electric and acoustic properties of foams,


Glassven, (2004),

Sodium silicate solution information,


Gohel, M.C., Amin, A.F., (1998),

Formulation optimization of controlled release diclofenac sodium microspheres using factorial design,

Development of matrix controlled release beads by extrusion-spheronization technology using a statistical screening design,

Controlled release pellets by extrusion-spheronization,

Gren, T., Bjerre, C., Camber, O., Ragnarsson, G., (1996),
*In vitro* drug release from porous cellulose matrices,

Gribble, C.D., (1988),
The silicate minerals,

Griffin, E.N., Niebergall, P.J., (1999),
Release kinetics of a controlled-release multiparticulate dosage form prepared using a hot-melt fluid bed coating method,

Handbook of Pharmaceutical Excipients, (2000),

Harris, B., Cooke, R.G., Hammett, F.W., Russell-Floyd, R.S., (1998),
Sol-gel composites – a low cost manufacturing route,
Harvey, C.C., (1996),
Halloysite: For high quality ceramics,

Heneghan, R., Byrne, R.S., Deasy, P.B., (2003),
The production of kaolin microparticles by extrusion-spheronization,
*Senior Sophister Research Project*, Trinity College Dublin, University of Dublin.

Hicks, D.C., Freese, H.L., (1989),
Extrusion and spheronizing equipment,

Higuchi, T., (1963),
Mechanism of sustained-action medication,
*J. Pharm. Sci.*, **52**, 1145-1149.

Response surface optimisation of high dose pellets by extrusion and spheronization,
*Int. J. Pharm.*, **100**, 71-79.

Imerys, (2004),
Ball clay information,

Ishizaki, K., Komarneni, S., Nanko, M., (1998a),
Powder compacts and green bodies for porous materials,
References

Ishizaki, K., Komarneni, S., Nanko, M., (1998b),
Applications of porous materials,

Ishizaki, K., Komarneni, S., Nanko, M., (1998c),
Sintering mechanisms and advanced sintering methods for porous materials,

Itokazu, M., Esaki, M., Yamamoto, K., Tanemori, T., Kasai, T., (1999),
Local drug delivery system using ceramics: vacuum method for impregnating a chemotherapeutic agent into a porous hydroxyapatite block,

Itokazu, M., Matsunaga, T., Kumazawa, S., Oka, M., (1994),
Treatment of osteomyelitis by antibiotic impregnated porous hydroxyapatite block,

Synthesis of antibiotic-loaded hydroxyapatite blocks by vacuum method and _in vitro_ drug release testing,
_Biomaterials_, 19, 817-819.

Jaiyeoba, K.T., Spring, M.S., (1980),
The granulation of ternary mixtures: the effect of the wettability of the powders,
_J. Pharm. Pharmacol._, 32, 386-388.

Plastic forming of ceramics: extrusion and injection moulding,
Sustained and controlled-release drug delivery systems,  
*Modern Pharmaceutics, 3rd Edition*, Banker, G.S., Rhodes, C.T., (Eds.), Marcel  

Jones, C.D., (1992),  
Method of preparing and storing a free flowing, frozen alimentary dairy product,  
U.S. Patent 5,126,156.

Jozwiakowski, M.J., Jones, D.M., Franz, R.M., (1990),  
Characterization of a hot-melt fluid bed coating process for fine granules,  

Julbe, A., Farrusseng, D., Guizard, C., (2001),  
Porous ceramic membranes for catalytic reactors – overview and new ideas,  

The fabrication and biochemical evaluation of alumina reinforced calcium  
phosphate porous implants,  

Juppo, A.M., Hellén, L., Pullinen-Strander, V., Kalsta, K., Yliuruusi, J., Kristoffersson,  
E., (1997),  
Application of mercury porosimetry in evaluation of extrusion-spheronisation  
process,  

Immobilization of lipase on a new inorganic ceramics support, toyonite, and the  
reactivity and enantioselectivity of the immobilized lipase,  
Preparation of multiple unit hollow microspheres (microballoons) with acrylic
resin containing tranilast and their drug release characteristics (in vitro) and
floating behaviour (in vivo),

Kelly, M.H., (2002),
Novel formulations for use in the oral cavity,
*PhD. Thesis*, Trinity College Dublin, University of Dublin.

Khalil, S.A.H., Mortada, L.M., El-Khawas, M., (1984),
The uptake of ampicillin and amoxycillin by some adsorbents,

Kikuchi, A., Kawabuchi, M., Watanabe, A., Sugihara, M., Sakurai, Y., Okano, T.,
(1999),
Effect of Ca\(^{2+}\)-alginate gel dissolution on release of dextran with different
molecular weights,

Knoch, A., (1994),
Cryopelletization,
*Multiparticulate Oral Drug Delivery*, Ghebre-Sellassie, I., (Ed.), Marcel Dekker,

Komlev, V.S., Barinov, S.M., Koplik, E.V., (2002),
A method to fabricate porous spherical hydroxyapatite granules intended for
time-controlled drug release,
*Biomaterials*, **23**, 3449-3454.

Porous ceramic bodies for drug delivery,
References

Kristensen, H.G., Schaefer, T., (1987),
A review on pharmaceutical wet-granulation,

Ku, C.C., Joshi, Y.M., Bergum, J.S., Jain, N.B., (1993),
Bead manufacture by extrusion-spheronization – a statistical design for process optimization,

Kumar, R., Kuloor, N.R., (1970),
The formation of bubbles and drops,

Calcium phosphate ceramics as drug-delivery system for anticancer therapy,
*Key Eng. Mat.*, **192**, 901-904.

Langer, R.S., Peppas, N.A., (1981),
Present and future applications of biomaterials in controlled drug delivery systems,

Lasserre, A., Bajpai, P.K., (1998),
Ceramic drug-delivery devices,

Law, M.F.L., (1996),
Excipient evaluation for extrusion-spheronization with indomethacin application,
*PhD. Thesis*, Trinity College Dublin, University of Dublin.
Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., (2003),
Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns,

Leo, E., Forni, F., Bernabei, M.T., (2000),
Surface drug removal from ibuprofen-loaded PLA microspheres,

Fabrication of porous polymeric matrix drug delivery devices using the selective laser sintering technique,

Novel pharmaceutical excipients,
*PhD. Thesis*, Trinity College Dublin, University of Dublin.

Characterisation of halloysite for use as a microtubular drug delivery system,
*Int. J. Pharm.*, **243**, 125-134.

Levis, S.R., Deasy, P.B., (2003),
Use of coated microtubular halloysite for the sustained release of diltiazem hydrochloride and propranolol hydrochloride,

Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50 D,
Lindner, H., Kleinebudde, P., (1994),
Use of powdered cellulose for the production of pellets by extrusion-spheronization,

Lindner, W.D., Lippold, B.C., (1995),
Drug release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress,

Linhardt, R.J., (1989),
Biodegradable polymers for controlled release of drugs,

Liu, D.M., (1996),
Fabrication and characterization of porous hydroxyapatite granules,

Liu, D.M., (1997),
Influence of porous microarchitecture on the _in-vitro_ dissolution and biological behaviour of porous calcium phosphate ceramics,

Liu, F.J., Chou, K.S., (2000),
Characterization of microstructure and properties of porous ceramics made by extrusion,

Liu, Y.F., Liu, X.Q., Wei, H., Meng, G.Y., (2001),
Porous mullite ceramics from national clay produced by gelcasting,
Lulewicz, J.D., Roux, N., (1998),
First results of the investigation of Li$_2$ZrO$_3$ and Li$_2$TiO$_3$ pebbles,

Lyckfeldt, O., Ferreira, J.M.F., (1998),
Processing of porous ceramics by ‘starch consolidation’,

Martin, A.N., (1993),
Diffusion and dissolution,

Mathivanar, R., Anderson, N., Harman, D., Skalsky, M., Ng, M., (1990),
_In vivo_ elution rate of drug eluting ceramic leads with a reduced dose of
dexamethasone sodium-phosphate,
_PACE_, 13, 1883-1886.

Mazzo, D.J., Obetz, C.L., Shuster, J., (1994),
Diltiazem hydrochloride,
_Analytical Profiles of Drug Substances and Excipients, Volume 23_, Brittain,

Mehta, A.M., (1989),
Evaluation and characterization of pellets,
_Pharmaceutical Pelletization Technology_, Ghebre-Sellassie, I., (Ed.), Marcel

Millili, G.P., Schwartz, J.B., (1990),
The strength of microcrystalline cellulose pellets: The effect of granulating with
water/ethanol mixtures,
_Drug Dev. Ind. Pharm.,_ 16, 1411-1426.
Molina-Sabio, M., Caturla, F., Rodríguez-Reinoso, F., Kharitonova, G.V., (2001),
Porous structure of a sepiolite as deduced from the adsorption of N₂, CO₂, NH₃
and H₂O,

Porous ceramics by powder processing,

Moore, D.M., Reynolds, R.C., (1997a),
Introduction and historical background,
*X-ray Diffraction and the Identification and Analysis of Clay Minerals*, Oxford
University Press, New York, pp. 3-27.

Moore, D.M., Reynolds, R.C., (1997b),
Structure and properties: General treatment,
*X-ray Diffraction and the Identification and Analysis of Clay Minerals*, Oxford
University Press, New York, pp. 104-137.

Moore, D.M., Reynolds, R.C., (1997c),
Identification of clay minerals and associated minerals,
*X-ray Diffraction and the Identification and Analysis of Clay Minerals*, Oxford

Moore, W.R., Graves, S.E., Bain, G.I., (2001),
Synthetic bone graft substitutes,

Moscou, L., Lub, S., (1981),
Practical use of mercury porosimetry in the study of porous solids,
Mukai, S.R., Nishihara, H., Tamon, H., (2003),
Porous properties of silica gels with controlled morphology synthesized by unidirectional freeze-gelation,

Murata, Y., Maeda, T., Miyamoto, E., Kawashima, S., (1993),
Preparation of chitosan-reinforced alginate gel beads – effects of chitosan on gel matrix erosion,
*Int. J. Pharm.*, **96**, 139-145.

Murray, H.H., (2000),
Traditional and new applications for kaolin, smectite, and palygorskite: a general overview,

Nagasawa, K., (1978),
Kaolin minerals,

Fabrication and characterization of extruded and spheronized beads containing carbopol® 974P, NF resin,

Potential use of gelcasting hydroxyapatite porous ceramic as an implantable drug delivery system,

The chemical constitution of clays,


The influence of process variables on the preparation and properties of spherical granules by the process of extrusion and spheronisation,


O’Connor, R.E., Schwartz, J.B., (1989),

Extrusion and spherization technology,


Synergy of polysaccharide mixtures in gelcasting of alumina,


Ono, I., Inoue, M., Kuboki, Y., (1996),

Promotion of the osteogenetic activity of recombinant human bone morphogenetic protein by prostaglandin E1,

*Bone*, **19**, 581-588.

Østberg, T., Vesterhus, L., Graffner, C., (1993),

Calcium alginate matrices for oral multiple unit administration: II. Effect of process and formulation factors on matrix properties,


Pabst, W., Kunes, K., Havrda, J., Gregorová, E., (2000),

A note on particle size analyses of kaolins and clays,

Paul, W., Nesamony, J., Sharma, C.P., (2002),
Delivery of insulin from hydroxyapatite ceramic microspheres: Preliminary in vivo studies,

Paul, W., Sharma, C.P., (1995),
Antibiotic loaded hydroxyapatite osteoconductive implant material – in vitro release studies,

Paul, W., Sharma, C.P., (1999),
Development of porous spherical hydroxyapatite granules, application towards protein delivery,

Microstructure of porous ceramics,

Pharmaceutical Codex, (1994),

Pierre, A.C., (1997),
Porous sol-gel ceramics,
*Ceram. Int.*, 23, 229-238.

Pillay, V., Fassihi, R., (1999),
*In vitro* release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract: I. Comparison of pH-responsive drug release and associated kinetics,

278
Pinto, J.F., Buckton, G., Newton, J.M., (1982),
The influence of four selected processing and formulation factors on the
production of spheres by extrusion and spheronisation,

Prendergast, R., Byrne, R.S., Deasy, P.B., (2002),
Investigation of cryopelletization for producing pseudo porous ceramics for drug
delivery,
*Senior Sophister Research Project*, Trinity College Dublin, University of
Dublin.

Price, R.R., Gaber, B.P., Lvov, Y., (2001),
*In-vitro* release characteristics of tetracycline HCl, khellin and nicotinamide
adenine dinucleotide from halloysite; a cylindrical mineral,

Queiroz, A.C., Santos, J.D., Monteiro, F.J., Gibson, I.R., Knowles, J.C., (2001),
Adsorption and release studies of sodium ampicillin from hydroxyapatite and
glass-reinforced hydroxyapatite composites,
*Biomaterials*, **22**, 1393-1400.

Reddy, E.S., Schmitz, G.J, (2002),
Superconducting foams,

Reed, J.S., (1995),
Common raw materials,
*Principles of Ceramics Processing, 2nd Edition*, John Wiley & Sons, New York,
pp. 35-53.

Rice, R.W., (1998),
Summary of porosity and microcracking effects, applications, special
fabrication, and engineering,
A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs,

Said, S., Al-Shora, H., (1980),
Adsorption of certain oral hypoglycaemics on kaolin and charcoal and its relationship to hypoglycaemic effects of drugs,
*Int. J. Pharm.*, 5, 223-228.

Salter, A.E., (2003),
Use of halloysite for agrochemical applications,
*PhD. Thesis*, Trinity College Dublin, University of Dublin.

Schmedders, T., Andresen, L., Koch, D., Grathwohl, G., (2001),
Porous materials by freeze-casting,
*Materials Week*, Munich, Germany.

Schneider, H., Okada, K., Pask, J.A., (1994),
Mullite synthesis,

Schröder, M., Kleinebudde, P., (1995),
Structure of disintegrating pellets with regard to fractal geometry,
*Pharm. Res.*, 12, 1694-1700.

Statistical output,
References

Sepulveda, P., Binner, J.G.P., (1999),
Processing of cellular ceramics by foaming and in situ polymerisation of organic monomers,

Sheppard, Jr., N.F., Mears, D.J., Straka, S.W., (1996),
Micromachined silicon structures for modelling polymer matrix controlled release systems,

Sherrington, P.J., Oliver, R., (1981),
Agitation,

Shinto, Y., Uchida, A., Korkusuz, F., Araki, N., Ono, K., (1992),
Calcium hydroxyapatite ceramics used as a delivery system for antibiotics,

Bioactive delivery systems for the slow release of antibiotics: incorporation of Ag⁺ ions into micro-porous hydroxyapatite coatings,

Siegel, R.A., (1989),
Modeling of drug release from porous polymers,

Reporting physisorption data for gas/solid systems with special reference to the determination of surface area and porosity,
Sivakumar, M., Panduranga Rao, K., (2002),
Preparation, characterization and in vitro release of gentamicin from coralline hydroxyapatite-gelatin composite microspheres,
*Biomaterials*, **23**, 3175-3181.

Soltmann, U., Böttcher, H., Koch, D., Grathwohl, G., (2003),
Freeze gelation: a new option for the production of biological ceramic composites (biocers),

Sood, A., Panchagnula, R., (1998),
Drug release evaluation of diltiazem CR preparations,

Stapleton, M.P., (1997),
Sir James Black and propranolol - The role of the basic sciences in the history of cardiovascular pharmacology,

On high-porous ceramic for pharmaceutical carrier,

Sweetman, S.C., (2002),

The kinetics of pentoxifylline release in vivo from drug-loaded hydroxyapatite implants,
Takahara, H., (1994),
The sound-absorption characteristics of particulate porous ceramic materials,
*Appl. Acoustics, 41*, 265-274.

Histological and biochemical evaluation of osteogenic response in porous hydroxyapatite coated alumina ceramics,
*Biomaterials, 17*, 1499-1505.

Dental high-speed cutting of porous-machinable-ceramic/resin composites and bovine enamel,

Tapia, C., Buckton, G., Newton, J.M., (1993),
Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronisation,

Thoma, K., Alex, R., Randzio, J., (1992),
Biodegradable controlled release implants based on tricalcium phosphate ceramic,

The role of reactive surface sites and complexation by humic acids in the interaction of clay mineral and iron oxide particles,

Torniainen, P.M., Chu, X., Schmidt, L.D., (1994),
Comparison of monolith-supported metals for the direct oxidation of methane to syngas,
*J. Catal., 146*, 1-10.
Türkoglu, M., Gürsoy, A., Ergőlü, L., Okar, I., (1997),
Effect of aqueous polymer dispersions on properties of diclofenac/alginate beads and in vivo evaluation in rats,
*S.T.P. Pharma Sci.*, 7, 135-140.

Twigg, M.V., Richardson, J.T., (2002),
Theory and applications of ceramic foam catalysts,

Uchida, A., Araki, N., Shinto, Y., Yoshikawa, H., Kurisaki, E., Ono, K., (1990),
The use of calcium hydroxyapatite ceramic in bone tumour surgery,

The use of ceramics for bone replacement,

United States Pharmacopeia, (2003),
United States Pharmacopeial Convention, Inc., USA.

Materials for biomedical applications,

van Olphen, H., (1963a),
Clay mineralogy,

van Olphen, H., (1963b),
Properties of hydrophobic sols,
van Olphen, H., (1963c),
   Electric double-layer structure and stability of clay suspensions,
   *An Introduction to Clay Colloid Chemistry*, John Wiley & Sons, Inc., New York,
   pp. 89-108.

van Olphen, H., (1987),
   Dispersion and flocculation,

   Use of enteric polymers for production of microspheres by extrusion-
   spheronization,
   *Pharm. Acta Helv.*, 72, 145-152.

Velde, B., (1992a),
   The clay perspective,
   *Introduction to Clay Minerals: Chemistry, Origins, Uses and Environmental

Velde, B., (1992b),
   Clays as minerals,
   *Introduction to Clay Minerals: Chemistry, Origins, Uses and Environmental

   Extrusion-spheronisation – A literature review,
   *Int. J. Pharm.*, 116, 131-146.

Wagner, J.G., (1969),
   Interpretation of percent dissolved-time plots derived from *in vitro* testing of
   conventional tablets and capsules,
   *J. Pharm. Sci.*, 58, 1253-1257.
References

Wan, L.S.C., Heng, P.W.S., Liew, C.V., (1993),
Spheronization conditions on spheroid shape and size,

Watanabe, A., Hayashi, T., (1976),
Microencapsulation techniques of Fuji Photo Film Co. Ltd., and their applications,

Wesseling, M., Bodmeier, R., (1999),
Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution,

Worrall, W.E., (1986),
Silica,

Ultrafiltration of soybean oil/hexane extract by porous ceramic membranes,

Ni(Al, Fe)2O4-TiO2 ceramic humidity sensors,

Pellets containing dihydropyridine derivatives process for the production thereof and use as rapid action dosage in heart and circulatory diseases,
U.S. Patent 5, 384, 129.
References

Means for containing active substances, having a shell of hydrophilic macromolecules, active substances and process for preparation thereof,
U.S. Patent 5, 405, 616.

Wunderlich, J.C., Schick, U., Werry, J., Freidenreich, J., (1996),
Shaped articles containing plant extract(s), in particular pellets, and their pharmaceutical or cosmetic use,

Yamamura, K., Iwata, H., Yotsuyanagi, T., (1992),
Synthesis of antibiotic-loaded hydroxyapatite beads and in vitro drug release testing,

Yamamura, K., Yotsuyanagi, T., (1992),
Adsorption and irreversible binding of adriamycin incorporated into hydroxyapatite beads,
*Int. J. Pharm.*, 79, R1-R3.

York, P., (2002),
The design of dosage forms,

Development and in-vitro evaluation of a multiparticulate sustained release theophylline formulation,

Production and characterisation of enteric beads,
*Int. J. Pharm.*, 125, 151-155.
Porous hydroxyapatite granules: Their synthesis, application and characterisation,

Improvement in the strength of reticulated porous ceramics by vacuum degassing,
Appendix 1

UV calibration curves used to determine the concentration of drugs in solution

(1) Diltiazem HCl in phosphate buffer pH 6.8

Analytical wavelength: 238 nm
Concentration (g/L) = \((\text{Absorbance} - 0.0136) / 50.612\)
\(R^2 = 0.9998\)

(2) Sodium benzoate in phosphate buffer pH 6.8

Analytical wavelength: 222.8 nm
Concentration (g/L) = \((\text{Absorbance} - 0.0069) / 58.633\)
\(R^2 = 0.9993\)

(3) Benzoic acid in phosphate buffer pH 6.8

Analytical wavelength: 221.8 nm
Concentration (g/L) = \((\text{Absorbance} - 0.0093) / 69.38\)
\(R^2 = 0.9996\)

(4) Propranolol HCl in phosphate buffer pH 6.8

Analytical wavelength: 222 nm
Concentration (g/L) = \((\text{Absorbance} - 0.0029) / 113.28\)
\(R^2 = 0.999\)
Analytical wavelength: 290 nm
Concentration (g/L) = (Absorbance + 0.0014) / 18.866
R² = 0.9998

(5) Diltiazem HCl in 0.1N HCl

Analytical wavelength: 238 nm
Concentration (g/L) = (Absorbance + 0.0037) / 50.04
R² = 0.9999

(6) Sodium benzoate in 0.1N HCl

Analytical wavelength: 230 nm
Concentration (g/L) = (Absorbance + 0.0012) / 73.387
R² = 1

(7) Benzoic acid in 0.1N HCl

Analytical wavelength: 230 nm
Concentration (g/L) = (Absorbance + 0.0059) / 88.12
R² = 0.9998

(8) Diltiazem HCl in water

Analytical wavelength: 236 nm
Concentration (g/L) = (Absorbance + 0.0065) / 50.402
R² = 1

(9) Sodium benzoate in water

Analytical wavelength: 224 nm
Concentration (g/L) = (Absorbance - 0.0014) / 54.891
R² = 1
(10) Benzoic acid in ethanol

Analytical wavelength: 226 nm
Concentration (g/L) = (Absorbance + 0.0088) / 87.373
$R^2 = 0.9996$

(11) Propranolol HCl in water

Analytical wavelength: 290 nm
Concentration (g/L) = (Absorbance - 0.0062) / 18.844
$R^2 = 0.9998$
Appendices

Appendix 2

Saturation solubility studies

(1) Diltiazem HCl in water at 26 °C

Mass dissolved after 24 h = 403 +/- 39 g/L
Mass dissolved after 48 h = 456 +/- 42 g/L

Average mass dissolved = 429.5 +/- 57 g/L

(2) Sodium benzoate in water at 26 °C

Mass dissolved after 24 h = 422 +/- 17 g/L
Mass dissolved after 48 h = 424 +/- 10 g/L

Average mass dissolved = 423 +/- 19 g/L

(3) Benzoic acid in ethanol at 26 °C

Mass dissolved after 24 h = 351 +/- 26 g/L
Mass dissolved after 48 h = 295 +/- 7 g/L

Average mass dissolved = 323 +/- 25 g/L

(4) Propranolol HCl in water at 26 °C

Mass dissolved after 24 h = 127 +/- 20 g/L
Mass dissolved after 48 h = 118 +/- 1 g/L

Average mass dissolved = 123 +/- 13 g/L
(5) Diltiazem HCl in phosphate buffer pH 6.8 at 37 °C

Mass dissolved after 24 h = 572 +/- 8 g/L
Mass dissolved after 48 h = 564 +/- 1 g/L

Average mass dissolved = 568 +/- 8 g/L

(6) Sodium benzoate in phosphate buffer pH 6.8 at 37 °C

Mass dissolved after 24 h = 394 +/- 15 g/L
Mass dissolved after 48 h = 393 +/- 1 g/L

Average mass dissolved = 394 +/- 15 g/L

(7) Benzoic acid in phosphate buffer pH 6.8 at 37 °C

Mass dissolved after 24 h = 7.74 +/- 0.25 g/L
Mass dissolved after 48 h = 8.42 +/- 0.05 g/L

Average mass dissolved = 8.08 +/- 0.26 g/L

(8) Propranolol HCl in phosphate buffer pH 6.8 at 37 °C

Mass dissolved after 24 h = 216 +/- 19 g/L
Mass dissolved after 48 h = 198 +/- 3 g/L

Average mass dissolved = 207 +/- 19 g/L

(9) Diltiazem HCl in 0.1N HCl at 37 °C

Mass dissolved after 24 h = 622 +/- 38 g/L
Mass dissolved after 48 h = 646 +/- 10 g/L

Average mass dissolved = 634 +/- 40 g/L
(10) Benzoic Acid in 0.1N HCl at 37 °C

Mass dissolved after 24 h = 4.96 +/- 0.02 g/L
Mass dissolved after 48 h = 4.62 +/- 0.18 g/L

Average mass dissolved = 4.79 +/- 0.18 g/L
### Appendix 3

**Pressure table used with PoreSizer 9320**

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Appendix 4

Model equations and parameter sets used to fit experimental dissolution data using Micromath® Scientist\textsuperscript{TM} for Windows\textsuperscript{TM}

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Appendix 5

Dissolution profiles of diltiazem HCl from intact and crushed samples of N-light N3 in phosphate buffer pH 6.8 at 37 °C
Appendix 6

Plot of Eqn. 5.3b fitted to the release data for diltiazem HCl from various porous ceramics in phosphate buffer pH 6.8 at 37 °C

(1) N-light N4

(2) Starlight SLK1000
(3) N-light N3 with PVP incorporated

(4) N-light N3 with Ethylcellulose 10 cps incorporated
Appendix 7

Extrusion-spheronization experimental designs and results

(1) Crossed d-optimal design used to investigate kaolin based pellet production

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Appendix 8

Extrusion-spheronization models

K = Kaolin, E = Ethanol, S = Sucrose, SS = Spheronizer speed, ST = Spheronization time

In all cases, insignificant terms not required to support the model hierarchy, have been eliminated.

(1) Fines yield

\[ \sin^{-1}\sqrt{\text{Fines yield}} = 0.01619 \times K - 0.03988 \times E + 0.01272 \times S - 3.289 \times 10^{-6} \times K \times SS + 0.001050 \times K \times ST + 1.273 \times 10^{-5} \times E \times SS - 0.004065 \times E \times ST - 3.212 \times 10^{-6} \times S \times SS - 3.953 \times 10^{-5} \times S \times ST - 1.249 \times 10^{-6} \times K \times SS \times ST + 4.837 \times 10^{-6} \times E \times SS \times ST + 1.632 \times 10^{-9} \times S \times SS \times ST \]

(2) Large pellet yield

\[ \sin^{-1}\sqrt{\text{Large pellet yield}} = -0.05055 \times K + 0.1819 \times E - 0.05473 \times S + 1.818 \times 10^{-5} \times K \times SS + 0.0005040 \times K \times ST - 7.041 \times 10^{-5} \times E \times SS - 0.001952 \times E \times ST + 2.937 \times 10^{-5} \times S \times SS + 0.003629 \times S \times ST - 2.501 \times 10^{-6} \times S \times SS \times ST \]

(3) Pellet yield

\[ \sin^{-1}\sqrt{\text{Pellet yield}} = 0.0660 \times K - 0.176 \times E + 0.0606 \times S - 2.47 \times 10^{-5} \times K \times SS - 0.00336 \times K \times ST + 9.58 \times 10^{-5} \times E \times SS + 0.0130 \times E \times ST - 2.47 \times 10^{-5} \times S \times SS - 0.00405 \times S \times ST + 2.57 \times 10^{-6} \times K \times SS \times ST - 9.95 \times 10^{-6} \times E \times SS \times ST + 2.57 \times 10^{-6} \times S \times SS \times ST \]
(4) Sphericity

\[
\ln\left(\frac{\text{Form PE} - 0}{1 - \text{Form PE}}\right) = 0.0180 \times K + 0.0131 \times E - 0.0332 \times S - 0.00116 \times K \times ST + 0.00450 \times E \times ST + 2.54 \times 10^{-5} \times S \times SS + 0.000585 \times S \times ST
\]
Appendix 9

Plot of values predicted by extrusion-spheronization models versus actual experimental values (values are in the transformed scale)

(1) Fines yield

(2) Large pellet yield
(3) Pellet yield

![Graph](image)

(4) Sphericity

![Graph](image)
Appendix 10

Cryopelletization experimental design and results

<table>
<thead>
<tr>
<th>Std</th>
<th>Run</th>
<th>Formulation</th>
<th>Sodium lauryl sulphate (% w/v)</th>
<th>Internal needle diameter (mm)</th>
<th>Drop height (cm)</th>
<th>Fall height (cm)</th>
<th>Pellet diameter (mm)</th>
<th>Form PE</th>
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Appendix 11

Cryopelletization models used to investigate the effects of production parameters on pellet diameter and sphericity

SLS = Sodium lauryl sulphate, IND = Internal needle diameter, DH = Drop height

(1) Pellet diameter

Formulation A

\[
\text{Pellet diameter} = 1.453 + 0.06743 \times \text{SLS} + 1.408 \times \text{IND} - 0.003524 \times \text{DH} - 0.1917 \times \text{SLS} \times \text{IND} - 0.007778 \times \text{SLS} \times \text{DH}
\]

Formulation B

\[
\text{Pellet diameter} = 1.664 + 0.06743 \times \text{SLS} + 1.408 \times \text{IND} - 0.003524 \times \text{DH} - 0.1917 \times \text{SLS} \times \text{IND} - 0.007778 \times \text{SLS} \times \text{DH}
\]

(2) Sphericity

Formulation A

\[
\ln\left(\frac{\text{Form PE} - 0}{1 - \text{Form PE}}\right) = 2.215 + 0.07154 \times \text{SLS} - 0.4807 \times \text{IND}
\]

Formulation B

\[
\ln\left(\frac{\text{Form PE} - 0}{1 - \text{Form PE}}\right) = 2.287 - 0.009167 \times \text{SLS} - 0.4807 \times \text{IND}
\]
Appendix 12

Plot of values predicted by cryopelletization models (Appendix 11) versus actual experimental values (values are in the transformed scale)

(1) Pellet diameter

![Graph showing predicted versus actual values for pellet diameter.]

(2) Sphericity data

![Graph showing predicted versus actual values for sphericity.]

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Appendix 13

Cryopelletization models used to investigate the effects of formulation parameters on pellet diameter and sphericity

These equations are given in terms of coded factors. The first coefficient is the difference of level 1 from the overall average; the second coefficient is the difference of level 2 from the overall average. The negative sum of both coefficients is the difference of level 3 from the overall average.

K = Kaolin, SS = Sodium silicate solution

(1) Pellet diameter


(2) Sphericity

\[
\]
Appendix 14

Plot of values predicted by cryopelletization models (Appendix 13) versus actual experimental values (sphericity values are in the transformed scale)

(1) Pellet diameter

(2) Sphericity data