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**Use of Computational Fluid Dynamics to investigate the
relationship between hydrodynamics and rates of
dissolution**

by

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being a thesis submitted for the degree of
Doctor of Philosophy in Pharmaceutics

at

University of Dublin
Trinity College

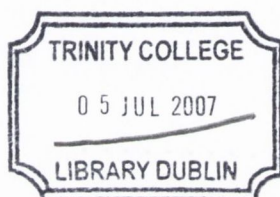
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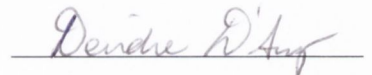


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DECLARATION

This thesis is submitted by the undersigned to the University of Dublin, Trinity College, for examination for the degree of Doctor of Philosophy. It has not been submitted for a degree at any other university. I myself carried out all the practical work except where duly acknowledged. The library of University of Dublin, Trinity College, may lend or copy this thesis on request, subject to the normal conditions of acknowledgement. This manuscript was written by me with the help of editorial advice from Dr. A. M. Healy and Prof. O.I. Corrigan.

A handwritten signature in cursive script, reading "Deirdre D'Arcy", written over a horizontal line.

Deirdre M. D'Arcy

Summary

The hydrodynamics within the paddle (900 ml), basket (900 ml) and Levy beaker (350 ml and 550 ml) (Levy et al., 1965) dissolution apparatuses were simulated using the computational fluid dynamics (CFD) package, FluentTM. Several methods to define convergence and to validate the CFD solutions were investigated.

The simulations within the paddle apparatus expanded on the work of McCarthy (2002), and included simulations of fluid flow around cylindrical compacts in different locations and of different dimensions in the base of the vessel. A rotating reference frame was used to simulate fluid flow around compacts located at the centre of the vessel base of the paddle apparatus and for the Levy beaker apparatus, and a multiple rotating reference frame was used for the paddle apparatus containing off-centre compacts. Flow in the basket apparatus was simulated using a periodic model, and the geometry of one-quarter of the basket and vessel. The basket grid wire geometry was approximated by using a 2-D geometry with perforations equal to the size of those in the wire mesh.

Simulations of the hydrodynamics in each apparatus at different agitation rates revealed flow characteristics which were similar in nature but changed in magnitude at each rotation speed. At lower agitation rates secondary flow features were less evident.

Flow within the basket apparatus was found to be primarily axial (upward) beneath the basket, with radial (outward) flow features at the basket sides. This was confirmed with flow visualisation studies.

Dissolution studies of compacts in the paddle apparatus, of corresponding dimensions and fixed locations to those simulated, revealed an increase in dissolution rate when moved from the centre of the vessel base to an off-centre position. Furthermore, following exposure for 1 hour to dissolution conditions, regions of preferential dissolution and erosion on some compact surfaces were observed. The increase in dissolution rate and regions of preferential dissolution on a compact surface was consistent with the CFD simulations of fluid flow around a compact surface, revealing an area of lower velocity in the central position, with velocity increasing off-centre, and higher velocities present in areas of preferential dissolution.

There was less variability observed in dissolution rate data from a compact fixed to a specific location in the vessel than that from a compact not fixed in any location.

The relationship between dissolution rate and CFD-generated velocity at the base of the vessel (location of a dosage form) in the Levy beaker apparatus was more complex in the larger 550 ml volume than the 350 ml volume. The stirrer was located further from the base of the vessel in the 550 ml volume, resulting in less agitation in this region at lower agitation rates than that seen in the 350 ml volume.

A similar relationship was observed between dissolution rate and CFD-generated fluid velocities in both the paddle and basket apparatus. This fluid velocity-dissolution rate relationship suggested a contribution to dissolution in the absence of forced convection i.e. dissolution under conditions of natural convection. On further investigation, the solubility, location and orientation of a dissolving surface was found to affect its dissolution rate under natural convection conditions. Several models relating dissolution rate to a function of fluid velocity were examined. Rather than using a function of the apparatus stirrer speed as a measure of fluid velocity, the velocity data used was from CFD-simulations of fluid flow around compacts in different locations in the paddle apparatus. Dissolution predictions within 2 standard deviations of the experimental data from the top planar surface of compacts were achieved, from a model using rates of shear at the dissolving surface instead of fluid velocity data (Nelson and Shah, 1975). When experimentally determined dissolution rates under natural convection conditions were added to the predictions using shear rate data, the dissolution rate predictions for the curved side surfaces also came within two standard deviations of the experimental data.

CFD-generated velocity data in the region that a dosage form would be located in any of the apparatuses was scaled to the *in vivo* dissolution or absorption rate from published *IVIVC* studies, for dosage forms where the release of the active ingredient does not rely on erosive or destructive forces. The calculated scaled velocity magnitudes are representative of that present *in vivo*, and were consistently lower than the velocity generated at compendially recommended agitation rates for the paddle apparatus (for example, 50 rpm).

The CFD simulations in this work give some insight into the relationship between fluid velocities and dissolution rates, and will aid in the comparison of dissolution rate data from different dissolution apparatuses.

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Publications and Presentations associated with this thesis

Publications:

1. Evaluation of hydrodynamics in the basket dissolution apparatus using computational fluid dynamics – Dissolution rate implications. *Eur. J. Pharm. Sci.* 27, 259-267, 2006. [D'Arcy, D.M., Corrigan, O.I., Healy, A.M.].
2. Hydrodynamic simulation (CFD) of asymmetrically positioned tablets in the paddle dissolution apparatus: Impact on dissolution rate and variability. *J. Pharm. Pharmacol.* 57, 1243-1250, 2005. [D'Arcy, D.M., Corrigan, O.I., Healy, A.M.].

Oral presentations:

1. “Use of computational fluid dynamics to analyse the effect of local hydrodynamics on dissolution rate in the paddle apparatus”. 26th Joint Research Seminar, Schools of Pharmacy, Queen's University Belfast/Trinity College Dublin, Belfast, 20th – 21st April 2004.

Posters:

1. “Dissolution under conditions of natural convection - investigating the effect of orientation and solubility” in *Proceedings from the EUFEPS Conference on When Poor Solubility Becomes an Issue: From Early Stage to Proof of Principles*. Verona, Italy, April 26th-27th, 2006. [D'Arcy, D., Fagan, F., O'Neill, E., Corrigan, O., Healy, A.M.].
2. “Dissolution modelling using computational fluid dynamics with high performance computing” in *Proceedings from the 3rd Annual National IRCSET Symposium*, Dublin, November 3rd, 2005. [D'Arcy, D.M., Corrigan, O.I., Healy, A.M.].
3. “Use of computational fluid dynamics to model fluid flow and interpret dissolution rate data for the basket dissolution apparatus” in *Proceedings from the 1st PharmSciFair*, Nice, France June 12th-17th, 2005. [D'Arcy, D.M., Corrigan, O.I., Healy, A.M.].

4. “Dissolution modelling of off-centre compacts in the Paddle Dissolution Apparatus” in *Proceedings from the 27th All-Ireland Schools of Pharmacy Research Seminar 2005*, Trinity College Dublin, March 21st-22nd, 2005. [D’Arcy, D.M., Corrigan, O.I., Healy, A.M.].
5. “Dissolution modelling using computational fluid dynamics with high performance computing” in *Proceedings from the 2nd Annual National IRCSET Symposium*, Dublin, November 2nd, 2004. [D’Arcy, D.M., Corrigan, O.I., Healy, A.M.].
6. “Analysis of variation in dissolution rate with position in the USP Paddle Apparatus using computational fluid dynamics” in *Proceedings from the European Conference on Drug Delivery and Pharmaceutical Technology*, Seville, Spain, May 10th-12th, 2004. [D’Arcy, D.M., Corrigan, O.I., Healy, A.M.].
7. “Effect of hydrodynamics on dissolution rate in the USP Dissolution Apparatus” in *Proceedings from the 1st Annual National IRCSET Symposium*, Dublin, November 7th, 2003. [D’Arcy, D.M., Corrigan, O.I., Healy, A.M.].

Abbreviations and Symbols

2-D	2-Dimensional
3-D	3-Dimensional
$\sim$	approximately
$\pm$	plus or minus
∞	infinity
$<$	less than
$>$	greater than
$\geq$	greater than or equal to
$\neq$	not equal to
∇	the vector differential operator $\left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right)$
α	rate of shear
ADS	Artificial Digestive System
AGV	Apparent Gastro-intestinal Velocity
AR	Agitation Rate
A	surface area
ANOVA	Analysis Of Variance
ASA	acetylsalicylic acid
AUC	Area Under the Curve
β	Exponent that X is multiplied by describing exponential relationship between Y and X
b	width of rectangular dissolving surface
BA	benzoic acid
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
χ	curvature parameter
$^{\circ}\text{C}$	degrees Celcius
C	Celcius
c	concentration
ca, cb	cell a and cell b, on either side of face, f .
c_s	concentration of a saturated solution
c_t	bulk concentration at time, t
c_0	bulk concentration at infinite dilution
$c_{\max}$	maximum plasma concentration
CFD	Computational Fluid Dynamics

cm	centimetre
δ_{hbl}	hydrodynamic boundary layer thickness
d_f	function of the momentum equation coefficients for cells on either side of the face, f
d	cylinder diameter
D_A	diameter of agitator
D	diffusion coefficient
DE	Dissolution Efficiency
Dept.	department
e_l	total energy per unit mass
EMA	European Medicines Evaluation Agency
ER	Extended Release
ϕ	function relating stirrer speed to velocity at dissolving surface
f	face
F	force
FDA	Food and Drug Administration (U.S. Dept. of Health and Human Services)
G	body force
G_r	Grashof number
g	gravity
g	gram
GB	gigabytes
GI	gastro-intestinal
GUI	Graphical User Interface
h	diffusion boundary layer
HCl	hydrochloric acid
H	cylinder height
HFMI	hydroflumethiazide
HPC	hydroxypropylcellulose
i	arbitrary direction 1
I	flow of matter to a surface
IR	Immediate Release
IVIVC	<i>In Vitro In Vivo</i> Correlation
j	arbitrary direction 2
J	flux
JP	Japanese Pharmacopoeia
K	mass transfer coefficient
k_d	dissolution constant

kg	kilogram
l	litre
LAR	Log agitation rate
LK	Log mass transfer coefficient
LV	Log CFD-generated local velocity value
L_c	characteristic length
L_p	length between 2 points, across a periodic boundary, which are periodically repeating
LIF	Laser Induced Fluorescence
μ	dynamic viscosity coefficient
μg	microgram
μm	micrometer/micron
m	metre
mg	milligram
min	minutes
ml	millilitre
mm	millimetre
M	molar
M	mass
MDT	Mean Dissolution Time
MR	Modified Release
nm	nanometre
(variable) ⁿ	Power to which (variable) is raised
n	sampling number
ν	kinematic viscosity
N	number of partitions in the fluid domain
NaCl	sodium chloride
NDA	New Drug Application
NIH	National Institutes of Health
ω	angular velocity ($= v_t/r$).
Ω	angular velocity of rotating reference frame
o1-o2	vertical planes on which UPE data was measured
ρ	ρ -value associated with a Student's t-test.
p	pressure
P_r	Prandtl number (analogous to the Schmidt number in mass transfer)
P_e	Peclet number
PDE	Partial Differential Equation
Ph Eur	European Pharmacopoeia

PIV	Particle Image Velocimetry
PRESTO!	PREssure Stagging Option pressure interpolation scheme.
Q	heat
θ	angle of inclination of the dissolving surface from the vertical
ρ	density
rpm	revolutions per minute
r	radius
$\vec{r}$	position vector
r_1	radius of tank
r_d	dimensionless radial co-ordinate
R	dissolution rate
R_a	Rayleigh number, defined as $P_r.G_r$
R_e	Reynolds number
R_t	amount of reference product dissolved at time, t
R^2	R-squared value – indicator between 0 and 1 indicating the closeness of estimated trendline data to the actual data
RAM	Random Access Memory
RSD	Relative Standard Deviation
s1-s3	horizontal planes on which UPE data was measured
s	seconds
S	entropy
S_c	Schmidt number (analogous to the Prandtl number used in heat transfer)
S_h	Sherwood number
S_t	Stanton number
SA	salicylic acid
SD	Standard Deviation
SEM	Scanning Electron Microscopy
τ_{ij}	stress tensor
TIM	TNO Intestinal Model
T	absolute thermodynamic temperature
t	time point, t
T_t	amount of test product dissolved at time, t
TM	trade mark
U	characteristic velocity of a system
UK	United Kingdom
UPE	Ultrasound Pulse Echo

USA	United States of America
USP	United States Pharmacopeia
UV	Ultra Violet
UWL	Unstirred Water Layer
v	velocity
v_x	velocity in x-direction
v_y	velocity in y-direction
v_z	velocity in z-direction
v_t	tangential velocity
v_c	circumferential velocity
V	volume
W	work done
w_t	weighting factor
w/v	weight per unit volume
x	x-axis direction or location in x-axis direction
X	distance from compact surface
y	y-axis direction or location in y-axis direction
Y	mass fraction of tracer
z	z-axis direction or location in z axis direction

Origin and Scope

As a drug must be in solution to be absorbed from the gastro-intestinal (GI) tract, dissolution testing is important in both the development and quality control of oral dosage forms. There are currently seven different compendial dissolution apparatuses (BP, 2005; Ph Eur, 2005; USP, 2005) which are used to set dissolution specifications and to determine dissolution rates of dosage forms. The paddle and basket apparatuses are the most widely used dissolution apparatuses, however despite their widespread use there are continuing problems with variability and reproducibility of dissolution test results with these apparatuses (Siewert et al., 2002; Qureshi and McGilveray, 1999). It has recently been demonstrated that the location of a dosage form within the paddle dissolution apparatus affects its dissolution rate (Kamba et al., 2003; Healy et al., 2002). From this it can be taken that the varying hydrodynamic conditions within dissolution apparatuses can influence the dissolution rate of a dosage form, potentially leading to dissolution test results which reflect differing hydrodynamic conditions rather than characteristics of the dosage form itself.

As the fundamental purpose of establishing dissolution specifications for an oral dosage form is to ensure that it dissolves *in vivo*, the development of a correlation between *in vitro* and *in vivo* dissolution results has been a goal in formulation development since the 1950's (Abdou, 1989). One of the first *in vitro in vivo* correlations was developed by Levy et al. (1965), using a beaker and stirrer apparatus (the Levy beaker dissolution apparatus). Replication of *in-vivo* conditions in an *in-vitro* test is an ultimate objective to facilitate *in vitro in vivo* correlations. Although it is not a compendial dissolution apparatus, the hydrodynamics within the Levy beaker dissolution apparatus are therefore also of interest as *in vivo* dissolution has been predicted from *in vitro* results using this apparatus and a time-scaling factor.

Computational fluid dynamics (CFD) has recently been used to investigate hydrodynamic conditions in the paddle dissolution apparatus (McCarthy, 2002). The work included simulations of the apparatus containing 900 ml of water at 37 °C with an agitation rate of 50 and 100 rpm. The hydrodynamics in the apparatus containing a large cylindrical compact located in the centre of the vessel at 50 rpm was also simulated. The identification of regions of highly variable fluid velocities within the fluid domain prompted the use of CFD for further investigation into the hydrodynamics of commonly employed dissolution apparatuses in the current work. The objectives of the current work were the following:

1. to investigate further the hydrodynamics within the paddle dissolution apparatus using CFD simulations;
2. to simulate the hydrodynamics within the basket and Levy beaker (Levy et al., 1965) dissolution apparatuses;

3. to interpret the impact of hydrodynamics on variability in dissolution testing;
4. to develop the relationship between fluid velocity and dissolution rates through the use of fluid velocity data in the region of the dissolving surface generated by CFD simulations;
5. to investigate the relevance of the hydrodynamics in the *in vitro* dissolution apparatuses investigated to *in vivo* hydrodynamic conditions.

1.0

Introduction.

1.1 Dissolution testing.

1.1.1 History of dissolution testing.

The solubility of a drug has been recognised to affect its bioavailability since the 1930's (Abdou, 1989), however studies relating *in vitro* dissolution to *in vivo* absorption were not carried out until the 1950's. Prior to this, the disintegration of a dosage form, usually a compressed tablet, was considered to be an indication that the active ingredient would be available for systemic absorption. The disintegration test became an official test in the British Pharmacopoeia (BP) in 1945 and in the United States Pharmacopoeia (USP) in 1950. Even then, however, it was recognised that disintegration does not imply dissolution of the active ingredient (Abdou, 1989). Several studies in the late 1950's and early 1960's attempted to correlate *in vitro* dissolution rates of an active ingredient with *in vivo* absorption rates. In 1965, Levy and co-workers developed a quantitative relationship between the dissolution rate and the absorption rate of several different aspirin formulations. A 3-bladed stirrer was used, in a Pyrex griffin beaker containing 350 ml of dissolution medium (Levy et al., 1965). This became known as the "beaker method" or the "Levy beaker dissolution apparatus". The results from this work, among others, prompted an interest in dissolution testing of dosage forms and investigation of the physicochemical factors affecting dissolution kinetics (Abdou, 1989). A consequence of the proliferation of research in the area of dissolution testing during this period was a corresponding increase in the number of apparatuses used for dissolution testing, and studies addressing the design of such apparatuses (Abdou, 1989). As a result there was a requirement for standardisation of the dissolution test apparatus, as by 1970 12 monographs in the USP incorporated a dissolution standard.

The basket dissolution apparatus (Apparatus 1) of Pernarowski was the first official compendial dissolution apparatus, having been originally proposed in 1968 (Pernarowski et al., 1968), and was introduced into the USP in 1970. It is now also included in the British, European and Japanese Pharmacopoeia, although the original BP device consisted of a flat-bottomed flask (British Pharmacopoeia, 1975, appendix XIX), and the original USP device had a concave-bottomed flask (United States Pharmacopoeia, 1975). However, there are many disadvantages associated with the basket apparatus, including inadequacy of mixing at slow speed, clogging of mesh openings by drug or excipient particles and hindered visual inspection of the disintegration process (Banakar, 1992).

In addition excessive variability has been noted in many older studies involving disintegrating USP prednisone calibrator tablets (Schuirmann 1980, Qureshi and McGilveray, 1995). These problems are considered to arise from the complex hydrodynamics present, with high shear in the vicinity of the basket which ejects the disintegrated dosage form particles through the wire basket (a "sieving" effect) and much lower agitation at the base where these particles tend to be deposited (Moriwara et al., 2002; Tandt et al., 1994). The paddle apparatus (Apparatus 2) became

official in 1978, and offered several advantages over the basket apparatus especially for disintegrating dosage forms (Cohen et al., 1990).

Although the paddle dissolution apparatus (Apparatus 2 of the United States and British Pharmacopeias) is the most widely used dissolution testing device in the pharmaceutical industry, it is recognised that there are difficulties in obtaining reproducible dissolution test results using the apparatus (Achanta et al., 1995; Cox and Furman, 1984; Qureshi and McGilveray, 1995; Qureshi and McGilveray, 1999). There are a number of sources of error which have been associated with variability in dissolution data including vessel alignment, curvature of the vessel, dissolved gases and sampling technique (Cox et al., 1978; Cox and Furman, 1982; Cox et al., 1982; Cox et al., 1983). Recognition of these factors has led to improved manufacturing of the dissolution apparatus and improved operator training (Cox et al., 1984). Despite these improvements, recent studies have revealed continuing difficulty in obtaining reproducibility in dissolution studies, in particular reproducibility of results from a number of different laboratories (Siewert et al., 2002). This has been attributed in part to varying hydrodynamics within the vessel, and it has been shown that there is a location-dependent variation in dissolution rate within the paddle dissolution apparatus (Healy et al., 2002; Kamba et al., 2003; Qureshi and McGilveray, 1999).

There are currently seven official compendial dissolution apparatuses (USP, 2005; Ph Eur 2005), but the paddle and basket apparatus remain the most commonly used apparatuses. The importance of dissolution testing of a dosage form was initially recognised through the relevance of dissolution to bioavailability, and as a result a goal of dissolution rate studies has been to develop *in vitro in vivo* correlations (*IVIVC*). In 1975 a notable addition to the BP was an appendix to the monograph on digoxin tablets to include a dissolution test. This followed the publication of several studies by a number of groups in the early 1970's in which a correlation was established between the *in vitro* and *in vivo* performance of digoxin tablets. These studies all found a correlation between dissolution rate of digoxin tablets and steady-state levels in normal volunteers (Shaw et al., 1973).

1.1.2 *In vitro in vivo* correlations (*IVIVC*) and applications of dissolution testing.

An *in vitro in vivo* correlation is defined as “the establishment of a relationship between measurable biological consequence (or parameter derived from a biological activity) produced by a dosage form and a measurable physicochemical characteristic of the dosage form” (Cohen et al., 1990). There are currently three levels of *IVIVC* officially recognised (FDA, 1997b):

Level A: This generally is generally a linear correlation, with a point-to-point relationship between *in vitro* dissolution and *in vivo* input (dissolution) rate. The *in vivo* and *in vitro* curves may be superimposable or may be related by a scaling factor. A level A *IVIVC* should be able to predict the *in vivo* rate from the *in vitro* data for the entire time course.

Level B: A level B correlation compares the mean *in vitro* dissolution time to the mean *in vivo* dissolution time or the mean *in vivo* residence time. Although all of the *in vivo* and *in vitro* data is used, it is not a point to point correlation and therefore does not reflect the actual dissolution profile.

Level C: A single point relationship between a specific dissolution parameter, for example the time to 50% dissolution and a specific pharmacokinetic parameter such as the time to maximum plasma concentration ($c_{\max}$), is established in a level C correlation. There is no reflection of the shape of the plasma-concentration-time curve in a level C correlation, which is a vital characteristic of extended release dosage forms. A multiple level C correlation relates one or more pharmacokinetic parameters to the *in vitro* dissolution rate at several time points.

A level A correlation is considered the most useful, and should be developed with at least two formulations demonstrating different *in vivo* profiles. A multiple level C correlation can be as informative as a level A correlation, however if a multiple level C correlation is possible a level A correlation is usually also possible and preferable. Level B correlations are the least useful from a regulatory perspective (FDA, 1997b).

The predictability of an *IVIVC* model should be demonstrated according to the regulatory guidelines. Predictability of an *IVIVC* model also contributes to “biowaivers” being granted in certain circumstances. A biowaiver is the waiving of the requirement to demonstrate bioequivalence using *in vivo* studies, and an *IVIVC* can be used as a surrogate for *in vivo* bioequivalence studies in certain circumstances. Comparative dissolution tests have been used to waive requirements for *in vivo* bioequivalence studies for immediate release dosage forms which are a lower strength to the approved product. With regard to extended release (ER) products, biowaivers may be granted in some circumstances such as certain changes in release controlling excipients, or approval of a lower strength of an approved product. In some instances, product *sameness*, or equivalence, may need to be demonstrated, following, for example, post-approval changes such as the manufacturing site or process or equipment changes in the manufacture of immediate release products. An *IVIVC* is not always necessary to demonstrate product “sameness” after a change in the approved manufacturing conditions. Details of the data required to demonstrate product equivalence is available in the guidance for industry on scale-up and post approval changes for immediate release (FDA, 1995) and extended or modified release (FDA, 1997c) dosage forms. In many cases dissolution rate data can be submitted following these manufacturing changes, and the similarity of the profiles assessed to demonstrate product equivalence. It is of importance, therefore, to have established appropriate dissolution test specifications. There are recommended approaches to establishing dissolution specifications, and for a new drug application (NDA) the dissolution specifications should be based on acceptable clinical bioavailability batches. For an ER dosage form, at least three time points are recommended to cover the early, middle and late stages of the dissolution profile (FDA, 1997b).

The paddle or basket apparatus are recommended, at common compendial agitation rates of, for example, 100 rpm for the basket apparatus and 50-75 rpm for the paddle apparatus. Further details of recommended dissolution testing conditions for immediate release dosage forms are supplied in the FDA guidance for industry on dissolution testing of immediate release dosage forms (FDA, 1997a). An established *IVIVC* will, of course, add value to any dissolution specifications as then the dissolution test becomes a predictor of *in vivo* performance rather than a demonstration of product equivalence. Use of dissolution rate profiles as a demonstration of product equivalence is using dissolution testing as a quality control tool. As *in vitro* dissolution testing will often be more discriminating and sensitive to changes in product quality than *in vivo* studies, it can detect changes in product quality before the *in vivo* performance is affected (FDA, 1997a). Dissolution testing has therefore gained widespread use as a tool employed in a quality assurance/quality control role. Consequentially, *in vitro* dissolution testing has also been used to assess the effect of process and formulation parameters on drug release rate in formulation development. *In vitro* dissolution tests for immediate release oral dosage forms are now recognised (FDA, 1997a) as having at least three distinct applications, being used to

- assess lot-to-lot quality of a drug product;
- aid in the development of new drug formulations;
- demonstrate continuing product equivalence and quality following certain changes in manufacture.

The same functions of dissolution testing can also be applied to the development and manufacture of modified release dosage forms. In order for dissolution test results to be of any value, however, robust methods for comparison of dissolution profiles must be established.

1.1.3 Comparisons of dissolution rate profiles.

Methods for comparison of dissolution profiles can be divided into three categories as follows:

- Statistical methods
- Model independent methods
- Model dependent methods.

Statistical methods involve statistical comparisons such as Student's t-test and ANOVA. A disadvantage with these methods is that a statistically significant difference does not necessarily imply a pharmaceutically relevant difference. For example, average dissolution rates from two different batches with a very low within-batch variability could show significantly different dissolution rates, but the actual difference between the rates for a particular case could be considered to be insignificant from a pharmaceutical point of view. Obviously the pharmaceutical significance of any difference is case-specific and is an issue which arises repeatedly when considering each method of comparison of dissolution profiles.

Many dissolution profiles do not exhibit simple linear zero-order release (which allows dissolution rates to be compared) however, and require more complicated statistical analysis than

a basic t-test. There have been numerous attempts at developing methods for comparing dissolution profiles independent of the release model. One of the most well-known methods is to use the difference factor (f_1) and similarity factor (f_2), defined as follows (Moore and Flanner, 1996):

$$f_1 = \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \times 100\%$$

$$f_2 = 50 \log_{10} \left\{ 1 + \left(\frac{1}{n} \sum_{t=1}^n w_t |R_t - T_t|^2 \right)^{-0.5} \right\} \times 100$$

Where n is the number of time points, R_t and T_t are the dissolution values of the reference and test products respectively at each time point t and w_t is an optional weighting factor. The similarity factor (f_2) is defined as a logarithmic reciprocal square root transformation of one plus the mean squared differences in percent dissolved between the test and reference products. It is recommended for use by both the FDA (FDA, 1995) and the European Medicines Evaluation Agency (EMA) (EMA, 2001) although the EMA documentation also refers to the use of model dependent and statistical methods. R_t and T_t are defined as % dissolved at each time point in the EMA guidance (EMA, 1999). If the f_1 value between a test and reference product is between 0 and 15, and the f_2 value is greater than 50, both products can be said to be similar. A disadvantage of the f_1 test is that a different value will be obtained if the designation of test and reference product is reversed.

The criterion of the f_2 value being greater than 50 is based on no more than a 10% difference at any time point. The similarity factor must be based on at least 3 time points, and from 12 individual values for every time point. Not more than one mean value should be of >85% dissolved, or the test will be biased towards similarity (EMA, 1999). It is not recommended by the FDA if the within-batch Relative Standard Deviation (RSD) is >15%, but in this case a multivariate model-independent approach should be used (FDA, 1997a). Advantages of the f_2 value are that it is easy to compute and results in a single number for comparison purposes (O'Hara et al., 1998). As the criterion of the f_2 value being greater than 50 is based on a cut off of 10% difference at any time point, it does not take variability into account. If there is a very low within-batch variation, a different f_2 cut-off value can be calculated to more accurately reflect differences between the test and reference batches. The f_2 value is insensitive to the shape of profiles and doesn't take into account unequal spacing of time (Costa, 2001), although the weighting factor can be employed to give more weight to different time points. Another disadvantage is that a statistical hypothesis cannot be formed using the f_2 value, and therefore the risk of type 1 (profiles are different when they are the same) and type 2 (profiles are the same

when they are different) errors cannot be evaluated (O'Hara et al., 1998). The similarity factor has been declared to be too liberal in concluding similarity, and due to the disadvantages outlined above has been termed a convenience criterion and not a criterion based on scientific facts (Costa and Lobo, 2001a). The f_1 and f_2 values are pairwise model-independent methods.

There are also ratio model-independent methods. The mean dissolution time (MDT), area under the release curve (AUC) and simple ratios of percent drug dissolved are examples of ratio model-independent methods. The dissolution efficiency (DE%) value has been proposed as a simple comparison method (Khan, 1975). It can be defined as the area under the dissolution curve up to a certain time point, t , expressed as a percentage of the area of the rectangle obtained by 100% dissolution in the same time. Mathematically this is expressed as:

$$DE\% = \frac{\int_0^t T_t \times dt}{T_{100\%} \times t} \times 100\%$$

where T_t is the percent drug dissolved at time, t .

This value does not, however, give any information on the shape of the profile.

Model-dependent comparison methods involve choice of a model most appropriate for the dissolution profile in question. This could involve a basic linear zero-order profile, a 1st order profile or an exponential, parabolic or sigmoidal profile. The Weibull model, which was adapted to the drug release process by Langenbucher (1972), can be applied to almost all kinds of dissolution curves as it includes a time scale factor, a term to address lag time and a shape factor to describe the shape of the curve. The dosage form could involve drug release from a matrix or from particles of the disintegrated dosage form. All of these factors should be taken into account when choosing an appropriate model. For example, release from a matrix will often be proportional to the square-root of time and a Higuchi model might be employed for this (Higuchi, 1961). When an appropriate model is chosen, comparison of the various parameters in the model can then be made. The difficulty is again in interpreting the importance of the differences in the calculated values.

In conclusion, a measure of comparison should not be taken in isolation but should be complimented with information on the shape of the profile, the timing of the samples, the within-batch variation and consideration of what would be an acceptable level of similarity to be considered pharmaceutically equivalent.

Due to the range of applications of dissolution testing in formulation development and manufacture, it is desirable to continually develop our understanding of the fundamental physical and chemical principles underpinning the process of dissolution testing. An increased knowledge of the factors affecting dissolution and drug release rates under the conditions experienced in the dissolution test could aid the ability to predict the effect of changes in both the conditions of the test and the formulation or processing parameters of the dosage form. This ability, in turn, could aid the design and understanding of both quality control and *IVIVC* studies. In the current work,

in-silico methods are used to simulate dissolution test conditions in order to gain further insight into the relationship between hydrodynamics and dissolution rate.

1.2 *In silico* tools in the pharmaceutical industry.

The term “*in silico*” refers to modelling research conducted with computers only (NIH, 2000). With the availability of computational resources of ever-increasing performance capabilities, and the introduction of commercially available software, *in silico* technology requiring high-performance computing power is being applied to a growing number of areas in the pharmaceutical industry. Within the area of formulation development and manufacture, *in silico* modelling of physical processes has resulted in process simulations. The aim of such simulations includes gaining a comprehensive insight into the underlying physical processes and the effect of specific process variables on process parameters, which in turn has the potential to improve process control and quality through process design. Additionally, as the cost of high-performance computing resources decreases, *in silico* simulations can offer a cost benefit over physical experimentation in terms of use of consumable resources. Processes which have been modelled with varying degrees of success include powder compaction (Michrafy et al., 2002), freeze-drying (Mascarenhas et al., 1997) and aerosol deposition in the oral cavity (Stapleton et al., 2000). In each case further research was required to optimise the predictability of the model, or to demonstrate its applicability. Nevertheless, identifying the shortcomings of the numerical model underpinning a process simulation aids in defining and characterising the process.

Computational fluid dynamics (CFD) can be defined as “the broad topic encompassing numerical solution, by computational methods, of the governing equations which describe fluid flow, the set of Navier-Stokes equations, continuity and any additional conservation equations or energy or species concentrations” (Cranfield University, 2003). CFD is an *in-silico* technology which can be used to gain further insight into hydrodynamics in any process involving fluid flow. In the field of pharmaceuticals, the hydrodynamic conditions present in dissolution studies are of interest in terms of their effect on dissolution rates, variability in dissolution test results and relevance to *in vivo* hydrodynamics conditions.

Recently, computational fluid dynamics (CFD) has been used to simulate the fluid flow in the paddle dissolution apparatus (McCarthy, 2002). In the current work, CFD will be used to further investigate the relationship between dissolution rate and hydrodynamic conditions in the paddle apparatus, and to investigate the hydrodynamics of the basket and Levy beaker dissolution apparatuses. In order to describe the nature and utility of the data which is generated using CFD, the user must have a basic understanding of fluid mechanics.

1.3 Fundamentals of fluid mechanics.

1.3.1. Laws governing motion for particles and material volumes.

1.3.1.1 Basic equations of motion and conservation.

In the treatment of fluid mechanics, the conservation of mass, linear momentum and energy are the principles which must be described by the relevant “balance” or conservation equations – the equations representing the fundamental physical laws which apply to the system of interest (Cramer, 2004).

The general form of a “balance” equation is that the time rate of *change* of a quantity is equal to the actions of the surroundings on the surface of a volume (containing a fixed mass of matter) plus the actions of the surroundings on the volume itself (Cramer, 2004).

The four universal physical laws relevant to fluid mechanics are:

- 1) The law of mass conservation (often referred to as the continuity equation in CFD)
- 2) The law of motion
- 3) 1st law of thermodynamics
- 4) 2nd law of thermodynamics

A volume which contains the same particles of matter at all times is known as a material volume, which is the basic form these laws are stated in (Sonin, 2001a). For a particle with infinitesimal volume $\delta V(t)$, density $\rho(t)$ and velocity $\vec{v}$, the laws are as follows (Sonin, 2001a):

1. Mass conservation:

$$\frac{d}{dt}(\rho \delta V) = 0. \quad \text{Equation 1.1}$$

This states that the mass of such a particle with an infinitesimal volume does not change (Sonin, 2001a).

2. Newton’s law of linear motion:

$$\frac{d}{dt}(\rho \vec{v} \delta V) = \delta \vec{F}. \quad \text{Equation 1.2}$$

This states that the product of a particle's mass and acceleration (relative to an inertial reference frame) is at every instant equal to the net force $\delta \vec{F}(t)$ exerted on it by the rest of the universe (Sonin, 2001a).

Newton's law applied to angular motion:

$$\frac{d}{dt}(\vec{r} \times \rho \vec{v} \delta V) = \vec{r} \times \delta \vec{F} \quad \text{Equation 1.3}$$

where $\vec{r}(t)$ is the particle's position vector, and $\times$ is the vector cross-product. This equation states that the rate of change of a particle's *angular* momentum is equal to the net torque exerted on the particle by the rest of the universe at every instant (Sonin, 2001a).

3. 1st Law of thermodynamics:

$$d(\rho e_1 \delta V) = \delta W + \delta Q. \quad \text{Equation 1.4}$$

This states that the increase of a material particle's total energy in a time interval, where e_1 is its total energy per unit mass, equals the work done, δW , on the material volume's boundary by forces exerted on it by the rest of the universe plus the heat, δQ , added to the particle boundary during this same time interval (Sonin, 2001a).

4. 2nd Law of thermodynamics:

$$d(\rho s \delta V) \geq \frac{\delta Q}{T}. \quad \text{Equation 1.5}$$

This law states that the increase of a particle's entropy (s), in a time interval, is greater than or equal to the heat added to the particle at the boundary, divided by the absolute thermodynamic temperature, T , during this time interval (Sonin, 2001a).

1.3.1.2 Navier-Stokes Equations.

The Law of motion, as applied to an infinitesimal fluid particle, can also be written as follows (Sonin, 2001b):

$$\rho \frac{Dv_i}{Dt} = \frac{\partial \tau_{ij}}{\partial x_j} + \rho G_i \quad \text{Equation 1.6}$$

where $\frac{D}{Dt}$ is the substantive derivative, defined as the operator: $\frac{D()}{Dt} \equiv \frac{\partial()}{\partial t} + \vec{v} \cdot \nabla()$.

This states at a particular point in time, the product of the mass per unit volume and the acceleration in the i-direction is equal to the net surface force per unit volume in the i-direction plus the body force per unit volume in the i-direction (summation of j over x, y and z is implied) (Sonin, 2001b). τ_{ij} defines the stress tensor and G_i is the body force. If compared to equation 1.2 it can be seen that this form of the equation attempts to characterise the forces which exert an effect on a material body. The body force term is quite straightforward, for example in a gravitational field the body force per unit mass is known. The surface tensor force, however, is more difficult to determine (Sonin, 2001b), but is related to both the pressure and the shear viscosity coefficient (μ) (Sonin, 2001b).

The Navier-Stokes equations can be simplified if the viscosity, μ , can be assumed to be uniform and ρ can be assumed to be constant, as is the case in a classical incompressible fluid. When τ_{ij} in the general equation of motion, equation 1.6, is expressed in terms of pressure and viscosity, the Navier-stokes equations written in full, in Cartesian coordinates, are:

$$\rho \left(\frac{\partial v_x}{\partial t} + v_x \frac{\partial v_x}{\partial x} + v_y \frac{\partial v_x}{\partial y} + v_z \frac{\partial v_x}{\partial z} \right) = -\frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_x}{\partial y^2} + \frac{\partial^2 v_x}{\partial z^2} \right) + \rho G_x$$

Equation 1.7

$$\rho \left(\frac{\partial v_y}{\partial t} + v_x \frac{\partial v_y}{\partial x} + v_y \frac{\partial v_y}{\partial y} + v_z \frac{\partial v_y}{\partial z} \right) = -\frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v_y}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} + \frac{\partial^2 v_y}{\partial z^2} \right) + \rho G_y$$

Equation 1.8

$$\rho \left(\frac{\partial v_z}{\partial t} + v_x \frac{\partial v_z}{\partial x} + v_y \frac{\partial v_z}{\partial y} + v_z \frac{\partial v_z}{\partial z} \right) = -\frac{\partial p}{\partial z} + \mu \left(\frac{\partial^2 v_z}{\partial x^2} + \frac{\partial^2 v_z}{\partial y^2} + \frac{\partial^2 v_z}{\partial z^2} \right) + \rho G_z$$

Equation 1.9

Fluid flow problems may be solved by integrating the Navier-Stokes equations along with the continuity equation and any other equations required for the boundary conditions of the problem under consideration. The approach to finding a solution involves attempts to simplify the equations and then to determine approximate solutions to the simplified situation (Levich, 1962).

1.3.1.3 Ideal fluids, real fluids and boundary layers.

To determine the solution to a hydrodynamic problem, the boundary conditions applying to the set of surfaces enclosing the space containing the fluid must be specified. A fluid with no viscosity is termed an ideal fluid, and this approximation is used in some real cases when viscous forces play a very minor role. Elimination of the viscosity term converts the Navier-Stokes equation to the Euler equation (Levich, 1962), which can sometimes be integrated in a general form as it constitutes a 1st-order equation rather than the 2nd-order Navier-Stokes equation. From this, for a given streamline in steady motion, it can be shown that

$$\frac{v^2}{2} + \frac{p}{\rho} + \frac{U}{\rho} = \text{Constant} \quad \text{Equation 1.10}$$

where U is a characteristic velocity of the system.

Equation 1.10 is known as Bernoulli's Theorem, which shows that from regions of higher (faster) flow to regions of lower flow the pressure changes in the opposite direction (Levich, 1962). In an ideal fluid, there is no interaction with a solid body in the fluid, as viscosity forces are not included. The velocity at a solid surface must become zero in reality, as there is no "slip" past the surface, but according to the equations of motion for an ideal fluid the fluid velocity at a solid surface is comparable to that distant from this surface (Levich, 1962). The "no slip" condition in a real fluid arises from intermolecular forces causing a fluid to adhere to the wall of a solid body (Schlichting, 1979). From this it can be taken that there is a thin region near the solid surface within which the bulk velocity decreases to zero (relative to the solid surface). This region is known as the hydrodynamic boundary layer, and is caused by viscous forces alone. In summary, the concept of an ideal fluid, without consideration of viscous forces, is not accurate within the hydrodynamic boundary layer.

Until the beginning of the 20th century, the field of fluid mechanics had diverged into a theoretical branch, dealing with the properties of ideal or Eulerian fluids, and the experimental branch of *hydraulics*, which had a more empirical approach to deal with the practical shortcomings of theoretical hydrodynamics. In 1904 L. Prandtl presented his paper "Fluid motion with very small friction" at the Mathematical Congress in Heidelberg, where he introduced the concept of the boundary layer near a solid body where friction in a fluid plays an essential role, thus establishing the importance of viscous forces (Schlichting, 1979). The thickness, δ_{hbl} , of the boundary layer cannot be precisely determined as the transition of the velocity to that of the bulk takes place asymptotically. In practical terms, however, the thickness of δ_{hbl} can be defined as, for example, the distance from the solid to where the velocity differs from the bulk by 1% (Schlichting, 1979). The value of δ_{hbl} will vary with the distance from the leading edge of the solid surface, the bulk velocity value and the shape of the solid body. Figure 1.1 illustrates the development of a boundary layer along a flat plate, where the bulk flow is in the direction x .

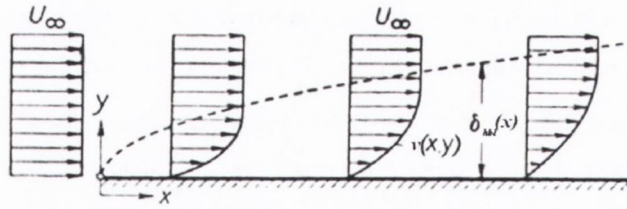


Figure 1.1. Diagram of a boundary layer developing over a flat plate. The flow is in the x direction, U_∞ represents the bulk flow velocity, v is the velocity within the boundary layer, $\delta_{hbl}(x)$ represents the thickness of the hydrodynamic boundary layer at the point x . Adapted from Schlichting, 1979.

All quantities within the boundary layer change rapidly in the direction of y , perpendicular to the boundary layer, representing the velocity gradient within the boundary layer, and gradually in the direction of x , the length of the solid body. The current work involves fluid mechanics which are much more complex than unidirectional laminar flow over a flat plate. Therefore, to illustrate the degree of complexity which can be introduced by simply changing the shape of the solid surface, two other situations are presented which are relevant to the current work. That of flow past a curved surface and flow in a pipe, or Hagen-Poiseuille flow.

Flow past a body with appreciable curvature, such as a sphere or cylinder, is non-streamlined (Levich, 1962). The difference in the boundary layer on a flat plate and on the surface of a cylinder is that within the boundary layer on a cylindrical surface the velocity and pressure passing around the surface varies. The diagram in Figure 1.2 shows flow over a curved cylinder, and separation of flow within the boundary layer.

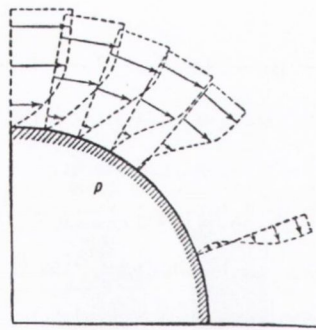


Figure 1.2. The development of separation within the boundary layer in a flow over a cylindrical surface. Taken from Levich, 1962.

According to Bernoulli's equation, the point at which the pressure is greatest is the point at which the velocity reaches zero, and is known as the stagnation point (Levich, 1962). The velocity can be considered to be at stagnation at the cylinder, increasing to the midpoint of flow over the cylinder and decreasing beyond this point. The pressure varies in the opposite direction, and is greatest at the stagnation point and increases over the downward region of the cylinder. The fluid within the boundary layer, however, moves with the pressure gradient in the upstream region of

the cylinder and against the pressure gradient in the downward facing region. The pressure in the opposite direction is known as the drag, and at some point will stop the flow within the boundary layer (Levich, 1962). After this point the flow will reverse, leading to what is known as separation of the boundary layer.

The situation of laminar flow within a pipe is illustrated in Figure 1.3. There is zero velocity at the wall of the pipe, and as the flow is surrounded by the pipe walls the velocity must be greatest at the centre of the pipe (Schlichting, 1979). At any particular radial value, the velocity is constant, and remains constant within the direction of flow once there is an adequate distance from the pipe entrance for the flow to have developed. The fluid is accelerated by the pressure gradient acting along the central axis, and retarded by frictional forces of the individual concentric layers of fluid exerting a shearing stress on adjacent layers. This type of laminar flow within a pipe exists only for fluids of relatively low velocities within a pipe of relatively small radius.

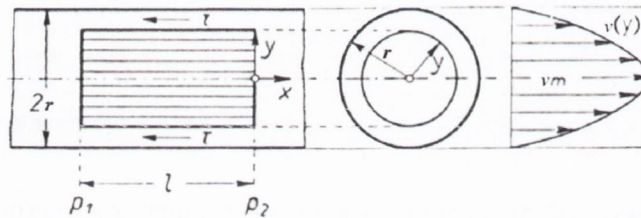


Figure 1.3. Laminar flow through a pipe of radius r . Flow is in the direction x , with velocity v , with the frictional shearing stress, τ , acting against the flow.

1.4 Dissolution theory.

1.4.1 Diffusion.

Fick's Laws of diffusion.

Diffusion occurs due to the random motion of molecules, leading to the mass transfer of molecules from areas of high concentration to areas of lower concentration (Martin, 1993).

Flux, J , is defined as the amount of material M flowing through a unit area A per unit time, t .

$$J = \frac{dM}{A \cdot dt} \quad \text{Equation 1.11}$$

The flux, J , is proportional to the concentration gradient, dc/dx :

$$J = -D \frac{dc}{dx} \quad \text{Equation 1.12}$$

This equation is known as Fick's first law, where D is the diffusion coefficient of the substance undergoing diffusion, c is the concentration and x is the distance of movement perpendicular to the surface of the source of the diffusing substance (e.g. a tablet surface). Fick's second law describes the rate of change of concentration with time at a definite location. The rate of change of concentration with time will depend on the amount of substance diffusing into or out of a given volume per unit time. Therefore it depends on the change in flux with distance within that finite volume:

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} \quad \text{Equation 1.13}$$

Differentiating equation 1.12 with respect to x and substituting $\frac{\partial c}{\partial t}$ from equation 1.13 gives us

Fick's second law:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad \text{Equation 1.14}$$

This equation, however, only describes the rate of change of concentration with time in the x direction. Diffusion in three directions may be shown as follows:

$$\frac{\partial c}{\partial t} = D \left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2} \right) \quad \text{Equation 1.15}$$

If sink conditions can be applied to the volume into which the solid is diffusing, then the concentration will not change with time at any particular point between the surface of the solid and the point at which the concentration reaches zero (infinite dilution). Such a system is said to

be at steady state – the rate of change of concentration with time will be zero and the following applies:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} = 0 \quad \text{Equation 1.16}$$

Equation 1.16 can be expanded, similar to equation 1.15, to define diffusion at steady state in all directions.

1.4.2 Dissolution.

Dissolution involves two basic steps: the dissolution of the solid at the solid-liquid interface, and the subsequent diffusion of the solute into the bulk. The first step usually occurs rapidly in comparison with the diffusion step, and it is this situation which will be considered in the current work. The dissolution at the interface can therefore be considered to form a saturated solution at the solid surface, and the diffusion of the solute into the bulk solution is the rate limiting step. In 1897, Noyes and Whitney (Noyes and Whitney, 1897) proposed the equation from which many models of dissolution have been derived:

$$\frac{dc}{dt} = k_d (c_s - c_t) \quad \text{Equation 1.17}$$

where k_d is known as the dissolution or proportionality constant, c_s is the saturated solubility and c_t is the bulk concentration at time, t (Abdou, 1989). Work by Nernst (1904), Brunner (1904), and their colleagues resulted in the proposition of the Nernst-Brunner equation:

$$-\frac{dc}{dt} = DA \frac{(c_s - c_t)}{Vh} \quad \text{Equation 1.18}$$

where A is the area of the dissolving surface, V is the volume of the dissolution and h is the thickness of the diffusion boundary layer. If the volume is constant and is kept large enough to ensure sink conditions are present, equation 1.18 can be reduced to:

$$-\frac{dM}{dt} = DA \frac{c_s}{h} \quad \text{Equation 1.19}$$

The diffusion boundary layer proposed in the Nernst-Brunner equation is the distance over which the solute in the saturated solution at the surface must diffuse to reach the bulk solution. The concentration in the bulk solution is uniform, provided the medium is well-stirred. There is a concentration gradient, therefore, between the saturated solution at the dissolving surface and the bulk solution where infinite dilution can be assumed, expressed as c_0 . The concentration gradient

occurs over the distance h , and can be expressed as $\frac{c_s - c_0}{h}$. **Equation 1.20**

It is clear from equation 1.19 that the dissolution rate will be increased if h decreases, and if A and D are kept constant the effect of altering h can be determined. The thickness of h has been shown to be related to velocity by the function

$$h \approx \frac{1}{v^n}$$

Equation 1.21

where experimental values of n have varied between 0.5 and 1 (Levich, 1962).

It is assumed by the Nernst-Brunner approach that the diffusion boundary layer, h , is a static layer at the solid surface, and that the concentration gradient is a linear function over h (Bircumshaw and Riddiford, 1952). That there is some fluid movement within the diffusion boundary layer has been demonstrated (Bircumshaw and Riddiford, 1952) and this is not contrary to the theory supporting the presence of the hydrodynamic boundary layer or the nature of diffusion. However, although the diffusional component of mass transfer is minimal compared to the convection component in the bulk solution, due to the generally low value of D in liquids, the importance of the contribution of diffusion increases within the diffusion boundary layer. This is analogous to the importance of viscous forces in fluid motion within the hydrodynamic boundary layer (Levich, 1962). Furthermore, the Nernst-Brunner model of dissolution is generally regarded as a qualitative model in a system where there is a moving fluid, as the value of h will vary with fluid velocity. Therefore, dissolution is governed by both the process of diffusion and convection, with convective forces, entraining dissolved particles, dominating in the bulk solution and diffusion dominating within the diffusion boundary layer, but both convection and diffusion play a part in each region. When convection is present in a liquid containing a solute, the movement of the solute (flux, J) in the x direction through a plane per unit time is the total of the sum of the convective and diffusive components:

$$J = cv - D \frac{\partial^2 c}{\partial x^2}$$

Equation 1.22

Equation 1.16 gives a diffusion rate with time, and from equation 1.22 it follows that 3-D convective diffusion can be expressed as:

$$\frac{\partial c}{\partial t} = D \left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2} \right) - \left(v_x \frac{\partial c}{\partial x} + v_y \frac{\partial c}{\partial y} + v_z \frac{\partial c}{\partial z} \right)$$

Equation 1.23

The velocity components in equation 1.23 can be determined through attaining a solution to the Navier Stokes equations specific to the problem in question, as discussed in section 1.3. The effect of D will be determined by the thickness of h at any particular point, (unlike the Nernst Theory, with the convective-diffusion model the thickness of h can vary along the surface due to motion within the layer), the solubility of the solute and the nature of the concentration gradient. The variation of c within h is not a linear function, as assumed by the Nernst-Brunner equation. Due to the persistence of fluid motion up to a point close to the solid surface within h , the concentration gradient is better described by a curve, with the h being equivalent to 0.893 times the total thickness of the concentration gradient (Bircumshaw and Riddiford, 1952).

In summary, when attempting to describe or predict dissolution rates from a surface where diffusion is the rate limiting step, “ h ” can be used as a predictive variable. However, rather than describing the thickness of the diffusion boundary layer for a particular system, h incorporates convective and diffusive elements from the surface to the bulk solution, and for a system is an average descriptor of a parameter which will vary from point to point. The nature and effect of h can be described using the convective-diffusion equation, and when sink conditions are applied and D , A and c_s are constant, the convective diffusion equation can be used to describe the dissolution process.

Using general convective diffusion theory, Levich (1962) calculated the thickness of h to be related to the hydrodynamic boundary layer divided by $(\nu/D)^{1/3}$, where ν is the kinematic viscosity. The term ν/D is known as the Prandtl number (or Schmidt number), and is of the order of 1000 for liquids such as water (Levich, 1962). Therefore, in an aqueous system, the magnitude of h can be expected to be in the region of 1/10 of the thickness of the hydrodynamic boundary layer.

As the thickness of h is related to both the thickness of the hydrodynamic boundary layer at a surface and the dissolution rate at that particular point on a surface, it can be deduced that the thickness of the hydrodynamic boundary layer will influence the dissolution rate. Knowledge of the local hydrodynamics in the vicinity of the dissolving surface, and the overall hydrodynamics within a fluid field in terms of uniformity of mixing, will therefore increase the ability to predict dissolution rates from a dosage form under specific dissolution test conditions. In the current work, CFD is used to simulate the hydrodynamics in defined flow field conditions through solving the equations outlined in section 1.3.

1.5 CFD using the software package “FluentTM”.

FluentTM is the commercial CFD software package which was used in the current work to obtain a solution to the flow fields of interest. The approach taken by FluentTM to solve the equations relevant to the hydrodynamics within the flow field is as follows (FluentTM User’s Guide, 2003):

- a) The fluid domain is divided into control volumes
- b) The governing equations are integrated within each control volume to produce algebraic equations for each discrete dependent variable, for example velocity or pressure. This is known as finite-volume discretisation of the governing equations.
- c) The discretised equations are linearised, and the linear equations are used to update the values of the discrete variables.

Each cycle of solving the equations and updating the variables is known as an iteration. The number of iterations needed to yield a usable solution depends on the complexity of the problem and the user requirements from the solution.

Creating a grid of control volumes.

When the fluid domain is divided into control volumes it is known as a “grid” or “mesh”. In the current work, the pre-processing package GambitTM was used to create the meshed fluid domain. GambitTM enables the construction of the geometry of the fluid domain, subsequent meshing of the geometry and assignation of continuum and boundary specifications. The construction and meshing of the geometry is carried out using a graphical user interface (GUI), where the user can specify the dimensions and positions of vertices, edges, faces and volumes to create 2-D or 3-D geometries as required. A mesh can then be applied to the geometry. This involves specifying the number or interval size of mesh nodes on an edge, which affects the level of mesh refinement on a face and in turn in a 3-D volume. Additionally, boundary layers can be inserted which define the spacing of mesh nodes on a face directly adjacent to a selected edge (Gambit User’s Guide, 2004). Boundary layers are useful in areas of the geometry where a high mesh density may be required, for example in areas of high velocity gradients near a wall. There are various meshing schemes available in GambitTM, creating mesh cells of hexahedral, tetrahedral, pyramidal or wedge shapes. GambitTM also enables the quality of the mesh to be examined using a range of quality descriptors. For example, the equiangle skew quality descriptor uses a function which produces a normalized measure of cell skewness. The maximum and minimum angles of the cell edges are compared to characteristic angles of an equilateral cell of the same form, for example 60° for a triangular or tetrahedral element, and 90° for a quadrilateral element. Equiangle skew values must fall between 0 and 1, where a value greater than 0.9 is considered to be of very poor quality (Gambit User’s Guide, 2004) and a value of 1 is a degenerate element. The aspect ratio is also commonly used as a measure of mesh quality. An aspect ratio of 1 denotes an equilateral element (Gambit User’s Guide, 2003), and in general it is best not to use cells with an aspect ratio greater than 5:1 (FluentTM User’s Guide, 2003). The quality of the mesh, in terms of skewness and refinement or

density, is a significant factor in determining solution accuracy and stability. This is especially relevant for swirling and rotating flows.

Boundary and continuum conditions are also specified in GambitTM. Boundary specifications refer to the characteristics of the model at each boundary, for example a wall or an inlet, and continuum specifications refer to the characteristics of the model within the domain, for example fluid or solid. The geometry, meshing and boundary/continuum specifications are then exported as a mesh file to the solver, FluentTM.

Using the solver, FluentTM.

The mesh file which is exported from GambitTM is then read (imported) into FluentTM and saved as a “case” file. Boundary and continuum specifications can be altered within FluentTM if necessary. The steps involved in using FluentTM to solve a fluid dynamics problem are outlined below (FluentTM User’s Guide, 2003):

1. Import and check the grid.
2. Choose the solver formulation.
3. Choose the basic equations.
4. Define the material properties and boundary conditions.
5. Adjust the solution controls.
6. Initialise the flow field and calculate a solution.
7. Examine the results.

Solver formulation.

In the current work, the default solver, a segregated implicit solver, was used. The segregated solver solves the relevant equations sequentially, whereas the other solver option provided by FluentTM, the coupled solver, solves the equations simultaneously. Both solvers are of comparable accuracy, however the coupled implicit solver may reach convergence faster but has greater memory requirements than the segregated solver (FluentTM User’s Guide, 2003). The term “implicit” relates to the manner in which the governing equations are linearised. The implicit form computes the unknown value in a cell using existing known and unknown values in adjacent cells. As result each unknown will appear in more than one equation, and these must then be solved simultaneously. This is the only linearisation option when using the segregated solver. The coupled solver also has an explicit option, in which the unknown values are computed using only existing values. An overview of the segregated solution method is presented in Figure 1.4.

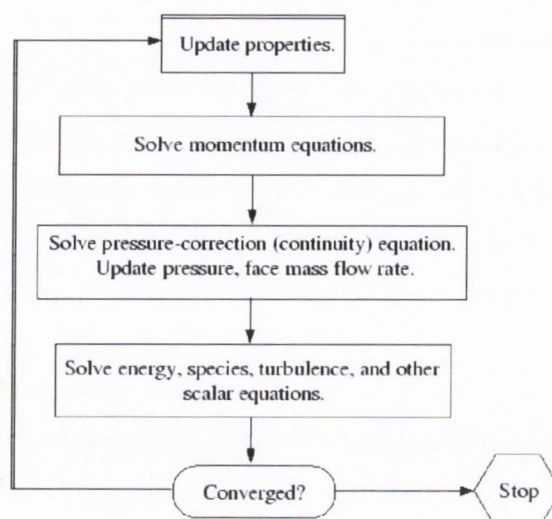


Figure 1.4. Overview of the segregated solution process. Taken from FluentTM User's Guide, 2003.

Choosing basic equations.

Choosing the discretisation scheme.

The default value for the discretisation scheme when using the segregated solver is 1st-order upwind. When converting the governing equations to an algebraic form which can be solved by numerical computation, accuracy to 1st- or 2nd-order can be specified. With the default 1st-order scheme, the quantity calculated at the centre of a cell for any variable is taken to be the cell average, and the quantity at the cell face is considered to be identical to the quantity in the cell centre. In the 1st-order upwind scheme, the quantity at the cell face of any variable is taken to be the quantity at the centre of the cell “upwind” or “upstream” to the cell face. The 2nd-order discretisation scheme is more complicated, achieving a higher order accuracy for the value of any variable at the cell face. A 2nd-order scheme gives more accurate results than a 1st-order scheme once the fluid flow is not aligned with the grid (which is always the case with an unstructured triangular or tetrahedral mesh), however it can be more difficult to attain solution convergence with a 2nd-order discretisation scheme (FluentTM User's Guide, 2003). The 1st-order upwind discretisation scheme was used in the current work.

Choosing the pressure-velocity coupling method.

FluentTM uses the discrete version of the continuity equation to derive an equation for pressure, and pressure-velocity coupling is required to do this (FluentTM User's Guide, 2003). A choice of two appropriate algorithms, SIMPLE and SIMPLEC are available in FluentTM when carrying out steady-state or time averaged calculations. SIMPLE uses a relationship between velocity and pressure corrections to ensure the conservation of mass, and to obtain a pressure field. With a guessed pressure field, the flux through a face on a cell will not satisfy the continuity equation and a correction must be applied which will satisfy the equation. The value for the pressure variable is obtained from this flux correction. The SIMPLEC algorithm is similar to SIMPLE, differing only

in the expression used for the face flux. SIMPLEC can yield a converged solution faster than SIMPLE in uncomplicated problems where pressure-velocity coupling is the main factor limiting convergence. In complicated flow the SIMPLE algorithm may be more appropriate. SIMPLE and SIMPLEC give similar convergence rates if a different modelling parameter is limiting convergence (FluentTM User's Guide, 2003).

Under relaxation factors.

Because the equations used in FluentTM are non-linear, it is necessary to control the change in any variable when updating the solution. An under-relaxation value is used to control this change. When using a rotating reference frame, as is the case in the current work, it is recommended to consider reducing the under-relaxation factors for velocities to obtain a converged solution (FluentTM User's Guide, 2003). If unstable behaviour is observed as the solution progresses, under-relaxation factors should be decreased further. Otherwise it may be possible to increase the under-relaxation factors as the solution progresses, provided the solution remains numerically stable.

Laminar and turbulence models.

In a time-averaged model, small scale fluctuations characteristic of turbulent flow are removed through manipulation of the exact governing equations. The result is a set of equations which are computationally less expensive to solve. Turbulence models can be employed when using FluentTM to determine any unknown variables which may be present in the time-averaged model, but use of a turbulence model adds to the computational expense of the solution.

Material properties and boundary conditions.

When the solver has been chosen and suitable solution algorithms identified to start the calculations for a case file, the material and boundary conditions must be specified. The boundary conditions for sides of the geometry enclosing the fluid are as described when using the GambitTM pre-processing software. For example a boundary condition of a pressure inlet or a vent can be applied to a specific zone. The motion of a wall must also be specified. For the continuum regions, the boundary conditions defined in the case file in FluentTM refer to the materials used, and the motion applied to these zones, to cause the flow field being modelled. The material used can be taken from a database in FluentTM or a user-defined material can be employed. The material used for a wall can also be defined. In the current work the default material of aluminium was used, as it was not a reacting surface. The motion applied to a wall can be in either the absolute or relative frame of reference. The motion used for the continuum (fluid) zones can be rotational or translational. As all of the flow domains in the current work consisted of rotational flow, with a boundary rotating through the flow field (i.e. an impeller of some kind) a rotating reference frame was therefore used.

Rotating reference frame.

Flow is usually modelled in an inertial or non-accelerating reference frame. When a rotating reference frame is used, the equations describing the motion of the flow include the rotation of the reference frame. In a situation where there is an impeller continuously rotating the fluid, the reference frame is rotating with the stirrer. As a result the continuous rotating motion of the stirrer is incorporated into the flow field. In Figure 1.5, the transformation of the coordinate system from a non-rotating reference frame to a rotating reference frame is illustrated.

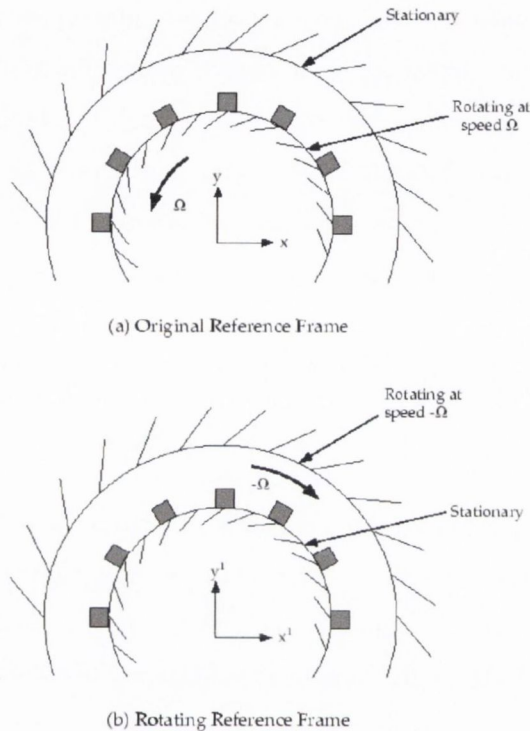


Figure 1.5. Transformation of a coordinate system to a rotating reference frame. Taken from **Fluent™ User's Guide, 2003.**

In Figure 1.5, the angular velocity of the rotating reference frame, Ω , is in the opposite direction when the impeller is stationary in the moving reference frame compared to when the impeller is moving through an inertial reference frame. In a case where there is “rotor-stator interaction” e.g. when baffles are present in the mixing tank, a simple rotating reference frame model is not adequate as the rotor-stator interaction cannot be simulated. In situations where the rotor-stator interaction is weak, a multiple reference frame model can be applied. In this situation, several reference frames are used. For each reference frame, it must be specified whether it is a stationary or rotating reference frame and the speed at which it is rotating.

Partitioning and adapting.

Once a flow domain has been divided into control volumes, the source and nature of the motion it will be subjected to and its material values defined, and the governing equations chosen, the calculations to obtain a solution can commence. There are a number of steps, however, which can be taken which will enable the solution calculations to proceed faster.

Partitioning.

If the computer being used to run the CFD software has more than one processor, the mesh can be partitioned to enable the computer to solve equations in each partitioned section at the same time. As the data must be fed between processors after each iteration, there is often a number of partitions after which further partitioning becomes counter-productive. In other words, if the mesh file is divided into N parts, the time to transmit data from each processor is greater than the time saved by the last partitioning, and the mesh file divided into $N-1$ parts would be more efficient.

Adapting.

Grid adaption can involve merging or dividing mesh cells, resulting in a coarser or finer mesh, but in the current work applies only to the division of cells. Adaption can be carried out before the solution commences, by, for example, refining the mesh in areas where the flow is expected to undergo steep velocity gradients. Mesh adaption can also be carried out as the solution progresses, with extra cells being added in areas which reveal unexpectedly complex flow features. The degree of mesh refinement which can be carried out through adaption is limited by the available memory.

Convergence criteria and residuals.

As a solution progresses, after each iteration the residual sum from each variable is stored. If a computer had infinite precision these residuals would eventually have a value of zero and a solution to the flow field would be obtained (FluentTM User's Guide, 2003). In reality, the residuals decrease to a small value and then level off. Residuals in FluentTM are by default presented as "scaled residuals", where the scaling factor is representative of the flow rate in the domain of that variable. Scaled residuals are a more appropriate metric by which to judge solution convergence than unscaled residuals (FluentTM User's Guide, 2003). Various approaches can be taken to decrease residuals as much as possible, such as altering the under-relaxation factors or refining the mesh. When the residuals will not decrease further the solution is said to have "converged". It is possible to define convergence criteria in FluentTM before the solution is commenced, and when these criteria are met the solution is considered converged and the solver ceases to iterate further. The criteria used by default is that the residual values for the continuity and velocity equations must decrease by a factor of 1000.

Writing case files, commencing the calculations.

When all of the required data is entered into the case file, including the mesh, solver formulations governing equations, material properties and boundary conditions, the case file is saved. This is done by choosing to “write” the case file in FluentTM. If any changes are to be made to the case file after the solving has commenced, the solution must be halted and the existing solution data at this point saved in a data file. After changes are made to the case file it must be written again. If these changes are to be applied to the solution data at this point, or to any other data file, FluentTM must read in the new case file and the desired data file to which the conditions of the case file are to be applied. If no data file is read into FluentTM, the solver will initialise the flow field and commence the calculations again from the beginning.

Initialisation of the flow field.

The solver must be supplied with an initial “guess” for the flow field in order for it to commence iterating through the flow field and calculating a solution. The default values for each variable are zero. If approximate or realistic values are known for any particular region or zone within the fluid domain these can be entered as initial values. Alternatively, the solver can compute average initial values from all of the cell zones, using pre-defined boundary conditions (FluentTM User’s Guide, 2003). After initialisation the solution can begin to iterate through the flow field.

Running the solver without the GUI.

Although the solution can be initialised and calculations commenced by using the drop-down menus available through the GUI, FluentTM can also be run in batch or background mode. If this option is used, the GUI is not available and the solver obtains inputs from, and stores the output in, files. The process is controlled from the inputs in the file eliminating the need for the user to be present to input these process controls and instructions. A particular advantage of running a solution in background mode is that the computer resources can be prioritised i.e. resources used to solve the solution rather than to produce the graphical output (FluentTM User’s Guide, 2003). This is a desirable situation when a large number of iterations are to be performed for a complex problem and was therefore an option used frequently in the current work. The initial problem set up in the case file and post-processing analysis of solution results can be carried out interactively using the GUI, only using the background mode while performing the calculations to obtain the solution.

Post processing.

When a satisfactory solution has been obtained, data may be output graphically or numerically. Surfaces such as planes, lines and points can be created in FluentTM at user-specified locations within the fluid domain and solution data displayed as, for example, colour coded contours or vectors of velocity data. Data from the created surfaces can also be reported numerically in many forms, for example as a maximum velocity data at a node (vertex) or cell (facet). An important post-processing feature is the ability to plot the change in residual with each iteration during the production of the data file being studied, to facilitate judging the convergence of the solution. Other facilities provided by the FluentTM package to analyse results include displaying mixing pathlines and animation of solution graphics (FluentTM User's Guide, 2003).

1.6 Other methods to measure fluid velocity values.

Quantitative fluid velocity measurements.

The term “pulsed light velocimetry” covers a range of techniques which measure the motion of regions of fluid by “marking” the fluid regions, then determining the position of these marked regions at two different time points (Adrian, 1991). This technique includes particle imaging velocimetry. The velocity, v , at a location, x , at time, t , is calculated using the relationship between the measured change in location, Δx , over a measured time period, Δt (Adrian, 1991):

$$v(x, t) = \frac{\Delta x(x, t)}{\Delta t} \quad \text{Equation 1.24}$$

The marker is usually a solid particle in a liquid but other methods can be used, for example molecules which fluoresce when activated by a laser beam, or liquid droplets in gases. When pulsed light velocimetry is used, the locations of the marked fluid regions are recorded using pulses of light, which photographically record the location of the fluid region (Adrian, 1991). Ultrasound pulse echo (UPE) uses a similar technique, where an ultrasound pulse is directed into fluid medium using a probe. The frequency at which the ultrasound pulse is generated is known. Solid particles within the fluid medium reflect the ultrasound pulse, and the frequency at which the returning ultrasound beam is detected by the probe is an indication of how fast the particle (and hence the fluid) is moving. In other words, it is the frequency shift of the ultrasound pulse which enables determination of fluid velocity (Diebold and Dressman, 2001). In laser Doppler anemometry, velocity measurements are taken where two laser beams cross. A particle crossing this point will cause the light to scatter, and the intensity of the scattered light can be measured. The frequency of the scattered light is used to calculate the velocity of the particle (Bocanegra et al., 1990).

Qualitative flow visualisation techniques.

Flow visualization can cover any technique which enables the fluid flow to be visualised, and the hydrodynamics and mixing patterns of a flow field can be qualitatively assessed. A common method involves injecting a dilute dye into the fluid medium and monitoring (visualising) its motion and thus the hydrodynamics from the point of injection into the fluid domain. The density and viscosity of the dye solution should be similar to the fluid being investigated. Physicochemical characteristics of the fluid medium, for example pH, can also be utilised to visualize fluid flow patterns. The hydrodynamics have been visualised around a dissolving salicylic acid tablet incorporating phenolphthalein indicator in a dissolution medium of dilute sodium hydroxide in the paddle dissolution apparatus at 25, 50 and 100 rpm. As the surface of the tablet dissolved, the pink colour of the phenolphthalein indicator in the clear sodium hydroxide dissolution medium indicates the flow direction above the tablet (Mauger et al., 2003). Laser induced fluorescence (LIF), where a light beam is used to excite molecules and the emitted light intensity is measured, can be used to visualise and quantify mixing in a flow field. Flow visualisation can be achieved by photography of the flow field capturing the fluorescence intensity (Unger and Muzzio, 1999).

1.7 Recent use of CFD, UPE and laser-Doppler techniques to analyse hydrodynamics in the paddle and basket dissolution apparatuses.

The hydrodynamics in a vessel containing 900 ml of water at room temperature (20°C) was simulated using CFD by McCarthy et al., 2002. Two approaches were used, using an unstructured grid with a multiple reference frame and a structured grid with a single rotating reference frame. It was concluded that the structured grid with the single rotating reference frame resulted in hydrodynamic data which was closer to the experimental laser-Doppler velocity data (Bocanegra et al., 1990) being used for validation purposes. Convergence criteria of a decrease in residual magnitude of 10^{-3} was used. An unstructured grid with a single rotating reference frame, or alternative convergence criteria (e.g. leveling of residuals) were not investigated. The hydrodynamics within the vessel at 25, 50 100 and 150 rpm were simulated. Hydrodynamics at 50 rpm around a compact (8.5 mm height plus 3 mm wax base) located at the centre of the vessel base were also simulated, with the high shear present at the lower 3 mm of the cylinder, consistent with experimental dissolution data revealing grooving at the base of a compact in this location (McCarthy et al., 2002). In the current work, the feasibility of using a single reference frame with an unstructured grid, different conformations of a multiple reference frame to that used by McCarthy et al. (2002) and criteria by which to judge convergence other than a decrease in residual magnitude of 10^{-3} will also be investigated.

CFD simulations of hydrodynamics in the paddle dissolution apparatus at 50 rpm (McCarthy et al., 2002) revealed secondary flow patterns which were in agreement with those previously predicted by laser-Doppler velocity data (Bocanegra et al., 1990). These secondary flow features included an eddy region at the tips of the paddles, inward radial flow beneath the paddle and flow patterns suggesting solid body rotation at the vessel base. Poor mixing between upper and lower portions of the vessel were suggested by Bocanegra et al. (1990) from the presence of separate axial recirculation flows in the upper and lower region of the vessel, however CFD simulated mixing pathlines demonstrated complete mixing in the vessel within 40-60 seconds at 25 rpm, with shorter times at higher rotation speeds. The CFD simulation also demonstrated axial recirculation patterns in the upper and lower regions of the vessel, however there was no dead-zone of mixing between the cylindrical and hemispherical paddle regions (McCarthy et al., 2002). A similar flow pattern to that suggested by Bocanegra et al. (1990) within the paddle apparatus was predicted from UPE data (Diebold, 2000). The magnitude of the low axial flow rate beneath the centre of paddle was also determined, and was found to vary with rotational speed of the paddle (Diebold, 2000). The hydrodynamics of the basket apparatus were also investigated using UPE data, and secondary axial and radial recirculation patterns were suggested to be present in addition to the rotational flow (Diebold, 2000). A schematic diagram of this flow pattern is presented in section 5.19, when CFD simulations of hydrodynamics within the basket apparatus are presented.

2.0

Materials and Methods.

2.1 Materials and Equipment.

2.1.1	Materials	Manufacturer/Supplier
	5 ml plastic syringes, Omnifix	Braun
	Benzoic acid	BDH Laboratory Supplies
	Mambrane filters, 0.45 µm	Pall (Gelman Sciences)
	Hydrochloric acid 37% w/v	Riedel-de Haën
	Needles, Sterican	Braun
	Paraffin wax, pastillated	BDH Laboratory Supplies
	Potassium dihydrogenphosphate (anhydrous)	Aldrich
	Prednisone calibrator tablets (USP Lot N)	USP
	Prednisone reference standard (USP Lot L)	USP
	Salicylic acid	BDH Laboratory Supplies
	Salicylic acid calibrator tablets (USP Lot O)	USP
	Salicylic acid reference standard	Elan
	Tcabag	Twinnings
	Tropaeolin dye (orange)	Fluka Chemica

2.1.2	Equipment	Supplier/Manufacturer
2.1.2.1	Software	
	Fluent TM version 6.1	Fluent Inc.
	Gambit TM , version 2.0.4	Fluent Inc.
	Microsoft Excel (Office 2000)	Microsoft
	Minitab, version 12	Minitab Inc.
	Origin version 7.5	OriginLab Corporation
2.1.2.2	Computational Resources	
	Dell 450 dual-processor workstation, 2GB RAM	Dell
	Linux operating platform	Red Hat Linux
2.1.2.3	Instruments	
	13 mm Hydraulic punch and die	Perkin-Elmer
	DT6 Dissolution Test Apparatus	Erweka
	Glass jars (natural convection studies)	Lennox
	Height gauge and centering tools	Vankel Ind.
	Hitachi S-3500N scanning electron microscope	Hitachi
	HP 8452A UV/visible spectrophotometer (and software)	Hewlett Packard
	Hydraulic press	Perkin-Elmer
	Magnetic stirrer hotplate	Stuart Scientific
	Pycnometer bottle	MBL
	Sartorius Balance BP121S	Sartorius
	Shaking water bath	Heto
	Stirrer (Levy beaker Dissolution Apparatus)	Nalge Inc.
	Waterbath (Natural convection studies)	Lauda

2.2 Methods

2.2.1 Computational fluid dynamics – geometrical model construction and flow simulations.

2.2.1.1 Paddle dissolution apparatus.

2.2.1.1.1 Vessel containing no compact, and the compact in the central position.

Construction and meshing of the vessel containing no compact and the compact in the central position.

The method used to create and mesh a model of the vessel containing no compact and a compact at the centre of the base was previously described in detail (McCarthy et al., 2003). GambitTM software was used to create the 3-D model of the apparatus. It was created to scale (U.S.P., 2005; B.P., 2005; Ph.Eur., 2005), with a total volume of 900 ml. The method consisted of creating edges corresponding to a 2-D section through one quarter of the hemispherical part of the vessel from the midpoint to the edge including the paddle. This edge was then rotated to create a 3-D version of a quarter of the hemisphere. A volume was cut out of this to define the width of the paddle as otherwise the paddle would have filled the entire top part of the hemisphere. This quarter was then reflected to create half a hemisphere, and this half further reflected to create the whole hemisphere. An edge was then created from the top of the hemisphere to a point which would be the top part of the cylindrical section of the vessel. All of the faces at the top of the hemisphere were then selected and “swept” along this edge to form the cylindrical part of the vessel attached to the hemisphere, including the paddle and the shaft. The completed geometry of the model as created in GambitTM is illustrated in Figure 2.1.

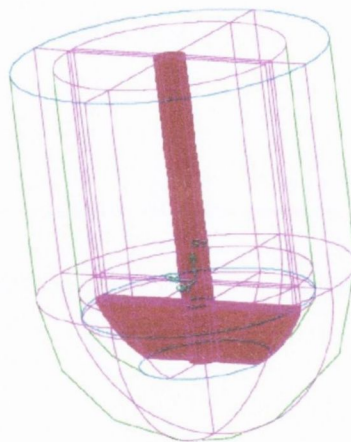


Figure 2.1. Geometry of empty paddle dissolution apparatus containing no compact constructed in the GambitTM pre-processor. The paddle volumes are highlighted in dark red, the remaining volumes consist of the vessel fluid.

Insertion of a compact in the central position.

The location of compact positions is described in Dissolution rate studies, section 2.2.2.3. A cylinder of 3 mm height and 13 mm diameter was created and located at the base of the vessel, such that the centre of the compact passed through the z axis. The edges of the compact met the vessel wall at 6.5 mm from the centre. This cylindrical volume, which represented the compact, was then surrounded by an “envelope”, a second cylindrical volume extending 1 mm both upwards and radially from the compact surface, i.e. 4 mm in height and 15 mm in diameter. This envelope was created to facilitate the creation of a very fine mesh at the compact surface. The volume of the compact and the envelope were then subtracted from the lower quadrant volumes forming the base of the hemispherical portion of the vessel. The result was four quadrant volumes to model the fluid in the lower region of the hemispherical portion of the vessel around the envelope, the envelope volume and the volume of the compact itself. As the compact surface touched the vessel base around the circumference of the lower planar surface, there was no modelling of fluid beneath the lower planar surface of the compact.

Meshing.

The next step consisted of meshing the model. The cooper meshing tool provided in Gambit™ was used to create a structured hexahedral mesh. It involves choosing source faces, usually roughly at opposite ends of a chosen volume, and mapping the mesh through the volume from one or more of these source faces onto the other(s). The manner in which the model is created results in the apparatus being divided into a number of different volumes, all of which must be meshed separately. It is essential, however, that the meshes on adjoining volumes are compatible with each other to facilitate the development of a continuous meshed domain.

In order to ensure that the hexahedra are as regular as possible, the aim is to mesh as many as possible of the source and non-source faces with a “Map” mesh, but due to the circular elements in the geometry this is not always possible. A Map mesh creates a regular structured grid of mesh elements (Gambit User’s Guide, 2003). As a mapped source face must be projected onto another mapped source face, the total amount of nodes on the source faces from which the mesh is protruding must equal the number of nodes on the face(s) onto which the mesh is being projected. Therefore all of the edges are carefully meshed first to define the number of nodes, which will lead to a particular amount of 2-D elements, which will facilitate the creation of a regular hexahedral 3-D mesh.

After meshing the model, the continuum and boundary specifications must be defined. That is, every volume must be declared to be either solid or fluid for the continuum specifications.

In this case, all volumes that are part of the shaft, paddle or vessel are solid, and the rest of the domain volumes are fluid, with the exception of the volumes defining the compact in the central position which are solid.

As regards the boundary specifications, the vessel wall is set to wall, as is the paddle and shaft. The liquid-air interface is defined as wall.

The meshed model is now ready to be exported to the solver, FluentTM.

Solver.

To apply the solver to a mesh, or grid, the mesh must first be read into the solver. The file is chosen and FluentTM reads it as a case file. A case file consists of all of the pre-determined specifications for solving a grid. Initially, the type of solver (in this case segregated) must be selected. This was done in the Define Models menu, and 3-D, steady time and absolute velocity were also the chosen options from this panel. In the materials panel, water at room temperature was entered, as this was the fluid used in generating the laser Doppler data which were used to validate the model (Bocanegra et al., 1990). It is possible also to use different fluids or to create user defined fluids. The dynamic viscosity of the water was changed to that of water at 37 °C ($0.0006943 \text{ kg m}^{-1} \text{ s}^{-1}$ (Visavanth and Natarajan, 1989)) for simulations of fluid flow around the compacts in the vessel once the model was validated, as experimental dissolution work was carried out at 37 °C. The angular velocity was set to rpm, and the fluid zone was set at an absolute rotational velocity of 50 rpm. This was relative to the velocity of the vessel wall which is stationary in the absolute frame (0 rpm) and stirrer wall which is stationary in the relative frame (stationary relative to the adjacent cells). In effect, it solves for a stationary paddle with moving fluid instead of vice-versa. This is termed a rotating reference frame (section 1.5).

The pressure discretisation scheme used was PRESTO!, momentum uses the 1st-order upwind scheme and SIMPLE C pressure-velocity coupling is selected.

A laminar model was used as opposed to one of the various types of turbulence models.

For the model containing the compact in the central position, the investigated boundary conditions applied to the liquid-air interface were wall (stationary in the absolute frame), wall (no shear) and a symmetry condition. The effect of these differences in boundary conditions were investigated in terms of the effect on mass transfer predictions from diffusion layer simulations (section 2.2.1.4). A periodic model of the paddle apparatus is also used in mass transfer predictions from diffusion layer simulations (details on periodic model approach are given in 2.2.1.2). Results from the simulation using the air-liquid interface defined as a stationary wall were used for all other applications.

For the model containing no compact, a solution was attained for simulated flow fields at 25, 50, 75, 100, 125, 150, 175 and 200 rpm.

Validation.

Validation involved comparing results from simulated fluid flow in a vessel containing no compact with previously determined laser Doppler velocities (Bocanegra et al., 1990) at numerous points throughout the fluid domain (Appendix 1). The method used was the C program,

COMPARE, developed by Kosiol (2000) and used by McCarthy (2002), and McCarthy et al., (2003), and the C program (COMPARE) was obtained by personal communication (McCarthy, 2003). The points were located at various radii on a series of five different horizontal planes throughout the vessel. Various under-relaxation factors involved in the mathematical algorithms used to solve the CFD model were modified until a solution consistent with the experimental data was obtained. This validation method is consistent with that used by McCarthy et al., (2003). Under-relaxation factors are involved in controlling the change of a variable value produced by each iteration. This control is necessary because of the non-linearity of the equations employed (FluentTM User's Guide, 2003). The model containing the compact in the central position was validated by defining the volume of the compact as fluid, and therefore simulating the hydrodynamics in a vessel filled with fluid only. Results were compared to laser Doppler velocities as for the original model containing no compact. Results for the simulations at agitation rates from 25-200 rpm were compared to previously published UPE velocimetry data (Diebold and Dressman, 2001), as detailed in section 2.2.1.2. The locations of the planes examined in the paddle apparatus were the same as those examined in the basket apparatus.

2.2.1.1.2 Vessel containing the off-centre compacts.

A single rotating reference frame is not suitable if baffles are present and presence of off-centre compacts results in a situation similar to the presence of baffles. Therefore a third domain must be created in the region of the off-centre compact (resulting in a multiple reference frame) (FluentTM User's Guide, 2003). A multiple reference frame model may be used if a baffle is situated such that the interaction between the stirrer and the baffle as the stirrer passes over the baffle is not significant. When modelled in this manner, the fluid flow in the region of the baffle is a simulated steady state approximation rather than a time-dependent solution which would model the changes in fluid flow with time around the baffle as the stirrer rotates. By definition a time-dependent solution is more accurate, but also more computationally expensive.

Flow around compacts in two off-centre positions, representing the positions that cylindrical compacts of benzoic acid were located in dissolution studies, was investigated. These locations are described and illustrated in section 2.2.2.3. In order to model fluid flow around tablets in the two off-centre positions, a horizontal plane was introduced into the vessel, at a level 1.6 cm above the base (0.9 cm below the stirrer). This was used to divide all of the outer quadrants and the volume above the tablet in two. A further face had to be introduced to join the outer edge of this plane to the bottom of the inner volume which surrounds the stirrer to facilitate meshing. These alterations to the model are illustrated in the quadrant shown in Figure 2.2. All volumes above the horizontal plane could be meshed using either the Map or Cooper scheme as before.

Structured mesh in the lower reference frame.

Below the plane, however, it was not possible to use a hexahedral meshing scheme without further dividing the bottom face to create a third mappable face which the upper face could be projected along to facilitate Cooper meshing.

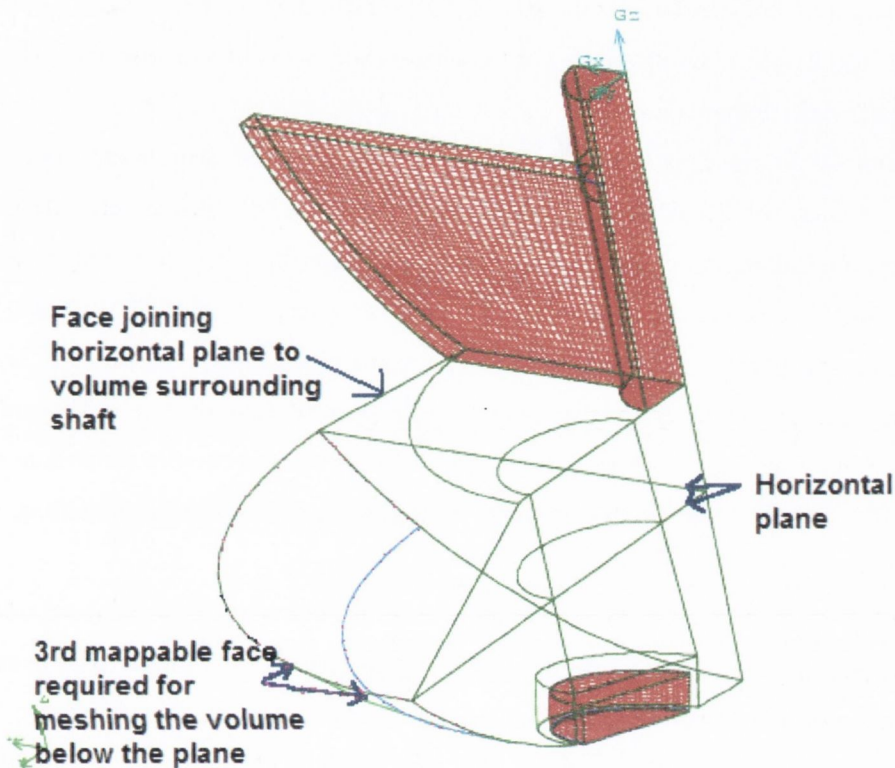


Figure 2.2. Diagram of one lower quadrant illustrating the new horizontal plane defined to divide the flow field in the paddle apparatus in two, enabling a multiple reference frame model to be used. The new faces required to facilitate structured meshing are also shown. One half of the off-centre compact, in position 1, is also shown.

The faces which made up the horizontal plane had to be duplicated, as the same face could not be used to form the boundary of two separate reference frames, however the two faces did have to have identical geometry and positioning. The stitch faces tool was then used to define the volumes. In specifying the continuum conditions, all fluid volumes above the plane were defined as “vessel fluid upper”, and below the plane as “vessel fluid lower”. There was a conformal (i.e. identical mesh nodes) grid at adjoining faces of the two reference frames. This requirement to use a conformal grid implies that the mesh spacing at this point must be suitable for meshing schemes above and below the plane. This restricts the available options for meshing both above and below the plane.

Unstructured mesh in the lower reference frame.

The above method resulted in the creation of a structured mesh in both the stationary and the rotating domain, however it was extremely difficult to reach the convergence criteria of a decrease in residual magnitude in the order of 10^{-3} . An initial solution was attained through solution-adaption methods (adapting the mesh in areas proving more problematic) as the solution evolves, however it was noted, on examining the residuals, that there were particular areas of the mesh where the residuals were consistently higher than in the overall domain. These areas were mainly located near the vessel wall in the lower part of the vessel (below the plane), and also near where the lower and upper fluid domains met.

Upon examination of the mesh, it was noted that the cells near the plane were very skewed (Equiangle skew values: (0.22% cells > 0.9, 287 cells (0.03%) > 0.98 = degenerate cells)) which would explain the difficulties in obtaining an accurate solution in this area. It was also noted that there was no pre-defined boundary layer inserted beside the lower vessel wall while the model was being built, as the geometry of this modified portion did not allow for this. In terms of meshing a model, a boundary layer consists of defining a specified number of cell-layers in the region next to a wall. These cells can have a defined thickness which provides for a more refined mesh in the region of the wall. This in turn allows for more accurate modelling of the hydrodynamic boundary layer.

In order to decrease the skewness of the cells, and to insert a boundary layer near all stationary walls, this lower portion of the vessel was meshed using an unstructured mesh. The model was built and the plane inserted as before, however it was not necessary to further divide the bottom face of the lower quadrants below the plane, as there was no third mappable face required for an unstructured mesh.

Boundary layers.

All of the boundary layers with the exception of that around the tablet surface had a 1st-row depth of 0.0002 m, and were made up of four rows. The growth factor was 1.5 in all areas of the wall above the spherical part of the vessel, and 1.2 in all areas below. A growth factor of 1.2 means that the second row of cells in the boundary layer is 20% thicker than the first row of cells (Gambit User's Guide, 2003). The boundary layers directly surrounding the tablet had a 1st-row depth of 0.00002 m, a growth factor of 1.2 and had six rows in total.

Size functions.

Size functions are similar to boundary layers in that they control the mesh characteristics in the proximity of the entities to which they are attached (FluentTM User's Guide, 2003). There are various types of size function, and the fixed type (employed in this model) defines the maximum element edge length as a function of distance from a defined source entity through a defined attachment entity. In other words, it is a function which defines the maximum length of any edge

of a given element (or mesh cell) when that element is a given distance from a source entity (e.g. a face on a volume) through an attachment entity (e.g. the volume). Therefore as the mesh proceeds from a face into a volume the size of the elements are controlled through the edge length being controlled at any particular distance from the source face.

The start size is the maximum element edge length for all mesh elements immediately adjacent to the attachment entity. The growth rate and distance are similar to a boundary layer. The size limit is the maximum allowable mesh element edge length either inside or outside the outer boundary of the size function.

When applying a size function, GambitTM defines a bounding box which it divides into subsections, then divides each section into further subsections and so on. If the number of subsections is small, computational time is saved, however some of the elements may only be approximations of the original size-function parameter. The number of subsections can be altered using the edit-defaults menu in GambitTM. The number of division steps in this model was six (default is ten).

It was not possible to mesh the particular geometry of the bottom quadrants using a tetrahedral mesh with boundary layers attached, and as a result size functions were attached instead. The source of the size function was the face defining the vessel wall in each quadrant. The attachment entity was the volume of the quadrant itself.

The parameters used are shown in Table 2.1.

Parameter	Position 1 3 mm tablet	Position 1 8.5 mm tablet	Position 2 3 mm tablet
Start size (m):	0.0002	0.0002	0.0002
Growth Rate:	1.2	1.2	1.5
Distance (m):	0.006	0.006	0.001
Size limit (m):	0.0015	0.0015	0.0015

Table 2.1. Parameters used when applying size functions to the lower quadrants of the vessel when simulating fluid flow around the compacts in positions 1 and 2 in the paddle apparatus.

The effect of the size function on the side face of a lower quadrant volume is evident in Figure 2.3. The mesh density at a series of isosurfaces at increasing distances from the source face to which the size function is attached is illustrated in Appendix 2.



Figure 2.3. Source face and side face of one of the lower quadrants in the paddle apparatus illustrating the continuous effect of the size function through the attachment entity.

Meshing.

The volumes of the tablet envelope, directly around the tablet, were meshed using a combined hexahedral and tetrahedral mesh with the Cooper scheme, and the tablet itself was meshed with a tetrahedral grid using the T-Grid scheme.

The volumes directly above the plane were meshed using a combination of hexahedral and tetrahedral elements with the Cooper meshing scheme. All other volumes were meshed using a structured hexahedral mesh with either the Cooper or Map meshing scheme as in the previous models.

The unstructured tetrahedral mesh is generally more versatile than the structured mesh, and as a result it was possible to mesh the quadrants around the tablet envelope without the need to create a new volume between the top of the tablet and the bottom of the face above. The final geometry of the hemispherical portion of the vessel used to model the off-centre tablets is shown in Figure 2.4, with the tablet in position 2.

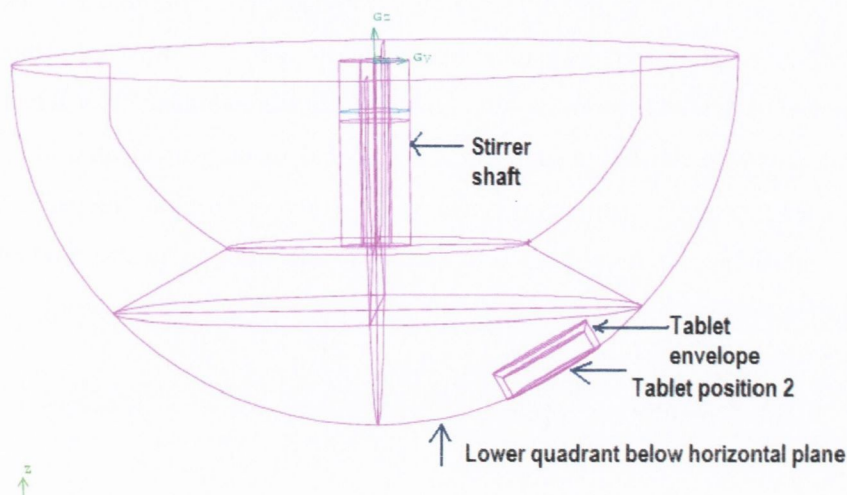


Figure 2.4. Final geometry of the hemispherical portion of the vessel containing off-centre compact (tablet) in position 2 in the paddle apparatus. The mesh is not shown for clarity.

Solver.

When this mesh was imported into FluentTM, the two fluid domains (upper and lower) were defined as rotating reference frames, however “vessel fluid upper” was defined as having an initial rotational velocity of 50 rpm, and “vessel fluid lower” an initial rotational velocity of 0 rpm. The compact (contained in vessel fluid lower) therefore has an absolute velocity of zero, as does the vessel wall in both upper and lower portions of the vessel. The stirrer wall is defined as being stationary relative to the adjacent cells, in other words a velocity of 0 rpm relative to the adjacent cells which have a velocity of 50 rpm. The model was run to convergence using the standard pressure discretisation scheme. The parameters for pressure-velocity coupling and momentum were not altered from those used for the model with the compact in the centre position.

Validation.

In order to ensure that the multiple reference frame model and meshing schemes were appropriate, the tablet volume was initially defined as fluid. This was essentially modelling fluid flow in an empty vessel. This was then run to convergence. Results were compared to laser Doppler velocities to validate the model (Bocanegra et al., 1990) using the method developed by Kosiol (2000). The tablet was then defined as solid and run to convergence. Convergence was determined when residuals would not decrease any further regardless of alterations in under-relaxation factors. Generally residuals had decreased by 10^{-3} to 10^{-4} at this point. Further convergence may have been limited by mesh size (which in turn is limited by available RAM). This is different to the original approach used by McCarthy (2002) and when modeling the vessel

containing no compact or a compact in the central position of achieving convergence when the residuals had decreased by a factor of 10^{-3} , with manipulations of the under-relaxation factors being used to achieve slight differences in the final solution. Altering under-relaxation factors can enable a solution to be achieved more rapidly, however when convergence is reached the solution should be similar (within the limits of the mesh size and mathematical algorithms employed) regardless of under-relaxation factors employed. This method of building the geometry, applying size functions, meshing and importing into FluentTM was used to create simulations of the compacts in both position 1 and position 2.

2.2.1.2 Basket dissolution apparatus.

Construction of basket apparatus.

Periodic Case.

As the basket by its nature consists of a fine wire grid, it was apparent that to build a geometry of the entire basket incorporating this grid would require an extremely fine mesh in order to create control volumes around the wire grid. As each wire grid opening is basically an interface between fluid within the basket and fluid outside the basket, and the wire between the openings is a wall between these two fluid domains, it was considered necessary to define separate control volumes around each of these openings. A fine, dense mesh was therefore produced both inside and outside the basket. To create a model of the entire vessel containing this basket mesh would require more memory (RAM) than was available to run the solution. To address this problem it was decided to create a periodic geometry. The principle of a periodic case is to model only a portion of the fluid flow when it is known that the physical geometry and the expected pattern of the flow solution have a periodically repeating nature (FluentTM User's Guide, 2003). The boundaries of this portion of the flow are termed periodic boundaries, and they are appropriate when the flow across two opposite planes in the model are identical. These planes can then be periodically linked. FluentTM treats the flow at a periodic boundary as though the opposing periodic plane is a direct neighbour to the cells adjacent to the first periodic boundary (FluentTM User's Guide, 2003).

The velocity (v) at a point on a periodic boundary is defined as follows:

$$v(\vec{r}) = v(\vec{r} + \vec{L}_p) = v(\vec{r} + 2\vec{L}_p) \dots$$

where $\vec{r}$ is the position vector and $\vec{L}_p$ is the length or distance to the same point on the opposite periodic boundary.

Swirling flow in a cylindrical vessel is an example of a potential application of periodic flow given in the FluentTM User's Guide (2003).

It was decided to model one-quarter of the basket apparatus as a periodic case. The geometry had to be of a repeating nature, therefore a rotationally periodic model was chosen as the geometry and flow are rotationally periodic. This consists of defining an axis of rotation, (which is the axis of rotation of the basket itself), and the repeating angle, which is 90 degrees for one-quarter of the apparatus. This resulted in a model with a very dense mesh which would have been impossible to run with the available RAM had the entire fluid domain been modelled.

Construction.

The construction of the basket grid involved the creation of a cylinder 27 mm in height and 11.1 mm in radius. This is consistent with the dimensions of the curved side grid of the basket in the USP and Ph. Eur. (U.S.P., 2005; Ph.Eur., 2005). A series of faces were then created on this curved face, which were 0.4 mm x 0.4 mm in area. The distance between the faces was 0.25 mm which is the diameter of the wire used in the wire grid. As the total area of this wire portion was approximately 470 mm², over 1000 of these faces would have to be individually created to create the apertures in the wire grid. Therefore the faces were copied and either translated vertically by 0.65 mm (to create vertical rows) or rotated by 3.355 degrees to create the horizontal rows. Once a whole row was created in either direction, the whole row could be copied. These faces had to then be subtracted from the original curved side of the cylinder, resulting in a cylindrical grid. Upon subtracting the faces, however, duplicate edges remained at the edge of the faces, and these edges had to be connected to eliminate the duplication. The cylindrical grid which was formed by this process was a 2-D face, as can be seen in Figure 2.5, as the wire diameter in reality is only 0.25 mm thick it was considered that this approach would provide a reasonable approximation of the fluid flow.

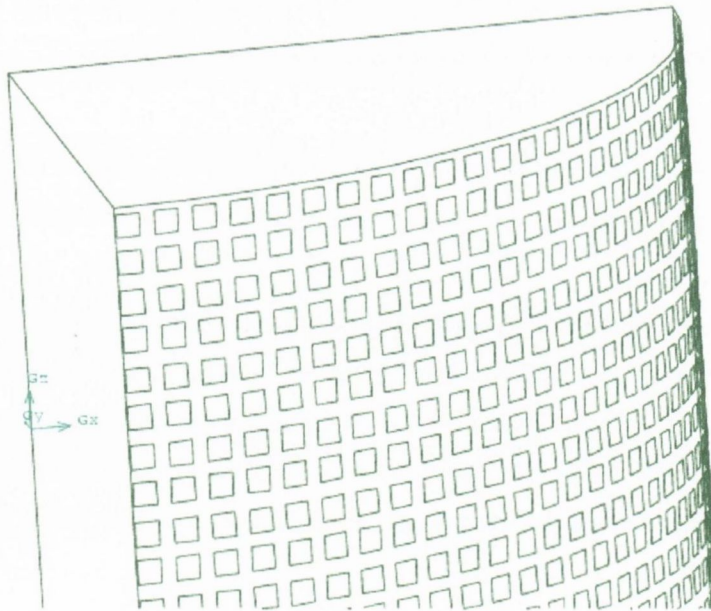


Figure 2.5. Part of the curved side wire grid of the basket in the periodic model of the basket apparatus, with apertures formed from individual faces.

Further quarter-cylinders were created to form the volume of the basket above the grid which attaches to the lid, the lid itself, and the lower portion of the basket. Both upper and lower portions have a lip extending approximately 1.4 mm out from the main portion of the basket, as can be seen in Figure 2.6. The grid on the bottom surface of the basket was created in a similar fashion to the curved side surface, that is a series of faces subtracted from the flat surface to create a 2-D grid.

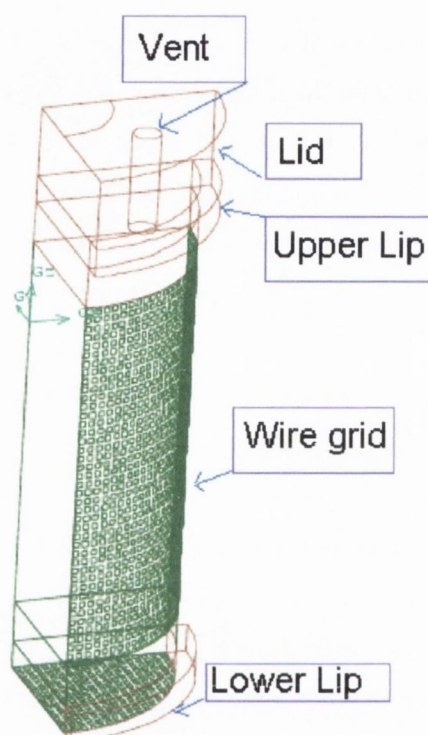


Figure 2.6. Completed quarter-basket with wire grid at the side and base, upper and lower lips, lid and vent, from the periodic model of the basket apparatus.

To facilitate meshing, the vessel was divided into several portions, each connected to a separate portion of the basket. The basket shaft was created from the top of the basket to the top of the vessel. A vent was inserted into the upper lid of the basket. In reality this is not a repeating feature as there is only one vent on the surface of the basket, however it was anticipated that this would not influence fluid flow patterns to an appreciable degree and was therefore included. A feature which was omitted from the model was the spring clips which hold the basket inside the lid. It was anticipated that the meshing of the volumes around the basket were too complex to incorporate this feature. The completed quarter-basket with vessel and with some of the lower sections of the vessel can be seen in Figures 2.7 and 2.8 respectively. Symmetry conditions were applied to the air-water interface for the 50 and 150 rpm simulations, and both symmetry and “wall” conditions were applied to this interface for the 100 rpm simulation. In the case of the model of the vessel with the tablet in the base, a quarter-cylinder (radius 6.5 mm, height 13 mm)

was inserted at the base of the “quarter-vessel” and the surface of this volume was defined as a solid wall.

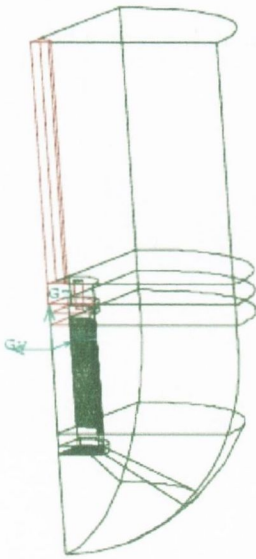


Figure 2.7. Completed quarter-basket and vessel, from the periodic model of the basket apparatus.

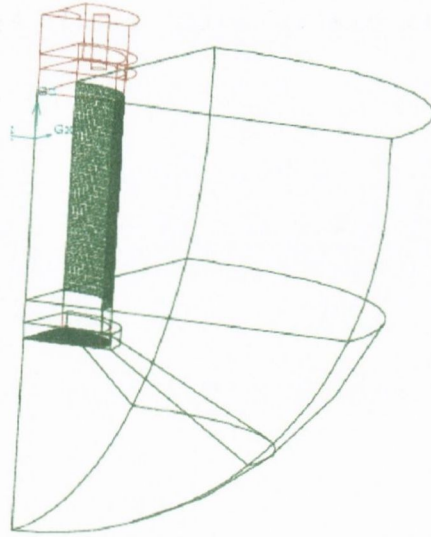


Figure 2.8. Quarter-basket with lower sections of vessel, from the periodic model of the basket apparatus.

Meshing.

Each edge on each of the faces which formed the grid apertures was assigned a mesh interval value of 1 to ensure that there was no more than one grid aperture associated with each control volume to accurately model fluid flow into and out of the basket. This interval assignment was then used as a basis to mesh the model. The majority of the volumes were meshed using the Cooper scheme. The volumes inside the basket were meshed using a tetrahedral scheme. The upper lip was mapped, and the portion of the vessel attached to this was submapped. The mesh contained both hexahedral and tetrahedral mesh elements.

Due to the complex nature of the face which constituted the wire grid, it was not possible to attach boundary layers to this wall. However, as the mesh was particularly fine to begin with, the range of element volume sizes in this model was approximately 1×10^{-12} m to 2×10^{-09} m. Most of the elements between 1×10^{-12} m and 5×10^{-12} m were in the region of the basket. As a comparison, the range of element volumes for the model of the paddle apparatus with the compact in the central position, for example, was approximately 5×10^{-12} m to 2×10^{-09} m. In this case, the elements that were in the range of 5×10^{-12} m to 1×10^{-11} m are within the boundary layer inserted around the side of the compact. Therefore it was considered that the elements in the region of the basket grid were refined adequately without inserting boundary layers.

Boundary and continuum specifications.

The faces at the periodic boundaries were assigned in pairs as periodic faces. Some of these periodic faces are illustrated in Figure 2.9. The basket and shaft faces and all of the walls of the vessel were defined as walls. The volumes of the vessel and the interior basket volumes were defined as fluid, and the shaft, basket lid and upper and lower lips were defined as solid.

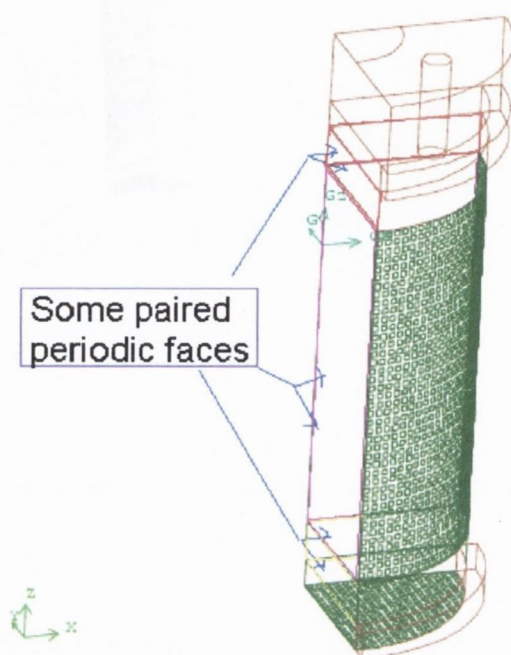


Figure 2.9. Example of some of the paired periodic faces at the boundaries of the quarter-basket, from the periodic model of the basket dissolution apparatus.

Solver.

The model was exported from GambitTM to FluentTM as a mesh file and then converted to a case file in FluentTM. The fluid domains were defined as a rotating reference frame similar to the models of the paddle apparatus. The periodic faces were assigned periodic boundary conditions in GambitTM and were automatically assigned as periodic faces in FluentTM.

A segregated, implicit time-averaged (steady) solver was used with a velocity formulation specified as absolute. The fluid was defined as water with a dynamic viscosity of water at 37 °C ($0.0006943 \text{ kg m}^{-1}\text{s}^{-1}$). The basket and shaft walls were defined as stationary in the relative frame, and the vessel walls as stationary in the absolute frame. The standard pressure discretisation scheme was used, with the SIMPLE-C pressure velocity coupling. The momentum discretisation scheme was first-order upwind. The initial under-relaxation factors used were 0.3 for pressure and approximately 0.35 for momentum. As the solution converged it was possible to increase the momentum under-relaxation factor.

Convergence Criteria.

The convergence criteria for x , y , and z velocities and the continuity equation were turned off, and plots of residuals for these variables were monitored. Although it would be expected that when these residual values start to level off a solution will have reached convergence, it was noted that velocities at particular locations continued to change after this point for each rotation speed examined. It is possible to monitor variables on a surface, in other words to use various surface integrals as convergence criteria (FluentTM User's Guide, 2003). When the variable ceases to change the solution can be considered converged. In the case of this model, the velocities tended to decrease long after the residuals had levelled, and most of the solutions took approximately 30,000 iterations to converge using these criteria. The surfaces used to monitor the velocities to determine convergence at each agitation rate were located on the planes where the previously published ultrasound-pulse-echo (UPE) velocity data was recorded (Diebold and Dressman, 2001). Horizontal (numbered s1, s2 and s3) and vertical (numbered o1 and o2) 2-D planes were defined in the solved flow-field corresponding to the planes on which the ultrasound-pulse-echo velocity data were previously recorded. These planes are illustrated in Figure 2.10.

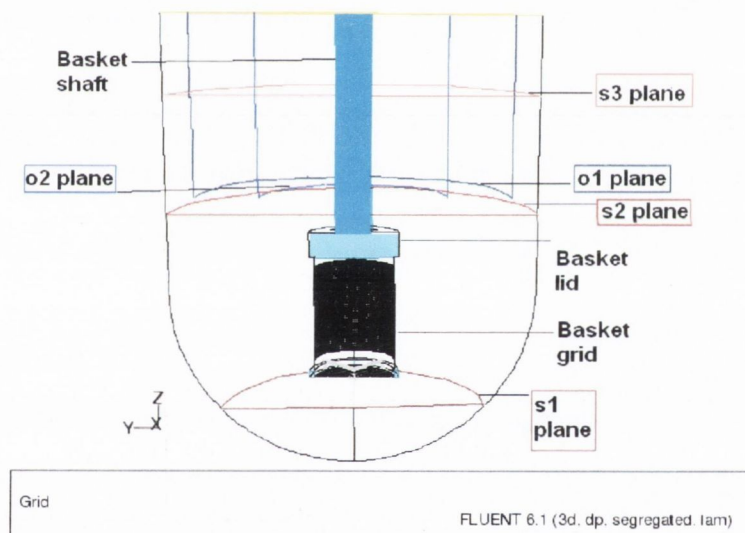


Figure 2.10. Horizontal (s1 to s3) and vertical (o1 and o2) planes on which tangential and axial velocities, respectively, were measured using the ultrasound-pulse-echo method (Dressman and Diebold, 2001), in the basket dissolution apparatus.

The velocities (facet maximum or minimum) examined were maximum tangential velocities (planes s1 to s3) and maximum (or minimum if in a downward direction) axial velocities on the o1 and o2 planes. The velocities were recorded at the same radial location on a particular horizontal plane at each iteration, and a different radial location was examined on each horizontal plane. For example, the radial locations examined from the 50 rpm solution were 7 mm from the centre (s1 plane), 36.4 mm from the centre (s2 plane) and 31.5 mm from the centre (s3 plane). These radii were defined as a ring-surface, each ring having a width of 1 mm. Similarly, a

different vertical location on vertical planes, o1 and o2, was examined. For the 50 rpm simulation these vertical points were 12.6 mm below the surface of the liquid (o1 plane) and 28.5 mm below the liquid surface (o2 plane). These surfaces are shown in Figure 2.11 and illustrate the nature of the distribution of data “sampling points” within the flow-field.

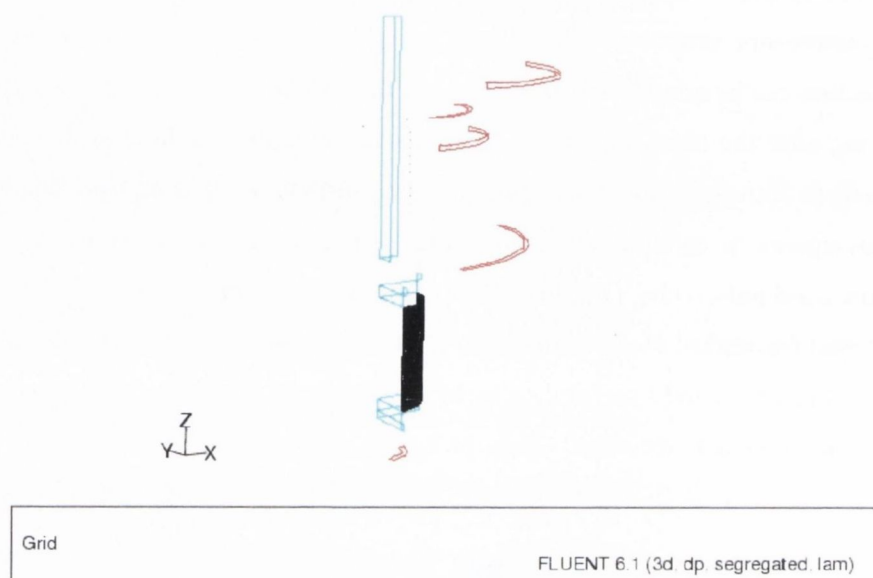


Figure 2.11. Illustration of surfaces defined in the 50 rpm flow field solution on which tangential and axial velocities were monitored to determine convergence, from the periodic model of the basket apparatus.

Validation.

The flow-field solution of the basket apparatus at 50 rpm was validated qualitatively using flow visualization studies. It was also validated quantitatively at 50, 100 and 150 rpm. Velocities were compared to previously published UPE velocity data (Diebold and Dressman, 2001), on the planes detailed in Figure 2.10. Velocity data could then be calculated for each plane as a whole or for particular locations on the plane corresponding to the exact locations at which the ultrasound-pulse-echo data was recorded. Average simulated tangential velocities on each horizontal plane were examined, and also the maximum and minimum simulated axial values on each vertical plane since average axial velocities were not very informative as the velocities in positive (upward) and negative (downward) directions generally cancelled each other out resulting in very low average values. These average values for each plane (or maximum/minimum axial values) were also plotted as a ratio to the average value of another of the planes and compared to equivalent ratios of maximal velocity data as measured by the ultrasound-pulse-echo method.

Velocity data for interpretation of dissolution rates.

The maximum velocity was calculated for a surface defined at the base of both the paddle and basket apparatuses. The surface was 8 mm in height from, and extended 12 mm on either side of, the centre point of the base of the vessel. Maximum velocity data within the basket itself was calculated from a plane which extended throughout the basket from the lower to upper surface, and from the centre of the basket to the side grid.

In order to calculate fluid velocity relative to the compact rotating in the basket, a number of horizontal 2-D rings (1 mm thickness) were defined, with several radii as follows: 0.0065 m, 0.0080 m, 0.0090 m, 0.0100 m. All were 0.003 m above the base of the basket as this was the approximate height of the compacts. As the radius of the benzoic acid compacts is 0.0065 m and the outer edge of the basket is at 0.0111 m this range of radii encompasses a range of locations at which the outer edge of a compact in the basket could be positioned. The maximum speed of the rotating tablet was then calculated to be the speed (ms^{-1}) that this outer edge would be travelling assuming it rotated consistently without change in position while situated on the base of the basket. The maximum difference in fluid velocity that this outer edge of the compact was exposed to relative to its own rotating velocity was then the difference between this speed and the lowest fluid velocity calculated at the corresponding radius from the rings defined above, as this difference was greater than the difference between the speed of the compact and the highest fluid velocity at the same radius.

2.2.1.3 Levy beaker dissolution apparatus.

Vessel and stirrer dimensions.

The dimensions of the vessel and stirrer were according to the specifications described by Levy and Hayes (Levy and Hayes, 1960), with modifications from Levy and Hollister (Levy and Hollister, 1964), where a 400 ml Pyrex Griffin beaker containing 350 ml of dissolution medium was used. Additionally a larger 600 ml volume Griffin beaker containing 550 ml was constructed (Corrigan, 1973). The stirrer was immersed to a depth of 0.027 m (Levy and Hayes, 1960).

Stirrer.

The stirrer used by Levy and Hayes (1960) and Corrigan (1973) was a 3-blade 5-cm-diameter polythene stirrer manufactured by Nalge Company Inc., New York. Dimensions were kindly supplied by Nalge (Europe) Ltd. of the current stirrer matching these specifications. These dimensions included further details required such as shaft diameter, length and stirrer radius.

These were as follows:

Stirrer radius:	0.02413 m $\pm$ 0.0010 m
Shaft diameter:	0.00635 m $\pm$ 0.0005 m
Shaft length:	0.46228 m $\pm$ 0.0076 m

The angle of the stirrer blades was not supplied, however measurement of the angle of the blade from the horizontal axis of the original stirrer used by Corrigan (1973) revealed an angle of approximately 45°. The blade was joined to the stirrer shaft by a section of plastic which was twisted at a 45° angle at the point at which it joined the shaft (see Figure 2.12).

The lower section of the stirrer (stirrer base) to which the blades were attached had a diameter of 0.012 m and a height of 0.011 m. The blades were attached at a point beginning approximately 0.005 m from the lower surface of the base. A height of 0.016 m for the upper part of the stirrer shaft ensured a total of 0.027 m stirrer height (from the base). This is equal to the depth to which the stirrer was immersed in the fluid (Levy and Hayes, 1960).

Other relevant stirrer measurements were:

Blade thickness:	0.0015 m
Blade diameter:	0.0165 m
Length of twisted portion (from blade to stirrer)	0.0025 m
Width of twisted portion	0.0060 m
Distance from bottom of twist to top of stirrer base (top of twist)	0.0050 m
Thickness of twisted portion – at 0° to the horizontal axis	0.0015 m
Thickness of twisted portion – at 45° to the horizontal axis	0.0050 m

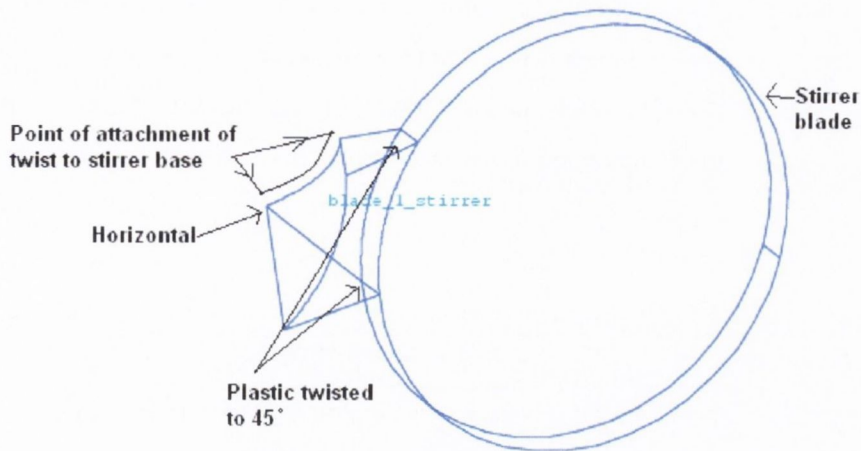


Figure 2.12. Diagram of a stirrer blade and twisted section attaching the blade to the stirrer base at a 45° angle, used in the construction of the stirrer of the Levy beaker apparatus.

Vessel.

The vessel dimensions used in the simulations of 350 ml and 550 ml fluid flow fields were as follows:

	350 ml	550 ml
Diameter	0.072 m	0.085 m
Height	0.086 m	0.099 m

Table 2.2. Dimensions used to create the 350 ml and 550 ml fluid volumes within the vessel of the apparatus.

The stirrer was positioned such that the stirrer base was 0.027 m from the upper surface of the vessel fluid.

Building and meshing the Levy dissolution apparatus in Gambit™.

Building the apparatus.

Building the stirrer.

The stirrer shaft was built by attaching two cylinders, one above the other. The upper cylinder had a diameter of 0.006 m and the lower one, which formed the stirrer base, a diameter of 0.012 m to conform to the specifications described. The first stirrer blade was built by creating a cylinder of diameter 0.0165 m and height 0.0015 m. This cylinder was rotated on the x axis by 45°, and moved from the central z-axis by 0.01676 m. This ensured that the outer edge of the blade was at 0.025 m from the central z-axis, conforming to an overall stirrer radius of 0.025 m, giving a stirrer diameter of 0.05 m as specified in Levy and Hayes, (1960). The inner edge of the stirrer was joined by four edges to the stirrer base. Faces were created between these edges using the skin

face tool. These faces were combined with the inner face of the blade and the section of stirrer base facing the blade to form the twisted volume attaching the blade to the stirrer. The stirrer blade and the twisted section volumes were combined as one group of volumes. This group was copied by rotation by 120° on the z axis, and a second copy was made by further rotation through 120° . The final result was the upper and lower sections of stirrer shaft, attached to three blades at 45° by twisted attachment sections. The completed stirrer is shown in Figure 2.13 within the fluid volume.

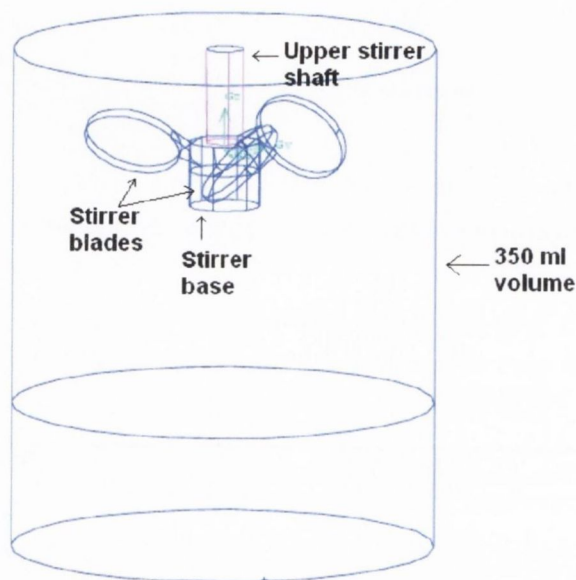


Figure 2.13. Completed geometry of stirrer at a depth of 0.0027 m within a 350 ml fluid volume of the Levy beaker apparatus.

Building the vessel.

The vessel of the apparatus containing the fluid volume was built by creating a cylinder with the appropriate height and diameter to enclose either a 350 ml or a 550 ml fluid volume as detailed in Table 2.2. The stirrer shaft and blade volumes were subtracted from the cylinder volume to create the fluid domain volume. A 350 ml fluid domain volume surrounding the stirrer is represented in Figure 2.13.

Meshing the apparatus.

Mesh counts were assigned to the edges of the stirrer faces as detailed in Figure 2.14. The faces were then meshed according to the tri-pave scheme. A mesh count of 160 was assigned to the upper and lower circumference of the vessel cylinder, and the fluid volume was then meshed according to the Tet/hybrid scheme. The resulting mesh had the following mesh quality attributes in the 350 ml vessel:

	1% of cells	0 cells
Equi angle skew	>0.64	>0.87
Aspect Ratio	>1.975	5.2

Table 2.3. Mesh quality attributes of the meshed fluid domain volume in the 350 ml Levy beaker apparatus.

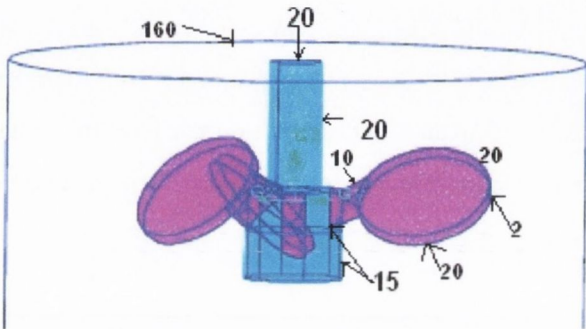


Figure 2.14. Mesh counts assigned to various edges of the Levy dissolution apparatus.

Although the apparatus had no boundary layers inserted, the element volumes in the cells around the stirrer were in the range 2.5×10^{-12} m to 2×10^{-10} m (550 ml volume) and 1.7×10^{-12} m to 1.2×10^{-10} m (350 ml volume). The largest cells in the fluid domain had a volume of 2×10^{-09} m (550 ml volume) and 1.2×10^{-09} m (350 ml volume).

Boundary and continuum conditions.

A boundary condition of “wall” was assigned to the vessel sides, bottom and upper surface of the fluid, and also to the stirrer faces. A continuum condition of “solid” was assigned to the stirrer and “fluid” was assigned to the fluid domain.

Solver.

Case File.

The meshed apparatus was exported as a mesh file from Gambit™ and imported into Fluent™ as a case file. A segregated, implicit time-averaged (steady) solver was used with an absolute velocity formulation. The fluid was defined as water with a viscosity of water at 37°C ($0.0006943 \text{ kg m}^{-1}\text{s}^{-1}$). The fluid was defined as a rotating reference frame, which rotated in the anticlockwise direction (the default z-axis direction of rotation in Fluent™). The direction of rotation of the stirrer in the Levy vessel was clockwise (Levy et al., 1965), however the stirrer blades on the replica Levy stirrer were at a 45° angle to the right (when viewed from above) whereas the blades on the simulated stirrer were at a 45° angle to the left. Thus the effect on

fluid flow should be comparable between the simulated and actual Levy apparatuses. The walls of the vessel were defined as stationary in the absolute frame, and the walls of the stirrer were stationary in the relative frame. The SIMPLE pressure velocity coupling algorithm was used and the momentum discretization scheme was first-order upwind. Simulations were carried out for 20, 50, 59, 100 and 174 rpm for the 350 ml volume, and 20, 59, 100 and 174 rpm for the 550 ml volume.

Convergence criteria.

The method used to determine convergence of the model was similar to that used for the basket apparatus as described in section 2.2.1.2. Velocities were recorded as facet maximum under the surface integrals menu panel at different points throughout the vessel. When the velocity value ceases to change the solution can be considered converged. The origin of the coordinate system lies at the centre of the stirrer shaft just below the point where the wider stirrer base meets the upper shaft. The surfaces examined were as follows, where *z* is the axial co-ordinate and *x* is the coordinate on the *x*-axis:

Horizontal plane	<i>z</i> (m) =-0.004	<i>z</i> (m) =-0.008	<i>z</i> (m) =-0.013
Radial coordinate (m)	0.006	0.006	0.006
	0.018	0.018	0.018
	0.030	0.030	0.030
Vertical plane	<i>x</i> (m) =0	<i>x</i> (m) =0	<i>x</i> (m) =0
Vertical coordinate (m)	-0.059	-0.029	0.0014

Table 2.4. The coordinates used to monitor surface maximum facet velocity values to judge convergence of the Levy apparatus.

The vessel walls were adapted using the hanging node method to a distance of 3 cells while converging the 350 ml 100 rpm model to increase convergence by attaining a maximal residual decrease. This case file was used for the 100 and 174 rpm simulations. The stirrer blades and walls were adapted during the 59 rpm simulation for the 550 ml volume and this case file was used for the 100 and 174 rpm simulations.

The pressure interpolation scheme was changed from standard to PRESTO! during the convergence of the 59 rpm (350 ml) simulation to investigate the effect of this scheme on convergence, and was maintained for the 100 rpm and 174 rpm simulations. The standard scheme was used for all of the 550 ml simulations, except that at 174 rpm where it was changed from standard to PRESTO! during the convergence.

Validation.

The simulation of the 350 ml volume at 59 rpm was validated qualitatively and indirectly validated quantitatively. The qualitative validation was carried out through comparison with written and photographic descriptions of fluid flow at 60 rpm in apparatuses using an identical stirrer and both a 1-litre concave-bottom vessel and a beaker identical to that in the simulation (Withey 1971, Withey and Bowker, 1971).

The indirect quantitative validation involved comparison of dissolution rate data from a rotating basket (at 50 rpm) and from the Levy beaker dissolution apparatus (Withey, 1971). The calculation of a ratio, of dissolution rate within one apparatus to the maximum fluid velocity the dissolving surface was exposed to within that apparatus (from CFD simulations), enabled the prediction of the maximum fluid velocity the dissolving surface was exposed to within a second apparatus, from the dissolution rate within the second apparatus. The maximum velocity at 0.005 m from the base of the Levy beaker dissolution apparatus at 59 rpm, on a plane which extended radially to 0.005 m from the centre, was predicted. The ratio of dissolution rate from a 1 cm³ cube of NaCl from within the basket of the basket dissolution apparatus at 50 rpm (Withey, 1971), to the maximum fluid velocity that a dissolving surface in the rotating basket was exposed to at 50 rpm (from CFD simulations), was calculated. Using this ratio, the dissolution rate from a 1 cm³ cube of NaCl at the base of the Levy beaker dissolution apparatus at 60 rpm was used to predict the maximum CFD-generated fluid velocity at 0.005 m from the base – representing a point midway up the side of the cube. The maximum fluid velocity on a horizontal plane extending to 0.005 m from the centre at 0.005 m from the base was determined from the CFD simulation at 59 rpm. This could then be compared to the predicted maximum velocity value. If the predicted CFD-generated velocity value was equivalent to the actual CFD-generated velocity value then the simulation was yielding expected velocity value results, and was considered validated.

The dissolution rate data (Withey, 1971) was plotted in the form

$(\% \text{ undissolved})^{1/3} = a + b (\text{time})$. As individual data were presented for the dissolution rate from 5 replicates in each case, a standard deviation (SD) can be calculated for the slope (dissolution rate), and a % relative standard deviation (% RSD) value calculated. This same % RSD value was used to calculate and display error bars for the predicted maximum velocity in the Levy beaker apparatus.

Investigation of the relationship between fluid velocities in the Levy beaker dissolution apparatus and dissolution rates.

Dissolution data from acetyl salicylic acid (ASA) and hydroflumethiazide (HFMI) were previously determined (Corrigan, 1973). These dissolution rates were determined from the top planar surface of disks of 0.013 m diameter. The disks manufactured by compression of 400 mg of either ASA or HFMI were dissolved in 0.1M HCl. They were covered in paraffin wax to expose only the top planar surface, and were placed in the centre of the base of the beaker (Corrigan, 1973). The

dissolution studies were carried out in agitation rate/apparatus dimensions corresponding to those simulated in the current work i.e. 350 ml and 550 ml, at 20, 59, 100 and 174 rpm. The radial planes used, from which the CFD generated velocity data was extracted to investigate the relationship between dissolution rate and fluid velocity in the apparatus, are illustrated in Figure 2.15.

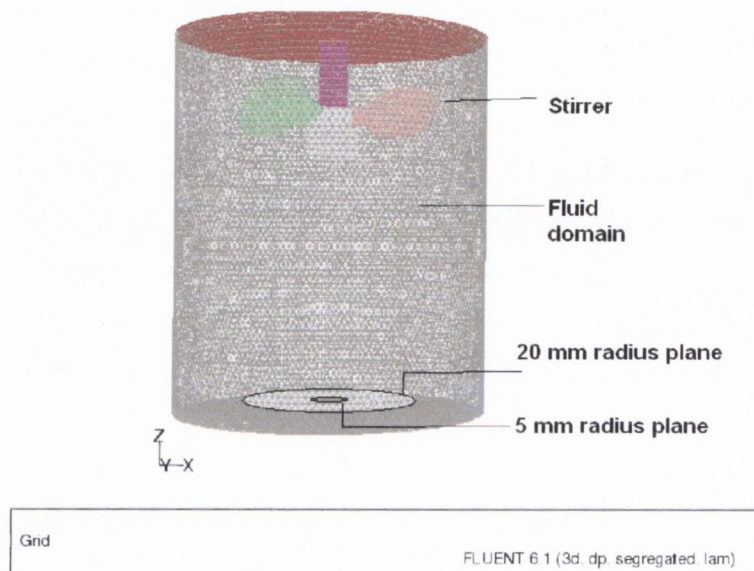


Figure 2.15. Radial planes from which velocity data was extracted and used to determine the relationship with dissolution rate data, in the Levy beaker apparatus geometry for the 350 ml volume. The central radial plane is 5 mm in radius, the outer plane extends to 20 mm radius, at 2 mm from the vessel base.

2.2.1.4 Mass transfer simulations

2.2.1.4.1 Simulation of diffusion boundary layer.

FluentTM does not facilitate the modelling of mass transfer in as much as a cell which has been defined as a solid cannot be redefined as a liquid without specifically halting the solver and redefining the entire volume defined by the cell as a liquid. It is possible, however, to define a solid face within the geometry as a source of a particular species. The approach taken therefore to model mass transfer was to define the faces of the solid compact as a source of saturated solution of benzoic acid. In order to be able to model convective-diffusion, the fluid flow in the vessel containing the compact was solved initially, thus each cell surrounding the compact contained a value for pressure, momentum and velocity in each direction which could be applied to the “saturated solution” which was “released” from the compact surface. The diffusion coefficient of benzoic acid in water or of salicylic acid was applied to this liquid to include the diffusion component of the convective-diffusion model, and the other properties were the same as water at 37 °C which was used to solve the fluid flow. The convective-diffusion of this saturated solution of benzoic acid was simulated in FluentTM by creating a mixture in the “materials” panel, whereby

the bulk of the mixture is made of water at 37 °C, and the other species consisted of what is considered to be a saturated solution of benzoic acid, with the appropriate diffusion coefficient and otherwise properties identical to that of water at 37 °C. This species was termed “tracer”. The tracer is released over time from the compact surface into the bulk. Therefore the solver is set to “unsteady” as it is now time-dependent. A series of data files were written at time intervals of 2 seconds to allow the solution to arrive at steady state. As the tracer released from the compact surface will be removed from the region of the compact at different rates depending on the flow variables already present in each cell, a simulation of the apparent diffusion boundary layer is visible in the vicinity of the compact surface.

The procedure used to change a case and data file (containing a converged solution of the fluid flow) to a case and data file to be used to simulate mass transfer is detailed in Appendix 3.

Using this method to simulate the diffusion of a saturated solution of benzoic acid through the solved flow field, six case and data files were written, each representing data after a time span of two seconds since the previous case and data files. In order to verify that steady state is achieved after 60 time steps, a line is created from the surface of the compact into the bulk in the same position in each case file. A profile can then be written by FluentTM of mass fraction of tracer at each point on this line. This can then be plotted against distance from the compact surface. If the simulation is at steady state the plots should not vary with time.

2.2.1.4.2 Mass transfer predictions.

In order to utilise the data generated by FluentTM of mass fraction of tracer present in the vicinity of the compact to predict mass transfer rates, it was necessary to devise a method by which an actual thickness of the apparent diffusion boundary layer could be estimated. This thickness is described by the term “ h ” in equation 1.20, reproduced here as equation 2.1:

$$dM/dt = DAc/h \quad \text{Equation 2.1}$$

where dM/dt is the change in mass with time, D is the diffusion coefficient, A is the surface area of the dissolving surface, c_s is the saturated solubility of the solute and h is the diffusion boundary layer (Nernst, 1904; Brunner, 1904).

As the mass fraction of tracer decreases exponentially with distance from the compacts’ surface (Appendix 4), theoretically the diffusion boundary layer is of infinite thickness and an appropriate cut-off point had to be determined. Using the experimental mass transfer results from the side surfaces in the central position, the average decrease in mass fraction of tracer to give this result could be calculated. The side surface of the compact in the central position was chosen as the reference surface as a) the shape of the compact did not change with time at this surface as it did

in the off-centre positions and b) the flow was more uniform around the whole of the central side surface than the central top surface.

A profile written for a line extending from the surface of the compact into the bulk, describing mass fraction of tracer at points along the line, can be plotted as mass fraction of tracer against distance from the compact surface. An exponential curve can be fitted to this line of the form

$$Y=e^{\beta X}.$$

Equation 2.2

The intercept of the line is 1, i.e. 100% saturated solution at the compact surface.

Y is mass fraction of tracer, X is distance (in μm) from the compact surface. To determine the boundary layer thickness on this line, it is necessary to find X when $Y=0.1$, as the distance from the surface at which the Y decreases to 10% was determined to be an appropriate point to mark the “edge” of the diffusion boundary layer (see section 4.2).

Rearranging equation 2.2 to find a value for X when $Y=0.1$ gives

$$(\ln 0.1)/\beta=X$$

Equation 2.3

This value for X is the equivalent of finding “ h ” for this line. As the apparent diffusion boundary layer thickness varies along the surface of the compact, it is necessary to get an overall average value of “ h ”. A series of lines were therefore created from the surface of the compact into the bulk, as illustrated in Figure 2.16.

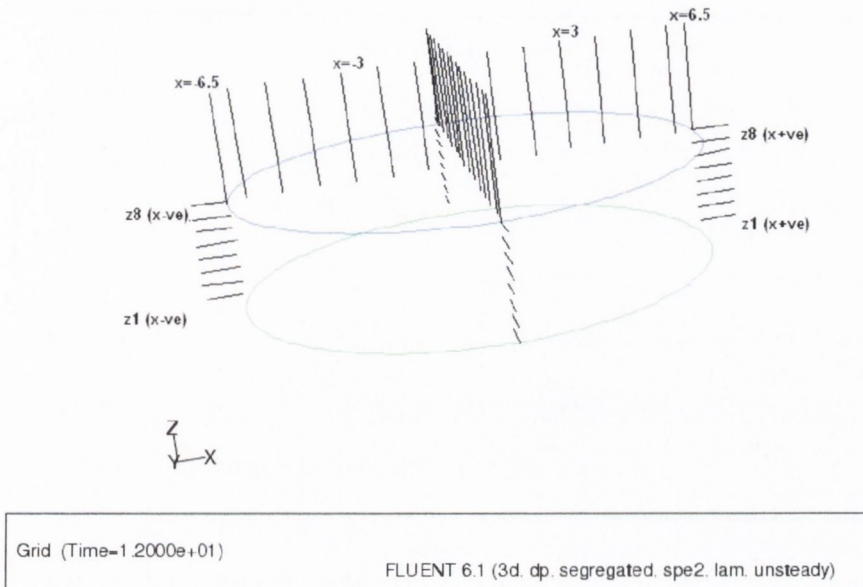


Figure 2.16. Diagram of lines created from the compact surface (position 1) into the bulk to plot profiles of mass fraction of tracer vs. distance from compact surface in diffusion boundary layer simulations in the paddle apparatus.

The top planar surface of the compact had a line extending from the centre of the compact into the bulk, and then lines radiating in four rows from the centre, along the x and y axes in both positive and negative directions, were created. The sides of the compact in the central position had 20 lines extending along the side into the bulk. In positions 1 and 2 there were 8 lines at each of four different positions (along the x and y axes, positive and negative directions) extending into the bulk, giving 32 side lines in total. They were named z1 (just above the base of the side surface) to z8 (at the top of the side surface) in the direction of each axis as illustrated in Figure 2.16.

The spacing and nomenclature of the lines from the top planar surface from the centre along the positive y axis to the edge of the surface is illustrated in Table 2.5. Lines in the directions of the negative y axis and positive and negative x axes were spaced identically and named in a similar manner, with the direction along the negative axis indicated with a negative integer, e.g. y-3.

	Line Spacing	Line name
Centre		y0
Line 1	1000 µm from centre	y1
Line 2	2000 µm from centre	y2
Line 3	3000 µm from centre	y3
Line 4	4000 µm from centre	y4
Line 5	5000 µm from centre	y5
Line 6	6000 µm from centre	y6
Line 7	6500 µm from centre (i.e. edge of tablet).	y6.5

Table 2.5. Spacing and names of lines from the centre of the top planar surface along the positive y axis to the edge of the surface.

The value of “ β ” from equation 2.2 varies with each line. In order to get an average value of “ h ” for the top planar surface an average value of “ β ” must be calculated.

$$(ln\ 0.1)/average\ \beta = h$$

Equation 2.4

Therefore each line is taken to represent a portion of the surface area of the compact. An average value of “ β ” is calculated for line 1 by adding the “ β ” value from line 1 in each of the four directions and dividing by 4, similarly for line 2 and so on to line 7. When an average value is calculated for each line, the values are multiplied by the fraction of surface area they represent, as shown in Table 2.6.

Line	Portion of compact (distance from centre represented)		Proportion of total area
Centre line:	0-500 microns		0.0059
Line 1	1000 μm from centre	(500 – 1500 μm)	0.0473
Line 2	2000 μm from centre	(1500 – 2500 μm)	0.0947
Line 3	3000 μm from centre	(2500 – 3500 μm)	0.1420
Line 4	4000 μm from centre	(3500 – 4500 μm)	0.1893
Line 5	5000 μm from centre	(4500 – 5500 μm)	0.2367
Line 6	6000 μm from centre	(5500 – 6250 μm)	0.2086
Line 6.5	6500 μm from centre	(6250 – 6500 μm)	0.0754

Table 2.6. Portion of the total surface area of the top planar surface which is represented by individual lines located at a specific distance from the surface centre.

Then each “ β ” value representing “ β ” for that portion of the compact surface area is added to give an overall average value of “ β ” for the top planar surface. Using equation 2.4 an overall value of “ h ” can then be calculated. From equation 2.1, dM/dt can be calculated using the following values for the variables D , A and c_s :

D (Diffusion coefficient of benzoic acid): (Edwards, 1951)	$1.236 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$
A (Area):	$1.327 \times 10^{-4} \text{ m}^2$
c_s (Saturated solubility of benzoic acid in 0.1M HCl): (Ramtoola and Corrigan, 1987)	$4.564 \times 10^3 \text{ g m}^{-3}$

The corresponding values for salicylic acid are

D (Diffusion coefficient of salicylic acid): (Edwards, 1951)	$1.132 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$
c_s (saturated solubility of salicylic acid in 0.1M HCl): (Corrigan, 1973)	$2.706 \times 10^3 \text{ g m}^{-3}$

To get an average “ β ” value for lines from the side surface a standard average can be calculated i.e. by adding all of the “ β ” values and dividing by 20 (central position) or 32 (positions 1 and 2) as each line represents an equal portion of the side surface area.

Calculated values of dM/dt can then be compared to experimentally derived values to determine the feasibility of using this method to predict mass transfer in the dissolution apparatus.

2.2.1.5 Determination of the hydrodynamic boundary layer thickness.

The thickness of the hydrodynamic boundary layer at the compact surface can be estimated by plotting velocity magnitude as a function of distance from the surface. The velocity values will increase with increasing distance from a value of zero directly at the surface, to a point at which the velocity starts to level off. The region where the velocity values cease to increase is considered to be the edge of the hydrodynamic boundary layer. Both the thickness of this layer and the velocity gradient within the layer can be examined in this manner. The velocity magnitude and distance from surface data were taken from the lines illustrated in Figure 2.16, from each compact in each position.

2.2.1.6 Determination of angular velocity, velocity magnitude and rate of shear values.

Angular velocity, velocity magnitude and rates of shear were taken from the CFD solutions either as average or maximum data reported in FluentTM as a surface integral on various lines as depicted in Figure 2.16, or as a surface integral at a point 1 mm from the compact surface. Data at 1 mm from the compact surface was taken from the top or side surfaces of the “tablet-envelope”, a volume defined in GambitTM around the compact in each position to facilitate meshing, as described in section 2.2.1.1. The surface integral data used in each calculation is described in section 4.3.

2.2.1.7 Determination of pressure gradients within the CFD simulated flow fields.

The pressure variable examined was the static pressure, which is the gauge pressure expressed relative to the operating pressure (FluentTM User's Guide, 2003). The operating pressure used for all simulations was the default option of atmospheric pressure at a reference point at the centre of the coordinate system. This corresponded to a point within the mass of the stirrer in the paddle and Levy apparatuses, and just below the basket lid in the basket apparatus.

2.2.2 **Dissolution rate studies.**

2.2.2.1 **Mechanical and chemical calibration of the dissolution apparatus.**

The paddle and basket stirrers were aligned within the vessels using a centering and height-adjustment tools. Chemical calibration was carried out according to the USP Apparatus Suitability Test guidelines (USP, 2005) with the exception that the salicylic acid reference standard used was not a USP reference standard. This involved using prednisone (disintegrating tablets containing 10 mg prednisone) with 500 ml water as the dissolution medium and salicylic acid (non-disintegrating tablets containing 300 mg salicylic acid) with 900 ml 0.05M pH 7.4 phosphate buffer (USP, 2005) as the dissolution medium. The test was conducted at 37°C and the % of labeled content dissolved from each tablet after 30 minutes at 50 rpm (prednisone) and 100 rpm (salicylic acid) must fall within the specified acceptance range (Table 2.7) for the apparatus to be considered suitable. The 30-minute sample is analysed by U.V. spectrophotometry at 242 nm (prednisone) and 296 nm (salicylic acid) and compared with solutions of known concentration of reference standards of prednisone and salicylic acid. One solution of known concentration of each reference standard for comparison with the test samples was used in each case. The concentration of prednisone reference standard solution used was 0.018 mg ml⁻¹ (apparatus 1) and 0.009 mg ml⁻¹ (apparatus 2). The concentration of salicylic acid reference standard solution used was 0.066 mg ml⁻¹ (apparatus 1 and 2). The test was carried out on six vessel-paddle combinations for apparatus 2 and three basket-vessel combinations for apparatus 1, as only these three baskets and vessels were used in dissolution tests using apparatus 1.

Apparatus	Range % Salicylic acid dissolved at 30 minutes, 100 rpm	Range of % Prednisone dissolved at 30 minutes, 50 rpm
1	23-29	54-78
2	17-26	28-54

Table 2.7. Acceptance ranges of % Salicylic acid (USP Lot O) and % Prednisone (USP Lot N) dissolved at 30 minutes

2.2.2.2 **Compact manufacture and coating.**

Cylindrical compacts of 500 mg benzoic acid and salicylic acid of 13 mm diameter and approximately 3 mm height were prepared as previously described (Healy et al., 2002) by compression at 10 tonnes for 10 minutes using a 13 mm hydraulic punch and die set and a hydraulic press. Cylindrical compacts of 1500 mg benzoic acid of 13 mm diameter and approximately 8.5 mm height were prepared in a similar manner. The benzoic and salicylic acid was passed through a 250 µm sieve before compression. The high pressures used ensured that the surface area of the compact available for dissolution was not increased by the presence of pores.

This was confirmed by scanning electron microscopy (SEM). In order to enable analysis of dissolution from the top planar surface alone of the compact, some of the compacts were coated on the curved side and bottom planar surface using paraffin wax. Similarly, some of the compacts were coated on the top and bottom planar surfaces to enable analysis of dissolution from the curved side surface only. The thickness of this coating was less than 1 mm in order to minimise interference with the hydrodynamics of the system.

2.2.2.3 Dissolution rate studies in the paddle dissolution apparatus.

Benzoic acid compacts of 13 mm diameter and approximately 3 mm height with either the top planar surface, the curved side surface, or the whole compact exposed were affixed, using double sided sticky tape, to one of three positions within the vessel, as illustrated in Figure 2.17. One of the positions was located in the centre of the base of the hemispherical portion of the vessel, this is referred to as the central position. The next position, position 1, was directly adjacent to this, and position 2 was directly adjacent to position 1. Dissolution studies were also carried out on compacts with the bottom planar surface coated in the central position, in order to determine the mass dissolved (if any) from this surface while affixed by the sticky tape to the vessel over the course of the dissolution experiment. Dissolution studies of salicylic acid compacts (13 mm diameter and approximately 3 mm height) were carried out in the central position only, and of benzoic acid compacts (13 mm diameter and approximately 8.5 mm height) were carried out in position 1 only.

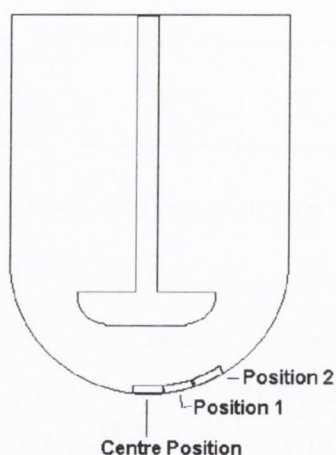


Figure 2.17. Schematic diagram of the location of compacts in the paddle dissolution apparatus.

In addition to the compacts fixed to the vessel as described above, six compacts were made which were not coated on any surface, and were not fixed to any position (diameter 13 mm, height approximately 3 mm). These were termed “control” compacts, as they represent the conditions

under which a dissolution study on this type of dosage form would normally be undertaken i.e. all surfaces exposed and not fixed to the wall of the vessel prior to dissolution. The results from dissolution studies using these control compacts could then be used to estimate the extent to which variability in dissolution results is due to random variation in the position of the compact when dropped into the dissolution vessel.

Dissolution studies using the paddle apparatus were performed using a dissolution medium of 900 ml 0.1M HCl with a paddle revolution speed of 50 rpm. The medium was deaerated according to the USP method (USP, 2005) and equilibrated at 37 °C. Samples were taken every 10 minutes for 1 hour from 6 replicates (3 replicates in studies of compacts with coated surfaces) for each compact position studied, and for the “control” compacts.

2.2.2.4 Dissolution rate studies in the basket dissolution apparatus.

Dissolution studies of benzoic acid using the basket apparatus were performed using a dissolution medium of 900 ml 0.1M HCl (deaerated and equilibrated as described in section 2.2.2.3) with a basket revolution speed of 50 rpm. Samples were taken every 10 minutes for 1 hour from 6 replicates. Dissolution studies using the same method were also carried out at 50, 100 and 150 rpm for benzoic acid and salicylic acid compacts, using 3 replicates.

2.2.2.5 Dissolution rate studies under conditions of natural convection.

Compacts of salicylic and benzoic acid were produced (diameter 13 mm, height approximately 3 mm), as described in section 2.2.2.2, and coated leaving either the top planar surface or curved side surface exposed. The dissolution medium was deaerated 0.1M HCl. Dissolutions were carried out for 2 hours at 37 °C. Four surface/orientation combinations were investigated: the top planar surface, the curved side surface, the lower planar surface, and the top planar surface positioned vertically i.e. at 90° to the standard horizontal orientation. To investigate the curved side surface and the top planar surface, the compacts were fixed to the lid of a jar containing 100 ml of dissolution medium. The jar was gently inverted to bring the compact in contact with the dissolution medium. Samples were taken every 30 minutes. This involved replacing the jar in the upright position, removing the lid and compact, and sampling from the dissolution medium. After sampling and replacement of the sample volume with fresh medium, the compact was replaced in the jar and gently inverted again. To investigate the lower planar surface and the top planar surface positioned vertically, the compacts were affixed to a piece of card and placed into a jar containing 100 ml of dissolution medium. A syringe and needle were used to slowly introduce more dissolution medium to fill the jar and cover the compact. The level of water in the water bath was maintained exactly level with the top of the jar. Sampling involved removing the card from the top of the jar, sampling from the medium, replacing the compact in the jar and

introducing fresh dissolution medium to fill the jar (replacing the sampling volume). Additional dissolution studies were carried out which involved a separate experiment for each time point for both the lower planar surface and the top planar surface of the compacts. This was to assess the impact of the sampling method on the natural convection conditions.

The surface/orientation combinations are detailed in Figure 2.18. The dissolution studies under natural convection conditions were carried out using 3 replicates in each case.

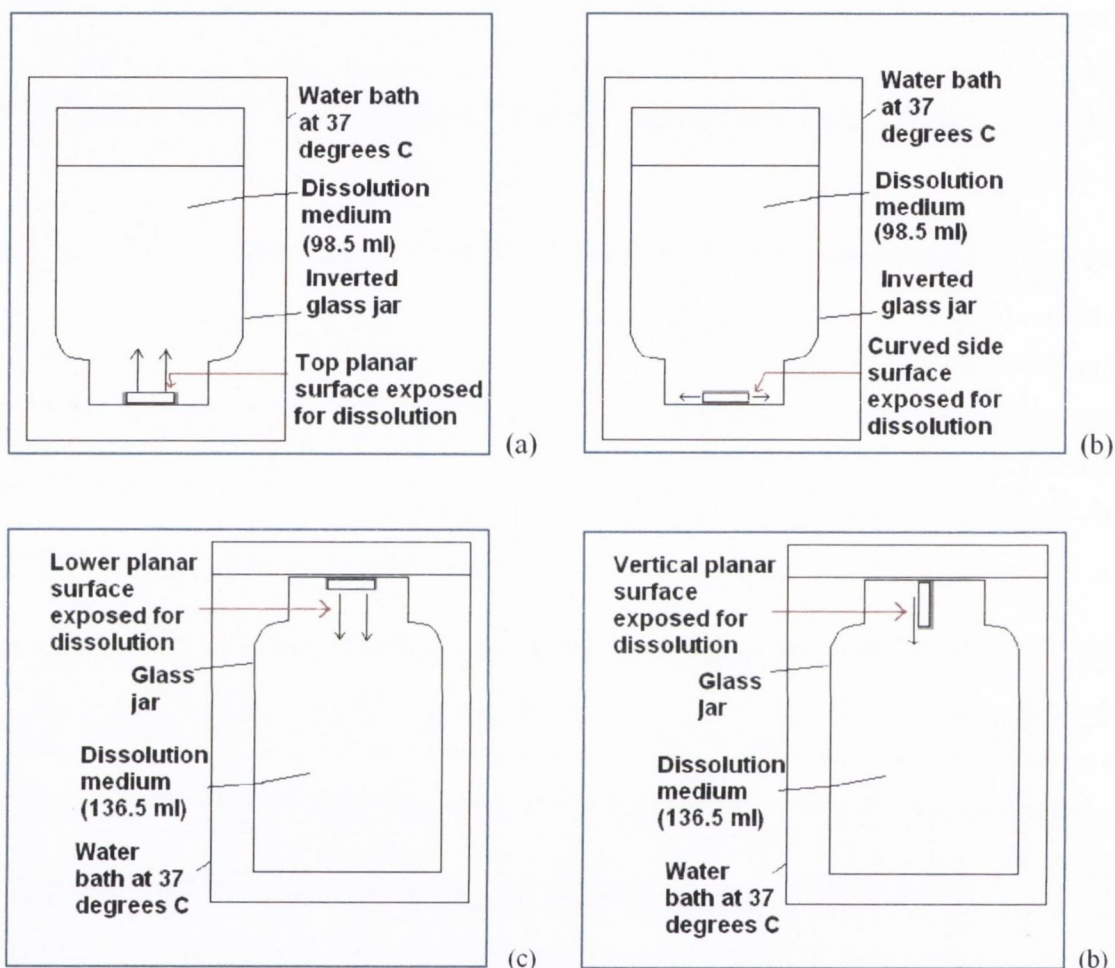


Figure 2.18. Surface/orientation combinations investigated under natural convection conditions: a) top planar surface, b) curved side surfaces, c) lower planar surface and d) top planar surface positioned vertically.

2.2.2.6 Sample analysis.

The dissolution medium samples from the dissolution studies were analysed by UV spectrophotometry, after filtration, using an absorbance wavelength of 274 nm (benzoic acid) or 296 nm (salicylic acid). Filter pore size was 0.45 μm . The absorbance was converted to mass of benzoic acid or salicylic acid present in the 5 ml sample by comparison with a standard curve. The standard curve was constructed from U.V. analysis of solutions of known concentrations of benzoic and salicylic acid in 0.1M HCl. Three replicates of each concentration were used for each

standard curve. A new standard curve was constructed each time a new set of dissolution results was to be analysed.

2.2.3 Saturated solution and bulk solvent density measurements.

The density of saturated solutions of benzoic acid in 0.1M HCl at 37 °C and of pure dissolution medium (0.1M HCl at 37 °C) was measured using a density bottle. The density of a saturated solution of salicylic acid in 0.1M HCl was determined by Walsh (2006), using the same method. The volume contained in and the weight of the density bottle were measured. Saturated solutions of benzoic and salicylic acid were prepared by adding three times the amount required for a saturated solution (benzoic acid: 4.564g l^{-1} (Ramtoola and Corrigan, 1987); salicylic acid 2.706g l^{-1} (Corrigan, 1973)) to the dissolution medium, and placing this in a sealed volumetric flask in a shaking water bath at 37 °C for 24 hours. Samples of the resulting solution were then taken, filtered, placed in the density bottle and weighed. Measurements were carried out in triplicate.

2.2.4 Surface porosity investigations – scanning electron microscopy (SEM).

The top planar surface of a benzoic acid compact was examined using a variable pressure scanning electron microscope to confirm that the compaction pressure used produced a non-porous surface. The surface was examined at magnifications detailing features of $\leq 10\text{ }\mu\text{m}$ (magnified x 3000), $\leq 25\text{ }\mu\text{m}$ (magnified x 1,800) and $\leq 50\text{ }\mu\text{m}$ (magnified x 700).

2.2.5 Statistical methods.

2.2.5.1 Dissolution rate comparisons.

The software package Minitab TM was used to carry out the statistical analysis of the dissolution rate data from the paddle dissolution apparatus. A one-way unstacked ANOVA was used to compare the dissolution rates from the dissolution of the compacts in each position, and from the control compacts. The data were taken from two different runs (3 replicates in each run) for each position by the same analyst within the same laboratory. The data from the two runs were pooled in each case and the ANOVA was therefore performed on 6 replicates in each position and for the control compacts. Thus the variability incorporated variability from both “within runs” and “between runs”. The results were compared using 95% confidence intervals.

Equivalence of dissolution rates, from compacts in the basket apparatus at 50 rpm and “control” compacts in the paddle apparatus at 50 rpm, and from compacts in different locations in the paddle apparatus, was tested using a two-sample t-test. A 95% confidence level was used to test for unequal means.

2.2.5.2 Variability comparisons.

The mean dissolution rates from each compact surface in each position in the paddle apparatus, as calculated using the ANOVA, and the standard deviation values, were used to calculate the RSD% for each position and for the control compacts. The RSD% involves dividing the mean by the standard deviation in each case and multiplying by 100.

When comparing RSD% values from this work to data from other studies, an RSD% was calculated for any relevant time point in the other studies detailed, and an average overall RSD% was then calculated from all time points for each particular comparison.

2.2.5.3 Repeatability comparisons.

Repeatability limits for dissolution rates from compacts within the paddle apparatus fixed to a position and for dissolution rates from control compacts were determined using the following formula:

$$\text{Repeatability limit} = 1.96\sqrt{2SD^2}$$

Where “SD” is the standard deviation. In this work, the SD value was taken from within a particular run from dissolution rates for compacts in each position and the control compacts. From these SD values, an SD² value was calculated, and an average SD² value determined for compacts either affixed to any position in the vessel, or unfixed.

2.2.5.4 Regression line equation.

A least squares regression analysis (of all of the individual dissolution rate data points rather than the averages) of the forced convection dissolution data and velocity data from the paddle and basket apparatuses was used to estimate a prediction range for the natural convection dissolution rate.

2.2.6 Flow visualisation studies.

Flow visualisation studies were carried out in the basket apparatus using the dye Tropaeolin and water. The solubility of Tropaeolin is 11% w/v in water (Horobin and Kiernan, 2002), and 10-20 mg of dye was used per 900 ml water. The upper cover of the water bath surrounding the apparatus holds the vessel in place, therefore it was not possible to remove the water bath but it was emptied to minimise the number of phases of different refractive indices through which a photograph was taken. As the main feature of interest in the simulated models of the hydrodynamics within the apparatus were the regions of high velocity radiating out from the side of the basket, the aim of the flow visualisation study was to examine the presence and nature of this flow feature.

A vertical strip of dye was incorporated onto an absorbent surface. This consisted of a porous paper bag (4.5 x 6 cm teabag). The width of the bag was folded to the height of the basket. The contents were evenly distributed and wetted thoroughly to ensure that the dye powder would adhere to the surface, and the bag was then rolled along the longitudinal axis to form a cylinder. This cylinder fitted into the basket and was not free to move except with the rotation of the basket. As a result the vertical strip of dye was constantly at the same point against the side grid of the basket. In this manner, the effect of the fluid flow around the side of the basket could be visualised through the patterns formed when the dye strip dissolved in the medium. Photographs were taken once the basket was lowered into the medium until the water became too coloured to visualise the patterns, which generally took approximately 30 seconds to 1 minute.

The basket was rotated at 50 rpm, immediately after being lowered into the water, as the flow patterns were less clear and the water became coloured faster at higher rotation speeds.

3.1 Introduction.

The location of a dosage form within the paddle dissolution apparatus has been shown previously to influence the dissolution rate (Healy et al., 2002; Kamba et al., 2003; Kukura et al., 2004; Baxter et al., 2005). It has also been demonstrated that dosage forms can stick to various positions on the vessel wall upon hydration (Dürig and Fassihi, 2000). The stirring speed or agitation rate of the paddle, therefore, can only be approximately associated with the dissolution rate, giving little or no information on the hydrodynamics at the dissolving surface.

This variation in dissolution rate with location of a dosage form will contribute to variability in dissolution results. In this chapter, both statistical methods (Student's t-test and ANOVA) and model dependent methods (the dissolution rate constant (k_d)) have been used to compare dissolution rates from different systems.

The apparatus suitability test is used for the dissolution apparatus to ensure that the apparatus/operator combination is operating optimally (Mirza, 2000). This test, however, uses calibrator tablets which reflect all of the factors of the apparatus which affect dissolution performance. Specific factors such as fluid flow and shearing at the dissolving surface cannot be accounted for using this test (Mauger, 1996).

CFD simulations of fluid flow within the apparatus containing compacts in different positions can be used to examine the hydrodynamic variables at the dissolving surface. This enables both the thickness of the hydrodynamic boundary layer around the compact and the magnitude of the velocities within this layer to be quantified.

CFD can also be used to examine the change in various hydrodynamic features within the flow field solution with agitation rate.

The objectives of this chapter were

- to examine the effect on the dissolution rate of varying the location of a cylindrical dissolving compact within the dissolution vessel of the paddle apparatus;
- to quantify the degree of variability in dissolution testing which is attributable to the random positioning of the compacts, when dropped into the vessel, and throughout the duration of the test;
- to investigate the relationship between the variation in dissolution rate with the variation in local hydrodynamics around compacts, located in varying positions, using CFD;
- to investigate the variation in hydrodynamics within the paddle apparatus at different rotation speeds using CFD.

3.2 Dissolution studies.

3.2.1 Calibrating the equipment.

3.2.1.1 Apparatus Suitability Test.

The results and acceptance ranges for prednisone Lot N and salicylic acid Lot O are presented in Table 3.1. The paddle dissolution apparatus passed the apparatus suitability test for both disintegrating tablets (prednisone) tested at 50 rpm and non-disintegrating (salicylic acid) tablets tested at 100 rpm. The test was carried out as described in section 2.2.2.1.

Tablet	Acceptance Range (Accepted range of % of labeled content dissolved at 30 minutes).	Result (Actual range of % of labeled content dissolved at 30 minutes; 6 prednisone tablets and 6 salicylic acid tablets were tested).
Prednisone	28-54%	33-42%
Salicylic Acid	17-26%	18-23%

Table 3.1 Acceptance ranges and achieved dissolution test ranges for the apparatus suitability test for the paddle dissolution apparatus.

There are three critical components that have to interact optimally together for the apparatus suitability test to give the best result. These are the analyst, the apparatus and the analytical procedure. A system suitability test (as opposed to mechanical calibration alone) ensures that the combination of these three components does not provide any significant bias to the results and lends credibility to the dissolution test results for this system (Mirza, 2000). The conformance of the apparatus suitability test results to the ranges specified in the apparatus suitability test must be in addition to routine monitoring of critical test parameters such as volume of dissolution medium, temperature and rotation speed of the apparatus (USP, 2005). The results of the apparatus suitability test imply that the combination of the dissolution apparatus components and operator technique give dissolution results that are in the range expected for a machine and operator that are operating without any notable bias. Therefore the suitability of the combination of apparatus and operator to conduct dissolution studies has been demonstrated.

3.2.1.2 Calibration Curves for analysis using UV spectrophotometer.

Sample calibration curves used are presented in Appendix 5.

3.2.2 **Dissolution from different surfaces of compacts in different locations in the paddle dissolution apparatus.**

3.2.2.1 **Dissolution from whole benzoic acid compacts (all surfaces exposed).**

Figure 3.1 shows dissolution test results from 6 replicates in the central position, position 1 and position 2. The lowest dissolution rate was from the compact in the central position, whereas there was no significant difference in dissolution rates from the compacts in positions 1 to 2, which were approximately 25% higher than the dissolution rate from the central position. The results of the ANOVA test comparing dissolution rates from whole compacts in the central position, position 1 and position 2 are presented in Table 3.2. These results also illustrate that there is no significant difference between the rates from the compacts in positions 1 and 2 (95% confidence intervals overlap) but that there is a significant difference between rates from each of these positions and the rate from the central position.

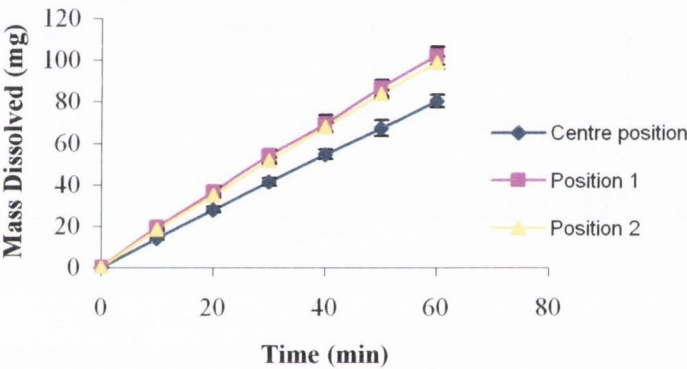


Figure 3.1. Mass benzoic acid dissolved (mg) vs. time (min) from compacts (height 3 mm, diameter 13 mm) in the central position, position 1 and position 2 in 900 ml 0.1M HCl in the paddle dissolution apparatus at 50 rpm.

Analysis of Variance					
Source	DF	SS	MS	F	P
Factor	2	0.077360	0.038680	59.55	0.000
Error	15	0.009743	0.000650		
Total	17	0.087103			

Individual 95% CIs For Mean Based on Pooled StDev			
Level	N	Mean	StDev
centre	6	0.53079	0.02364
pos1	6	0.68002	0.03249
pos2	6	0.65677	0.01828

Pooled StDev = 0.02549

0.720

0.540 0.600 0.660

Table 3.2 Results of one-way ANOVA of dissolution rates from whole benzoic acid compacts in the central position, position 1 and position 2, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

A t-test for equal means also demonstrates that rates from the central position and either position 1 or 2 ($p=0$) are not equal (in this case rates from both positions 1 and 2 are greater than the rate from the centre), but that there is no significant difference between rates from positions 1 and 2 ($p=0.17$).

3.2.2.2 Dissolution from the top planar surface.

Dissolution rates from benzoic acid compacts where the side and bottom surfaces were coated with paraffin wax revealed a similar pattern to dissolution from whole compacts. Again, the lowest dissolution rate was from the central position and the dissolution rate from positions 1 and 2 were higher. Figure 3.2. shows the dissolution rate from the top planar surface from the compacts in each of the positions central, 1 and 2.

Similar to the results from the whole compact, an ANOVA on the results from the central position, position 1 and position 2 reveal overlapping 95% confidence intervals for positions 1 and 2 (indicating that the rates are not different), but no overlap between confidence intervals for the rate from the central position and the rates from either positions 1 or 2. A t-test for unequal means revealed that the mean dissolution rate is different between that from compacts in either position 1 or 2 and the central position ($p=0.003$, centre vs. position 1; $p=0.018$, centre vs. position 2) at the 5% significance level. In this case both of the off-centre mean top planar surface dissolution rates are greater than the dissolution rates from the top planar surface in the centre position, but the mean dissolution rates from the top planar surface in positions 1 and 2 cannot be considered different ($p=0.533$).

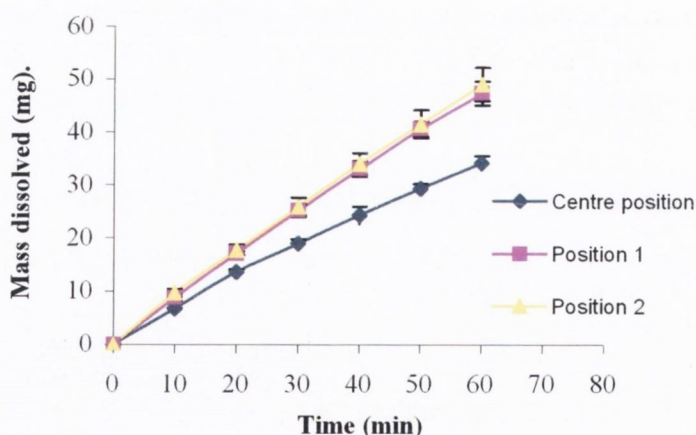


Figure 3.2. Mass benzoic acid dissolved (mg) vs. time (min) from the top planar surface only of benzoic acid compacts (height 3 mm, diameter 13 mm) from each of positions centre to 2, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

3.2.2.3 Dissolution from the curved side surface.

As illustrated in Figure 3.3, once again both positions 1 and 2 give a higher benzoic acid dissolution rate than the central position, but there is no significant difference between positions 1 and 2.

Again, the ANOVA revealed overlapping 95% confidence intervals between dissolution rates from positions 1 and 2 but not between rates from either position 1 or 2 and the central position. Results from the t-tests for equal means of dissolution rates from the side surfaces of the compact support a difference between rates from the central position and position 1 ($p=0.0250$) and the central position and position 2 ($p=0.023$) at the 5% significance level, but no difference between the mean dissolution rates from positions 1 and 2 at the 5% significance level ($p=0.79$).

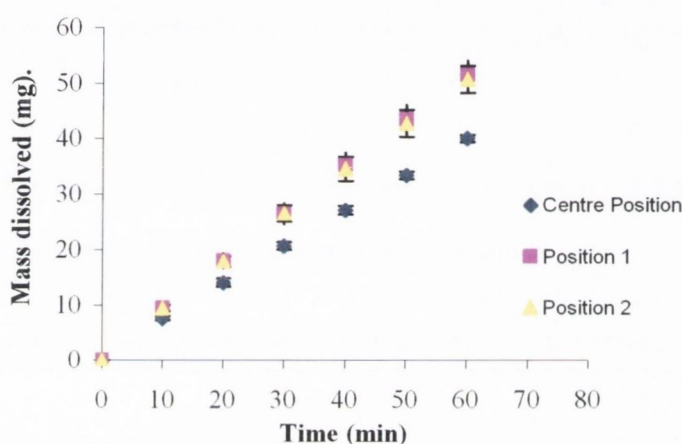


Figure 3.3. Mass benzoic acid dissolved (mg) vs. time (min) from the curved side surface only of benzoic acid compacts (height 3 mm, diameter 13 mm) from each of positions centre to 2, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

3.2.2.4 Comparison of variation between top planar surface and curved side surface.

The mass of benzoic acid dissolved at 60 minutes was compared for the whole compact, top planar surface only and curved side surface only. The results can be seen in Figure 3.4. As there seems to be a greater variation between centre and off centre positions from the top planar surface than the curved side surface, the rates per unit surface area from the top planar surface and the curved side surface were compared. Table 3.3 shows dissolution rates from whole compacts and the top planar and curved side surfaces alone for the compacts in different positions. There was a greater dissolution rate from the curved side surface than the top planar surface in the central position at a 5% significance level ($p=0.004$). The rate for the whole compact has been adjusted to take into account a small amount of dissolution which occurs from the bottom surface which is affixed to the vessel. This was found to be $0.0837 \text{ mg min}^{-1}$ for the compact in the central

position. As this bottom surface is not exposed to varying currents it was taken to be the same rate in each position.

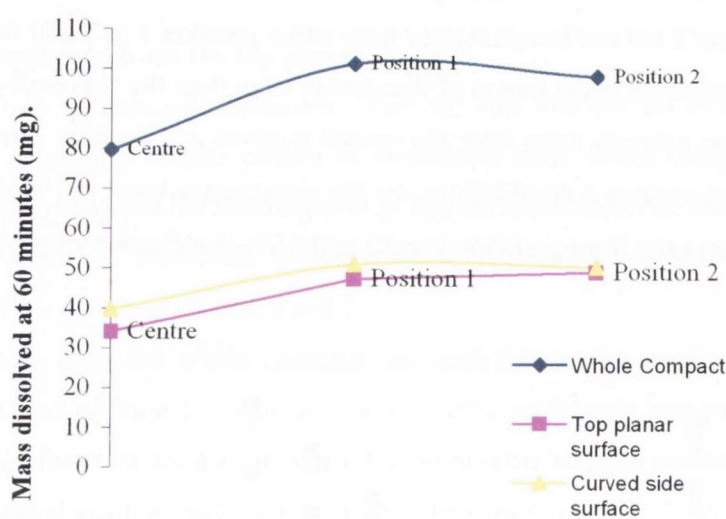


Figure 3.4. Mass benzoic acid (mg) dissolved at 60 minutes from whole compact, top planar surface alone and curved side surface alone for benzoic acid compacts (height 3mm, diameter 13mm) for positions centre, 1 and 2, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

Surface	Compact position	Rate (mg min ⁻¹)	Rate (mg min ⁻¹ cm ⁻²)
Whole compact	Centre	1.2712	0.4980
	Position 1	1.6499	0.6464
	Position 2	1.5927	0.6240
Top planar surface	Centre	0.5967	0.4496
	Position 1	0.8157	0.6146
	Position 2	0.8413	0.6338
Curved side surface	Centre	0.6747	0.5507
	Position 1	0.8702	0.7104
	Position 2	0.8584	0.7007

Table 3.3. Dissolution rate in mg min⁻¹ and mg min⁻¹ cm⁻² from different surfaces of the benzoic acid compact in different positions, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

The increase in dissolution rate that was measured as a compact’s location is varied from the centre of the base of the vessel to the off-centre positions supports previously published results of an increase in dissolution rate as a compact is moved from the centre of the base of the vessel

(Kamba et al., 2003; Kukura et al., 2004). In the current work, an increase in dissolution is shown from both top planar and curved side surfaces, although the increase in dissolution rate is greater from the top planar surface than the curved side surface. In addition, the dissolution rate from the curved side surface of the compact in the central position is greater per unit surface area than that from the top planar surface. It can be concluded therefore that, in conjunction with the hydrodynamics in the vessel varying between the central position and the off-centre positions, the top planar surface of the compact in the central position is subject to different hydrodynamic forces to the curved side surface.

3.2.2.5 Dissolution from 8.5 mm compacts.

Dissolution test results from benzoic acid compacts of 13 mm diameter and approximately 8.5 mm in height have been previously published (Healy et al., 2002). Grooves formed on these compacts following dissolution for 1 hour in 0.1M HCl were consistent with the expected effect from radial inflow around a compact at the centre of the base of the paddle apparatus from CFD simulations (McCarthy et al., 2003). It was therefore considered that this compact was located in the region of the centre of the base of the vessel. For comparative purposes, dissolution tests in the current work were also carried out on compacts of 8.5 mm in height in position 1, the results of which are shown in Figure 3.5.

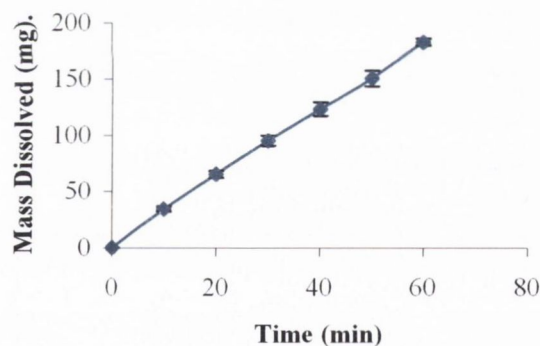


Figure 3.5. Mass benzoic acid dissolved (mg) versus time (min) from a compact 8.5 mm in height, diameter 13 mm, situated in position 1, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

The dissolution rate from position 1 was found to be $2.9931 \text{ mg min}^{-1}$. If dissolution from the bottom surface is assumed to be the same as for a compact affixed to the central position ($0.0837 \text{ mg min}^{-1}$) then the adjusted rate from the top and sides of an 8.5 mm compact in position 1 is $2.9094 \text{ mg min}^{-1}$.

This result from the whole compact (including the bottom surface) can be compared to that obtained by Healy et al., (2002) for a compact of the same size which was assumed to be in (but not affixed to) the central position. The dissolution rate in that case was $2.578 \text{ mg min}^{-1}$. The

weight of these 8.5 mm compacts (approximately 1.5 g) was probably a factor contributing to these compacts falling to the centre of the base of the vessel without being fixed to this position prior to dissolution. In describing the dissolution from the compact in the centre of the vessel, the dissolution rate constant, k_d , was used (Healy et al., 2002). The k_d value is equal to the diffusion coefficient (for benzoic acid) divided by the thickness of the aqueous diffusion boundary layer. For the benzoic acid compacts in the central position k_d was reported to be $15.4 \times 10^{-4} \text{ cm s}^{-1}$ (Healy et al., 2002). This figure also accounts for dissolution from the lower surface of the compact. The k_d value for the lower surface alone, however, is also presented in the previous work. If the k_d value is corrected to take into account the dissolution from the top and sides only, the resulting k_d value is approximately $18.6 \times 10^{-4} \text{ cm s}^{-1}$. The k_d value for the compact affixed to position 1 in the present work was $22.21 \times 10^{-4} \text{ cm s}^{-1}$. The magnitude of the increase in dissolution rate from the central position to position 1, therefore, for these compacts (approximately 19%) was not as great as for the smaller 3 mm compacts (approximately 25%). This may be explained by the following:

- a) the compact in the previous work was not fixed in the central position, and therefore may have been slightly off centre and subject to higher velocities in the surrounding dissolution medium. It may also have been lifted momentarily from the base by the fluid movement thereby exposing the bottom surface for dissolution while lifted.
- b) as described in section 3.2.2.4 the change in dissolution rate with distance from the centre of the vessel for the smaller 3 mm compacts is mostly attributable to varying dissolution from the tops of the compacts. In this case the dimensions of the compact tops were the same for the 8.5 mm compacts as for the 3 mm compacts. As the sides were that much bigger (8.5 mm vs. 3 mm), the proportion of dissolution occurring from the compact tops is smaller and therefore the variation with positioning in this manner is less.

3.2.3 Statistical analysis of dissolution results.

3.2.3.1 Dissolution from control compacts – Analysis of variability in routine dissolution testing procedures.

It has been noted that a non-swellable dosage form will not remain stationary on the base of the paddle dissolution apparatus under routine testing procedures (Baxter et al., 2005), but is likely to move about in an erratic fashion. In the same study, a higher degree of variability was noted for tablets placed in the centre of the base of the dissolution vessel compared to those placed at a distance of 21 mm from the centre. Dissolution rates from the control compacts (compacts not affixed to any position, as described in section 2.2.2.3) are compared to those in a fixed position in Table 3.4.

The dissolution rates from the control compacts were higher than those from the compacts in the central position but lower than the compacts in position 1. There is greater variability in the dissolution rates from these control compacts than from the compacts in any of the fixed positions. This is quantified in Table 3.4 using the relative standard deviation (RSD)% value. The RSD% value of 7.7% from the control compacts is notably higher than that from position 1 which is 4.8%. This is of a similar magnitude to the RSD% value from the central position which is 4.5%. The RSD% value from position 2 is lower again at 2.8%.

The slightly higher RSD% values in position 1 and the central position compared to position 2 may be due to the fact that in this region of the vessel there is a significant change in dissolution rate with a minor change in position (as is evident from the dissolution results presented in Figure 3.1.). As a consequence of this, small variations in the experimental positioning of these compacts for dissolution will lead to more noticeable variation in dissolution results in comparison to the positioning of compacts in position 2. As there is no significant difference in dissolution rates between positions 1 and 2 a variation in positioning of the compact in position 2 will have less of an effect on the repeatability of the dissolution results. The RSD% value of 7.7% is taken from dissolution data from two different runs (3 replicates per run), performed by the same analyst within the same laboratory. This RSD% value is comparable to values obtained from two other studies, using the same apparatus, when the components of variance from within the same laboratory only are considered (i.e. variance components from “between laboratories” is ignored). In the first study, data from non-disintegrating USP salicylic acid calibrator tablets sampled at 30 minutes only, and glibenclamide tablets sampled at intervals from 10 to 120 minutes were used (Qureshi and McGilveray, 1999). As the dissolutions in the current work were undertaken for 60 minutes the data was compared to glibenclamide dissolution data from 10 to 60 minutes only, and an average RSD% calculated over this time period. From the “within lab variance” data provided in this study, an RSD% value of 8.4% for the salicylic acid tablets and an average RSD% value of 7.1% for the glibenclamide tablets were calculated. In the second study (Siewert et al., 2002), data from glibenclamide tablets sampled at intervals from 10 to 60 minutes were also used. There was no “within lab” variance component given in this study, so the “within analyst” and “between analyst” components were added. It was considered that this was comparable to the variability in the current work attributable to “within analyst” and “between runs”. The average RSD% value calculated in this manner from the glibenclamide dissolution results was 7.1%. It can be concluded, therefore, that when the dissolution rate of a tablet is tested in the paddle dissolution apparatus using the routine testing procedures, an RSD% value in the approximate range of 7% to 8.5% can be expected from any particular laboratory.

Compact Position	Average Dissolution Rate (mg hour ⁻¹)	Standard Deviation	RSD%
Centre	81.3	3.6	4.5
Position 1	104.2	5.0	4.8
Position 2	100.6	2.8	2.8
Control (not fixed to any position)	91.1	7.0	7.7

Table 3.4. Average Dissolution Rate, Standard Deviation and RSD% from benzoic acid compacts in each of centre position, position 1 and position 2, and compacts not fixed in a position (control compacts), in 900 ml 0.1M HCl in the paddle dissolution apparatus at 50 rpm.

3.2.3.2 Analysis of decrease in variability in dissolution testing by fixing compact position.

Repeatability Limit.

The repeatability limit is defined as “the value less than or equal to which the absolute difference between two test results obtained under repeatability conditions may be expected to be with a probability of 95%” (Mullins, 2003), and is expressed as :

$$1.96\sqrt{2(SD)^2}$$

Where *SD* is the standard deviation.

It is assumed that repeatability conditions apply within a single analytical “run”. It is also possible to estimate repeatability from historical data involving numerous runs, where an $(SD)^2$ value is calculated from each run, allowing an average $(SD)^2$ value to be obtained for all runs. In this case the repeatability limit calculated still applies to the differences between two measurements *within* a particular run, as the estimate for *SD* used in the calculation is taken from the average of within-run *SD* values.

All data for the uncoated compacts fixed in the central position, position 1 and position 2 and the control compacts were obtained from 2 separate runs in each case. The dissolution rate (in mg hour⁻¹) was calculated for each of 3 replicates, in two different runs. The $(SD)^2$ values from these dissolution rates were then averaged, to get an average $(SD)^2$ value where the position is fixed, and an average $(SD)^2$ value when the position is not fixed. For these calculations, had the data been pooled for both runs, between-run variability would also have affected the *SD* value, as the different runs were carried out on different days, with new media. By calculating the within-run variability the difference in results is more likely to reflect true random variation.

The rates for each system are presented in Table 3.5.

Run 1				
Dissolution	Centre	Position 1	Position 2	Control
Rate	74.81	101.83	97.00	85.14
(mg hour ⁻¹)	82.80	97.00	101.94	95.00
	80.02	100.89	97.23	93.49
Run 2				
Dissolution	Centre	Position 1	Position 2	Control
Rate	83.18	109.56	103.78	99.35
(mg hour ⁻¹)	85.28	107.15	101.48	93.44
	81.65	108.44	102.07	80.39

Table 3.5. Dissolution Rates in mg hour⁻¹ for benzoic acid compacts in central position, position 1 and position 2 and not fixed to any position (control compacts), in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm. Results are presented in each case for two separate dissolution runs (n=3 for each run).

The SD values, $(SD)^2$ values and average $(SD)^2$ values for systems with positions fixed and unfixed are detailed below in Table 3.6.

	SD (mg hour ⁻¹)	$(SD)^2$ (mg hour ⁻¹) ²		Average $(SD)^2$ (mg hour ⁻¹) ²
Run 1				
Centre	4.06	16.46	Position fixed	6.16
Position 1	2.56	6.54	Position unfixed	61.15
Position 2	2.79	7.77		
Control	5.31	28.18		
Run 2				
Centre	1.82	3.32		
Position 1	1.20	1.45		
Position 2	1.19	1.43		
Control	9.70	94.11		

Table 3.6. The standard deviation (SD) value, $(SD)^2$ value for each position within each run and the average $(SD)^2$ value for a benzoic acid compact with a fixed position and that not fixed in any fixed position (control compact); from dissolution data in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

From these average $(SD)^2$ values, the repeatability limit when the position is fixed would be 6.881 mg hour⁻¹. The repeatability limit where the position is not fixed (the control compacts) would be

21.676 mg hour⁻¹. As can be seen from the Table 3.5, if the repeatability limit calculated when compact position is fixed (6.881 mg hour⁻¹) was applied, both of the runs for the control compacts (position unfixed) would have failed, as both runs have differences between dissolution rates which are greater than 6.881 mg hour⁻¹.

In summary, to apply repeatability limits to dissolution testing which were derived from data from compacts in a fixed position in the dissolution vessel would result in more stringent repeatability limits than those derived from compacts not in a fixed position. As repeatability limits are designed to reflect the limits within which results subject to random variation should fall, any discernible source of bias in calculating these results should be eliminated. The purpose of a dissolution test is to quantify and monitor the dissolution characteristics of a dosage form (which would be subject to random variation), and not the variation within the dissolution apparatus. As the contribution to variation from positioning within the dissolution vessel has been demonstrated and quantified, it would seem reasonable to consider that this source of variation be eliminated as much as possible. In other words, allocated positioning of a dosage form within the apparatus, or a modification of the design of the apparatus ensuring consistency of dosage form position is recommended. A number of methods to address this have been considered. Placing a hydrophilic matrix tablet (verapamil HCl, guar gum and filler, (Dürig and Fassihi, 2000)) between two meshes maintaining it in the bottom third of the apparatus resulted in a dissolution rate standard deviation $\leq 3\%$ compared to $\leq 22\%$ in the unmodified paddle apparatus at 50 rpm (Dürig and Fassihi, 2000). Stationary baskets have been employed to hold three types of extended release felodipine tablets above the paddle apparatus (Wingstrand et al., 1990). The effect of placing salicylic acid tablets within a stationary basket at the base of the rotating filter apparatus has been compared to a tablet held in place with a nichrome wire at both the side and the centre of the vessel (Vongvirat et al., 1981). The use of the basket above the paddle (Wingstrand et al., 1990) resulted in RSD% values less than 6% at all sampling points, up to 24 hours in the case of one formulation, with the exception of the earliest 2-hour sampling point. The rapid increase in strain rate along the vessel wall from the centre of the base of the vessel noted from CFD simulations of the paddle apparatus, containing no compact (Kukura et al., 2004), undoubtedly contributes to this variability in dissolution testing. The use of CFD to model and examine the varying hydrodynamics around compacts placed in different positions offers further insight into the sources of variability in the apparatus.

3.3 CFD simulations of compacts in different positions in the dissolution apparatus.

3.3.1 Validation of hydrodynamic simulations.

Velocity data was used from the CFD simulations of the models of the paddle apparatus with compacts in the central position, position 1 and position 2, where the compact volume was defined as liquid, using the same specifications as the other fluid volumes in the vessel to simulate the dissolution medium. In other words, a vessel containing no compact was modelled, but using the same mesh which was used in simulating the vessel containing a compact in each position. Axial, radial and tangential velocity data from the same locations within the flow field as those used by Bocanegra et al., (1990), were plotted as a function of the radial location relative to the location of the rotating paddle, in the manner that the laser Doppler velocity data were plotted by Bocanegra et al., (1990). The resulting graphs are presented in Appendix 6, with reproductions of the graphs published by Bocanegra et al., (1990), for comparative purposes. The CFD generated flow fields were qualitatively and quantitatively similar to those produced using laser Doppler velocimetry, for the compacts located in the central position. The compacts located in positions 1 and 2 were also qualitatively and quantitatively similar to the laser Doppler data, with the exception of more erratic data from the CFD simulations at a point close to the interface between the lower and upper fluid volumes of the multiple reference frame. This corresponds to data on Figure A6.4.d and A6.4.e or the plane at $Z=-0.461$ using the Bocanegra coordinate system (Appendix 1) (Bocanegra et al., 1990). The graphs from both above and below (including near the base of the vessel where the compact was located) this plane, however, displayed velocity data which was consistent with the physical laser Doppler data. The method using the multiple reference frame to simulate hydrodynamics in the paddle apparatus with the off-centre compacts was therefore considered appropriate, as when the compacts were defined as fluid the resulting flow field produced hydrodynamic data which was similar to the physical data measured using the laser Doppler velocimetry method.

3.3.2 Analysis of hydrodynamics present in the dissolution apparatus containing compacts in different locations through CFD simulations of hydrodynamics around compacts in each position.

CFD simulations of fluid flow in the apparatus containing compacts situated in the central position, position 1 and position 2 were analysed.

The CFD simulation of fluid flow in the vessel containing the compact in the central position shows the compact lying in a region of very low velocity. This is due to a vortex formed between the lower surface of the paddle and the centre of the hemispherical base. Figure 3.6 shows a

vertical plane through the mid-section of the vessel containing the compact in each position from the CFD simulations.

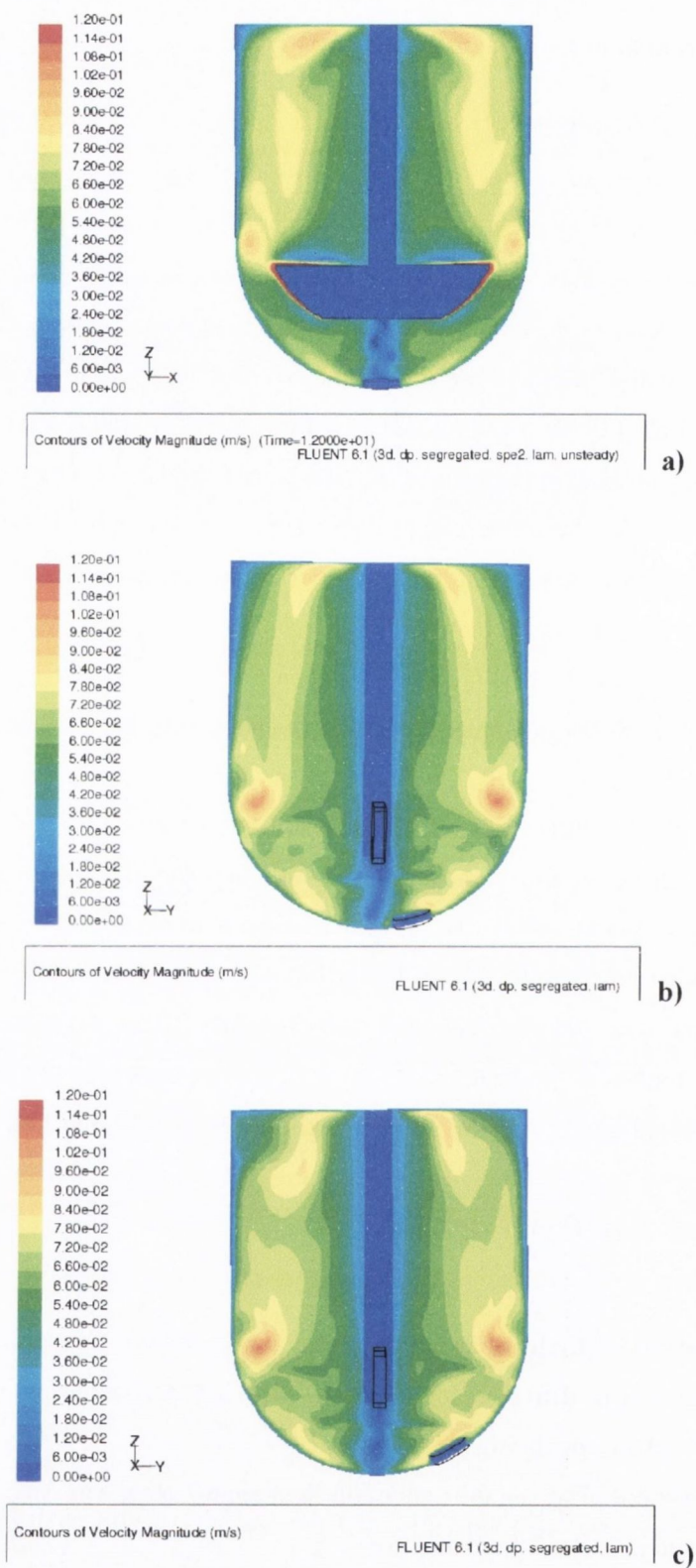


Figure 3.6. Contours of velocity magnitude on a vertical plane midway through the vessel of the paddle apparatus containing 900 ml at 50 rpm with a compact in a) central position, b) position 1 and c) position 2.

The low velocity vortex can be clearly seen between the surface of the compact in the central position and the bottom of the paddle, and between the base of the vessel and the bottom of the paddle where the compacts are positioned off-centre.

Figure 3.7 shows velocity vectors from the CFD simulations of the vessels with the compacts in a) central position, b) position 1 and c) position 2. These vectors are at a distance of 1 mm from the sides of the compacts, which is approximately the edge of the hydrodynamic boundary layer for the central compact (McCarthy et al., 2004). It is evident from these images that the velocities around the sides of the compacts are of a similar average magnitude in each position, although there are regions around positions 1 and 2 where there are higher velocities visible than around the central compact. Figure 3.7 also shows velocity vectors 1 mm from the top of the compacts in d) central position e) position 1 and f) position 2. The lower velocity in the region of the compact in the central position is in stark contrast to the velocities surrounding the compacts in positions 1 and 2. The increase in velocity magnitude to which the off-centre compact is exposed is not as evident around the sides of the compacts compared to the tops of the compacts in Figure 3.7. This is due to the fact that although a distance of 1 mm from the surface of the compact would be approximately at the edge of the hydrodynamic boundary layer in the central position, the thickness of the hydrodynamic boundary layer varies around the off-centre compact surfaces. Variation within the hydrodynamic boundary layer is described in section 3.3.4 where velocity vectors around the off-centre compacts reveal differences in the velocity gradients around the sides of the compacts. Although generally the thickness was less than 1 mm around the off-centre curved side surfaces, there are regions of the displayed surface (Figure 3.7) at 1 mm from the sides of the compacts that are likely to be within the hydrodynamic boundary layer or located in regions of low bulk velocity. The overall velocities shown in Figure 3.7.b and 3.7.c are therefore lower than would be anticipated at the edge of the boundary layer.

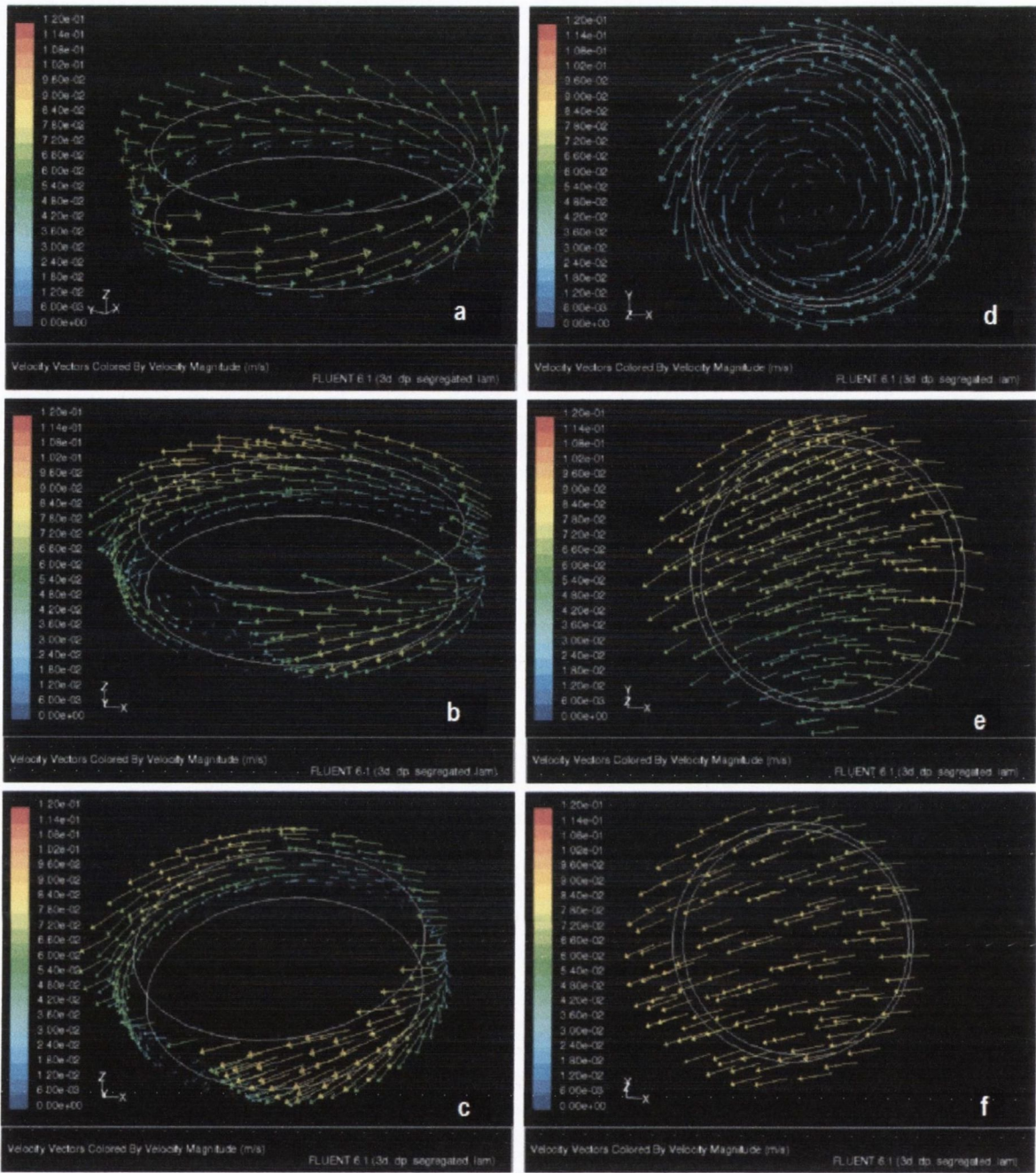


Figure 3.7. CFD-generated vectors coloured by velocity magnitude at a distance of 1 mm from the side of the compact in a) centre position, b) position 1 and c) position 2, and at 1 mm from the top of the compact in d) centre position, e) position 1 and f) position 2.

3.3.3 Relationship between velocity and mass transfer.

The relationship between the maximum value of velocity magnitude at a distance of 1 mm from various compact surfaces (i.e. top planar surface and curved side surface in each position), as determined from CFD data, and dissolution rate from these surfaces are shown in Figure 3.8. Data was taken from a distance of 1 mm from the compact surface as this was determined to be the approximate thickness of the hydrodynamic boundary layer at the top planar surface of a compact in the central position (McCarthy et al., 2004). There is an increase in dissolution rate

corresponding to an increase in the maximum velocity in the region of the compact, as obtained from the CFD simulations. The increased dissolution rate can be attributed to the compact being removed from the low velocity vortex region in the centre of the base of the vessel, and therefore being exposed to higher velocities once in an off-centre position. These maximum velocity values are of a comparable magnitude to those calculated from experimental fluid resistance data (Kamba et al., 2003) in regions corresponding to those regions where the off-centre compacts were located in the current work, at a 50 rpm paddle rotation speed. The fluid velocity data calculated from the fluid resistance data (Kamba et al., 2003) is compared to CFD velocity data in Table 3.7.

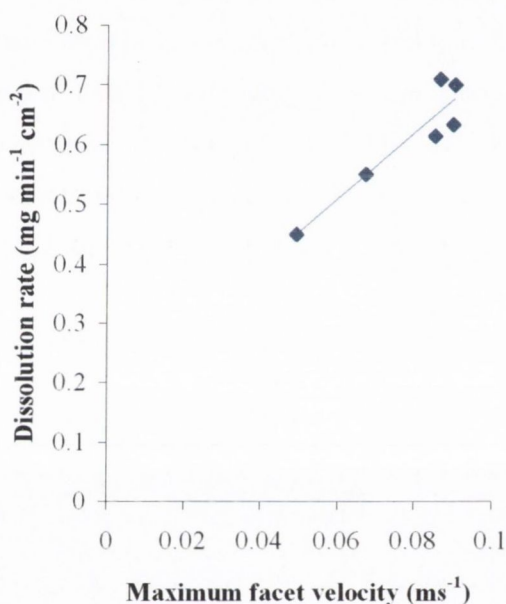


Figure 3.8. Dissolution rate ($\text{mg min}^{-1} \text{cm}^{-2}$) from different surfaces of both centred and off-centre benzoic acid compacts, in 900 ml 0.1M HCl in the paddle dissolution apparatus at 50 rpm vs. maximum facet velocity value (ms^{-1}) from CFD-generated data.

Data from Kamba et al., (2003).		
Distance from centre (mm)	20	28
Velocity (ms^{-1})	0.081	0.098
Data from CFD	Position 1	Position 2
Distance of outer edge from centre (mm)	18.3	28.9
Maximum facet velocity (ms^{-1}) (side)	0.0865	0.0903
Maximum facet velocity (ms^{-1}) (top)	0.0853	0.0899

Table 3.7. Velocity values in the paddle dissolution apparatus calculated from fluid resistance data (Kamba et al., 2003) compared to maximum fluid velocity data in the same region generated using CFD simulations of the paddle apparatus containing 900 ml dissolution medium at 50 rpm.

3.3.4 Analysis of the effect on compact shape of varying hydrodynamic environments after dissolution for one hour.

On removal of the compacts from the dissolution medium after 1 hour of dissolution, it was noted that the 3 mm high compacts in positions 1 and 2 were sloped on one side. This side was facing into the direction of fluid flow, but was orientated slightly more towards the centre on the compact in position 1 than that in position 2. Figure 3.9.a shows a photograph of the compact after dissolution for 1 hour in position 1, where the left hand side of the compact was facing the centre of the vessel, and Figure 3.9.b shows velocity vectors surrounding the compact on a plane through the centre of the vessel. The insert at the top left corner of Figure 3.9.a depicts the compact prior to dissolution. The variation in the velocity gradient in the region around the compact which influenced the formation of this sloped edge can clearly be seen in Figure 3.9.b. Figure 3.10.a is a photograph of the compact after dissolution for 1 hour in position 2, parallel to the centre of the vessel and facing into the fluid flow. Again the insert depicts the compact prior to dissolution for comparison. Figure 3.10.b shows velocity vectors on a plane through the compact in position 2 from the same angle, that is the front of the compact is facing the centre of the vessel.

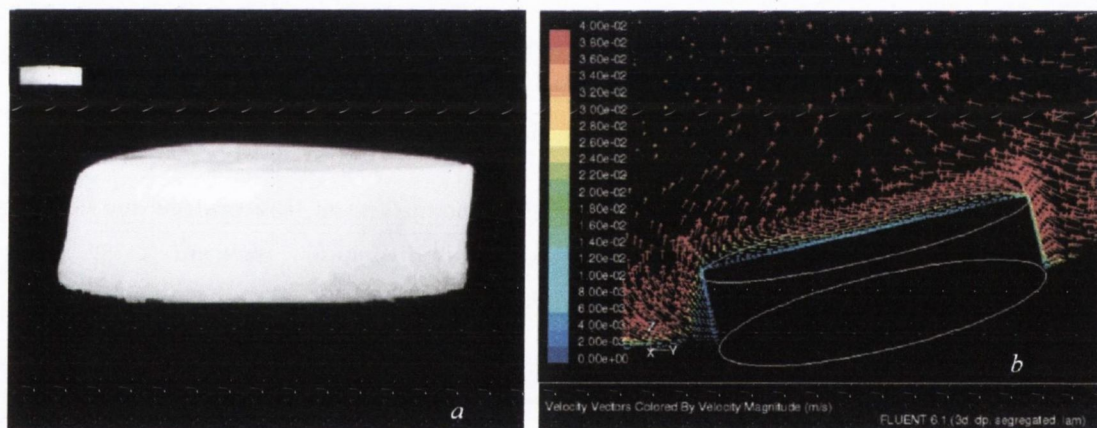


Figure 3.9. a) Photograph of benzoic acid compact after undergoing dissolution for 1 hour in position 1, in 900 ml 0.1M HCl at 50 rpm in the paddle apparatus. The left hand side of the compact was facing the centre of the base of the vessel.

b) CFD-generated vectors coloured by velocity magnitude surrounding the compact in position 1, at a vertical plane midway through the vessel, from simulations of the paddle apparatus at 50 rpm. The centre of the base of the vessel is to the left of the picture.

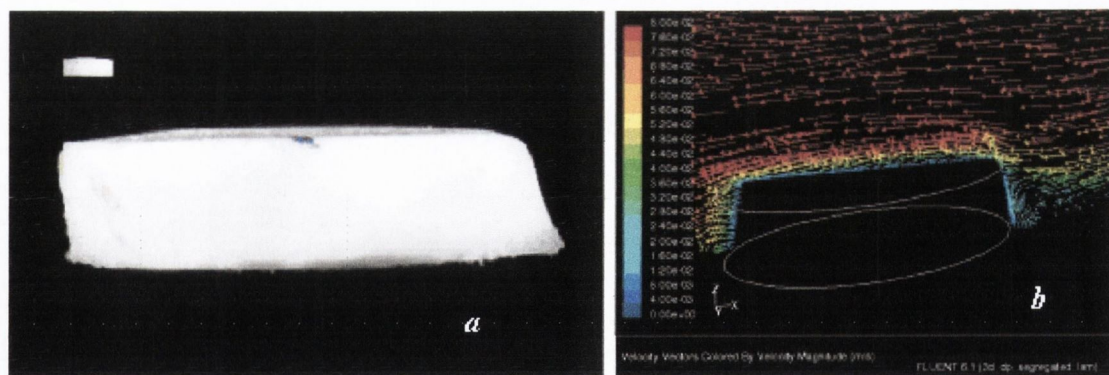


Figure 3.10. a) Photograph of benzoic acid compact after undergoing dissolution for 1 hour in position 2, in 900 ml 0.1M HCl at 50 rpm in the paddle apparatus. The front of the compact was facing the centre of the base of the vessel.

b) CFD-generated vectors coloured by velocity magnitude surrounding the compact in position 2, at a vertical plane perpendicular to that through the centre of the vessel, from simulations of the paddle apparatus at 50 rpm. The front of the compact in this picture is facing the centre of the base of the vessel.

In the previous work, it was noted that a groove formed around the bottom 3 mm of the 8.5 mm compact during dissolution (Healy et al., 2002). CFD simulations of the vessel containing no compact showed a high inward radial component around the base of the vessel consistent with preferential erosion towards the base of the compact. In the current work it was also noted that there was grooving on the 8.5 mm compact in position 1 but it was not uniformly distributed about the base of the compact. Two grooves were formed, one on the side of the base of the compact which faced into the rotating fluid and the other on the opposite side. A ridge was evident at the back of the compact where the two grooves met. These grooves and the ridge can be seen on examination of the photographs in Figures 3.11 and 3.12. CFD simulations of this compact in position 1 show patterns of inward radial fluid flow and tangential velocities around the compact consistent with this grooving effect, as can be seen in Figure 3.13. A slight hump which formed on the side of the top planar surface of this compact can also be seen on the left of the photo in Figure 3.12, and the lower velocity region influencing the formation of this hump can be noted from the CFD output in Figure 3.13.



Figure 3.11. Photograph of the 8.5 mm benzoic acid compact after dissolution for 1 hour in position 1, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm. The left hand side of the image was facing the centre of the vessel. The groove on the side of the compact facing into the fluid flow is facing the front, and the end of this groove, the diagonal ridge and the beginning of the groove on the far side of the compact are also visible here.

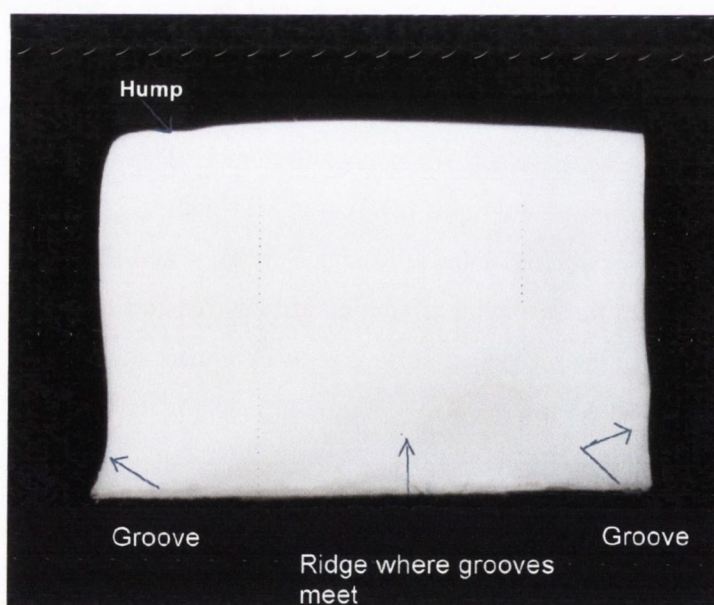


Figure 3.12. Photograph of the 8.5 mm benzoic acid compact after 1 hour of dissolution in position 1, in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm. This photograph is at a 90° angle to that in Figure 3.11. The left hand side of the image was facing into the fluid flow, the far side of the image (away from the camera) was facing the centre of the vessel. Again the grooves formed on both sides of the compact can be seen, and diagonal ridge where both grooves meet is barely visible in the centre.

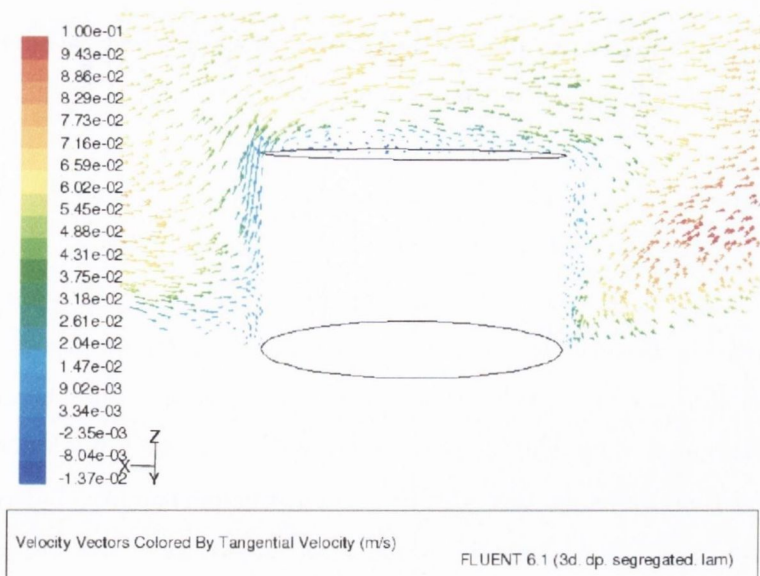


Figure 3.13. CFD-generated vectors coloured by tangential velocity around the 8.5 mm compact as shown from the same angle as in Figure 3.12. The direction of fluid flow and the variation in tangential velocity magnitude can easily be seen to have influenced the shape of the compact after dissolution.

3.3.5 Comparison of thickness of and velocities within the hydrodynamic boundary layer of the 3 mm compacts.

3.3.5.1 Velocity data adjacent to the top planar surface.

The thickness of the hydrodynamic boundary layer at the compact surface can be estimated by plotting velocity magnitude as a function of distance from the surface. The velocity values will increase with increasing distance from a value of zero directly at the surface, to a point at which the velocity starts to level off. The region where the velocity values cease to increase is considered to be the edge of the hydrodynamic boundary layer. Both the thickness of this layer and the velocity gradient within the layer can be examined in this manner. Figure 3.14 shows the velocity profile with increasing distance from the compact surface at five different points along the top planar surface. This compact is in the central position. The point described by the legend y_0 is at the centre of this surface, y_3 and y_{-3} are 3 mm from the centre in the positive and negative directions along the y axis, respectively, and similarly $y_{6.5}$ and $y_{-6.5}$ are 6.5 mm from the centre in the positive and negative directions along the y axis. The points along the surface and the lines radiating from them, along which data is taken to plot velocity profiles used to analyse the hydrodynamic boundary layer around the off-centre compacts, are described in Figure 2.16. The points and lines for the centrally positioned compact are the same with the exception of the z points along the curved side surface, where 20 z points are used radiating in one direction from the central compact, in place of the 8 z points radiating in each direction along the x and y axes used in the off-centre compacts. Further details of the positions of these lines from which the hydrodynamic profiles extending from the surface of the compacts were constructed is given in section 2.2.1.4.2.

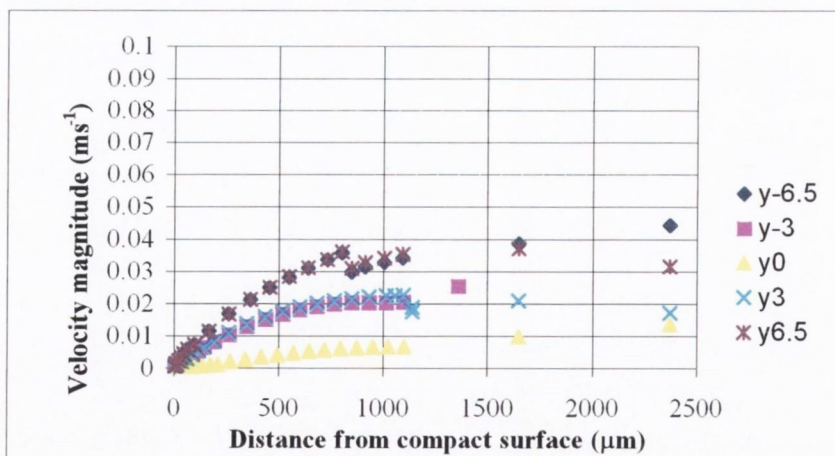


Figure 3.14. CFD-generated velocity magnitude data vs. distance from top planar surface of compact in the central position, from simulations of 900 ml in the paddle apparatus at 50 rpm.

As would be expected from the CFD data shown in Figures 3.6 and 3.7.d, the velocity is lowest in the centre of the top planar surface (evident from the point y_0), and increases with increasing distance outward horizontally from the centre. The thickness of the hydrodynamic boundary layer

is approximately $1000\ \mu\text{m}$ for all points along the surface, but the maximum velocity reached is between 0.03 and $0.04\ \text{ms}^{-1}$ at the outer edges of the compact, compared to approximate values of 0.005 and $0.01\ \text{ms}^{-1}$ at the centre of the compact. The uneven profiles at the edge of the hydrodynamic boundary layer for the lines $y_{6.5}$ and $y_{-6.5}$ are most likely due to the edge effects experienced at these outer edges of the top surface. Hydrodynamics at the edge of a dissolving surface can be complex as there are converging flow patterns from both the side and top surfaces. Figures 3.15.a and 3.15.b show the lines at the same points from the top surfaces of the compacts in positions 1 and 2, respectively.

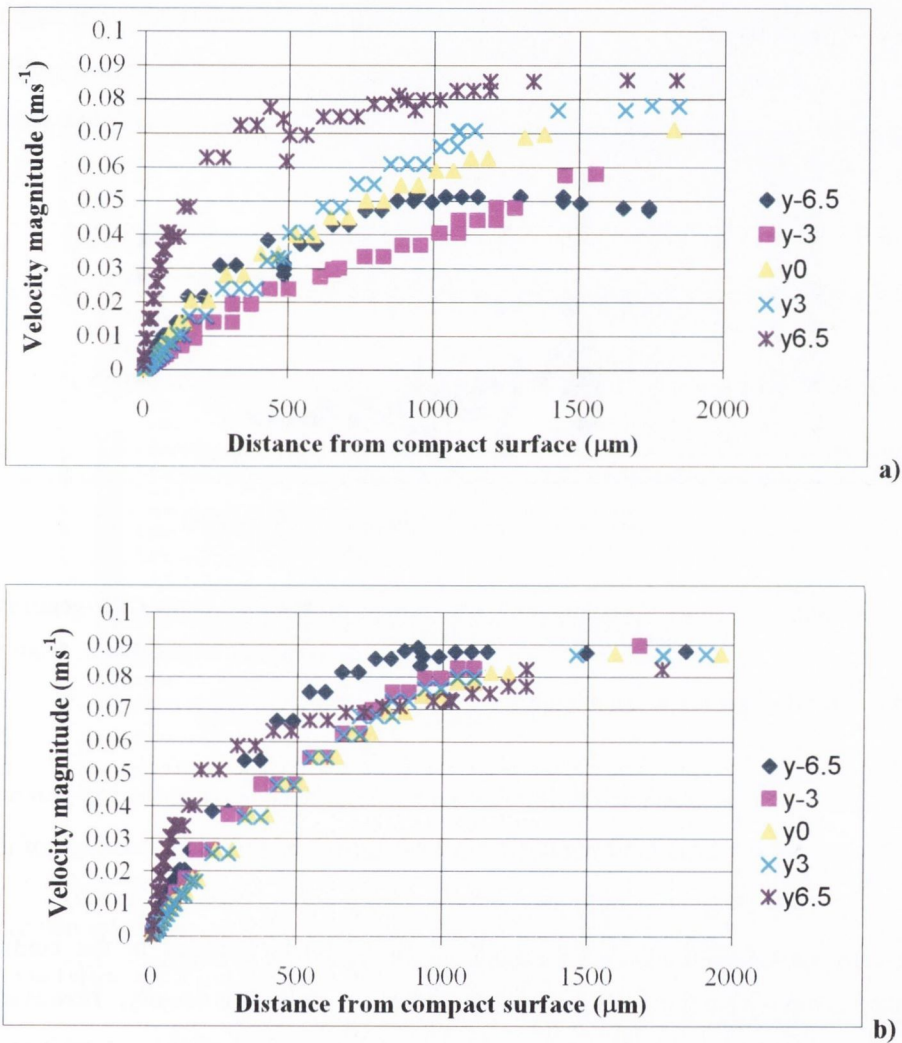


Figure 3.15. CFD-generated velocity magnitude data from profiles extending from points on the y-axis vs. distance from the top planar surface of the compact in a) position 1 and b) position 2, from simulations of 900 ml in the paddle apparatus at 50 rpm.

In the case of the compacts in positions 1 and 2, the centre of the base of the vessel is along the y axis in a negative direction. It can be seen in Figure 3.15.a that the velocity profiles at the $y_{-6.5}$ and y_{-3} are in a lower velocity region, and the velocity increases along the positive y direction.

This is as expected as the points on the top surface of compact at y-6.5 and y-3 are nearer the low velocity vortex in the centre of the vessel. The profile for y-6.5, in particular, illustrates the influence of this low velocity region as the velocity profile starts to decrease at approximately 1000 μm from the compact surface, which indicates the beginning of the central low velocity region interfering with the compact's hydrodynamic boundary layer. For all of these velocity profiles from position 1, the edge of the hydrodynamic boundary layer is at 1000 to 1500 μm from the compact surface. Although this implies a thicker hydrodynamic boundary layer than that around the compact in the central position, there is little change in velocity magnitude with distance from the compact surface at 1000 μm from the surface for all profiles along the y-axis, as illustrated in Figure 3.16.

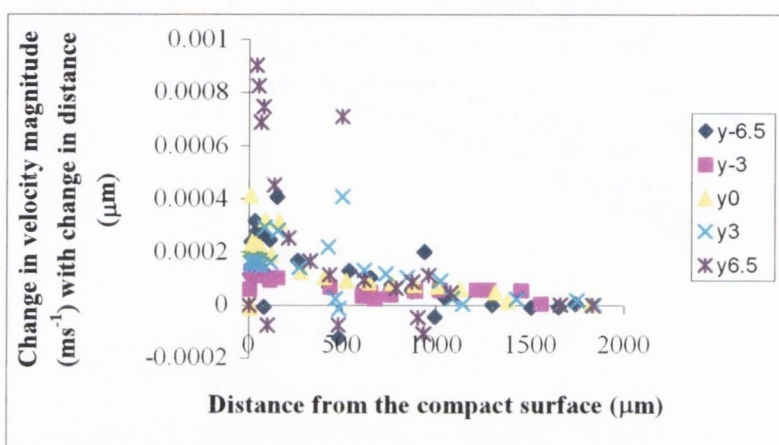


Figure 3.16. Change in velocity magnitude with change in distance from CFD-generated velocity data vs. distance from the top planar surface (y lines) of the compact in position 1, from simulations of 900 ml in the paddle apparatus at 50 rpm.

The actual velocities at the edge of the hydrodynamic boundary layer at the top planar surface of the compact in position 1 are much higher than those above the top planar surface of the compact in the central position, ranging from approximately 0.06 (y-3) to 0.085 ms^{-1} (y6.5).

It could be interpreted that the levelling off of the velocity profiles in the central position illustrates the region where the velocity reaches that of the bulk flow locally. However, as can be seen from Figure 3.6, the bulk flow above the top planar surface of the compact in the central position is not representative of the overall bulk velocity within the apparatus, but is of the flow within the apparatus in the low-velocity region under the paddle. It has been postulated (Beckett et al., 1996) that the low velocity vortex region above the compact in the central position can result in the rate controlling step of drug release being the rate of release from this low velocity region to the bulk medium rather than the rate of release under sink conditions. Costa and Lobo (2001b) also suggested that regions of low fluid velocity will affect the concentration gradient and therefore the dissolution rate in dissolution testing. The measured dissolution rate from the low velocity vortex region may therefore incorporate release of dissolved benzoic acid from this

vortex region into the bulk in addition to dissolution from the compact itself. In this scenario, the thickness of the hydrodynamic boundary layer at the compact surface would be a poor indicator of the overall measured dissolution rate within the vessel. The velocity profiles from Figure 3.15.b begin to level off at approximately 1000 μm from the compact surface. Again, velocities are much higher here than in the central position, with all of the profiles levelling off within the approximate range of 0.07 to 0.09 ms^{-1} . An interesting feature to note from this graph is the profile for the y6.5 point. As the hydrodynamics within the vessel generally consist of an increase in velocity with increase in distance from the centre of the base of the vessel, it might be expected that this profile at the outer edge of the compact surface would illustrate the fastest velocity, whereas in fact it is the slowest. Again, local flow features can account for this as the lower velocity at this point is influenced by liquid flowing radially inward being obstructed by the side of the compact and forming a low velocity pool at this edge, as can be seen at the right hand side of Figure 3.17.

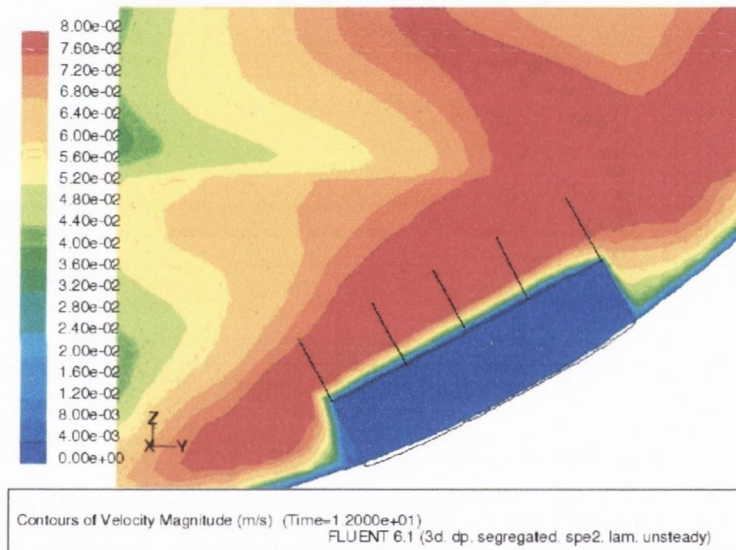


Figure 3.17. CFD-generated contours of velocity magnitude around the compact in position 2 from simulations of 900 ml in the paddle apparatus at 50 rpm. The lines (y-6.5 to y6.5) from which the profile data was taken are illustrated.

The velocity profiles are shown at points along the x-axis direction on the top planar surface of compacts in position 1 (Figure 3.18.a) and position 2 (Figure 3.18.b).

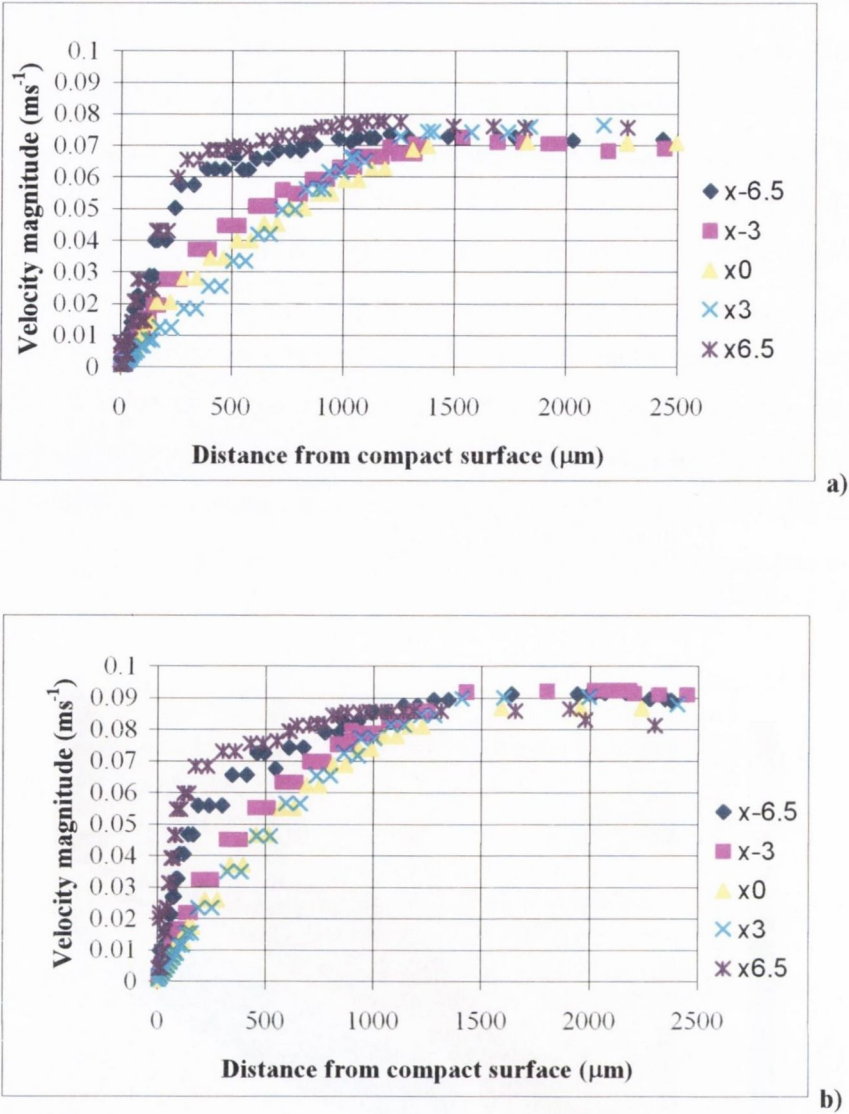


Figure 3.18. CFD-generated velocity magnitude data from profiles extending from points in the x direction vs. distance from the top planar surface of the compact in a) position 1 and b) position 2, from simulations of 900 ml in the paddle apparatus at 50 rpm.

A similar pattern is visible in both of these graphs. The points are plotted along the x axis from the edge facing into the rotating fluid flow to the opposite edge, along the centre of the compact surface. In both position 1 and position 2 the profiles at both outer edges of the compacts level off at approximately 1000 μm from the surface, but the profiles from points away from the edges are estimated to level off at 1500 μm. However, as was the case with the profiles from the lines in the direction of the y-axis, there is little change in velocity magnitude with distance from the compact surface at a distance of 1000 μm as illustrated in Figure 3.19.

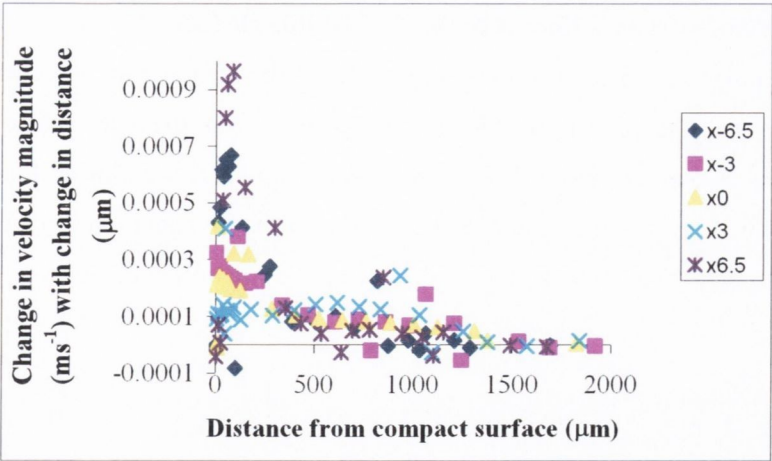


Figure 3.19. Change in velocity magnitude with change in distance from CFD-generated velocity data vs. distance from the top planar surface (x lines) of the compact in position 1, from simulations of 900 ml in the paddle apparatus at 50 rpm.

The maximum velocity from profiles from lines in the direction of the x-axis is in the range of 0.07 to 0.08 ms⁻¹ and 0.08 to 0.09 ms⁻¹ for position 1 and position 2 respectively. As the flow is approximately parallel to this row of points, it would be expected that the slope would be steepest for the profile of the line at x6.5, as the hydrodynamic boundary layer would not be developed at this point, and that the profiles further along the surface would demonstrate the developing hydrodynamic boundary layer. The fact that the slope of the profile at the far edge opposite that facing into the flow is similar to that of the profile at the edge facing into the flow is another example of the complex nature of the flow in the apparatus. In this case the effect of the fluid being drawn down over the far edge has decreased the thickness of the boundary layer, as illustrated on the left hand side of Figure 3.20.

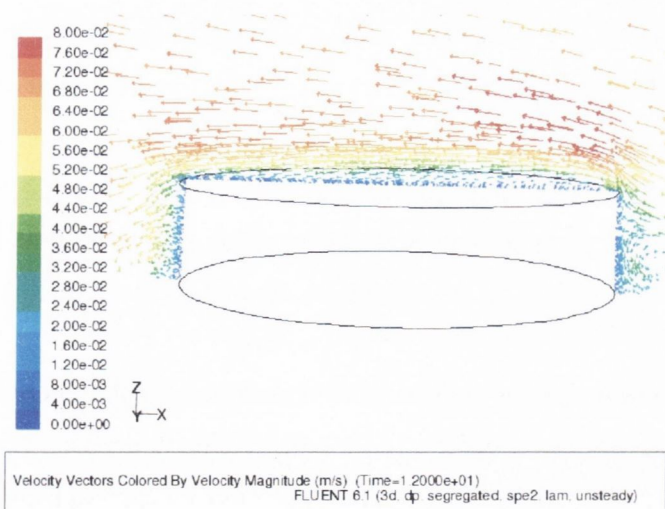


Figure 3.20. CFD-generated velocity vectors over the compact in position 1, from simulations of 900 ml in the paddle apparatus at 50 rpm. The decreased thickness of the hydrodynamic boundary layer at the outer edge of the top planar surface is visible.

3.3.5.2 Velocity data adjacent to the curved side surface.

As the hydrodynamics are consistent around the sides of the compact in the central position, it is only necessary to examine velocity profiles in one direction from the side surface of the compact. These profiles are shown in Figure 3.20. The points examined are almost 1 mm apart on the compact surface, with z1 being just above the bottom of the compact, and z18 being just below the top of the compact. The point at z10 is half way up the side of the compact.

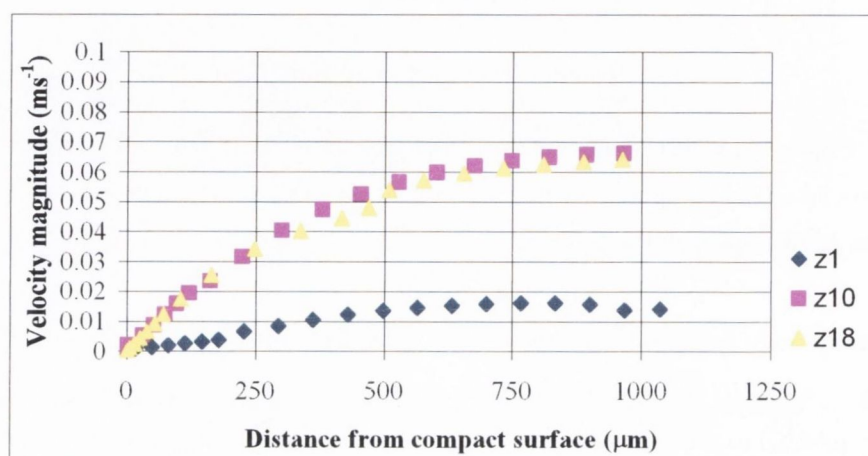


Figure 3.21. CFD-generated velocity magnitude data from profiles extending from the curved side surface vs. distance from the curved side surface of the compact in the central position, from simulations of 900 ml in the paddle apparatus at 50 rpm.

It is clear from the graph in Figure 3.21 that the bottom of the compact is in a very low velocity region. This is due to the profile also incorporating the hydrodynamic boundary layer of the vessel wall. The velocities at the bottom of the compact do not exceed 0.02 ms^{-1} at any distance from the surface. On the other hand, it would seem that there is little, if any, difference between the velocities experienced at a point half way up the side surface or near the top of the side surface, where velocities reach a range of 0.06 to 0.07 ms^{-1} , and the edge of the hydrodynamic boundary layer appears to be at $1000 \mu\text{m}$ from the compact surface. These velocities are higher than those present at the edge of the hydrodynamic boundary layer over the top planar surface of the compact in the central position, which are in the range of 0.03 to 0.04 ms^{-1} as described in section 3.2.4.1. This corresponds to the increase in dissolution rate from the curved side surface compared to the top planar surface, as described in section 3.1.2.4.

Due to the off-centre positioning of the compacts in positions 1 and 2, there is no consistent flow pattern around the sides of the compacts. As a result, velocity profiles were examined in each direction on each axis. This resulted in four sets of profiles for each of positions 1 and 2, one set each in the positive and negative directions along the x and y axes. Figure 3.22 shows velocity profiles from the curved side surface of the compact in position 1, facing toward the centre of the vessel (negative y direction) and from the other side of the compact facing toward the outer edge

of the vessel (positive y direction). Similar to the profiles from the central position, there was almost 1 mm between the points profiled, with z1 being just above the bottom of the compact, z4 being half way up along the curved side surface and z7 being just below the top of the compact.

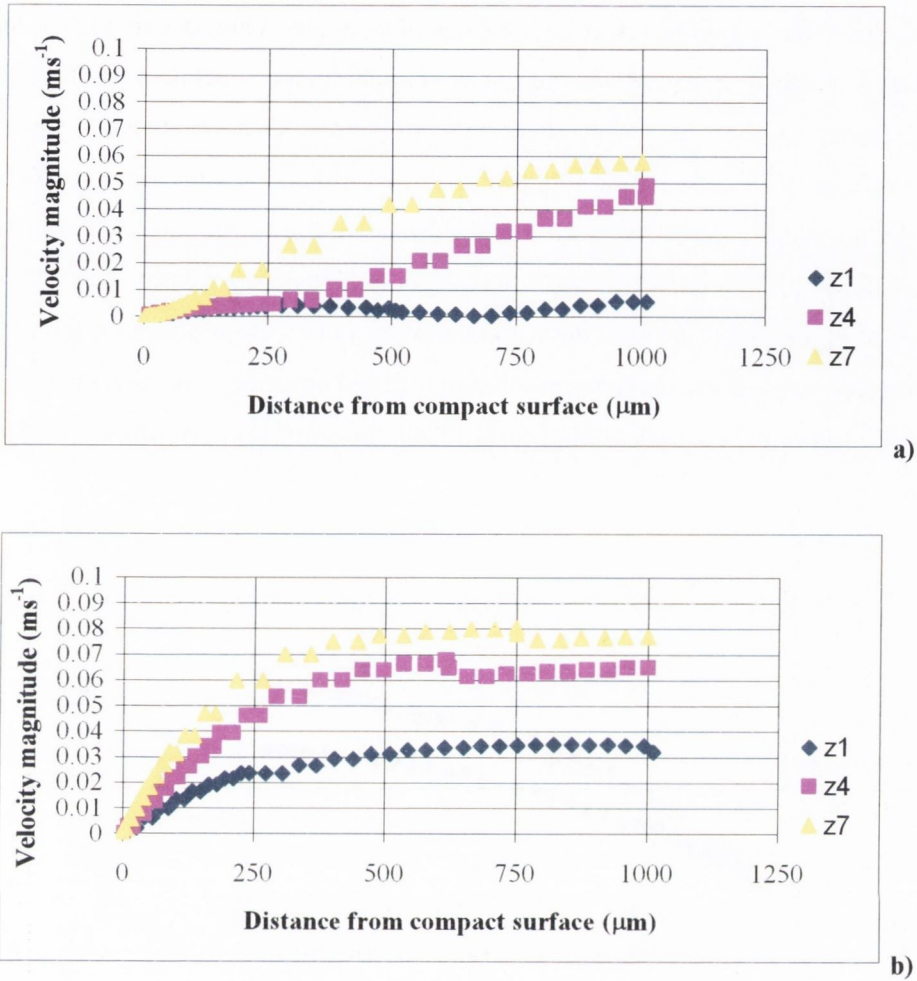


Figure 3.22. CFD-generated velocity magnitude data from profiles extending from the curved side surface in a) the negative direction along the y-axis and b) the positive direction along the y-axis vs. distance from the curved side surface of the compact in position 1, from simulations of 900 ml in the paddle apparatus at 50 rpm.

The corresponding profiles (not shown) from the side of the compact in position 2 are very similar. The profiles in the negative y-axis direction (Figure 3.22.a) correspond to the sloped edge of the compact after one hour of dissolution in position 1 as shown in Figure 3.9.a. It is evident from these velocity profiles that the velocity magnitude towards the bottom of the compact (z1 profile) in this direction is in the region of 0.005 ms⁻¹. The z1 profile increases only marginally before decreasing again, illustrating the presence of low velocity magnitudes due to the adjacent central low velocity vortex region and the presence of the hydrodynamic boundary layer of the wall of the vessel itself. The velocity profiles in the positive direction along the y axis (Figure 3.22.b) illustrate that there is a lower velocity towards the bottom of the compact in this direction also compared to further up the sides of the compact. This lower velocity, however, is in the region of 0.03 to 0.04 ms⁻¹. The photograph of the compact following dissolution in Figure

3.9.a does not show a slope on this side. This would imply that either the difference between velocities at a particular surface must be greater than a certain value to influence the shape of the dissolving surface, or that above a certain value an increase in velocity will not influence the dissolution rate. The possible effect of low velocity regions resulting in higher local solute concentrations, thereby increasing the diffusion boundary layer thickness in this region, may explain the former theory. The effect of increasing agitation intensity above a particular point resulting in no increase in dissolution rate for the same formulation above that point (Shah et al., 1992) has been documented. This may explain the latter theory that above a certain value an increase in velocity at a particular surface will not influence dissolution rate.

The profiles in Figure 3.23 are from the compact in position 2, from points on the compact side surface extending into the surrounding dissolution medium along negative and positive directions of the x axis. Again, the corresponding profiles from the compact in position 1 (not shown) are very similar.

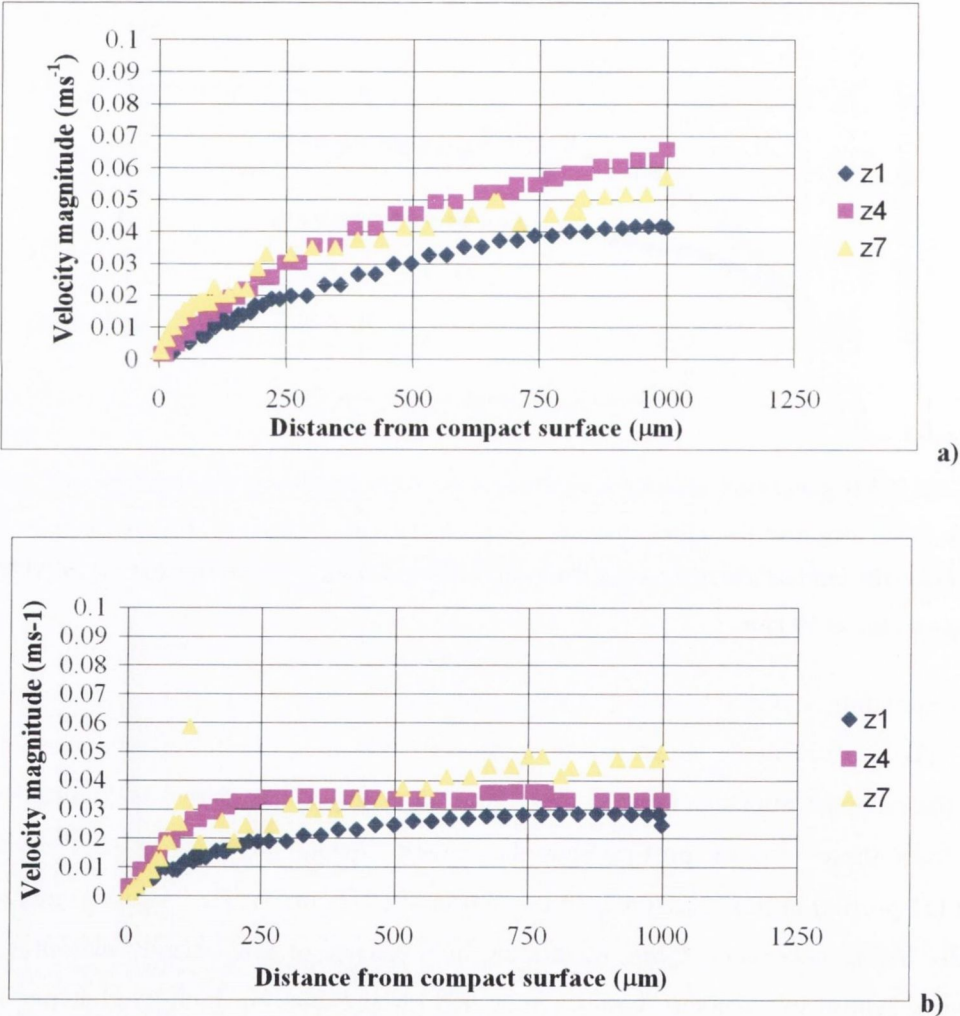


Figure 3.23. CFD-generated velocity magnitude data from profiles extending from the curved side surface in a) the negative direction along the x-axis and b) the positive direction along the x-axis vs. distance from the curved side surface of the compact in position 2, from simulations of 900 ml in the paddle apparatus at 50 rpm.

An interesting feature of the profiles in the negative direction along the x axis is the fact that the z4 profile (that is the profile at half way up the curved side surface) shows higher velocities than the z7 profile, which is near the top of the compact. This feature is also present on the profiles from the compact in position 1. On further investigation of the CFD simulations of the fluid flow field around the compact in position 2, it was found that the fluid flowing radially inward around the compact appears to be slowed by meeting fluid flowing over the top of the compact and pooled at the front of the compact (the side facing the low velocity region in the centre of the vessel). Flow along the side of the compact at the level of the z4 profile point is also slowed in a similar manner, but at a different point to where the profile is plotted, and to a lesser degree. The radial velocity vectors shown in Figure 3.24 are on a vertical plane at the end of the lines along which the velocity profiles in Figure 3.23.a are plotted.

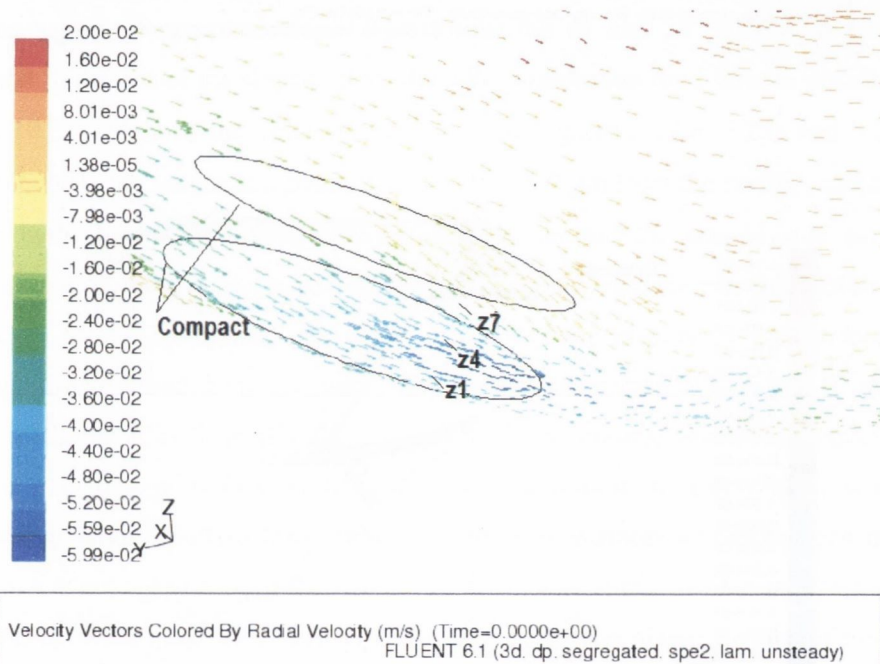


Figure 3.24. CFD-generated vectors coloured by radial velocity on a vertical plane at the end of the lines depicted (z1,z4 and z7), on which the velocity profiles are plotted, from simulations of fluid flow around the compact in position 2, in 900 ml in the paddle apparatus at 50 rpm.

The inward radial velocity is a negative velocity value, and the darker blue velocity around the z4 region can clearly be seen here, indicating a higher inward radial velocity in the z4 region. Figure 3.25.a and 3.25.b show vectors of velocity magnitude on horizontal planes, where the planes are located at the level of the z4 and z7 lines, respectively.

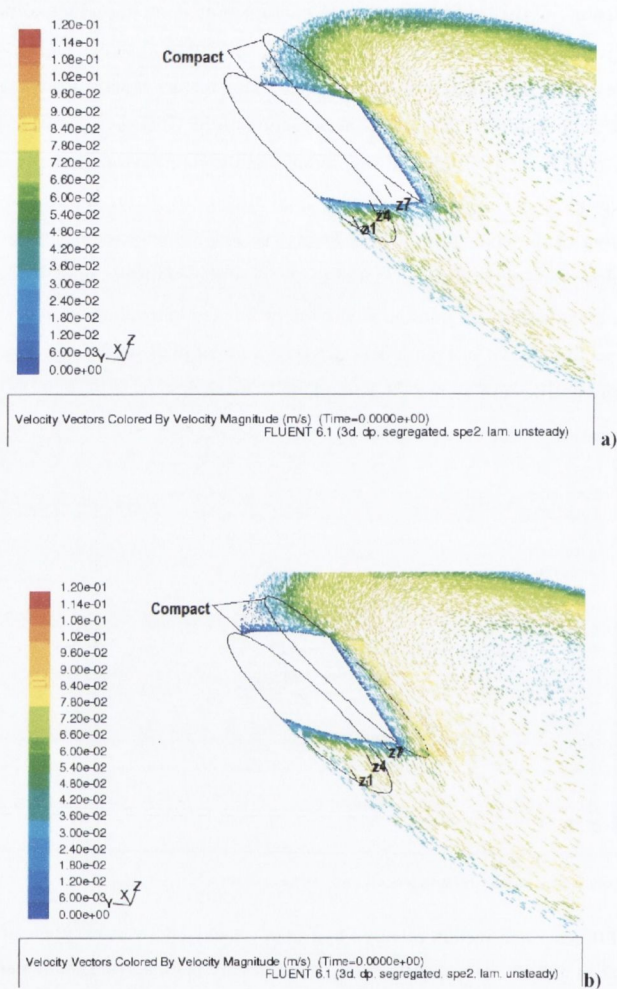


Figure 3.25. CFD-generated vectors coloured by velocity magnitude on a horizontal plane around the compact in position 2 at the level of a) z_4 and b) z_7 , from simulations of fluid flow around the compact in position 2, in 900 ml in the paddle apparatus at 50 rpm.

In this case, as the vectors are coloured by velocity magnitude, the darker the blue colour the lower the overall velocity at this point. It can be seen that the line corresponding to the z_7 profile is mostly in a region where the velocities are in the range of 0.03 to 0.04 ms^{-1} . The line corresponding to the z_4 profile is in a region which reaches velocities in the approximate range of 0.055 to 0.065 ms^{-1} . There is a region of lower velocity on this plane, but it is just beyond where the z_4 profile line lies, towards the centre of the vessel. The nature of the flow in this region is a further illustration of the variable flow that a dosage form may be subject to in the paddle

dissolution apparatus. Additionally, the nature of the graphs in Figure 3.23.a and the explanation for the higher velocity at the z4 profile compared to the z7 profile as detailed, serve to reinforce the fact that velocity data at single points in isolation are not enough to describe overall flow patterns in a complex geometry and flow regime such as that described in the present work. To further complicate matters, the CFD solutions presented here are time-averaged solutions. Strain measurements across a tablet surface in the centre of the vessel has been noted to be a time dependent feature (Kukura et al., 2003), which could imply that there are facets of the local flow around the compacts in the current work which are not shown in the time-averaged solution. Finally, it can be seen from Figure 3.23.b that there is an unusual profile for the z7 point. Although the profile eventually levels off, there appears to be a rapid initial increase in velocity near the surface. This initial velocity increase to velocity values in the region of 0.06 ms^{-1} , compared to values of approximately 0.03 ms^{-1} for the z1 and z4 profiles, is likely to have influenced the formation of the slope at this edge after dissolution for 1 hour in position 2, as seen in Figure 3.10.a. Most of the velocity profiles from Figures 3.22.a, 3.23a and 3.23.b show a levelling of the velocity values at a point around $750 - 1000 \text{ }\mu\text{m}$ from the surface, indicating that in general the hydrodynamic boundary layer is thinner around the curved side surface of the compacts in these positions than above the top planar surface, with the exception of the area of the compact facing the centre of the vessel (the profiles in the negative y axis direction). The velocity magnitude reached, however, is in many cases in the region of 0.06 to 0.07 ms^{-1} , whereas in the case of the profiles from the top surfaces of the compacts, velocities frequently reached values of 0.08 to 0.09 ms^{-1} before levelling off. The dissolution rate from the top surfaces of the compacts was generally slightly lower than from the side surfaces as can be seen in Table 3.3. This difference is not significant in the case of the top planar surface of the compact in position 2 ($p > 0.05$), and is of marginal significance in the case of the top planar surface of the compact in position 1 ($p > 0.045$). It is clear from these results that it is both the overall thickness of the hydrodynamic boundary layer and the velocity gradient encountered within this layer which influences dissolution rate. This supports the general theory (Bircumshaw and Riddiford, 1952) that a surface that is exposed to increased velocity should have a corresponding decrease in the thickness of the effective diffusion boundary layer, but that this relationship is dependent on the geometry of the system. Furthermore the evidence of such wide variations in velocity around each compact surface and the different dissolution rates from both the different surfaces and from different regions of the same surface support the concept (Grijseels et al., 1981) that the thickness of the effective diffusion layer varies substantially along a surface.

3.4 CFD simulations of hydrodynamics within the paddle dissolution apparatus at different agitation rates.

3.4.1 Validation

The simulation of the hydrodynamics within the paddle apparatus at 50 rpm, containing no compact, was validated by comparing the velocities with previously published laser Doppler velocimetry data, as described in section 2.2.1.1.1. The graphs used in the comparisons are included in Appendix 6. Data from different regions within the vessel at agitation rates from 25 rpm to 200 rpm, in increments of 25 rpm, were also compared to ultrasound-pulse-echo (UPE) velocity data (Diebold and Dressman, 2001). The planes on which the tangential (s1-s3) and axial (o1-o2) CFD and UPE velocity data were compared are detailed in Figure 3.26, superimposed on the contours of velocity magnitude from the 50 rpm flow field on a vertical plane through $y=0$.

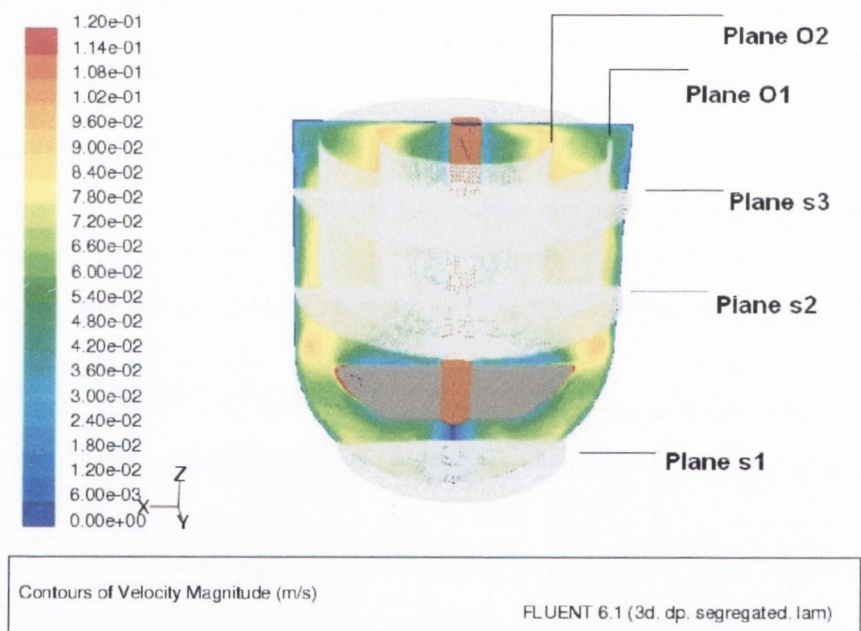


Figure 3.26. Planes on which the tangential (s1-s3) and axial (o1-o2) previously published UPE velocity data was recorded (Diebold and Dressman, 2001), superimposed on the contours of velocity magnitude (ms^{-1}) on a plane through $y=0$ from the 50 rpm flow field solution, in 900 ml in the paddle apparatus.

The simulated tangential velocity data from the s1-s3 planes at agitation rates of 25 to 200 rpm is plotted against the data recorded using the UPE method in Figure 3.27. It can be seen that the error bars, representing the standard deviations from the UPE measurements, do not always cross the line of identity, implying that the CFD data does not always fall within the range of the standard deviations from the UPE data. Overall, however, there was a good quantitative

agreement between the UPE measured velocity data and the data from CFD simulations. This was despite the fact that the CFD data was from a time-averaged solution whereas the UPE method recorded maximum velocity data.

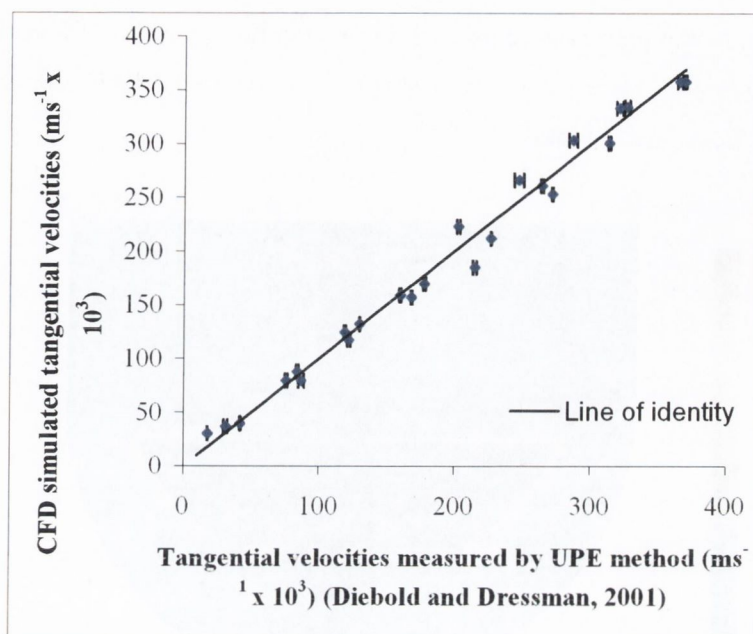
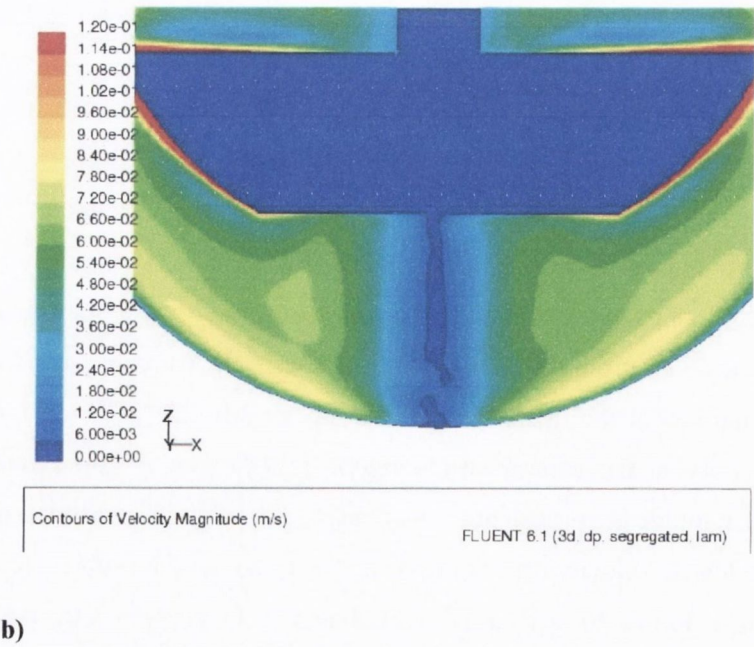
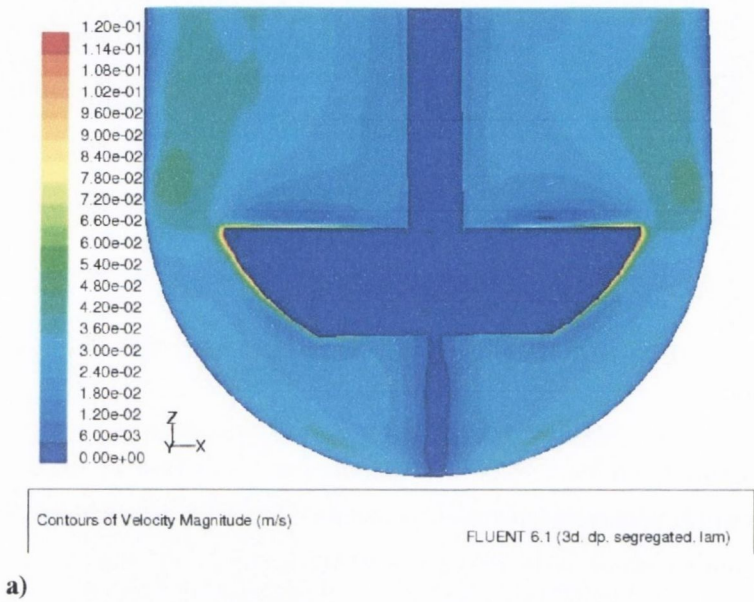


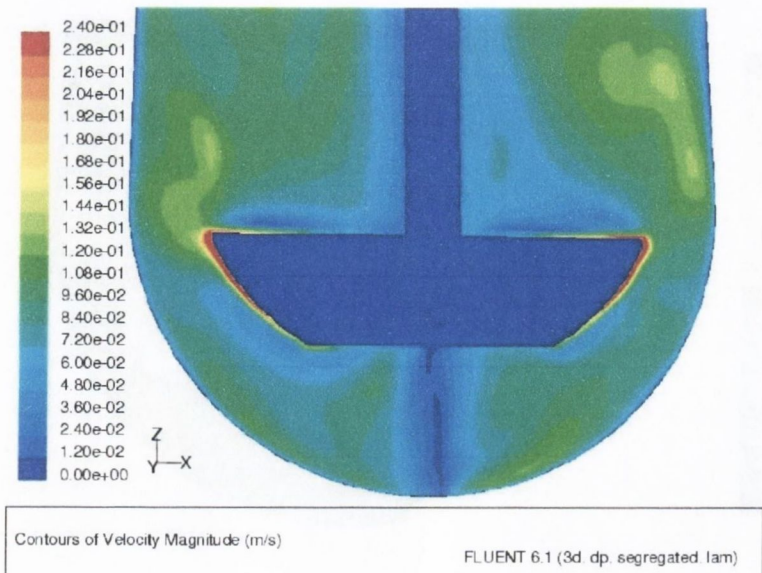
Figure 3.27. Tangential velocities from CFD simulations calculated at the UPE measurement locations, on planes s1-s3, vs. tangential velocities measured by UPE (Diebold and Dressman, 2001). Data is taken from rotation speeds of 25-200 rpm in 900 ml in the paddle apparatus.

3.4.2 Hydrodynamic features in the base of the vessel.

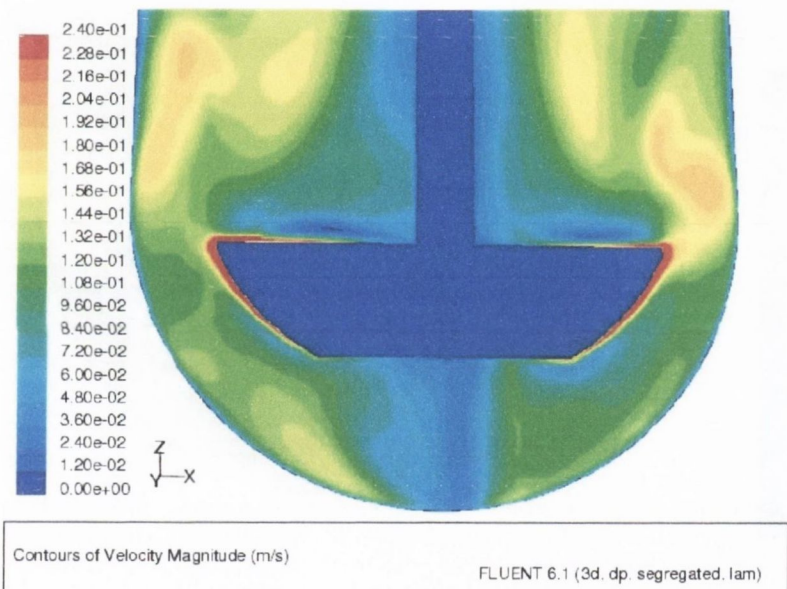
Contours of velocity magnitude in the lower region of the vessel, at rotation speeds of 25 to 200 rpm, on a vertical plane through $y=0$, are shown in Figure 3.28 a-h. In order to examine the contours at a similar level of detail at each rotation speed, the scale of velocity magnitude used to display the contours was increased at 75, 125 and 175 rpm. It is clear from the contours that there is a consistent feature of a low velocity area beneath the paddle at the centre of the vessel at each rotation speed. The radial extent of this region is greater on the plane from the 25 rpm simulation than the 50 rpm simulation. The fragmented nature of the central vortex region at 50 rpm, illustrated in Figure 3.28.b, suggests that it is a dynamic rather than a static feature. Although increasing the display scale from $0\text{--}0.12 \text{ ms}^{-1}$ to $0\text{--}0.24 \text{ ms}^{-1}$ for the contours of 75 and 100 rpm facilitates the comparison of the hydrodynamic features at different agitation rates, it should be noted that the velocity in the central vortex region at 100 rpm is approximately 0.02 ms^{-1} . Velocities of this magnitude are prevalent throughout the vessel at 25 rpm, implying that a dosage form located in the lowest velocity central region at 100 rpm would be subject to velocities of the same magnitude as a dosage form located in the higher velocity off-centre regions at 25 rpm. Considering dissolution rates as a function of stirring rate without reference to dosage form location could therefore be misleading. Another feature which should be noted is the fluid flow at

either side of the centre. At both 25 and 50 rpm this is symmetrical in nature, but this no longer appears to be the case at higher agitation rates. When interpreting these contour images, it should be recalled that the data is from time-averaged simulations. The lack of symmetry in the fluid flow extending from the centre and the uneven nature of the central vortex are most likely to be the result of the more complex flow regimes at higher rotation rates. Additionally, the increased difficulty with increasing agitation speed in obtaining a converged CFD solution will promote inaccuracies in the flow field solution.

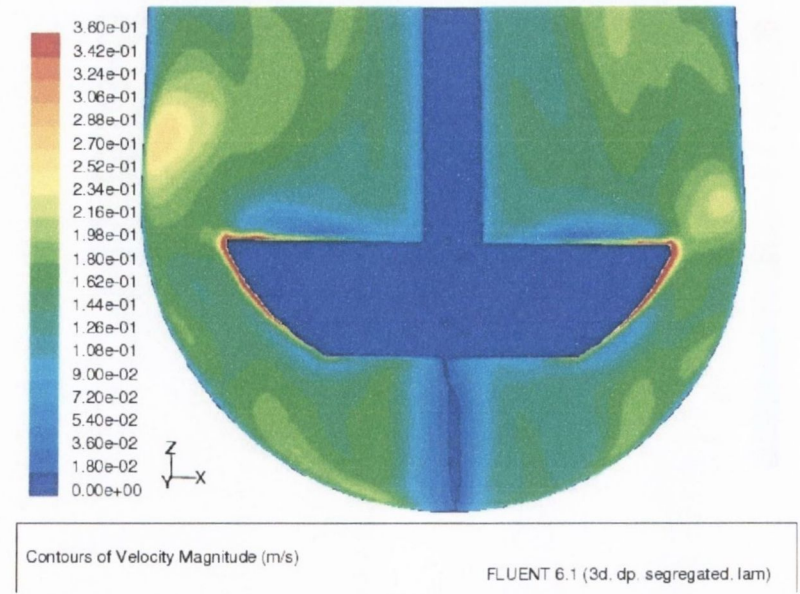




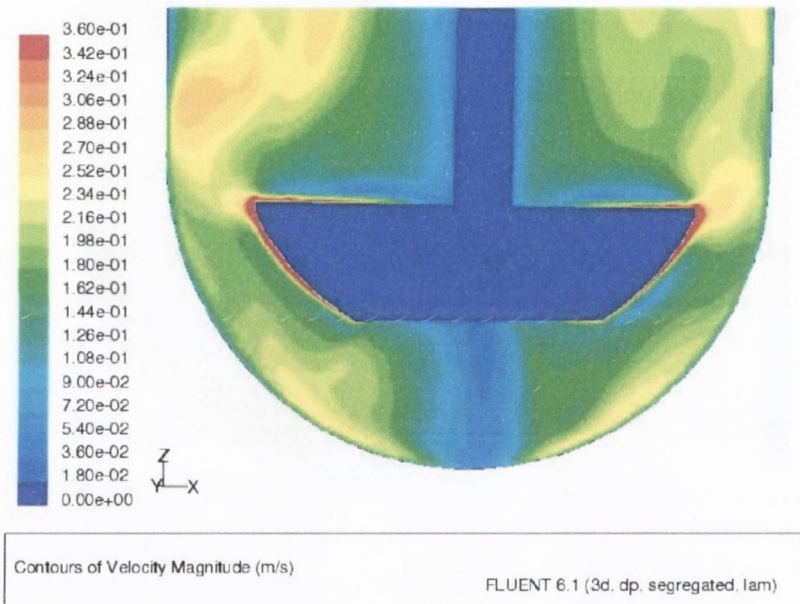
c)



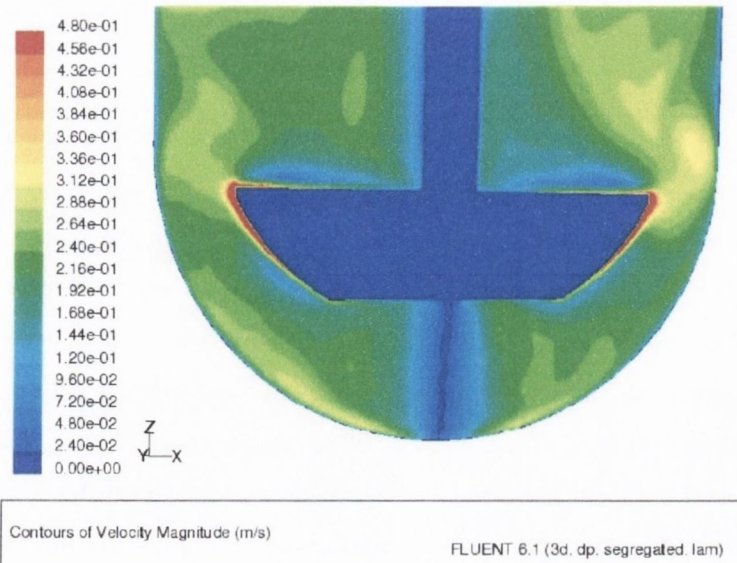
d)



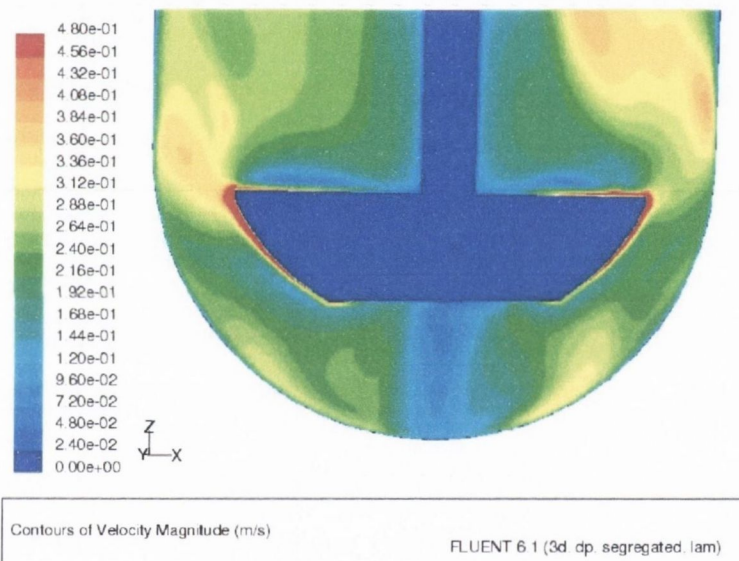
e)



f)



g)



h)

Figure 3.28 CFD-generated contours of velocity magnitude (ms^{-1}) on a vertical plane through $y=0$ at rotation speeds of a) 25 rpm, b) 50 rpm, c) 75 rpm, d) 100 rpm, e) 125 rpm, f) 150 rpm, g) 175 rpm, h) 200 rpm, from simulations of 900 ml in the paddle apparatus.

Regardless of the agitation speed used, however, it is evident that the hydrodynamics at the base of the vessel are highly variable in nature, which will affect the variability and discriminatory ability of the dissolution test.

3.5 Conclusions.

It can be concluded that the location of a dosage form within the vessel of the paddle dissolution apparatus can have a significant effect on the dissolution rate. The dissolution rate is lowest from any surface of a dosage form located at the centre of the base of the vessel compared to that located off-centre, but there is a greater increase in dissolution rate from the top planar surface than from the curved side surface when a compact is moved from the centre to an off-centre position. The magnitude of the increase in dissolution rate is also dependent on the geometry and aspect ratio of a cylindrical dosage form. The greatest variation in dissolution rate occurs between the centre of the vessel base and immediately off-centre, with no significant increase in rate when a dosage form is located increasingly further from the centre, at 50 rpm. Fixing the location of a dissolving cylindrical compact decreases variability compared to an unfixed compact, regardless of the location the compact is affixed to.

CFD can be successfully used to model fluid flow around compacts in different locations in the vessel, resulting in hydrodynamic data which can be used to gain an insight into variation in dissolution rates. The lower velocity region above the compact in the central position corresponds to the lower dissolution rate from this position. The velocity in the region of the dissolving compact can therefore be directly related to the mass transfer rate. CFD can also be used to predict regions of a surface of a non-disintegrating dosage form which may undergo preferential dissolution and erosion due to the nature of the local hydrodynamics to which different surface regions are exposed. Similarly, local hydrodynamic data generated by CFD can be used to determine the shape of the hydrodynamic boundary layer around a dissolving surface. The shape of this layer has been shown to be highly complex within the systems modelled due to the complex nature of the rotating flow and the shape and location of the compacts within the flow. Variability in dissolution testing, therefore, will arise not only from overall hydrodynamic variation with dosage form location, but also unpredictable hydrodynamic variation within regions of the surface of a dosage form.

When investigating the hydrodynamics within the paddle apparatus at different agitation rates, it is evident from CFD data that, from 25 to 200 rpm, there is a consistent feature of a low velocity region in the centre of the vessel beneath the paddle. The actual velocity within this region, however, can only be considered to be low in relation to the velocity magnitudes within the rest of the vessel at that rotation speed. As the rotation speed increases, the flow becomes more complex in the lower region of the vessel, and any resulting time-dependent hydrodynamic features within the flow field will only be approximated by a time-averaged model. A dosage form will, however, be exposed to variable velocities within the vessel regardless of rotation speed. The effect of this variation on dissolution rate at a particular agitation rate is likely to be specific to the dosage form being tested.

4.0

Mass transfer predictions from dissolving compacts in the paddle dissolution apparatus.

4.1 Introduction

In this section, the effective diffusion layer including diffusion in all directions and convection near to the surface is modelled within the limits of the mesh refinement. As expected, (Grijseels et al., 1981) the diffusion boundary layer varies around each surface and in any area of any particular surface.

Additionally, there have been many models of dissolution based on relating mass transfer rates to agitation rather than the thickness of the diffusion boundary layer (Grijseels et al., 1981). Prior to the use of CFD in this field, however, it was only feasible to relate mass transfer to the known rate of agitation of the stirrer, the dissolving surface itself (if it was being agitated) or velocity data determined from velocimetric methods such as laser Doppler velocimetry, which, though providing data on the flow field, yields a much more sparse range of data than CFD. The objectives of this section of the work are

- to attempt to utilise the simulated diffusion layer to estimate an approximate value of the diffusion boundary layer thickness. This will be used to estimate mass transfer from compacts in various positions, of different dimensions and different materials;
- to utilise velocity and shear rate data in the vicinity of the compound surface, generated by CFD, to predict the rate of mass transfer. These predictions can be compared to models using a function of the agitation rate to predict dissolution rates. It can be then determined whether CFD generated data can yield accurate predictions of dissolution rates from different surfaces of compacts in different locations within the same apparatus and under the same dissolution conditions.

4.2 Predicting mass transfer through simulation of the diffusion boundary layer.

4.2.1 Use of profiles of “tracer” fraction as a function of distance from compact surface to illustrate simulation steady state and to determine the “edge” of the diffusion boundary layer.

Steady state.

Figures 4.1 and 4.2 shows a series of plots of mass fraction of tracer against distance from compact surface at 2 second intervals up to 60 timesteps, or 12 seconds. The plots do not vary with time at 60 timesteps, (in fact, there is little variation beyond the 10 time step point) and simulations were run for this length of time. Steady state was achieved by this point for all of the surfaces in each position. The “double” distance values for each value of mass fraction of tracer, evident in Figure 4.2, is characteristic for all of the plots from the off-centre compacts. As an unstructured mesh was used for these models, each line from which a profile is written obviously passes through two different mesh elements which are allocated different spatial (distance) values, but which record the same value of tracer.

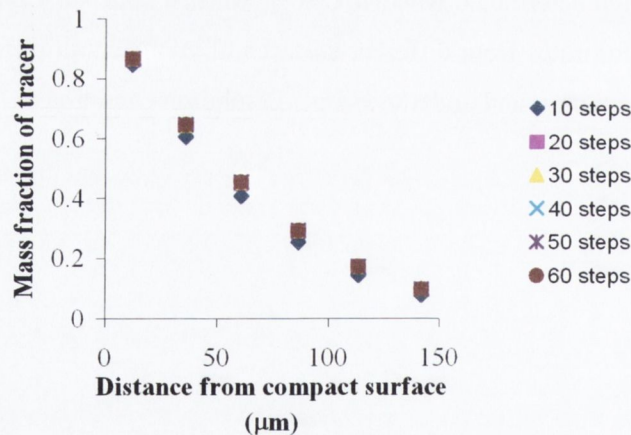


Figure 4.1. Mass fraction of tracer vs. distance from compact surface on line y=3 from the salicylic acid centre position simulation. Data generated from CFD simulations of diffusion of tracer through a flow field of 900 ml in the paddle apparatus at 50 rpm.

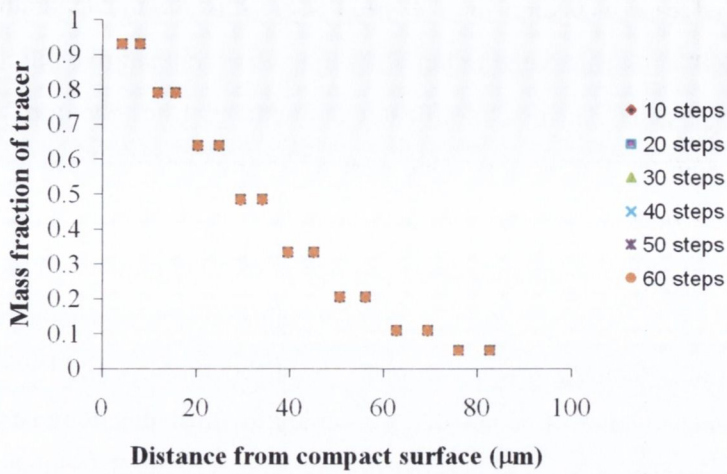


Figure 4.2. Mass fraction of tracer vs. distance from compact surface on line y=3 from benzoic acid position 2 simulation. Data generated from CFD simulations of diffusion of tracer through a flow field of 900 ml in the paddle apparatus at 50 rpm.

Determination of a cut-off value to mark the “edge” of the diffusion boundary layer.

It was found that the point at which the fraction of tracer reached approximately 10% of its value at the side surface of the compact in the central position resulted in a value for “*h*” comparable to the experimental results. The decrease in mass fraction of tracer from the central side surface for CFD models with four different boundary conditions (as detailed in section 4.2.2) are shown in Table 4.1.

Boundary condition	% tracer defining “edge” of boundary layer
Top wall stationary no shear	12.56
Top wall symmetry	11.88
Top wall stationary	9.54
Periodic model	6.70
Average	10.17

Table 4.1. The % tracer resulting in a calculated boundary layer thickness which gives a dissolution rate equal to the experimentally determined rate from the curved side surface, using equation 2.1, from models of 900 ml in the paddle dissolution apparatus at 50 rpm, with the benzoic acid compact in the central position, using different boundary conditions.

The thickness of the diffusion boundary layer using a 10% cut-off value is comparable to that calculated using the equation proposed by Levich for diffusion boundary layer thickness:

$$h = 1.61D^{1/3} \nu^{1/6} \omega^{-1/2}$$

Equation 4.1

where the value used for ω is taken from the speed of the stirrer in the apparatus. Using equation 4.1, the thickness of “ h ” is calculated to be 70.88 μm . For comparative purposes, the values of “ h ” calculated from CFD convective-diffusion simulations from the top planar surfaces in positions 1 and 2 using the 10% cut off value were 67.75 μm and 73.37 μm respectively. Thus it is apparent that the thickness of the diffusion boundary layer at which the fraction of tracer decreases to 0.1 of its value at the dissolving surface is of a magnitude appropriate for use with equation 2.1. The problem of the infinite boundary layer has been encountered previously in numerical analysis of a rotating disk in stationary fluid (Southard et al., 1992). A value of “ h ” was calculated using equation 4.1, however, in order to fulfil the boundary conditions at an infinite distance from the source, an optimal thickness of $3h$ was determined. In the current work, therefore, the value of h at which the mass fraction of tracer had decreased to 0.1 of its value at the dissolving surface was used when predicting mass transfer rates using equation 2.1.

4.2.2 Dissolution rate predictions - Central Position

As there is no accurate method to define the air-water interface at the top of the vessel in FluentTM (i.e. where the surface of the fluid in the vessel meets the air in the surrounding environment), a number of different boundary conditions were applied to this surface. The validations of the vessel containing no compact and the vessels containing the compacts in different positions where the compact volumes were defined as fluid (as described in section 2.2.1) were carried out satisfactorily with this surface defined as a solid stationary wall (the default option). It was anticipated that this may impose a degree of drag on the fluid, and therefore two other options were investigated for the compact in the central position, “no shear” wall and symmetry conditions.

Results obtained from a model solved using periodic boundary conditions were also examined.

4.2.2.1 The effect of different boundary conditions on mass transfer predictions from the central position.

“No shear” wall.

This option consisted of defining the surface as a wall, which was stationary relative to the adjacent cells but had a specified shear stress of zero.

Symmetry conditions.

Symmetry conditions are used when a system which is symmetrical (symmetrical geometry and symmetrical fluid flow) is being modelled. As it is symmetrical, only one half needs to be modelled and the symmetry condition is attached to the plane of symmetry. This is obviously not

the case at this air-water interface, however it may also be used to model conditions of zero shear slip walls in viscous flows (FluentTM User's Guide, 2003).

Symmetry boundary conditions may be summarised as follows (Fluent^{TMF} User's Guide, 2003):

- Zero normal velocity at a symmetry plane
- Zero normal gradients of all variables at a symmetry plane

A disadvantage is that symmetry conditions are applied to all equations.

Periodic boundary.

Periodic boundary conditions may be applied if the physical geometry of interest and the expected pattern of fluid flow have a periodically repeating nature. In this case mass transfer data were calculated from a situation where only half of the vessel was modelled (with the geometry divided vertically through the centre as the geometry is symmetrical through this plane although the flow is not). In this situation the air-water interface was defined as a stationary wall. Due to the rotation of the paddle the rotating flow has a periodically repeating nature. Periodic modelling is further described in section 2.2.1.2, as applied to the basket apparatus.

Table 4.2 shows the results of the mass transfer predictions from the compact in the central position with the air-water interface defined as a wall stationary in the absolute reference frame, a wall stationary in the relative frame with zero specified shear, with symmetry conditions attached and also the results from the model with periodic boundaries (air-water interface as wall stationary in absolute frame).

Air-water interface boundary condition:	Surface	CFD prediction (mg hour ⁻¹)	Experimental Rate (mg hour ⁻¹)
Wall stationary in absolute frame	Centre Top	22.10	35.80 ± 1.49
	Centre Side	41.46	40.48 ± 0.84
	Whole compact (top and side)	63.56	76.27 ± 3.78
Wall stationary in relative frame with zero specified shear:	Centre Top	18.30	35.80 ± 1.49
	Centre Side	36.58	40.48 ± 0.84
	Whole compact (top and side)	54.88	76.27 ± 3.78
Symmetry conditions:	Centre Top	22.44	35.80 ± 1.49
	Centre Side	37.56	40.48 ± 0.84
	Whole compact (top and side)	60.00	76.27 ± 3.78
Periodic model:	Centre Top	19.85	35.80 ± 1.49
	Centre Side	47.67	40.48 ± 0.84
	Whole compact (top and side)	67.52	76.27 ± 3.78

Table 4.2 Mass transfer predictions for the benzoic acid compact in the central position from CFD simulations using different boundary conditions for the air-water interface, and from a simulation using periodic boundary conditions, of 900 ml in the paddle apparatus at 50 rpm.

Although mass transfer predictions from the side surface of the compacts correlate reasonably well in all cases with experimental data, the top planar surface predictions are a large underestimation of the experimental rate in all cases. This is thought to be due mainly to the fact that the CFD simulations show a very high concentration of tracer at the centre of the top planar surface of the compact (visible in Figure 4.3), and a very thick boundary layer is therefore calculated at the centre of this surface. This is presumably due to the tracer entering the “dead space” of fluid above the compact (visible in Figures 3.6 and 3.7.d) and therefore not being “swept away” by the motion of the surrounding fluid.

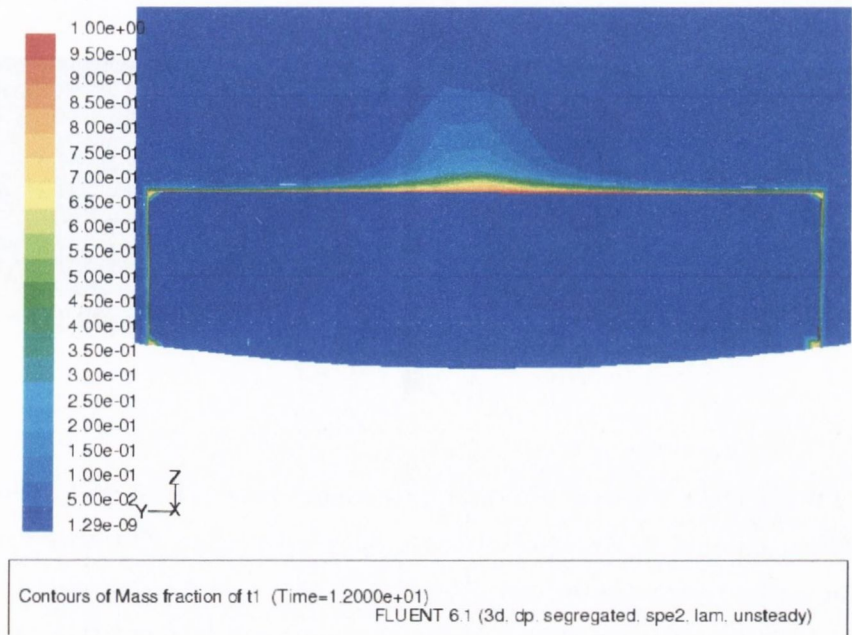


Figure 4.3. Distribution of tracer under convective-diffusion CFD-simulations from the surface of the compact in the central position in 900 ml in the paddle apparatus at 50 rpm. The area of high concentration at the centre of the top surface is visible.

It is possible, however, that this vortex which appears to be directly at the centre of the compact surface is actually a dynamic feature. In other words, that the region of the compact surface which was exposed to this very low fluid velocity was altered in a time dependent nature but was at all times at some point near the centre of the top planar surface. The following pictures in Figures 4.4 and 4.5 are taken from flow field solutions with a stationary wall and symmetry condition applied to the air-water interface, respectively. These are examples of how the nature of this central vortex region is altered in different flow field solutions with respect to its position on the top planar surface.

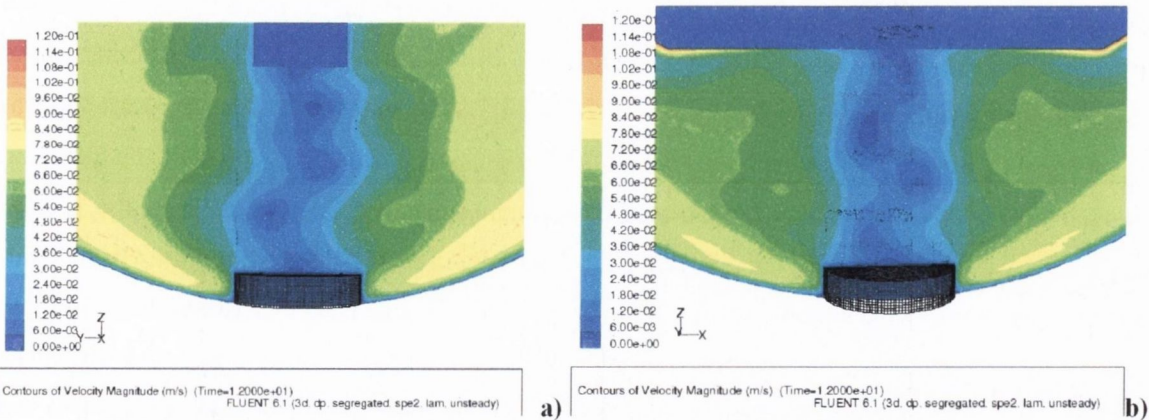


Figure 4.4. CFD-generated contours of velocity magnitude from a flow field solution, with a stationary wall condition applied to the air-water interface, showing the nature of the vortex region on the top planar surface of the compact in the central position on a) a vertical 2-dimensional plane at $x=0$ and b) a vertical 2-dimensional plane at $y=0$. Data taken from simulations of 900 ml in 0.1M HCl in the paddle apparatus at 50 rpm.

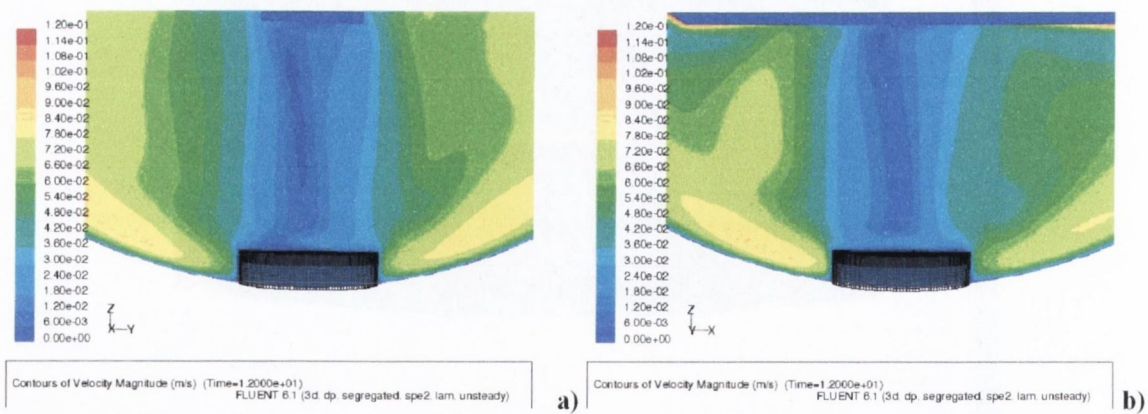


Figure 4.5. CFD-generated contours of velocity magnitude from a flow field solution, with a symmetry condition applied to the air-water interface, showing the nature of the vortex region on the top planar surface of the compact in the central position on a) a vertical 2-dimensional plane at $x=0$ and b) a vertical 2-dimensional plane at $y=0$. Data taken from simulations of 900 ml in 0.1M HCl in the paddle apparatus at 50 rpm.

From the results in Table 4.2 it is apparent that defining the air-water interface as a wall stationary in the absolute frame gives the most accurate result when predicting mass transfer rates from the compact in the central position. This was the condition used also with the periodic model. Although the periodic model gives a better prediction overall for the combined top and sides, the prediction for the side surface alone is not as accurate as the results from the entire model with no periodic boundary (117.76% vs. 102.42% of the experimental rate for the periodic vs. standard model respectively). In addition, as can be seen from Table 4.2 the periodic model gives a lower prediction of mass transfer from the top planar surface than the standard model. In summary use of the standard entire model with no periodic boundaries, with the air-water interface defined as a stationary wall in the absolute frame, gives the most accurate results for mass transfer prediction from the compact in the central position. An issue which must be considered in terms of the predicted dissolution rates from the top planar surface of the compact in the central position is that of natural convection. The 10% cut-off value to determine the effective “edge” of the diffusion boundary layer, which is in fact a feature of theoretically infinite thickness, described in section 2.2.1.4.2., was established by correlation with the experimental dissolution rate data. Any contribution from natural convection (induced by density differences between the saturated solution and the bulk medium) to the dissolution rate is therefore already accounted for in the situation of the central side surface, where there is continuous tangential flow adjacent to the dissolving surface. As a result, although there is no simulated density difference between the tracer and the bulk dissolution medium in the CFD simulations, in reality the more dense saturated solution at the dissolving surface would be removed by the bulk flow convection. At the top planar surface, however, the lack of significant fluid motion, particularly at the centre of the dissolving surface, could result in the pooling of the more dense saturated solution. In this

situation the density difference between the bulk flow and the saturated solution could affect the local hydrodynamics and consequently the dissolution rate from this surface. The incorporation of the mass dissolved in stagnant fluid from the top planar surface with the predicted dissolution rate using the simulated diffusion boundary layer is investigated further in section 5.7.

4.2.2.2 The effect of prolonged dissolution in the central position on the shape of the top planar surface of a benzoic acid compact.

Although no “peak” was noted on the top planar surface of the compact in the central position after dissolution for 1 hour, the fact that all CFD solutions simulated a much thicker diffusion layer at the centre of this top planar surface prompted investigation of the shape of this top planar surface after a prolonged dissolution. It was noted after 5 hours of dissolution in the central position a “peak” did develop in the centre of the top planar surface of a compact in this position, as can be seen in the photograph in Figure 4.6.



Figure 4.6. Photograph of a benzoic acid compact after 5 hours dissolution in the central position. The “peak” which developed can be seen in the centre of the top planar surface.

The development of the peak would suggest that, although the dissolution profiles from the top planar surface in the central position exhibited zero order linear dissolution rates over the hour that they were examined (as shown in Figure 3.2), dissolution from this surface does not remain uniform over a longer time period. As the dissolution rate obviously decreases with distance from the edge of the surface to enable formation of the central peak, the rate from this surface must change with time. The changing surface area with the formation of the peak, and the extent of the surface exposed to different velocity magnitudes will influence the dissolution rate. The rate predicted from the CFD diffusion boundary layer simulations are possibly closer to a rate from this surface at a later time point, however if the experimental rate were decreasing with time then this would be an instantaneous or “snapshot” prediction only.

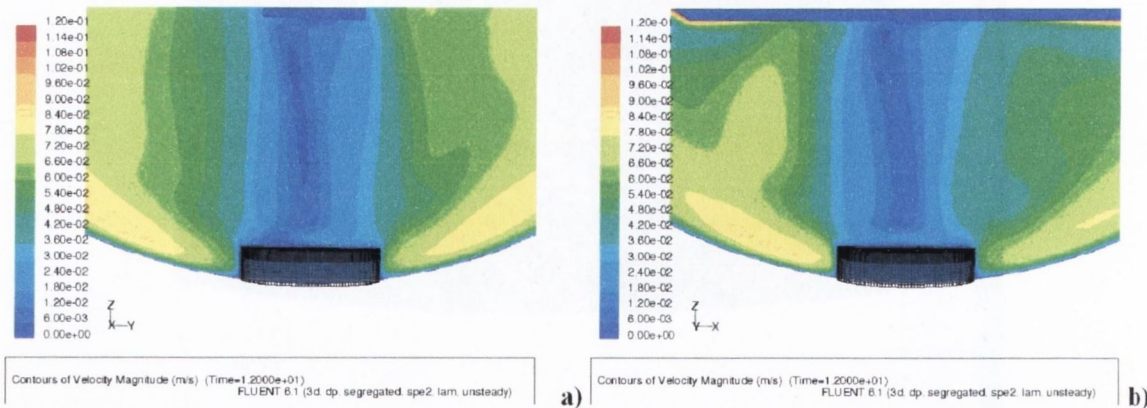


Figure 4.5. CFD-generated contours of velocity magnitude from a flow field solution, with a symmetry condition applied to the air-water interface, showing the nature of the vortex region on the top planar surface of the compact in the central position on a) a vertical 2-dimensional plane at $x=0$ and b) a vertical 2-dimensional plane at $y=0$. Data taken from simulations of 900 ml in 0.1M HCl in the paddle apparatus at 50 rpm.

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4.2.2.3 Comparison with predicted rate for a salicylic acid compact.

The dissolution profile of a 1-hour dissolution of a cylindrical 500 mg compact of salicylic acid in the central position is shown in Figure 4.7.

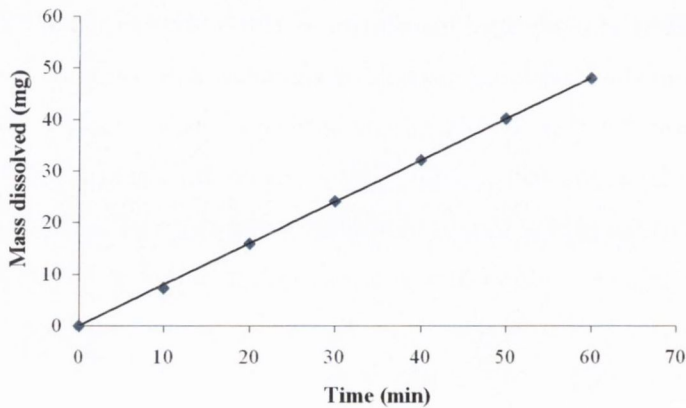


Figure 4.7. Mass of salicylic acid dissolved (mg) vs. time (min) from a compact located in the central position in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

The predicted dissolution rate from a compact in the central position using the solubility and diffusion coefficient of salicylic acid in the CFD diffusion simulation is shown in Table 4.3. The predicted rate is compared to the dissolution rate with a correction applied for dissolution from the lower planar surface (assuming the same % dissolved for this surface as the benzoic acid compacts).

Surface	CFD Predicted rate (mg hour ⁻¹)	Actual rate whole compact (mg hour ⁻¹)	Actual rate adjusted for dissolution from lower surface (mg hour ⁻¹)
Top surface	12.78		
Side surface	22.20		
Whole compact	34.98	48.15 ± 2.79	45.19 ± 2.79

Table 4.3. Comparison of CFD predicted dissolution rates and actual dissolution rates for salicylic acid compacts in the central position in the paddle apparatus in 900 ml 0.1M HCl at 50 rpm; CFD-generated data from simulations of 900 ml in the paddle apparatus at 50 rpm.

The CFD predicted dissolution rate of salicylic acid expressed as % of the actual dissolution rate (approximately 77%) corrected for dissolution from the bottom surface, compares well to the value for the predicted dissolution rate of benzoic acid under the same experimental conditions (83.33% of experimental dissolution rate) (Table 4.2). This method for simulating diffusion and therefore dissolution using CFD solutions is of comparable accuracy for dissolution of two different diffusion-controlled compounds.

4.2.3 Predicting dissolution rates from compacts located in off-centre positions.

Although optimal boundary conditions were described in section 4.2.2.1 for predicting mass transfer from the compact in the central position, these cannot be taken to be optimal conditions for predicting mass transfer from any of the off-centre positions as the model used to simulate the fluid flow is quite different. As described in section 2.2.1.1.2., the model for the compact in the central position used a single rotating reference frame, whereas that for the off-centre positions used a multiple reference frame. This model incorporates the use of two fluid domains with data being transferred between the two. The effect of the boundary condition applied to the air-water interface is therefore not necessarily predictable from the known effect of each boundary condition in the model with the compact in the central position. As a result two boundary conditions were investigated, that of the interface defined as a wall stationary in the absolute frame (which gave the best results from the compact in the central position and was also the condition used to validate all of the models), and a symmetry condition being applied to the interface. The mass transfer predictions from the off-centre benzoic acid compacts are shown in Tables 4.4 and 4.5 for compacts in positions 1 and 2 respectively. The experimental dissolution data from each surface in each position is also presented, with the data from the whole compacts adjusted to account for dissolution from the lower planar surface.

As can be seen from Table 4.4, the model with the symmetry condition applied gives slightly better results overall for position 1, as predictions from each surface fall within 20% of the experimental value. It should be noted that these CFD predictions apply to dissolution from the compact at the beginning of dissolution, when the surface area is equivalent to that in the model. Although the surface area remains relatively constant in the central position after 1 hour of dissolution, the variation in the hydrodynamic environment in the region of the off-centre compacts causes the compact to change shape during dissolution, as outlined in section 3.3.4. The predicted dissolution results for both air-water interface conditions in position 2 are very similar as shown in Table 4.5.

Air-Water interface boundary condition	Surface	CFD Prediction (mg hour ⁻¹)	Experimental rate (mg hour ⁻¹)
Wall as stationary in absolute frame	Top planar surface	38.56	48.94 ± 2.07
	Side surface	48.11	52.21 ± 3.14
	Top and side surfaces combined (position 1)	86.67	99.12 ± 4.98
Symmetry condition applied	Top planar surface	39.79	48.94 ± 2.07
	Side surface	51.93	52.21 ± 3.14
	Top and side surfaces combined (position 1)	91.72	99.12 ± 4.98

Table 4.4. Comparison of CFD predicted vs. actual dissolution rates from surfaces of benzoic acid compacts in position 1, using different boundary conditions for the air-water interface; CFD-generated data from simulations of 900 ml in the paddle apparatus at 50 rpm.

Air-Water interface boundary condition	Surface	CFD Prediction (mg hour ⁻¹)	Experimental rate (mg hour ⁻¹)
Wall as stationary in absolute frame	Top planar surface	36.23	50.48 ± 3.17
	Side surface	55.80	51.50 ± 2.80
	Top and side surfaces combined (position 2)	92.03	95.56 ± 2.80
Symmetry condition applied	Top planar surface	36.74	50.48 ± 3.17
	Side surface	57.52	51.50 ± 2.80
	Top and side surfaces combined (position 2)	94.26	95.56 ± 2.80

Table 4.5. Comparison of CFD predicted vs. actual dissolution rates from surfaces of benzoic acid compacts in position 2, using different boundary conditions for the air-water interface; CFD-generated data from simulations of 900 ml in the paddle apparatus at 50 rpm.

When plotting the concentration of “tracer” against distance from the compact surface for the profiles along the positive x axis from the side surface of the compact in position 2, it was observed that for both simulations the curve was a very poor fit ($R^2= 0.52$ for wall condition, 0.47 for symmetry condition models) for the z8 (at the top of the side surface) profile, as shown in Figure 4.8. The equation for this curve also resulted in the calculation of a much thinner diffusion boundary layer at this point than anywhere else on the compact surface. This was in the region

where the compact side surface was sloped during dissolution as seen in the photograph in Figure 3.10.a. The solution to the fluid flow in this region resulted in the very first points plotted having a low fraction of tracer. This may also be influenced by the shape of the mesh at this point as each mesh cell only holds one value, and the calculated distance from the compact surface does not account for the differing width in this direction of each mesh cell. As a result of the poor fit of this z8 profile, an average rate was calculated from the side surface omitting this point. This rate was 47.85 and 46.53 mg hour⁻¹ for the symmetry and stationary wall models, respectively. A graph of “β values” against distance from the bottom of the side surface is shown in Figure 4.8. The bottom of the side surface is at z1 and the top is at z8. The “β value” is the value of “β” when the curve is fitted to the mass fraction of tracer vs. distance from compact surface, as described in section 2.2.1.4.2. The equation of the curve is of the form $Y=e^{-\beta X}$, where Y is the mass fraction of tracer and X is the distance from the compact surface. Therefore “β” is the function that varies with each profile to describe the varying thickness of the hydrodynamic boundary layer.

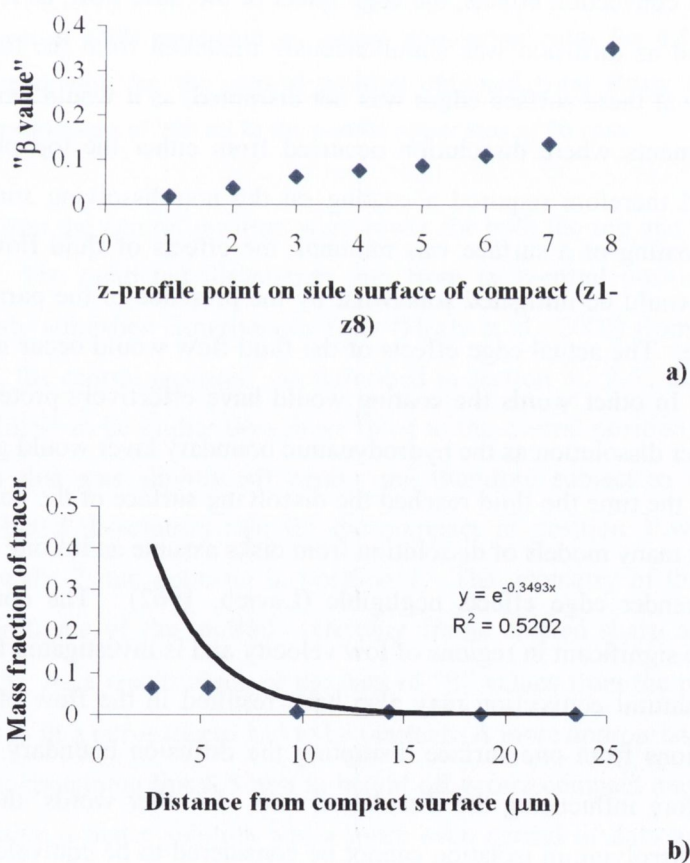


Figure 4.8. a) Variation of “β value” along the compact side on the positive x axis in position 2 illustrating the higher β value at z8, and b) the plot of mass fraction of tracer vs. distance from compact surface for the profile at z8 with the poorly-fitting equation yielding the β value.

The deviation of the z8 “β value” is apparent in Figure 4.8.

In summary, there is little difference between applying the symmetry condition and the stationary wall condition to the air-water interface in predicting dissolution rates from the simulations of fluid flow around off-centre compacts in the paddle apparatus. Care should be taken when determining an average effective diffusion layer at any surface using this method, as sporadic results from an individual profile at the surface can noticeably alter the predicted rate. It should be noted also that the total measured dissolution rate from the top and side surfaces of the compact does not always equal the sum of the measured dissolution rates from these surfaces. This is due to the edge effects (Schlichting, 1979) and effects of natural convection. If a stream is flowing over a flat plate in the direction of its length, the boundary layer is no longer found to be 2-dimensional at the edge of the plate. Rather, secondary flows arise in the region very close to the edges, causing the local skin-friction coefficient to vary irregularly both in the direction of and perpendicular to the main flow direction. The skin friction is a measure of the drag on a body as it moves through a fluid (Shlichting, 1979). Although the “tracer” material used in the diffusion simulations had a density equal to that of the dissolution medium and would therefore not incorporate natural convection effects, the edge effect of the fluid flow, as it affected dissolution, would be simulated as diffusion was simultaneously modelled from the top and side surfaces. Simulation of flow at these surface edges was not disrupted, as it would have been in the actual dissolution experiments where dissolution occurred from either the top planar or curved side surfaces alone and therefore required a coating on the non-dissolving surface. Although the thickness of the coating of a surface was minimal, the effects of fluid flow at the edge of the uncoated surface would be mitigated somewhat by the presence of the paraffin wax coat at the edge of the surface. The actual edge effects of the fluid flow would occur instead at the edge of this wax coating. In other words the coating would have effectively protected the edge of the surface from greater dissolution as the hydrodynamic boundary layer would generally be expected to have formed by the time the fluid reached the dissolving surface of the coated compacts. It is for this reason that many models of dissolution from disks assume an infinite disk radius, or a disk large enough to render edge effects negligible (Levich, 1962). The contribution of natural convection may be significant in regions of low velocity and is investigated further in section 5.7. The presence of natural convection may also have resulted in the flow of mass under natural convection conditions from one surface disrupting the diffusion boundary layer in an adjacent surface and therefore influencing the dissolution rate. In other words, the sum of rates from adjacent surfaces dissolving in isolation cannot be considered to be equivalent to the rate from a system of adjacent surfaces dissolving simultaneously. This has been demonstrated previously through investigation of dissolution rates from different surfaces of salicylic acid tablets placed in different positions in a rotating filter-magnetic basket apparatus. The ratio of the sum of dissolution from individual surfaces to the combined dissolution from these surfaces was found to vary with agitation rate. Natural convection was demonstrated to contribute to this variation (Vongvirat et al., 1981).

4.2.4 Predicting dissolution rates from compacts of different dimensions.

The results for predicted dissolution rates from compacts of 13 mm diameter and 8.5 mm height in the central position and position 1 are presented in Table 4.6.

Surface	CFD predicted rate (mg hour ⁻¹)	Experimental rate (data for central position taken from Healy et al., 2002)
Centre Side	80.42	118.50 ± 8.00
Centre Top	17.46	32.48 ± 1.75
Centre Whole	97.86	146.21
Position 1 Side	96.55	
Position 1 Top	65.01	
Position 1 Whole	161.56	174.56 ± 1.11

Table 4.6. Comparison of CFD predicted vs. actual dissolution rates for 8.5 mm benzoic acid compacts. Experimental data for the central position obtained from Healy et al., 2002; CFD-generated data from simulations of 900 ml in the paddle apparatus at 50 rpm.

The predicted rates from the central position were lower for both the top and side surfaces than the measured rates. The predicted dissolution rate from the central position, however, was compared to previously published experimental rates (Healy et al., 2002) from compacts located in, but not affixed to, the central position. As described in section 3.2.2.5., the dissolution from these compacts was likely to be higher than those fixed to the central position as they may have moved to a position that was slightly off centre and therefore subject to rapidly increasing velocities. The predicted dissolution rate for the compact in position 1 was of comparable accuracy to that from the 3 mm compact in position 1. The geometry of this model with the compact in the lower frame of the multiple reference frame created sharp angles which were problematical to mesh. As a result, much of the data of “ β ” values from the profiles around the surface were difficult to fit a curve to and had to be omitted. A more appropriate geometry for the lower reference frame containing this 8.5 mm in height off-centre compact may facilitate a more even mesh and therefore a better solution and a more even spread of data around the surface. One possible approach to this is to have curved interface between the lower and upper reference frames, depicted diagrammatically in Figure 4.9.a., rather than the current situation of a flat interface, depicted in Figure 4.9.b.

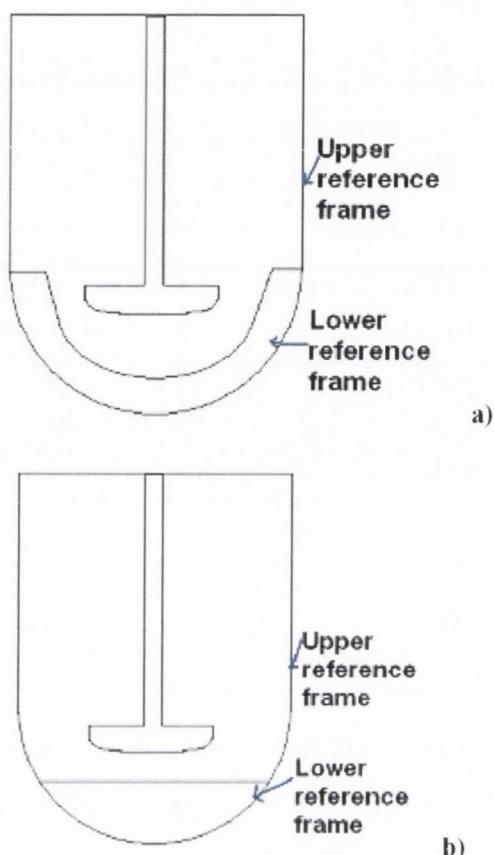


Figure 4.9. Diagrammatic representation of the geometry of the (a) proposed and (b) currently used multiple reference frames.

It can be concluded that, within the systems examined, this method for predicting dissolution rates through simulation of convective diffusion is of similar accuracy for compacts in different locations, of different dimensions and consisting of differing materials which dissolve by a diffusion-controlled mechanism. Areas of improvement for this method would ideally consist of

- incorporation of density differences to model the natural convection component;
- enabling the shape change with time of the dissolving surface to be incorporated into the prediction;
- a method to determine numerically (rather than through experimental calibration) the decrease in mass fraction of tracer which would be achieved to signal the “edge” of the diffusion boundary layer;
- ensuring that rate of production of “tracer” from the source was inhibited by increasing local concentrations at any point, rather than the constant source production of tracer as is currently the case.

4.3 Use of CFD-generated velocity and maximum shear rate data at the solid-liquid interface to predict dissolution rate.

4.3.1 Calculation of a local angular velocity value.

There have been several attempts to relate angular velocity (ω) and dissolution rate from a stationary disk in a rotating fluid, generally describing a correlation between dissolution rate and $\omega^{1/2}$. Levich derived the following expression for diffusional flow *to* the surface of a rotating disk:

$$I \approx 1.9D^{2/3}v^{-1/6}\omega^{1/2}r^2c_0 \quad \text{Equation 4.2}$$

where I is total flow of matter to the disk surface, v is the kinematic viscosity, r is the disk radius and c_0 is the concentration of solute in the bulk. In the equation for diffusional flow *from* a rotating disk the c_0 term would be replaced by c_s , the saturated solubility of the solute in the solvent. In this case the angular velocity would be calculated from the rotation rate of the disk. The case of a stationary disk in a rotating fluid is similar to that of a rotating disk in a stationary fluid, with some notable differences:

- The surface of the stationary disk is not uniformly accessible to the rotating fluid (Khoury et al., 1988; Colton and Smith, 1972) as the mass transport is dominated by the edges of the disk with a much thicker diffusion boundary layer developing in the central vortex region.
- The relationship with ω is more difficult to determine, as the rate of rotation of the stirrer is not necessarily the value for ω at the disk surface. In the absence of flow field velocity data, however, the value of ω for the rotating stirrer is used.

To account for the fact that the surface is not uniformly accessible, the relationship between dissolution rate and dissolving disk radius has been investigated. The dissolution rate was found to be proportional to the disk radius to the power of 3/2 (Khoury et al., 1988). This is in comparison with r^2 for a stationary disk in a rotating fluid (i.e. the area of the dissolving surface is πr^2). In addition, the dissolution rate was related to the variables C_s , $D^{2/3}$, $v^{-1/6}$, $\omega^{1/2}$, $r^{3/2}$ by an experimentally determined proportionality constant. This constant was calculated from dissolution data from hydrocortisone alcohol and acetate, yielding values of 1.25 and 1.4 respectively, resulting in an average of 1.33.

The final equation therefore is

$$R = 1.33 c_s D^{2/3} v^{-1/6} \omega^{1/2} r^{3/2} \quad \text{Equation 4.3}$$

(Khoury et al., 1988).

Two important differences between the experimental set up used to calculate equation 4.3 and the experimental set up used in the current work are that:

- a) The dissolution apparatus used by Khoury et al. (1988) incorporated a tablet holder with the dissolving surface facing downwards in a flat-bottomed vessel, with a rotating magnetic stirrer on the base of the vessel. A degree of natural convection may have interfered with dissolution in this system. In addition, the convex base of the dissolution vessel used in the current work could have resulted in a different relationship between dissolution rate and fluid velocity to that in a flat-bottomed vessel.
- b) Although the compacts in the off-centre positions, positions 1 and 2, are stationary in a rotating fluid, the axis of rotation of the fluid is not located at the centre of the surfaces of these compacts. Therefore the top planar surface is possibly more uniformly accessible than the top planar surface of the compact in the central position, and the relationship with $r^{3/2}$ may not hold for these surfaces.

Table 4.7 shows the predicted dissolution rates from the top planar surfaces of the 3 mm high compacts in each position. The predictions use equations 4.2 and 4.3 above, using the average angular velocity across the top surface of the compact, and also the angular velocity calculated from the apparatus stirring speed. The average angular velocity across the top surface of the compact is calculated from the maximum angular velocity on each of a series of lines extending from the compact surface, situated from the side of the compact facing the centre of the vessel to the outer edge (i.e. along the y-axis). These lines are described in Figure 2.16.

	Centre	Position 1	Position 2	Using ω calculated from apparatus stirring speed
ω (s ⁻¹)	6.467	6.785	3.992	5.236
Predicted dissolution rate (mg hour⁻¹)				
Equation 4.2 (Levich, 1962).	40.96	41.95	32.18	36.85
Equation 4.3 (Khoury et al., 1988)	35.56	36.42	27.94	32.00
Experimental dissolution rate (mg hour⁻¹)	35.8	48.94	50.48	

Table 4.7. Predicted dissolution rates from the top planar surfaces of the benzoic acid compacts using equations 4.2 and 4.3, using the average angular velocity value at the surface of the compact and the calculated angular velocity from the apparatus stirring speed.

The calculated average values of ω near the dissolving surface are of interest in that they are higher than the calculated value from the apparatus stirring speed, and lower in position 2 than the central position and position 1. Equation 4.3 assumes solid body rotation (constant angular

velocity), and it has been previously demonstrated that the fluid above the compact in the central position undergoes solid body rotation (McCarthy et al., 2003). However, the lower calculated angular velocity above the compact in position 2, compared to that above the compacts in the central position or position 1 (Table 4.7), suggests that mechanics of the fluid rotation above the compact in position 2 no longer conforms to the ideal solid body rotation situation. Both the angle of the compact and the hemispherical shape of the vessel base could have contributed to the lower ω value at position 2. The predicted dissolution rate from equation 4.3, for a compact in the central position, using the ω value from near the dissolving surface, is closer to the experimental value than the predicted rate using ω from the apparatus stirring speed. As the predictions for the off-centre positions were too low, an attempt was made to predict the dissolution rate using equation 4.2 as this assumes a uniformly accessible surface which should be the case for the top planar surface of the off-centre compacts. Although the predictions were higher using equation 4.2, they still fell short of the experimental rate, particularly for position 2. In summary, the use of the rotating disk/stationary fluid equation (equation 4.2) or the use of the stationary disk/rotating fluid equation (equation 4.3) is not applicable for stationary compacts in a rotating fluid when they are positioned off-centre to the axis of fluid rotation. Equation 4.2 predicts the dissolution rate from the compact in the central position when the ω from the apparatus stirring speed is used. Equation 4.3 gives a more accurate prediction for the compact in the central position when the value for ω used is that at the dissolving surface rather than that calculated from the apparatus stirring speed.

4.3.2 Calculation of a local Reynolds number

The Reynolds number (Re) is a dimensionless term which describes the ratio of fluid momentum per unit area per unit time (Bircumshaw and Riddiford, 1952). It takes the general form UL_c/ν where U is a characteristic velocity, L_c is a characteristic length and ν is the kinematic viscosity. It is often used to describe the point at which a flow regime changes from laminar to turbulent flow. In the situation of a rotating impeller in a cylindrical vessel, the Reynolds number can be defined in several ways including: $\omega r_1^2/\nu$ (Colton and Smith, 1972), where r_1 is the radius of a cylindrical tank and $\rho AR(D_A)^2/\mu$ (Kukura et al., 2003), where AR is the rotational speed of the agitator, D_A is the diameter of the agitator, ρ is the fluid density and μ is the fluid viscosity. In both of these cases the characteristic length used is a feature of the apparatus. When relating Re to dissolution rate, it is also possible to use a feature of the dissolving surface as the characteristic length. For example, the diameter of the dissolving surface across the direction of fluid flow in a flow through cell (USP dissolution apparatus 4 (USP, 2005)) (Cammarn and Sakr, 2000) and the radius of a dissolving disk (Colton and Smith, 1972; Mauger et al., 2003) have been used. As the dissolution rates in the current work were determined from the same apparatus at the same stirring speed, it would not be possible to relate the dissolution rate to the Reynolds number using

the conventional Re definitions. The characteristic length from the apparatus would be identical, and the velocity term calculated from the stirring speed would also remain constant resulting in the same Re being calculated regardless of compact location within the vessel. Therefore, Re values were calculated using local CFD-determined velocity values and a characteristic length related to the dissolving surface. The velocity component used was the maximum velocity magnitude at 1 mm from the compact curved side or top planar surface, and the characteristic length was the compact radius. A log-log plot, of dissolution rate per unit surface area from the top and side surfaces in each position vs. the local Re , yields a slope of 0.672 (R^2 0.901) as illustrated in Figure 4.10.

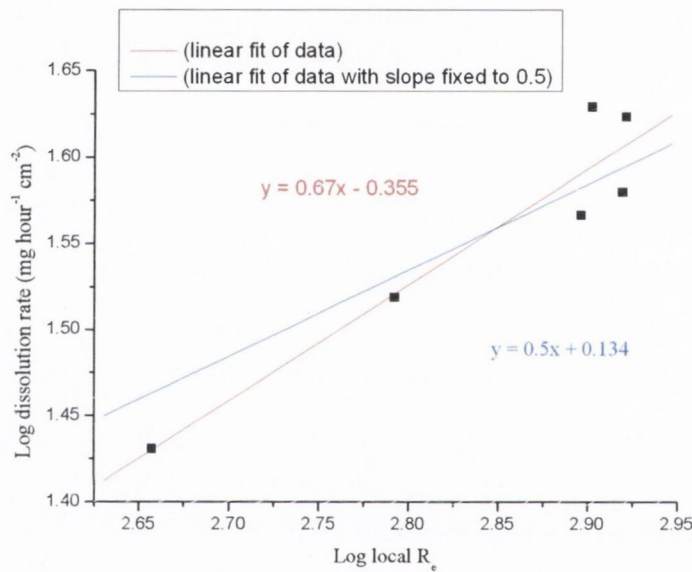


Figure 4.10. Log dissolution rate of benzoic acid ($mg\ hour^{-1}\ cm^{-2}$) vs. log local Re , from top and sides surfaces of compacts in the central position, position 1 and position 2. Local Re calculated from CFD-generated velocity magnitude data at 1 mm from the compact surface in each position, from simulations in 900 ml in the paddle apparatus at 50 rpm. A line through the data fitted to a slope of 0.5 is also illustrated.

Dissolution rate has been related to $Re^{0.5}$ (Cammarn and Sakr, 2000; Grijseels et al., 1981; Colton and Smith, 1972), assuming laminar flow, and a line is also drawn through the data in Figure 4.8 with a fixed slope of 0.5. The R^2 value for this line is 0.842.

Dissolution in turbulent forced convection has been related to $Re^{0.9}$ (Levich, 1962), and the slope of 0.672 in Figure 4.10 implies that there is a turbulent element to the fluid flow around the dissolving compact surfaces. However, flow around the side of the compact in the central position is primarily tangential (as evident in Figure 3.7.a), and would therefore be anticipated to be less turbulent than the flow around the off-centre compacts, as the centre of the compact surface is at the axis of rotation for the tangential flow. The flow over the top surfaces is also

primarily tangential in nature and would therefore be expected to be laminar, as can be seen in Figure 3.7.d-f. A log-log plot of dissolution rate per unit surface area vs. Re similar to that in Figure 4.10 is constructed in Figure 4.11, but only including data from the top planar surfaces and the side surface in the central position.

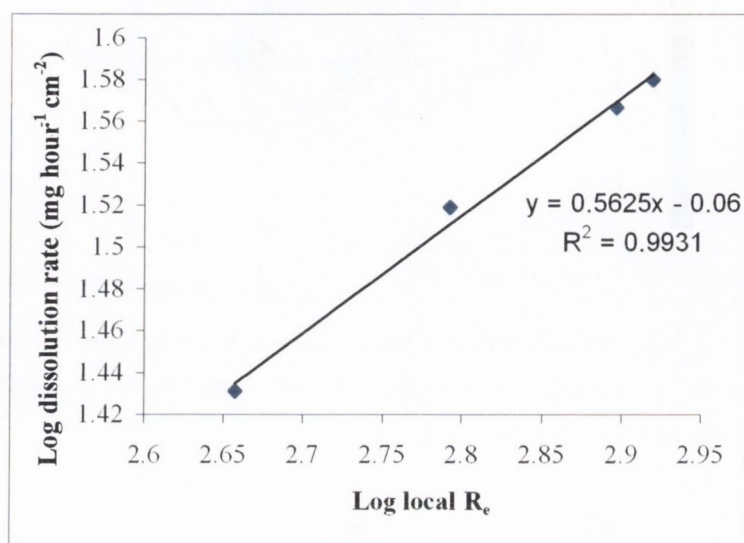


Figure 4.11. Log dissolution rate of benzoic acid ($\text{mg hour}^{-1} \text{cm}^{-2}$) vs. Log local Re from the top planar surfaces and the side surface in the central position only. Local Re calculated from CFD-generated velocity magnitude data at 1 mm from the compact surface in each position, from simulations in 900 ml in the paddle apparatus at 50 rpm.

The slope of 0.56 in Figure 4.11 is closer to the exponent of 0.5 associated with laminar flow, implying that flow around the side of the compact in the central position is laminar in nature. A further implication of the reduction of the exponent on elimination of the data from the off-centre side surfaces is that there is a degree of turbulent flow around these side surfaces. Regions of the side surfaces of the compacts where the flow is not smooth laminar flow but rather subject to the development of swirls or eddies when the fluid in the central vortex is in contact with the compact surface is evident in Figure 3.7.b (position 1) and 3.7.c (position 2). Additionally, disturbance of the laminar flow at the compact side is seen in Figure 3.10.b.

A plane was created around the sides of the compacts in positions 1 and 2 in order to identify regions of turbulent fluid behaviour. The location of this plane around the compact in position 2 is illustrated in Figure 4.12, and the planes in relation to the paddle, for orientation purposes, are shown in Figure 4.13.a (position 1) and 4.13.b (position 2).

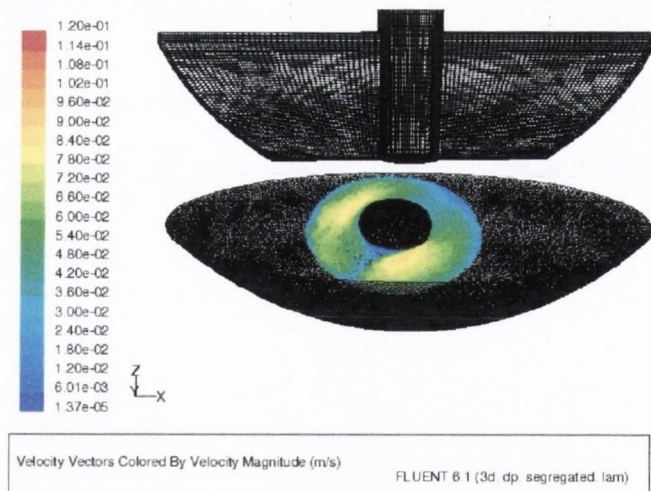


Figure 4.12. Plane of CFD-generated vectors coloured by velocity magnitude around the compact in position 2, including the lower portion of the vessel wall and the paddle, from simulations of 900 ml in the paddle apparatus at 50 rpm.

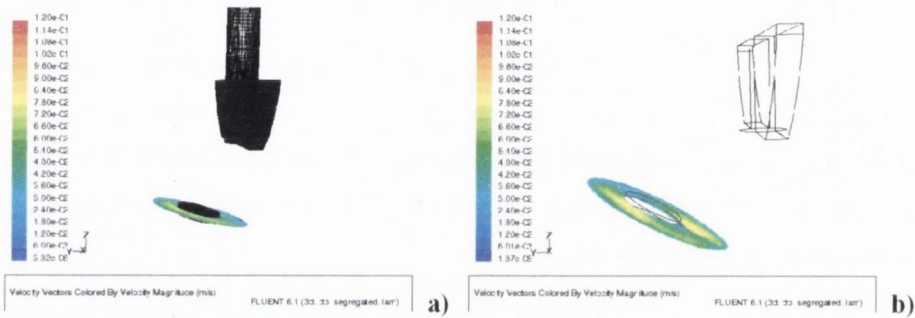


Figure 4.13. Planes of CFD-generated vectors coloured by velocity magnitude around the compact in a) position 1 and b) position 2, including paddle for orientation, from simulations of 900 ml in the paddle apparatus at 50 rpm.

The plane around the sides of the compact in position 1 illustrating a region of potential turbulence is shown in Figure 4.14.a, and vectors of swirling flow in this region are presented in Figure 4.14.b.

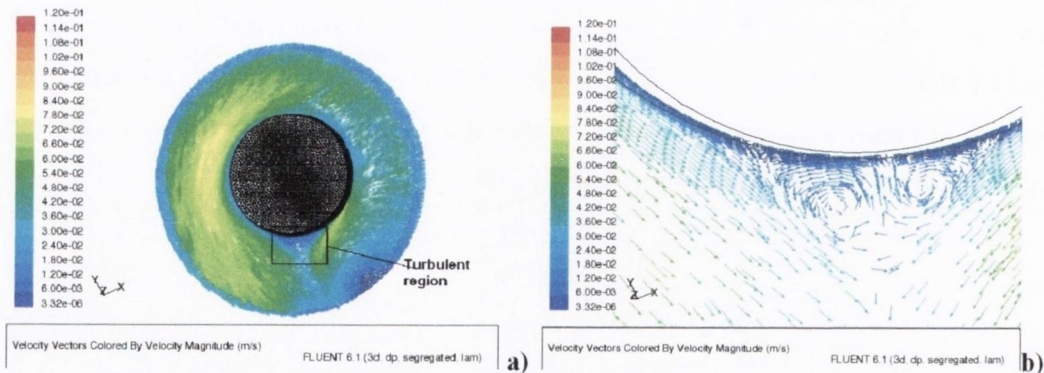


Figure 4.14. CFD-generated vectors coloured by velocity magnitude around the compact in position 1 on a plane illustrating a) turbulent region and b) swirling fluid within the turbulent region. Data taken from simulations of 900 ml in the paddle apparatus at 50 rpm.

As turbulence is by its nature time-dependent and unpredictable, “active” turbulence cannot be captured in a time-averaged simulation. However, swirling fluid such as that presented in Figure 4.14.b would suggest the potential for development of turbulence in this region.

In a similar manner, the plane around the compact in position 2 with potentially turbulent regions is illustrated in Figure 4.15.a and vectors of swirling flow in this region is presented in Figure 4.15.b.

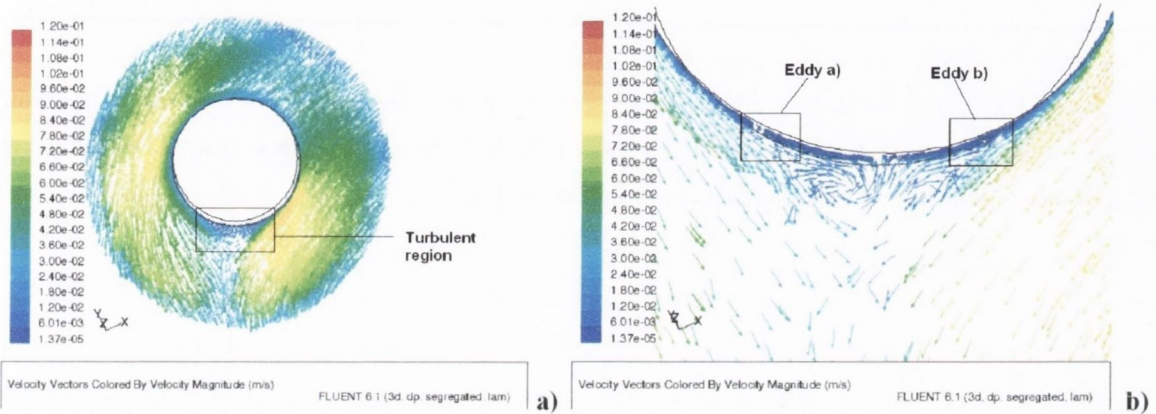


Figure 4.15. CFD-generated vectors coloured by velocity magnitude around the compact in position 2 on a plane illustrating a) turbulent region and b) swirling fluid within the turbulent region. Data taken from simulations of 900 ml in the paddle apparatus at 50 rpm.

In addition to the swirling fluid flow depicted in the region of the compact sides presented in Figure 4.15.b, smaller eddies or flow instabilities could also be identified closer to the compact surface, suggesting potential boundary layer detachment. Although these are present in regions of very low fluid velocities, the presence of eddies imply that the flow is not entirely laminar at these points. This would support the concept of turbulent flow or flow instabilities developing in some regions of the vicinity of the side surfaces of compacts in these off-centre positions. The vectors in eddy regions a and b of Figure 4.15.b are shown in Figure 4.16.a and 4.16.b respectively.

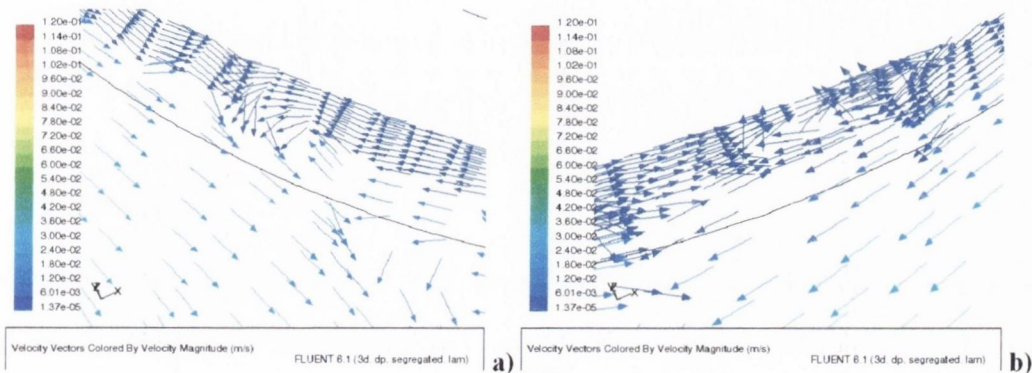


Figure 4.16. CFD-generated vectors coloured by velocity magnitude in the region of Eddy a (a) and Eddy b (b), around the compact surface in position 2. Data taken from simulations of 900 ml in the paddle apparatus at 50 rpm.

The critical Reynolds number is the number at which the flow changes from laminar to turbulent. Comparison of the calculated R_e for the different surfaces examined enables a critical R_e within this system to be determined. These numbers are presented in Table 4.8.

	Top Central	Top Position 1	Top Position 2	Side Central	Side Position 1	Side Position 2
R_e	423	748	799	620	799	834

Table 4.8. Calculated local Reynolds numbers for the top and side surfaces in the central position, position 1 and position 2, from velocity data from CFD simulations of fluid flow around the compacts in each position, in 900 ml in the paddle apparatus at 50 rpm.

From Table 4.8, some turbulent features could be expected when R_e is approximately 800 for the system under investigation. It should be noted that the R_e is a dimensionless relative term. Using a different characteristic length will obviously change the number, and R_e comparisons should only be made between systems for which the R_e has been calculated using a similar method.

Models to predict dissolution rate using both the Reynolds number and the Peclet number (P_e) have been used. The Peclet number in a system incorporating a rotating disk in a stationary fluid is defined as $r^2\omega/D$. In the case of a stationary disk/rotating fluid, the discrepancy between the ω value calculated from the stirrer speed and the appropriate ω value at the dissolving surface must be addressed. This discrepancy can be accounted for by using a function of ω , ($\phi\omega$), to relate the dissolution rate to stirrer speed. The following equation was used by Mauger et al., (2003)

$J=0.77(D/r)(R_e)^{1/2}\phi^{1/2}(P_e/R_e)^{1/3}c_s$

Equation 4.4

where J is the dissolution rate per unit area. A value of 0.4 for ϕ was used by Mauger et al. (2003) to accurately predict salicylic acid dissolution rates from the paddle dissolution apparatus at both 50 and 100 rpm. The value of 0.4 was taken to be reasonable from laser Doppler velocity data produced by Bocanegra et al., (1990). The equation was originally presented by Colton and Smith (1972) in the form

$S_tS_c^{2/3}R_e^{1/2} = 0.768\phi^{1/2}.$

Equation 4.5

S_t is the Stanton number ($k/\omega r_1$), where k is the mass transfer coefficient, and r_1 is the radius of the tank. A local Stanton number is also defined, $k/\omega L_c$, where L_c in this situation relates to the dimensions of the mass transfer surface. S_c is the Schmidt number (ν/D), which is also known as the Prandtl number, especially when discussing heat transfer rather than mass transfer problems. Values of ϕ from 0.44 to 0.49 for a laminar flow regime were calculated. The experimental set up used to study mass transfer consisted of a flat-bottomed cylindrical vessel and 5 plates of

compressed benzoic acid. The plates with the smallest and largest radius were disks, and the plates with outer radii in between these values were annular rings. The radial coordinate used in the work, therefore, is the outer radial coordinate of the dissolving surface. In the derivation of the above equation, the assumption is made that the base of the tank is infinite. To address this, the authors derived a second equation taking the relative radial position of the dissolving surface into account:

$$S_t S_c^{2/3} R_e^{1/2} = 0.572 \phi^{1/2} [1 - r_d]^{-1/4} \quad \text{Equation 4.6}$$

where r_d is a dimensionless radial coordinate, r/r_1 , r being the radial coordinate of the dissolving surface. As the current work uses velocity data from CFD, it is anticipated that the ϕ term would be redundant in these equations, as the velocity is not related to the stirrer speed. Predictions of dissolution rate were made using both equation 4.4 and equation 4.6, omitting the ϕ term in each case. A number of approximations had to be employed due to the different nature of the dissolving surface (an off-centre disk) and the shape of the hemispherical vessel base. The P_e number used was (the tangential velocity (v_t)*the disk radius of the dissolving surface)/ D . Tangential velocity values were also used to calculate R_e . The radial coordinate used was the tablet radius in each case, as the outer radial coordinate was not applicable to a disk placed at an angle on the hemispherical base. Similarly, as the compacts are placed on the hemispherical surface, the distance from the surface of each compact to the nearest edge is the same and the same value for r_d in equation 4.6 was used for each position. The value for the radius of the base of the tank was taken to be the radius of the hemisphere, 0.051m. The results from predictions of dissolution from the top planar surface using equations 4.4 and 4.6 are shown in Table 4.9.

Predicted dissolution rate (mg hour ⁻¹)	Central position	Position 1	Position 2
Equation 4.4: (maximum velocity) mg hour ⁻¹	54.4	72.4	74.8
Equation 4.4: (average velocity) mg hour ⁻¹	44.8	64.5	71.1
(ϕ)	(0.64)	(0.58)	(0.50)
Equation 4.6: (maximum velocity) mg hour ⁻¹	41.8	55.7	57.5
Equation 4.6: (average velocity) mg hour ⁻¹	34.4	49.6	54.6
(ϕ)	(1.08)	(0.97)	(0.85)
Experimental rate (mg hour ⁻¹)	35.8 ± 1.49	48.9 ± 2.07	50.5 ± 3.17

Table 4.9. Dissolution rate predictions from the top planar surface of the benzoic acid compacts located in the central position, position 1 and position 2, using equations 4.4 and 4.6. Predictions utilise both average and maximum tangential velocity data at 1 mm from the compact surface. The ϕ value is a measure of accuracy of the tangential velocity value when used in these equations.

As can be seen from Table 4.9 an average tangential velocity at 1 mm from the compact surface results in a more accurate prediction than maximum fluid velocity data. Despite the approximations used in equation 4.6, the dissolution rate predictions for the compact in the central position and in position 1 were within 1 standard deviation of the experimental rate. The accuracy of the prediction can be assessed using the ϕ term. In the original equation the ϕ term related the stirrer speed velocity to the velocity near the compact surface. A ϕ value of 1 ($\phi\omega = \omega$) using local velocity data would therefore imply that an accurate velocity value (ω) had been used to predict dissolution from this equation. The ϕ values presented of 1.08 (centre position) and 0.97 (position 1) (i.e. which, if incorporated into equation 4.6 as $\phi^{1/2}$, would result in a prediction of a dissolution rate equivalent to the experimental rate) calculated from the results of equation 4.6, using average tangential velocity data, support the use of the local CFD-generated velocity data with this model. The prediction for the compact in position 2, however, is higher with a ϕ value of 0.85. This may be due to inaccuracies in the local velocity data, but is more likely to be due to this prediction model being unsuitable for the compact at this angle in the hemispherical vessel.

4.3.3 Calculation of a local shear rate for mass transfer prediction.

Drug dissolution models have been developed to theoretically predict dissolution rates from both rectangular and circular disk surfaces incorporating a term (α) describing the rate of shear in the boundary layer rather than a velocity term (Nelson and Shah, 1975). The model for dissolution rate (R) from a circular disk surface was presented as:

$$R = 2.157 D^{2/3} c_s \alpha^{1/3} r^{5/3} \quad \text{Equation 4.7}$$

The dissolution rate from a rectangular surface was presented as:

$$R = 0.808 D^{2/3} c_s \alpha^{1/3} b L_c^{2/3} \quad \text{Equation 4.8}$$

The width of the rectangular surface is described by b and the length (in the direction of fluid flow) as L_c .

Experimental work (Nelson and Shah, 1975) supported the theory in terms of the exponents to which each variable was raised, with the exception of the geometrical orientation for a rectangular surface. It was considered that this was due to non-ideal behaviour of the boundary layer as the experimental set-up consisted of a rotating stirrer with the flat dissolving surface held in place by a vertical rod, parallel to the axis of rotation of the flow. Flow visualisation revealed that the boundary layer along the dissolving surface was affected by eddies from the main stream, whereas the theoretical equation assumes ideal boundary layer behaviour. Additionally, the shear rate could not be directly measured and was assumed to be a function of the apparatus stirring speed (Nelson and Shah, 1975). Dissolution experiments using a different experimental system, involving controlled laminar flow past the dissolving surface in a dissolution cell, yielded results that were within 10% of the results predicted by the theoretical model for a circular disk surface. The shear rate was calculated as a function of volumetric flow rate (Shah and Nelson, 1975).

It is possible to extract shear rate data from FluentTM CFD solutions. Maximum shear rate data from individual lines extending from the top compact surface into the bulk, as described in Figure 2.16, was averaged and the resulting value used with equation 4.7. The lines at the edge of the top surface were not used in order to eliminate edge effects. The shear rate is greatest in the region near the compact surface where the lines are located, as illustrated for the compact in position 1 in Figure 4.17.

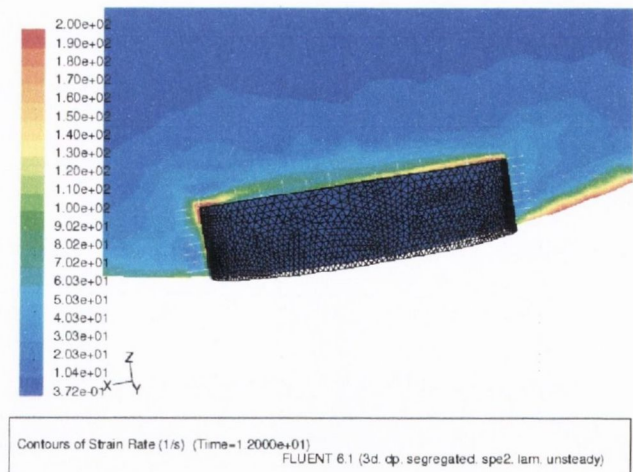


Figure 4.17. Contours of shear rate (strain rate) in the region of the compact in position 1, from CFD-generated data of the fluid flow around the compact in 900 ml in the paddle apparatus at 50 rpm.

The predicted dissolution rates from the top planar surfaces using equation 4.7 are presented in Figure 4.18, along with experimental dissolution rates for comparison. The predicted dissolution rates from the side surfaces, using equation 4.8, are shown in Figure 4.19. The value for b (the width of the dissolving rectangular surface) was taken to be the height of the side surface. The value for L_c (the length of the dissolving surface in the direction of fluid flow) was taken to be the length of the perimeter of the compact.

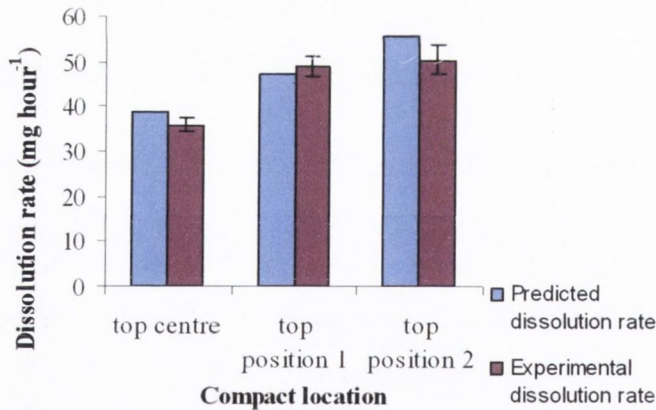


Figure 4.18. Experimental and predicted (equation 4.7) dissolution rates in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm, from benzoic acid compact top planar surfaces in the central position, position 1 and position 2.

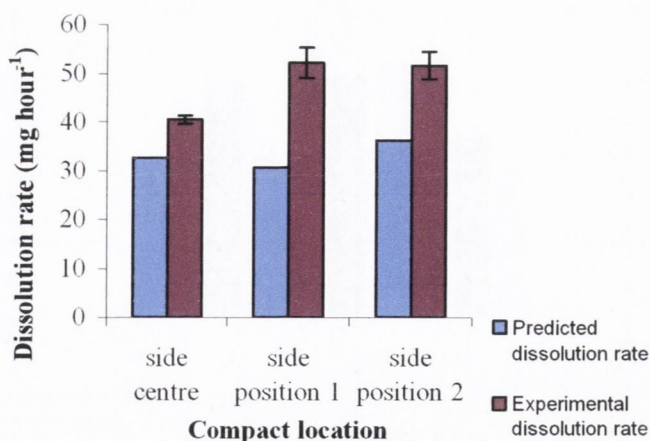


Figure 4.19. Experimental and predicted (equation 4.8) dissolution rates in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm, from the curved side surfaces of benzoic acid compacts in the central position, position 1 and position 2. L_c taken to be compact perimeter.

It is clear from Figure 4.19 that the predicted dissolution rates for the curved side surfaces from equation 4.8 are much lower than the experimentally measured rates. Although application of the model to a curved surface and a complicated flow regime may result in inaccuracies, including the power to which the shear rate value is raised, the assignation of appropriate dimensions for the characteristic length and width of the dissolving surface were investigated prior to investigating the model's inadequacies in this situation. In the central position, the flow around the compact sides is primarily tangential. Thus the curved side surface is in effect the direction along which the fluid is flowing. In this situation use of the compact perimeter length as the value for L_c would seem appropriate. In the off-centre positions, although there is a large component of tangential fluid flow, the compacts are not located at the centre of the axis of rotation. The length therefore, in the direction of fluid flow, could be approximated as half of the perimeter, as the fluid flows past the curved surface and onwards around the vessel. As there are two halves of the side surface dissolving, the width of the rectangle could be considered to be double the compact height. Figure 4.20 shows predicted dissolution rates using these new dimensions, with experimental dissolution rates for comparison.

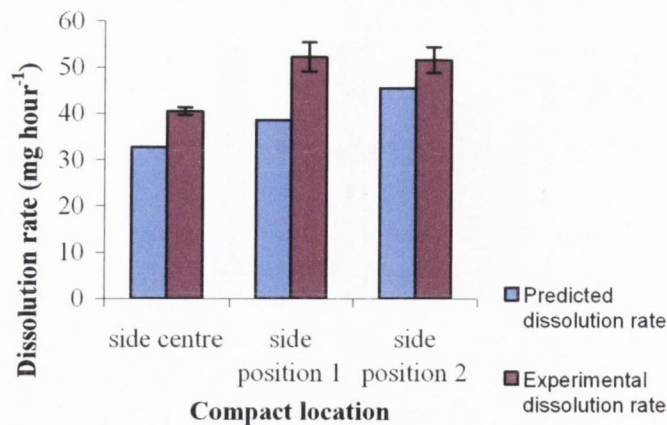


Figure 4.20. Experimental and predicted (equation 4.8) dissolution rates in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm, from the curved side surfaces of benzoic acid compacts in the central position, position 1 and position 2. For the off-centre compacts, L_c is taken to be compact perimeter/2, b taken to be height of side surface x 2.

It is obvious that predicted dissolution rates in Figure 4.20 are closer to the experimental values than those presented in Figure 4.19.

However, despite the improvement in the dissolution predictions through the use of a more appropriate dimension in the case of the off-centre compact side surfaces, the shear rates from these surfaces would seem to be too low to accurately predict the dissolution rate using equation 4.8. A log-log plot of dissolution rate vs. shear rate for the surfaces examined is presented in Figure 4.21.

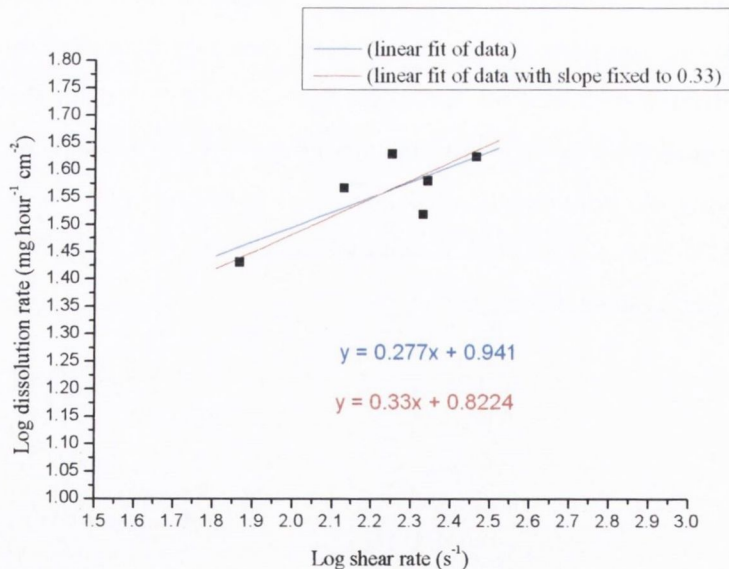


Figure 4.21. Log dissolution rate vs. log shear rate from top and side surfaces of benzoic acid compacts in the central position, position 1 and position 2, in 900 ml in the paddle apparatus at 50 rpm. Shear rates are from CFD-generated velocity data near the compact surface. A line through the data fitted to a slope of 0.33 is also illustrated.

It is clear from Figure 4.21 that the relationship between dissolution rate and $\alpha^{1/3}$ does not hold for all of the data investigated. The line fitted to the data, with a slope of 0.277 ($R^2 = 0.607$), is a better fit to the data than the line fitted to a slope of 0.33 ($R^2 = 0.584$). However, if the data for the curved side surfaces in the central position and position 1 (which yield predicted dissolution rate data that is furthest from agreement with the experimental data presented) are removed as outliers, there is a satisfactory relationship between dissolution rate and $\alpha^{0.3}$, as shown in Figure 4.22. This is in reasonable agreement with the exponent of 1/3 used in equation 4.7.

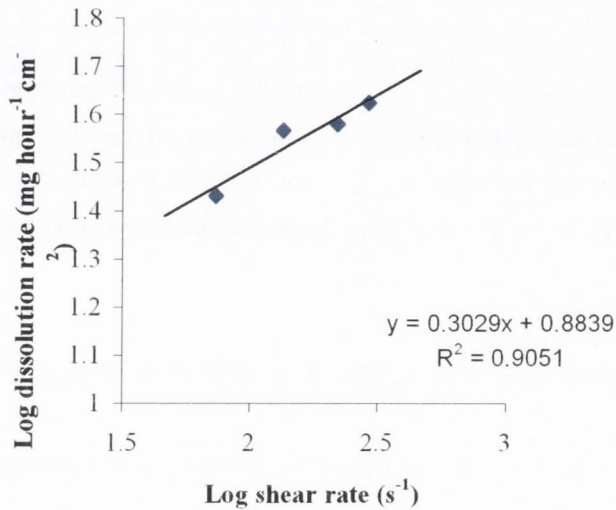


Figure 4.22. Log dissolution rate vs. log shear rate from top of benzoic acid compacts in the central position, position 1 and position 2, and the side surface of the compact in position 2, in 900 ml in the paddle apparatus at 50 rpm. Shear rates are from CFD-generated velocity data near the compact surface.

The shear rate values for the curved side surfaces were calculated from an average of maximum shear rate values from lines extending from the sides into the bulk. The lines used were z1, z4 and z7 in each direction along each axis. The z8 value was not used to eliminate edge effects. As the shear rates at many of these lines were affected by low velocity fluid regions at sides of the compact facing away from the general flow direction, the calculated average may have been lower than the effective value. Furthermore, the shear rates calculated around the sides of the compacts are based on fluid flow past a curved surface. A deviation from the predicted behaviour of the model used in equations 4.7 and 4.8 is expected in the case of flow past a curved surface (Shah and Nelson, 1975).

Contours of shear rates around the compacts in position 2 on a vertical plane at $x=0$ are shown in Figure 4.23. The high shear strain area at the top left hand corner (z7) is in contrast to the lower shear rate at the bottom right hand corner (Z1).

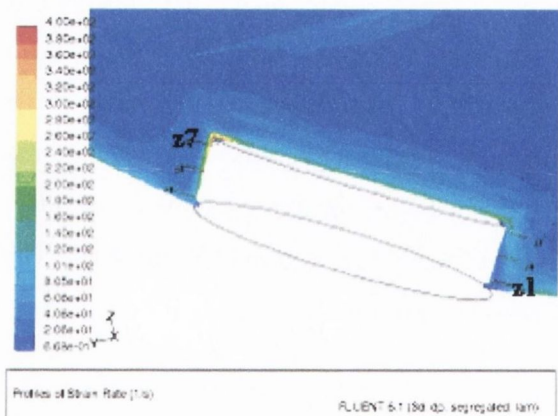


Figure 4.23. CFD-generated contours of shear strain around the compact in position 2, on a vertical plane at $x=0$, in 900 ml in the paddle apparatus at 50 rpm.

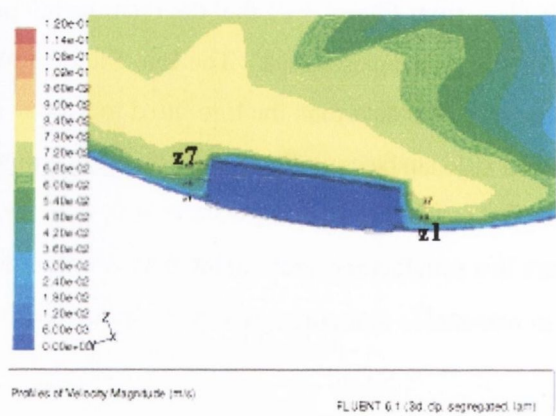


Figure 4.24. CFD-generated contours of velocity magnitude around the compact in position 2, on a vertical plane at $x=0$, in 900 ml in the paddle apparatus at 50 rpm.

The contours of velocity magnitude on the same plane influencing these shear rates are visible in Figure 4.24.

In addition to the surface being curved rather than flat, it has been shown that in a situation of low flow rates and inverted orientation (i.e. downward facing horizontal surface) there is a contribution from natural convection (Nelson and Shah, 1975). As some of the curved side surfaces are located in regions of low fluid velocity, and fluid is free to flow vertically along the surface, it is anticipated that natural convection will play a part in dissolution from these curved side surfaces and contribute to the shear experienced at this surface. The contribution of natural convection to the dissolution rate predicted from equations 4.7 and 4.8 will be investigated in section 5.7.

4.4 Conclusions

The diffusion layer thickness was used to predict dissolution rates using simulated diffusion boundary layers from top planar and curved side surfaces in the central position, position 1 and position 2. The diffusion boundary layer thickness was specified in terms of a specific decrease in concentration of benzoic acid saturated solution determined from the relationship between the dissolution rate and the diffusion boundary layer from the curved side surface in the central position. Dissolution rates were within 20% of the experimental value for all surfaces, materials and compact dimensions with the exception of the top planar surface in the central position and position 2, which underpredicted the dissolution rate. As a prolonged dissolution study of a compact in the central position revealed the development of a central “peak”, consistent with that predicted by the CFD simulation of the diffusion boundary layer, it is possible that the simulated diffusion boundary layer could be more aptly employed to predict dissolution rates over a longer time period. The predicted dissolution rate from the top planar surface of the compact in position 2 was also lower than the experimental rate. The importance of the fit of the curve to the calculated “ β ” values is highlighted in terms of the curved side surface of position 2, and a more accurate dissolution rate was predicted from the side surface when outlying “ β ” values were omitted. The fact that the predicted dissolution rates were generally less than the experimental rates suggests a significant contribution to the dissolution rate from natural convection. Use of the simulated diffusion boundary layer thickness to predict dissolution rates can give an approximate estimate of the magnitude of the dissolution rate from each surface in each position only.

Several dissolution models relating the dissolution rate to angular velocity (ω) were examined. Although the dissolution rate from the top planar surface in the central position could be accurately predicted from a local CFD-generated ω value, predicted rates from the off centre compacts were less accurate. The dissolution rate from the top planar surface in the central position and position 1 was predicted with reasonable accuracy employing average ω velocity data, using an equation which accounted for a finite dissolving surface and the effect of the edge of the vessel (equation 4.6). Some approximations had to be made to account for the angle of the compacts and the hemispherical nature of the vessel base. A local value for Re can be used to determine surfaces which may be exposed to some turbulence in the surrounding fluid. CFD vectors can illustrate these turbulent regions and the Re values of the fluid surrounding the surfaces under investigation can be used to determine a critical Re for the system, where the flow can no longer be considered laminar.

Dissolution rate predictions using CFD-generated shear rate data are in good agreement with experimental dissolution rate data (within ~10%) from the top planar surfaces in each position. The predictions from the side surfaces, however, underestimate the dissolution rate. Modification of the appropriate dimensions to use in relation to the direction of fluid flow around a circular surface improved the predictions for the off-centre side surfaces. The shear rate at the side

surfaces, however, is too low to accurately predict dissolution rates with the model employed in this section. The contribution of dissolution from natural convection, particularly in areas of low velocity, will possibly increase the effective shear rate at the side surfaces. It is possible, therefore, to accurately predict dissolution rates from the CFD-generated simulations using hydrodynamic data alone without simulation of diffusion from the surface. Angular velocity and shear rate data, with appropriate consideration of the geometry of the surface and the vessel, combined with investigation into the contribution of natural convection to the local hydrodynamics, potentially result in accurate dissolution rate predictions from different surfaces, in different locations, in the paddle apparatus using CFD simulations.

5.0

Investigation of hydrodynamics in the basket dissolution apparatus and determination of dissolution rates under natural convection conditions.

5.1 Introduction.

In order to improve our understanding of the hydrodynamics present in the basket dissolution apparatus, differences in dissolution profiles for various pharmaceutical dosage forms, both within the basket and outside the basket at the base of the vessel, have been examined recently and comparisons have been made with dissolution within the paddle dissolution apparatus (Mori-hara et al., 2002). There is evidence to suggest that dissolution rates are similar for a non-disintegrating tablet placed inside the rotating basket and at the base of the vessel in the paddle apparatus at the same agitation speed (Mori-hara et al., 2002). This is despite the fact that there is much greater dissolution from the lower surface of the tablet when placed in the rotating basket compared to when it is placed at the bottom of the vessel in the paddle apparatus (Mori-hara et al., 2002). When the tablet is placed at the bottom of the vessel of the basket apparatus dissolution is much slower, with the dissolution rate constant from the tablet in this position at 100 rpm being equivalent to that from the tablet inside the basket at 50 rpm (Mori-hara et al., 2002).

The aim of this work is

- to examine the hydrodynamics present in a simulation of the flow field within the basket dissolution apparatus generated using CFD. The fluid flow patterns can then be compared both within the basket and outside the basket at the base of the vessel;
- to compare hydrodynamics in the basket apparatus to the hydrodynamics in the paddle dissolution apparatus to aid interpretation of differences in dissolution data between the two official methods;
- to investigate the relationship between the dissolution rate from a compact within both the paddle and basket apparatuses and the hydrodynamics in the region of the dissolving compact. This relationship between dissolution rate and hydrodynamics at the dissolving surface should be similar regardless of the apparatus in which the dissolution is taking place. An attempt is made to predict dissolution from dissolving compacts within the basket apparatus at different agitation rates from the relationship between dissolution rate and fluid velocity at the dissolving surface;
- to extend this dissolution rate – fluid velocity relationship to determine the magnitude of dissolution occurring under conditions of natural convection, as CFD only simulates forced convection;
- to identify areas of low velocity in both the paddle and basket apparatus and to determine and the maximum possible contribution from natural convection to the dissolution rate in these low velocity regions, as natural convection can influence dissolution rates under forced convection of low velocity (Fee et al., 1976);

5.2 Solution convergence.

Convergence of the solutions for each agitation rate in the basket apparatus was judged by monitoring the decrease in residuals and the change in velocity data at specific locations. The decrease in residuals as the 50 rpm solution converges is shown in Figure 5.1. Although the residuals do not decrease further after approximately 15,000 iterations, it can be seen from Figure 5.2 that the velocities on each surface continue to change. The levelling of velocity values at a range of data sampling points as shown in Figures 5.2 (50 rpm), 5.4 (100 rpm) and 5.6 (150 rpm) contributes to the assurance that the solution has converged adequately. The solution was therefore judged to be converged when these velocities stopped changing. In some cases the solution was judged as converged when the velocities stopped changing in a particular direction i.e. the exact velocity value might be marginally different on iterating further through the solution, however if this difference is a slight increase when the velocity value was consistently decreasing up to this point, the solution was taken to be converged. The residuals show a similar pattern, where rather than levelling off smoothly, they alternate around a particular magnitude. This is evident in Figure 5.1, in addition to Figures 5.3 and 5.5, which show the decrease in residuals with solution from the 100 rpm and 150 rpm simulation respectively. Figure 5.4, which shows the change in velocity with iteration on the surfaces examined while converging the 100 rpm solution, illustrates the situation where the velocity does not stop changing with iteration but stops changing in one direction. This is particularly evident on the s1 and s2 surfaces (as described in Figure 2.10, section 2.2.1.2) in Figure 5.4, from approximately 30,000 iterations onwards. Figure 5.6, which shows velocity values as the 150 rpm solution converges, also displays this feature (of alternating values rather than a smooth levelling of values with a converged solution) very obviously for the s1 and s2 surfaces. This may be representative of instability of the solution at this high agitation speed. The time-averaged solution will not simulate any time dependent features, and these will be more prevalent at a higher agitation speed.

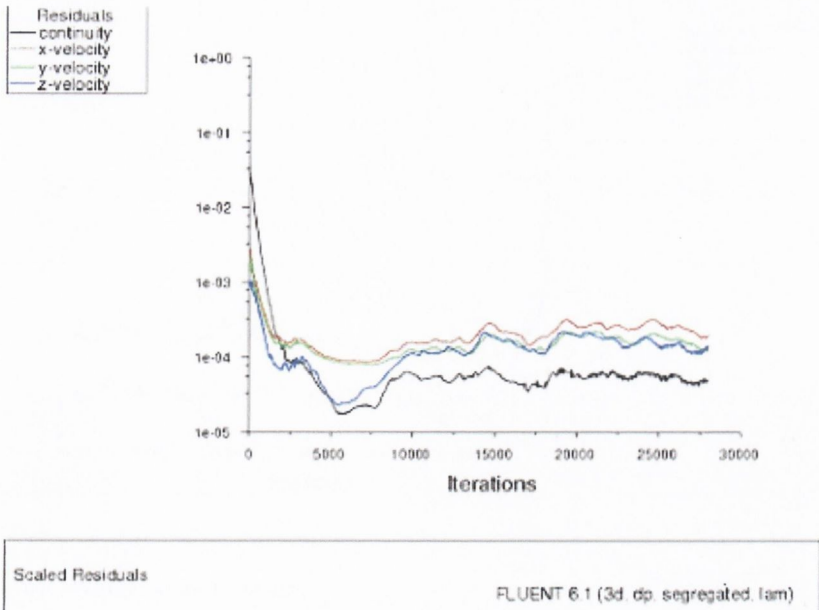


Figure 5.1. Change in residual magnitude with iteration in the convergence of the 50 rpm 900 ml CFD simulation of the flow field in the basket apparatus.

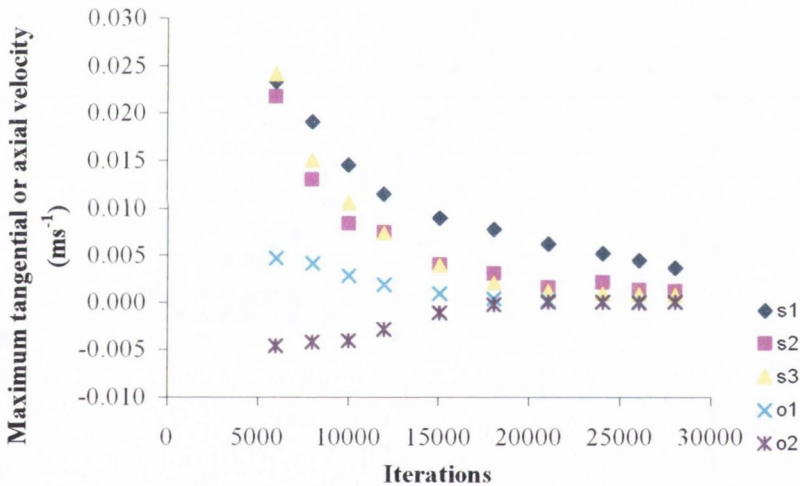


Figure 5.2. CFD-generated maximum tangential (s1-s3) or axial (o1 and o2) velocity vs. iterations when solving the flow field for the 900 ml volume at 50 rpm in the basket apparatus.

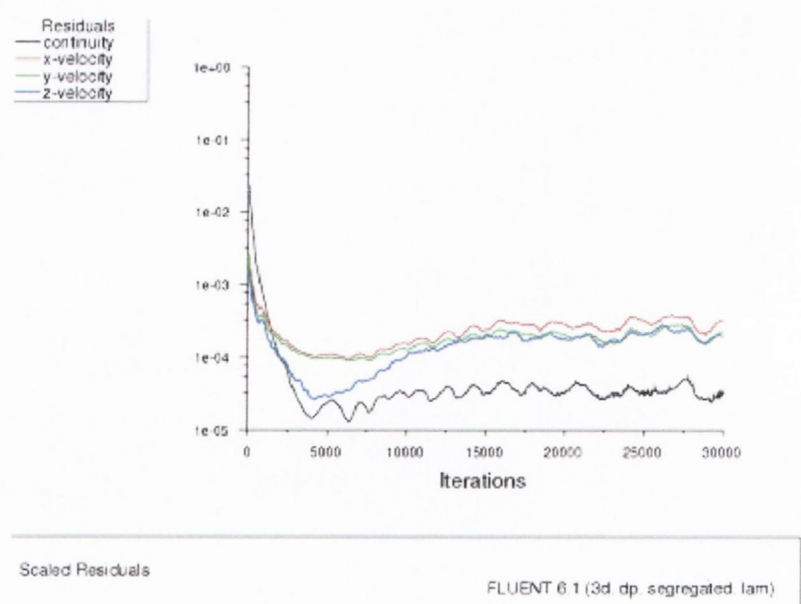


Figure 5.3. Change in residual magnitude with iteration in the convergence of the 100 rpm 900 ml CFD simulation of the flow field in the basket apparatus.

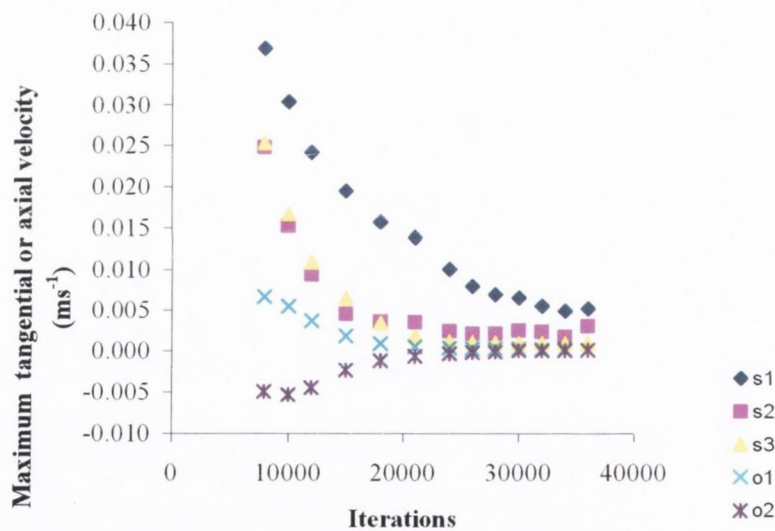


Figure 5.4. CFD-generated maximum tangential (s1-s3) or axial (o1 and o2) velocity vs. iterations when solving the flow field for the 900 ml volume at 100 rpm in the basket apparatus.

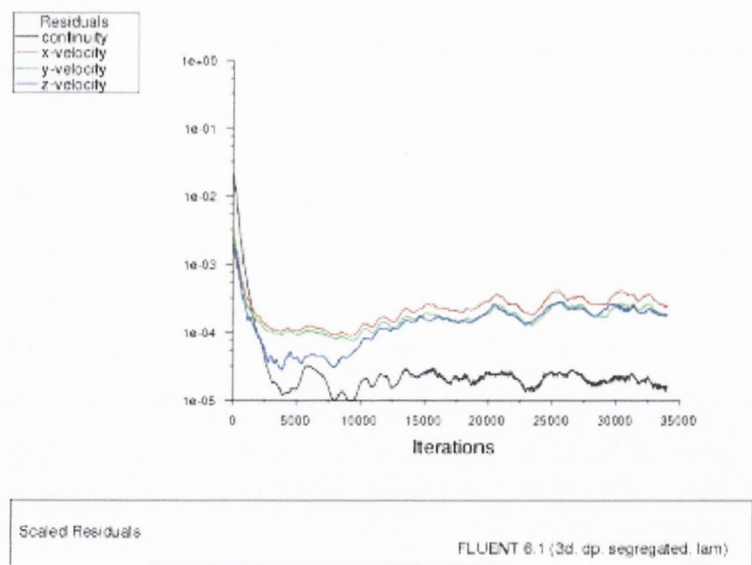


Figure 5.5. Change in residual magnitude with iteration in the convergence of the 150 rpm 900 ml CFD simulation of the flow field in the basket apparatus.

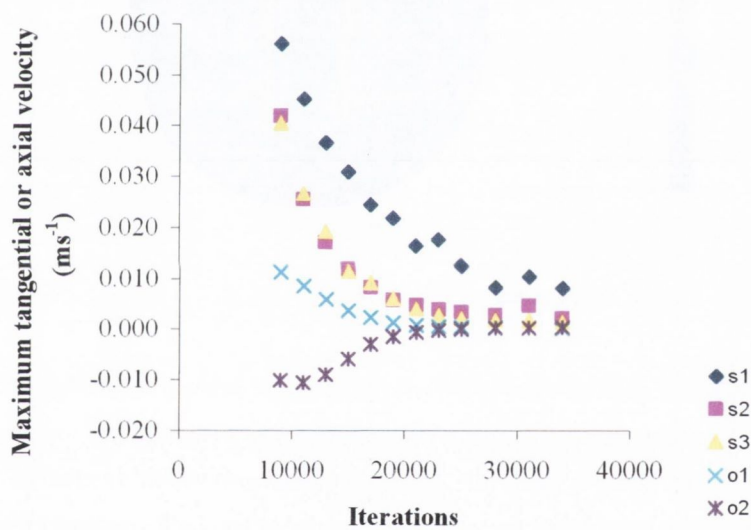


Figure 5.6. CFD-generated maximum tangential (s1-s3) or axial (o1 and o2) velocity vs. iterations when solving the flow field for the 900 ml volume at 150 rpm in the basket apparatus.

5.3. Qualitative and quantitative validation.

5.3.1 Qualitative validation.

The contours of velocity magnitude around the outside of the basket at 50 rpm, displayed in Figure 5.7, show regions of higher velocity radiating from the side of the basket. These high velocity regions are also present at 100 and 150 rpm as can be seen from the velocity vectors from the Figures 5.11 and 5.16 in section 5.4. The CFD simulations generated have several of these high velocity regions at the side of the basket. In the 50 rpm simulation there is one above the lower lip and one below the upper lip.

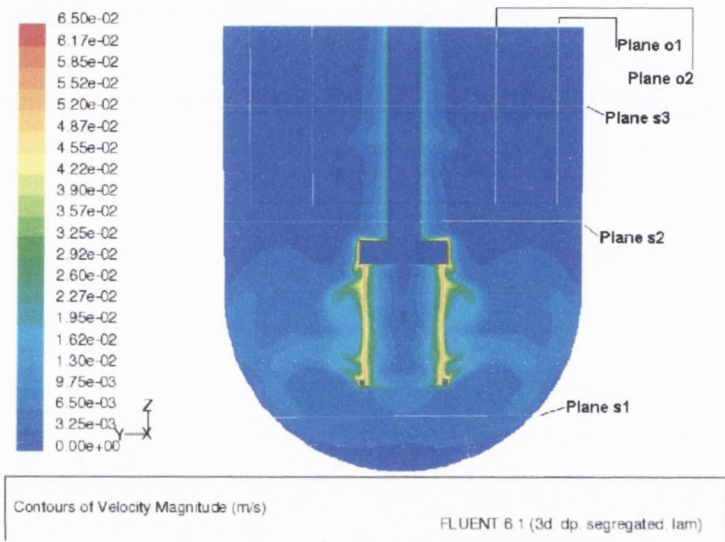


Figure 5.7. CFD-generated contours of velocity magnitude around the basket at 50 rpm. The regions of higher velocity radiating from the side of the basket are visible in the image. Also shown are the horizontal (s1 to s3) and vertical (o1 and o2) planes on which tangential and axial velocities respectively were measured using the ultrasound-pulse-echo (UPE) method (Diebold and Dressman, 2001).



Figure 5.8. Photograph of dye radiating outwards from the side of the basket at 50 rpm. Three distinct streams of radiating dye are visible here: one above the lower lip, one below the upper lip and one almost midway up the side of the basket.

Photographs taken to visualise the flow (Figure 5.8), by the method described in section 2.2.6, reveal high velocity domains projecting horizontally from the side of the basket similar to those generated by the CFD model (Figure 5.7). There was a consistent radial emanation of dye from just above the bottom lip. In addition there was generally a region further up the side of the basket where a further emanation was visible. It is expected that all of the fluid around the sides of the basket will have similar consistent features such as the presence of regions of high radial velocity. The exact location of these regions, the distance to which the high velocity radiates outwards until it dissipates and the patterns of the swirls or eddies formed are less predictable time-dependent features. Therefore the overall pattern of fluid-flow at the side of the basket at any one time will be quite complex. The time-averaged CFD model has captured the consistent patterns described above, but the time-dependent features of these patterns could not be represented by the time-averaged CFD simulation. An additional feature noted in the flow visualisation studies was that, although the water coloured within approximately 30 seconds of immersing the basket in the medium, the upper portion of the vessel remained clear for longer. This indicates a region of very low mixing in the upper portion of the vessel, consistent with the low velocities in the upper portion of the vessel, illustrated in Figure 5.7.

Considering the presence of the regions of high velocity radiating from the side of the basket and the area of low velocity in the upper portion of the basket demonstrated using the flow visualisation technique, these results give confidence that CFD provides a representative model of the system hydrodynamics.

5.3.2 Quantitative validation.

Simulated tangential and axial velocity values in the apparatus were compared to values reported using an ultrasound-pulse-echo (UPE) technique (Diebold and Dressman, 2001). The simulated values from the CFD model were found to be lower than the measured velocities, possibly due to the velocities recorded by the ultrasound method being maximum values at a particular location on each plane, whereas the simulated flow-field is a time-averaged solution. Average simulated tangential velocities on each plane were examined, and also the maximum and minimum simulated axial values on each plane since average axial velocities were not very informative as the velocities in positive (upward) and negative (downward) directions generally cancelled each other out resulting in very low average values. When these average values for each plane (or maximum/minimum axial values) are plotted as a ratio to the average value of another of the planes, the ratios correspond well to equivalent ratios of maximal velocity data as measured by the UPE method. Figure 5.9 shows average plane velocity ratios of s1 to s2, s3, o1 and o2 and ratios of s3 to s1, s2, o1 and o2 at 50, 100 and 150 rpm from CFD simulations (maximum or minimum velocities in the case of the axial data from o1 and o2) plotted against ratios of velocity data determined by Diebold and Dressman (2001) using UPE. It can be concluded that there is a correlation between ratios of simulated and experimental observations. In other words, time-averaged CFD solution yields information about velocities in one region of the vessel relative to another at 50, 100 and 150 rpm which is similar to the relative differences between measured time-dependent maximum values in the corresponding regions of the vessel determined using the UPE method.

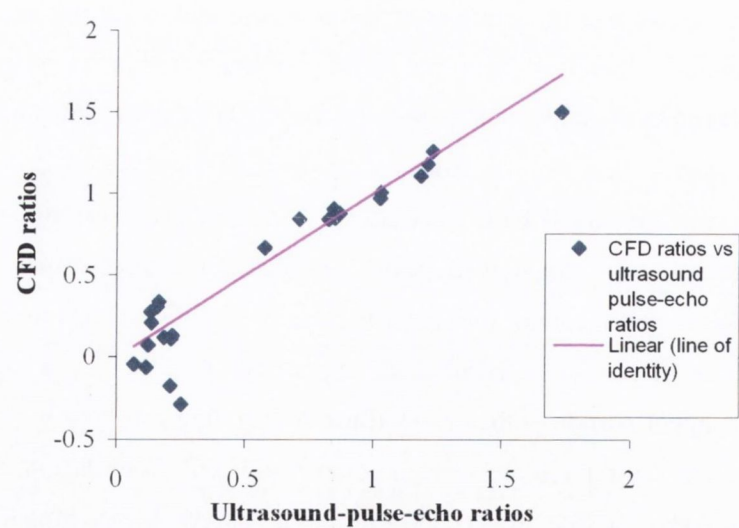


Figure 5.9. Ratios of s1 to s2, s3, o1 and o2 and ratios of s3 to s1, s2, o1 and o2 at 50, 100 and 150 rpm from average plane velocities from CFD simulations (maximum or minimum plane velocities in the case of the axial data from o1 and o2) vs. ratios of velocity maxima at particular locations on plane s1 to s2, s3, o1 and o2, and on plane s3 to s1, s2, o1 and o2 from ultrasound-pulse-echo (UPE) data (Diebold and Dressman, 2001), also measured at 50, 100 and 150 rpm.

Unfortunately, none of the points on the planes detailed in the UPE data (Diebold and Dressman, 2001) were in or near the basket itself, where the highest velocities were present, and where a dosage form would be placed.

The maximum simulated velocity on a plane through the basket itself at 50 rpm is $57 \times 10^{-3} \text{ ms}^{-1}$, while the maximum velocity recorded by Diebold and Dressman (2001) at planes where measurements were made was $9 \times 10^{-3} \text{ ms}^{-1}$. The greatest difference between the CFD simulation of the basket apparatus at 50 rpm and the UPE measurements at the same speed is only $5 \times 10^{-3} \text{ ms}^{-1}$ (occurring on the s2 plane). Thus, the magnitude by which the CFD values were lower than the UPE values is minimal when compared to the overall velocities present in both the basket and paddle apparatus.

It can be seen in Figure 5.10 that although tangential velocity data from the CFD model of the paddle apparatus did not, in general, fall inside the error bars of the measurements recorded by UPE, there was a good correlation between the two methods over the range of velocities examined. The degree to which the values in the basket apparatus differ from the UPE values is also evident in Figure 5.10.

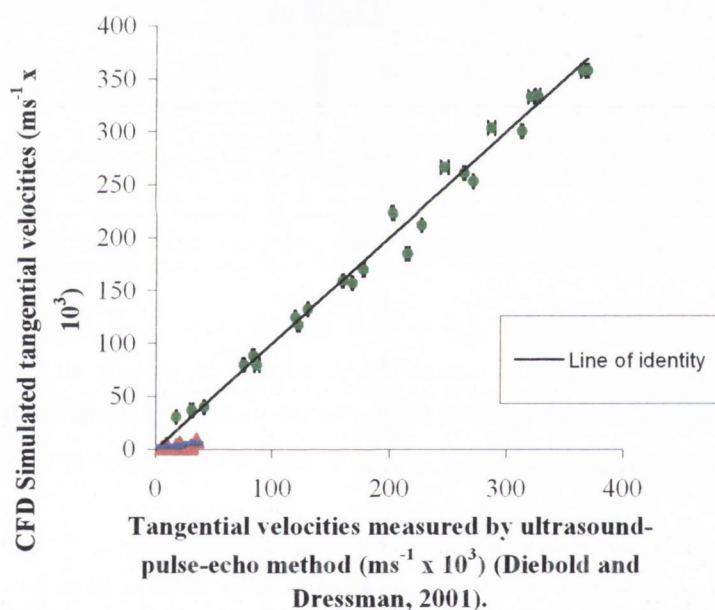


Figure 5.10. Tangential velocities from CFD simulations calculated at the ultrasound-pulse-echo measurement locations vs. tangential velocities measured by ultrasound-pulse-echo (Diebold and Dressman, 2001). Data from the paddle apparatus (●) is taken from rotation speeds of 25 to 200 rpm, and from the basket apparatus (▲) at 50, 100 and 150 rpm. “Basket plane average” data (—) is the average CFD-generated velocity value from the entire plane of measurement (s1, s2 and s3) rather than the exact location on the plane that the velocities were measured by the UPE method.

5.4 Hydrodynamic features.

The velocity vectors in the region of the basket (at 100 rpm) in Figure 5.11 show an upward axial flow under the basket, and some outward radial flow at the base of the basket. This implies that a dosage form at the base of the basket is exposed to higher velocities at the outer edge of the basket. The upward axial flow would contribute to the fluid motion at the bottom of the basket which results in a similar degree of dissolution from the bottom surface of a tablet in the basket as from the side and top surfaces (Moriwaka et al., 2002). Fluid motion from natural convection, as discussed in section 5.7, also possibly contributed to the dissolution from this lower surface.

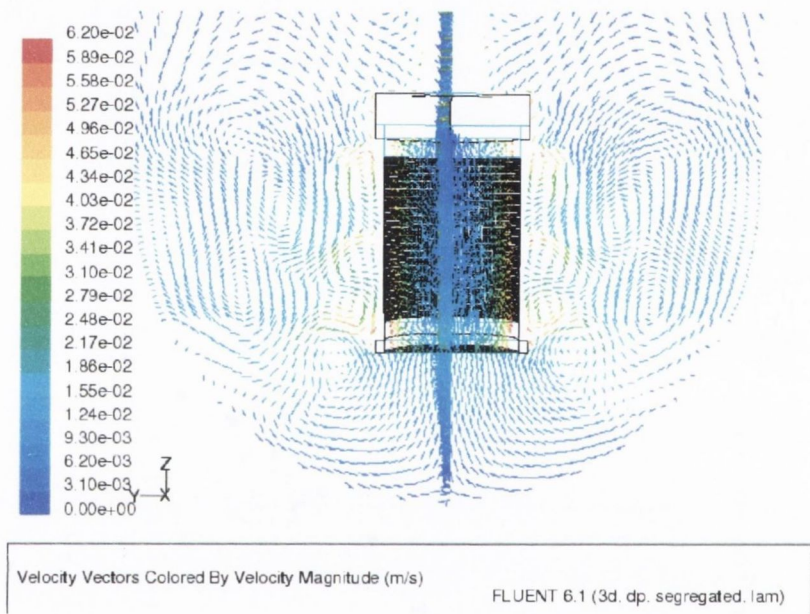


Figure 5.11. CFD-generated vectors coloured by velocity magnitude on a vertical plane at $x=0$ through the flow field, from simulations of 900 ml in the basket apparatus at 100 rpm. For clarity, only 1 vector in 9 is shown and vectors of velocity greater than or equal to 0.062 ms^{-1} are shown in red.

There is a degree of both inward (negative) and outward (positive) radial flow within the basket, as seen in Figure 5.12, and axial velocities in the upward and downward directions, as seen in Figure 5.13, which might result in a dosage form being subject to variable velocities.

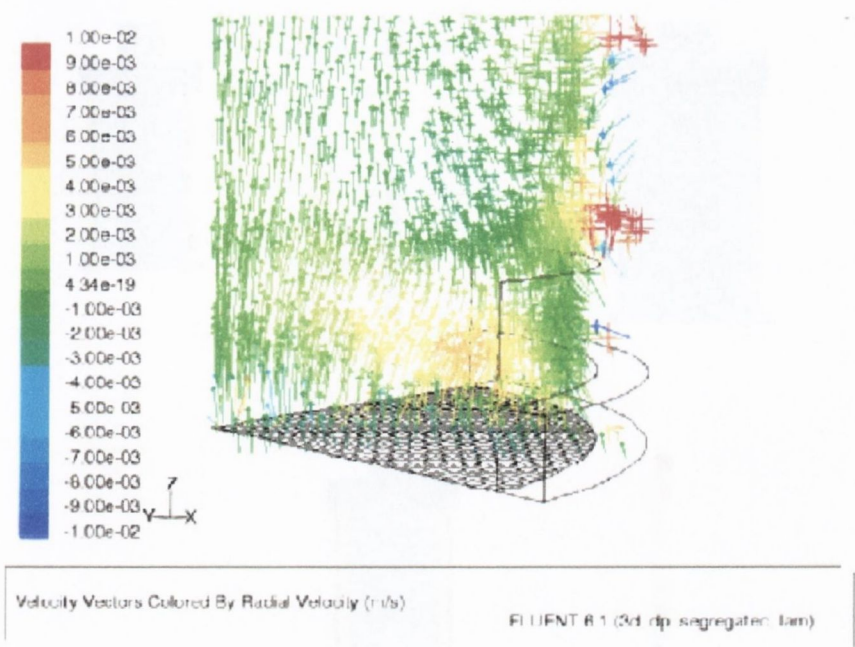


Figure 5.12. CFD-generated vectors coloured by radial velocity in the lower portion of the basket; from simulations of 900 ml in the basket apparatus at 100 rpm.

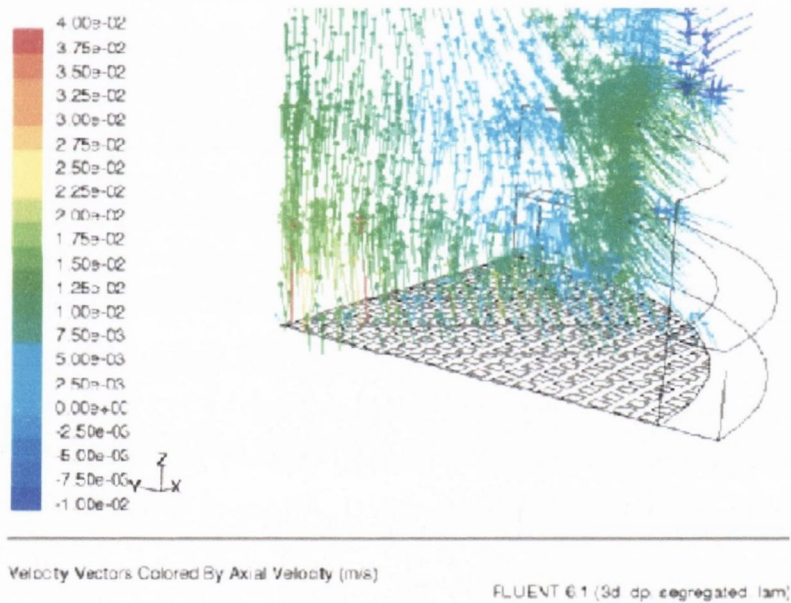


Figure 5.13. CFD-generated vectors coloured by axial velocity in the lower portion of the basket; from simulations of 900 ml in the basket apparatus at 100 rpm.

The velocity magnitude within the basket at 50, 100 and 150 rpm is displayed in contours in Figure 5.14.

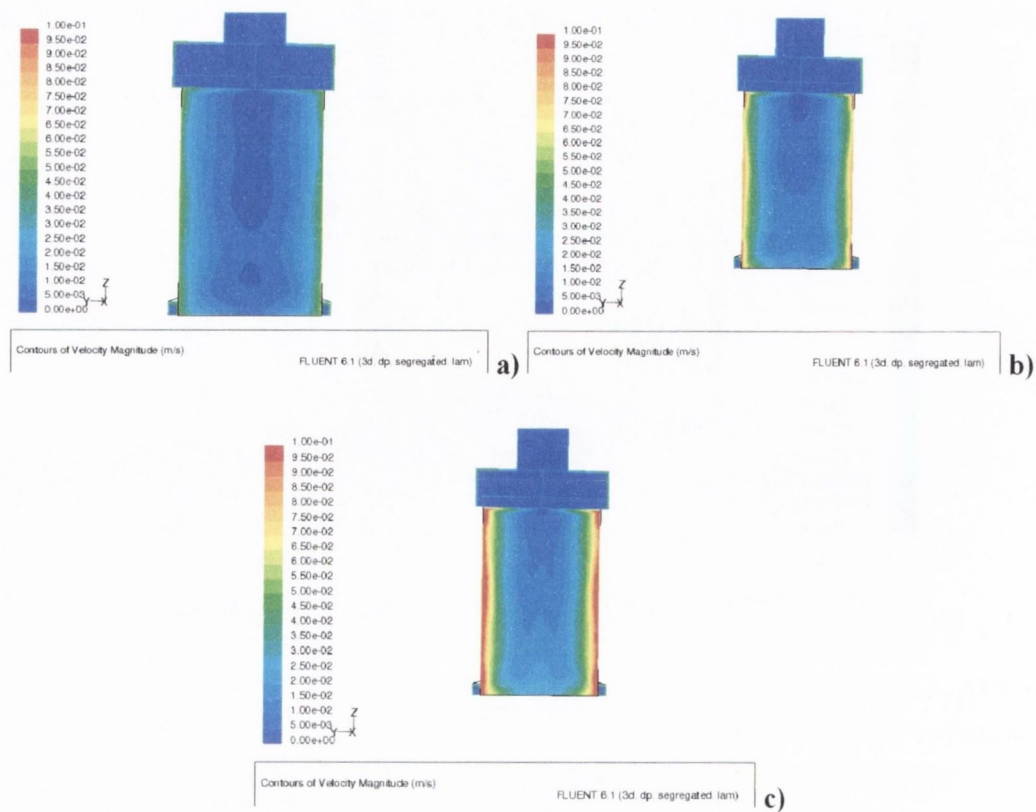


Figure 5.14. CFD-generated contours of velocity magnitude in the basket from simulations of 900 ml in the basket apparatus at a) 50 b) 100 and c) 150 rpm.

From Figure 5.14 it is evident that within the basket the velocity increases from the centre of the basket towards the basket sides which are rotating. Although the velocity distribution inside the sides of the basket grid appears uniform, with the exception of a region of slightly higher velocity at the lower end of the centre of the basket compared to the upper end, the velocity distribution directly outside the basket wall is much more complex (Figure 5.11). The slightly higher velocity at the centre of the bottom of the basket in Figure 5.14 is likely to be influenced by upwards axial flow entering the basket, as described in Figure 5.11. This axial flow is shown in greater detail at each rotation speed in Figure 5.15.

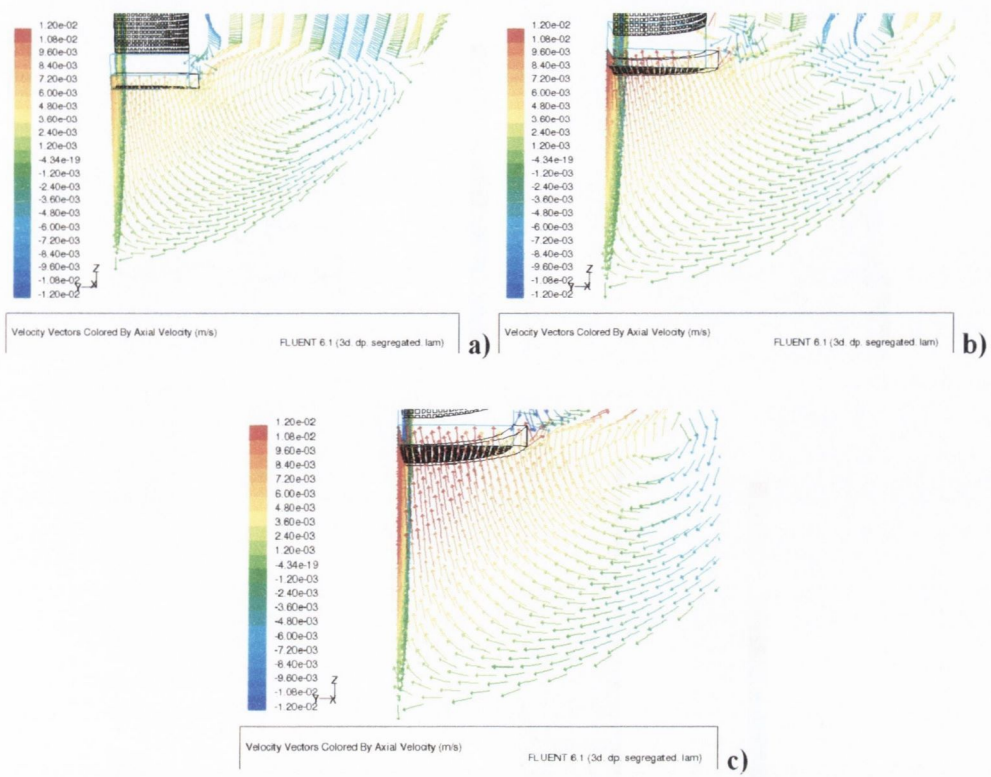


Figure 5.15. CFD-generated vectors coloured by axial velocity underneath the basket; from simulations of 900 ml in the basket apparatus at a) 50 b) 100 and c) 150 rpm. Only 1 vector in 5 is shown for clarity.

It is clear from Figure 5.15 that there is positive axial flow underneath the basket at each rotation speed investigated. This is generated as a part of the secondary flow patterns which result from the regions of radial outflow at the basket sides, as described in section 5.3. Velocity vectors coloured according to the radial velocity values are presented in Figure 5.16.

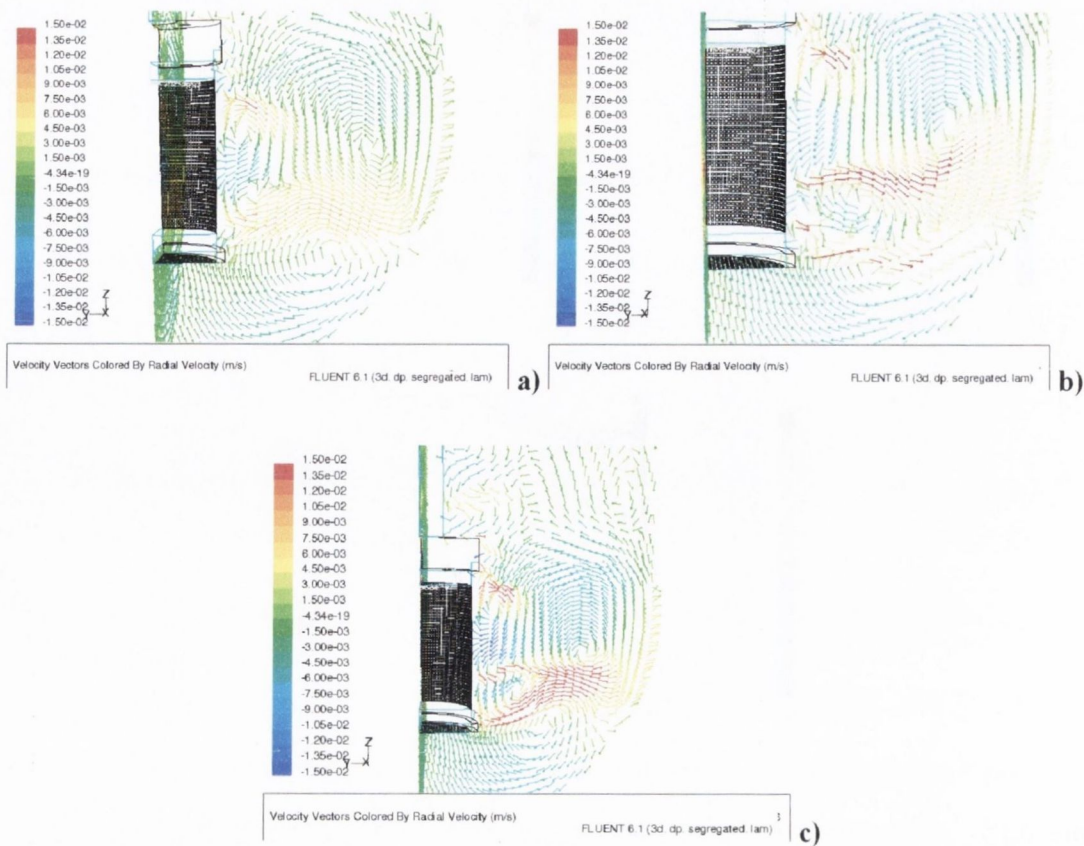


Figure 5.16. CFD-generated vectors coloured by radial velocity; from simulations of 900 ml in the basket apparatus at a) 50, b) 100 and c) 150 rpm. Only 1 vector in 9 is shown for clarity.

The radial velocity vectors in Figure 5.16 indicate the regions of fluid flowing radially outward from the basket wall. Although there is some radial inward (negative) flow in each case, the magnitude is not as great as the radial outflow. As a result there are complex swirling features produced, as the fluid which has flowed outwards radially undergoes axial movement. There is both upward and downward axial movement of the fluid, but as can be seen in Figure 5.17 a larger component of the fluid at the level of basket sides travels in the negative (downward) axial direction. This is balanced by the positive axial flow upwards and into the basket.

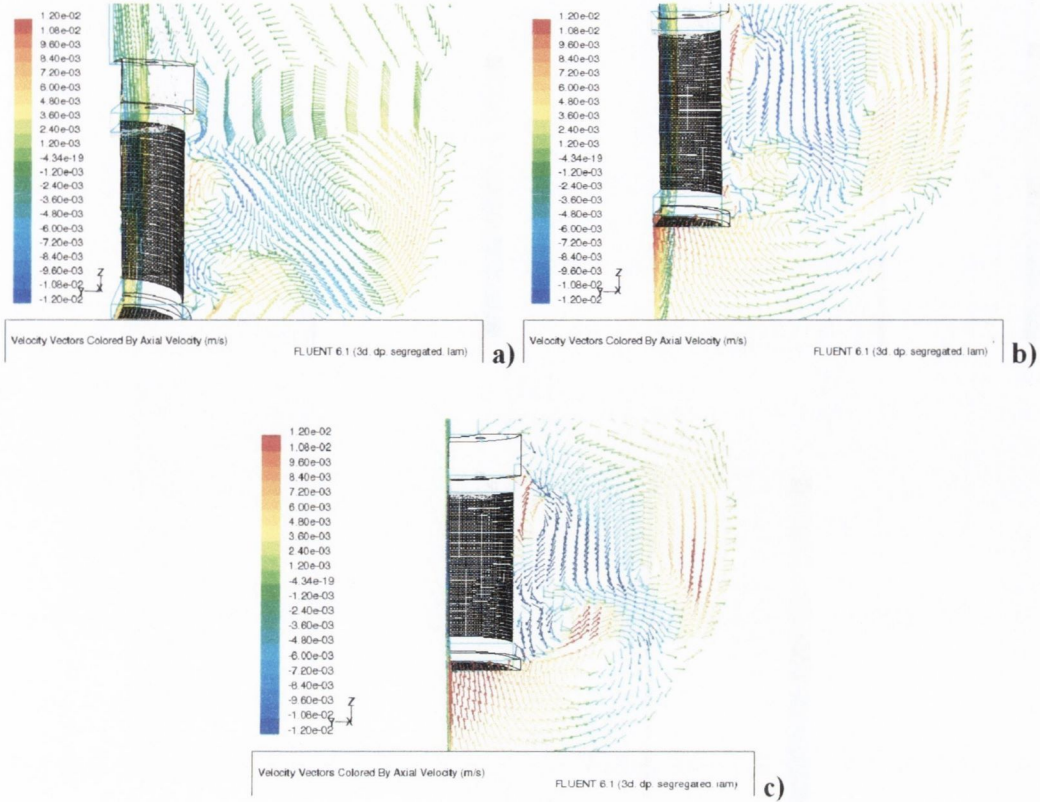


Figure 5.17. CFD-generated vectors coloured by axial velocity; from simulations of 900 ml in the basket apparatus at a) 50, b) 100 and c) 150 rpm. Only 1 vector in 9 is shown for clarity.

Although there is a considerable downward flow from the level of the basket sides, which is compounded by the curvature in the lower region of the vessel to produce the strong positive axial flow underneath the basket, there is also a degree of positive axial flow from the level of the basket into the upper region of the vessel. This results in a positive axial flow in the upper region of the fluid domain (above the basket), which is countered by negative axial flow at the shaft, resulting in the formation of swirls or eddies in the region of the surface of the rotating basket. These are evident in Figure 5.18.

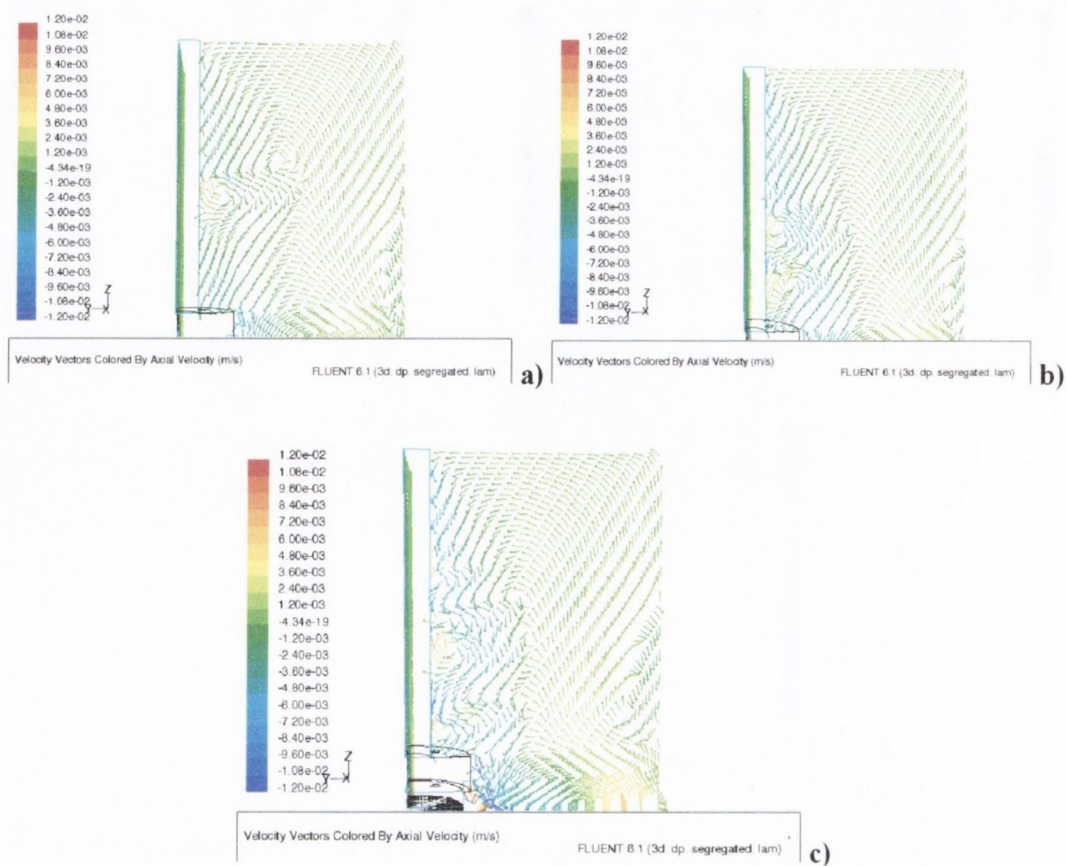


Figure 5.18. CFD-generated velocity vectors coloured by axial velocity in the upper region of the fluid domain; from simulations in 900 ml in the basket apparatus at a) 50, b) 100 and c) 150 rpm. Only 1 vector in 5 are shown for clarity.

The complex secondary flow patterns generated by the CFD simulations can be compared to the postulated flow pattern within the basket apparatus presented by Diebold (2000), reproduced in Figure 5.19

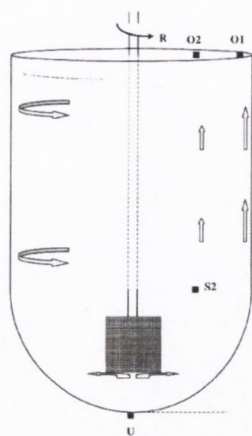


Figure 5.19. Suggested fluid flow pattern within the basket apparatus from UPE data (Diebold, 2000).

The upward axial flow in the upper region of the fluid domain is consistent with the flow fields simulated using CFD. The CFD simulations, however, suggest radial outflow from the basket sides and predominantly upward flow beneath the basket, whereas the flow pattern suggested by Diebold (2000) shows upward flow and outward radial flow beneath the basket. Despite the variation in axial and radial fluid dynamics in the basket apparatus, there is little variation in tangential fluid flow away from the walls of the basket itself. Figure 5.20 illustrates the variation in tangential velocity in the basket apparatus at 150 rpm. It is clear that in both the lower and upper regions of the flow field there is little variation in tangential velocity, with the exception of the region adjacent to the basket walls, and some increase in tangential velocity persists as far as the edge of the vessel at the level of the basket.

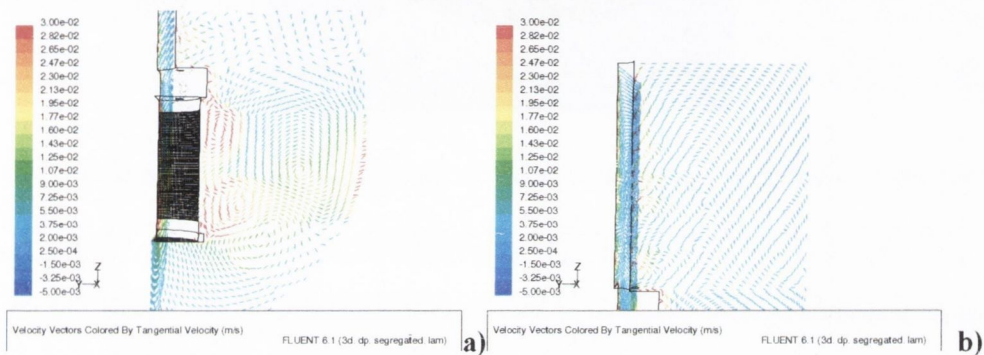


Figure 5.20. CFD-generated vectors coloured by tangential velocity at a) the region of the apparatus level with the basket and b) the upper region of the fluid domain; from simulations of 900 ml in the basket apparatus at 150 rpm. Only 1 vector in 9 is shown in (a) and 1 vector in 5 is shown in (b) for clarity.

The lower velocities present above the basket compared with the velocities at the level of the basket itself are consistent with the dye studies in Figure 5.21. In this photograph the upper region of the media is less coloured than the region adjacent to the basket and beneath the basket. Although the region of the fluid adjacent to the basket side is expected to be more coloured, as the basket side is the source of the dye, the increased colour below the basket compared to above the basket implies a greater extent of mixing between the fluid region adjacent to the basket and that beneath the basket, compared to the mixing between the lower and upper regions of the vessel. This is also consistent with the qualitative validation in section 5.3.1, where low velocities were described in the upper portion of the vessel corresponding to less visible dye in the upper portion of the vessel in the photograph in Figure 5.8.

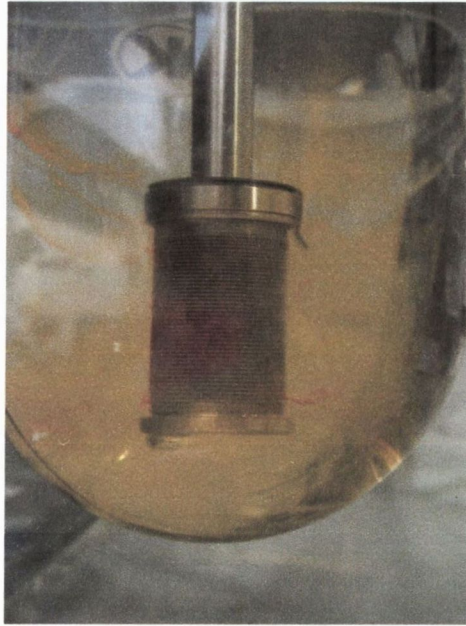


Figure 5.21. Photograph of the extent of dye mixing in the media in the basket apparatus.

The various “swirls” visible on the CFD images of velocity vectors in the region of fluid adjacent to the basket side are evidence of the complex flow phenomena which are present in the basket apparatus. Caution should be exercised, however, in interpreting the importance of the exact location of these swirls. In Figure 5.22 tangential velocity vectors are presented from the 100 rpm simulation using both wall and symmetry conditions at the air-water interface. Although the velocity magnitudes are very similar, as are the overall hydrodynamic characteristics, the location and size of the various swirls and eddies vary with each simulation. It must be accepted, therefore, that the boundary conditions used in the CFD solution itself will influence the nature of the “swirls” simulated.

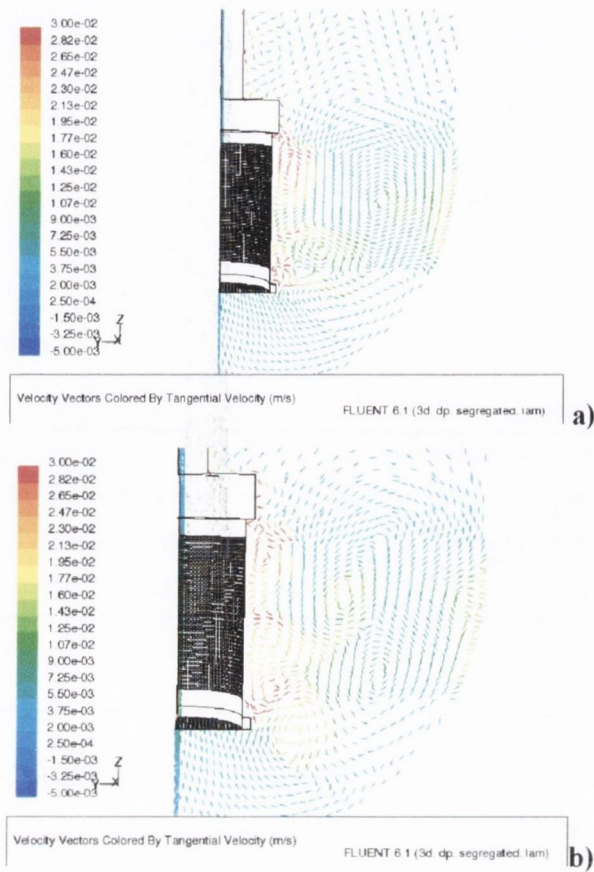


Figure 5.22. CFD-generated vectors coloured by tangential velocity from simulations of 900 ml in the basket apparatus using a) wall and b) symmetry conditions at the air-water interface. Only 1 vector in 9 is shown for clarity.

As these are essentially time-dependent features, it can be concluded that the nature and location of the swirls are subject to variation. However, they are present in each simulation regardless of boundary conditions at the air-water interface, or rotation speed used, and can therefore be assumed to contribute to the secondary flow characteristics present in the apparatus.

5.5 Effect of hydrodynamics on dissolution rate – comparisons between regions in the basket apparatus and between the paddle and basket apparatuses.

5.5.1 Apparatus suitability test.

The basket dissolution apparatus passed the apparatus suitability test for both disintegrating tablets (prednisone) tested at 50 rpm and non-disintegrating (salicylic acid) tablets tested at 100 rpm. The results and acceptance ranges for prednisone Lot N and salicylic acid Lot O are presented below in Table 5.1.

Tablet	Acceptance Range (Accepted range of % of labelled content dissolved at 30 minutes).	Result (Actual range of % of labelled content dissolved at 30 minutes; 3 prednisone and 3 salicylic acid tablets were tested).
Prednisone	54-78%	59-77%
Salicylic Acid	23-29%	24-28%

Table 5.1. Acceptance ranges and achieved dissolution test ranges for the apparatus suitability test for the basket dissolution apparatus.

5.5.2 Relationship between velocity and mass transfer.

The velocities present in each apparatus, at 50 and 100 rpm, are compared in Figure 5.23. Velocities in the region of the base of the vessel of the basket apparatus were found to be very low in general, ranging from approximately 0.003×10^{-3} to $3.5 \times 10^{-3} \text{ ms}^{-1}$ at 50 rpm to 0.006×10^{-3} to $4.5 \times 10^{-3} \text{ ms}^{-1}$ at 100 rpm. Velocities within the basket, on the other hand, ranged from approximately 0.5×10^{-3} to $57 \times 10^{-3} \text{ ms}^{-1}$ at 50 rpm and 1×10^{-3} to $114 \times 10^{-3} \text{ ms}^{-1}$ at 100 rpm. In the paddle apparatus, velocities at the base of the vessel ranged from approximately 0.8×10^{-3} to $80 \times 10^{-3} \text{ ms}^{-1}$ at 50 rpm.

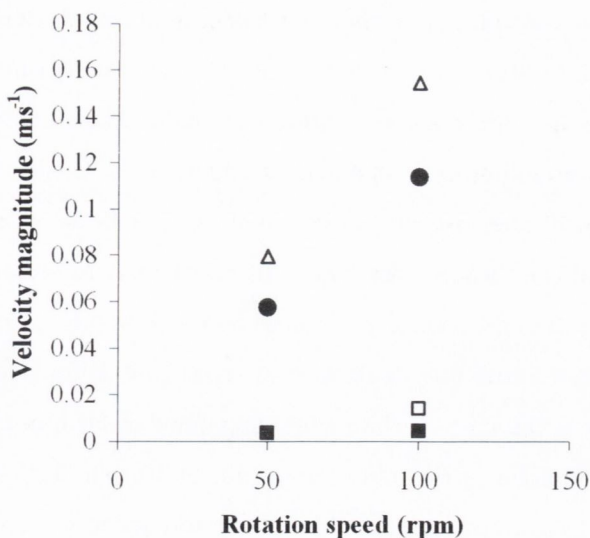


Figure 5.23. CFD-generated velocity magnitude vs. rotation speed for locations within the basket (●), at the base of the vessel of the basket apparatus (within 12 mm of the centre) (■), at the base of the vessel of the paddle apparatus (within 12 mm of the centre) (Δ) and above a tablet placed at the base of the vessel of the basket apparatus (□).

The maximum velocity at the base of the paddle apparatus at 50 rpm ($80 \times 10^{-3} \text{ ms}^{-1}$) is lower than the maximum velocity within the basket of the basket apparatus at 100 rpm ($114 \times 10^{-3} \text{ ms}^{-1}$). This comparison is of interest as these are common operating speeds for the respective apparatuses, and are recommended, for example, in the development of an *IVIVC* using *in vitro* dissolution test data (FDA, 1997b).

It has been shown that there is greater dissolution from the lower surface of a dosage form within the basket than at the base of the paddle apparatus at the same rotation speed (Moriwara et al., 2002). The similar fluid velocity magnitudes within the basket and at the base of the paddle apparatus at each rotation speed from the CFD simulations supports the equivalent dissolution rate from a non-disintegrating tablet placed in each of these positions (Moriwara et al., 2002). Although the velocity relative to the surface of a dosage form in the basket will be less than the overall velocity magnitude due to the concurrent rotation of the dosage form itself, when the increased dissolution from the lower surface of the tablet inside the basket is accounted for it is feasible that the dissolution rate could be equivalent to that of a dosage form at the base of the paddle apparatus. The low velocities at the base of the vessel of the basket apparatus are not, however, consistent with the observation of Moriwara et al. (2002) that dissolution from a tablet in this position at 100 rpm is equivalent to dissolution from a tablet inside the basket at 50 rpm. In order to investigate this further, a CFD model of the basket apparatus (at 100 rpm) with a tablet at the base of the vessel was solved, and the solution yielded velocities in the region of $14 \times 10^{-3} \text{ ms}^{-1}$ above the tablet. Although this is still lower than the velocities recorded in the paddle apparatus at 50 rpm ($80 \times 10^{-3} \text{ ms}^{-1}$) and inside the basket at 50 rpm ($57 \times 10^{-3} \text{ msec}^{-1}$), it represents a

significant increase in velocity compared to the base of the vessel where velocities in the region of $4.5 \times 10^{-3} \text{ ms}^{-1}$ were determined at 100 rpm without the tablet in place. As the dissolution studies performed by Morihara et al. (2002) were carried out using salicylic acid in a phosphate buffer medium of pH 7.4, there may have been a contribution from natural convection to the dissolution of salicylic acid arising from its solubility at this pH, $\sim 10 \text{ mg/ml}$ at 37°C (Ramtoola and Corrigan, 1987), and the resultant density and viscosity effects that this solubility would introduce at the dissolution interface. Natural convection effects may also contribute to the dissolution rate from the lower surface of a tablet within the basket, as described in section 5.6.

In the present work it was also found that there was no significant difference in dissolution rate from benzoic acid compacts at the base of the paddle apparatus at 50 rpm (1.52 mg min^{-1}) and benzoic acid compacts in the basket of the basket apparatus at 50 rpm (1.50 mg min^{-1}) ($p > 0.05$). The CFD simulation of the basket apparatus does not take into account erosion from the basket sides, movement of the compact within the basket, or disturbances in fluid flow within the basket caused by the presence of the compact itself.

A correlation was demonstrated in section (3.3.3) between the dissolution rate from different compact surfaces and the CFD simulated maximum velocities at a distance of 1 mm (approximately at the edge of the hydrodynamic boundary layer, as discussed in section 3.3.5) from the compact surface in the USP paddle apparatus. In order to further investigate this relationship, velocities at various points within the basket relative to a compact rotating at these points (as described in section 2.2.1.2) were calculated. These velocities are presented in Table 5.2.

Radius	Relative velocity (ms^{-1})		
	50 rpm	100 rpm	150 rpm
0.0065	0.0240	0.0515	0.0785
0.008	0.0276	0.0607	0.0934
0.009	0.0283	0.0637	0.0962
0.01	0.0254	0.0597	0.0950
Average	0.0263	0.0589	0.0914

Table 5.2. Calculated relative velocities that the compact surface would be exposed to at 50, 100 and 150 rpm in the basket apparatus. The velocity is equal to the difference between the speed at which the compact would be rotating with the basket at a defined radius within the basket, and the minimum fluid velocity (data from the CFD simulation) at this radius.

The average of the velocities relative to the compact, as detailed in Table 5.2, is an estimate of the maximum relative fluid velocity the rotating compact would be exposed to within the basket. The dissolution rate from the basket apparatus at 50 rpm is plotted against this maximum relative

velocity in Figure 5.24, together with the corresponding data (maximum facet velocity at 1 mm from the compact surface) from the paddle apparatus.

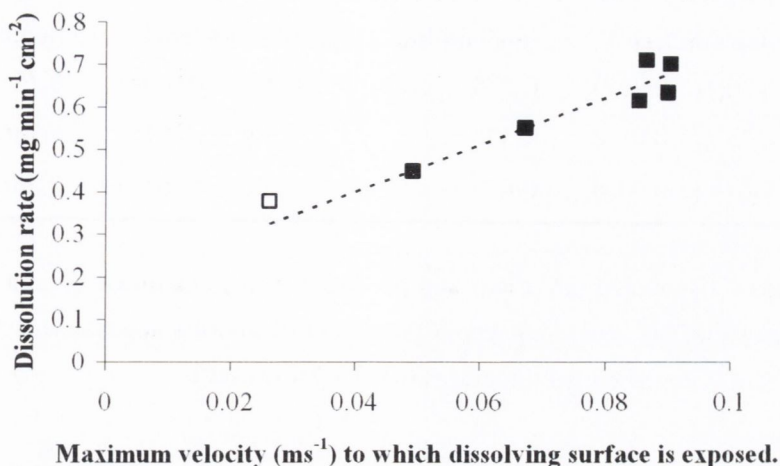


Figure 5.24. Dissolution rate of benzoic acid in $\text{mg min}^{-1}\text{cm}^{-2}$ from different compact surfaces within the paddle apparatus (■) and whole compacts within the basket of the basket apparatus (□) vs. maximum facet velocity (ms^{-1}), or maximum relative velocity (data from the basket apparatus) to which the dissolving surface is exposed.

A reasonable linear relationship is evident having a positive intercept on the y- axis. This positive intercept indicates dissolution in the absence of forced convection i.e. the dissolution rate in natural convection. The equation of the line ($R^2 = 0.9051$), by least squares regression (of all of the individual dissolution rate data points, rather than averages) was:

$$\text{Dissolution Rate (mg min}^{-1}\text{cm}^{-2}) = (4.62 \times \text{Velocity (ms}^{-1})) + 0.254. \quad \text{Equation 5.1}$$

Equation 5.1 was divided by the values for the diffusion coefficient (D) and saturated solubility (c_s) of benzoic acid, and multiplied by the corresponding values for salicylic acid ($D = 1.132 \text{ m}^2 \text{ s}^{-1} \times 10^{-9}$, $c_s = 2706 \text{ g m}^{-3}$ respectively, (Ramtoola and Corrigan, 1987; Corrigan, 1973). This resulted in a version of equation 5.1 modified to relate the dissolution rate of salicylic acid to the maximum velocity (ms^{-1}) the dissolving surface is exposed to:

$$\text{Dissolution rate}_{\text{salicylic acid}} (\text{mg min}^{-1}\text{cm}^{-2}) = (2.509 \times \text{Velocity (ms}^{-1})) + 0.138 \quad \text{Equation 5.2}$$

Dissolution rates from benzoic and salicylic acid compacts in the basket apparatus at agitation rates of 50, 100 and 150 rpm (O'Neill, 2006) were compared to rates predicted from equation 5.1 (benzoic acid) and modified equation 5.1, equation 5.2, for salicylic acid dissolution rate predictions.

Actual and predicted dissolution rates, using equations 5.1 and 5.2, from the basket dissolution apparatus at different rotation speeds, are compared in Table 5.3.

	Benzoic acid		Salicylic Acid	
Agitation	Actual	Predicted	Actual	Predicted
rate (rpm)	Dissolution Rate	Dissolution Rate	Dissolution Rate	Dissolution Rate
	(mg.min ⁻¹ cm ⁻²)	(mg.min ⁻¹ cm ⁻²)	(mg.min ⁻¹ cm ⁻²)	(mg.min ⁻¹ cm ⁻²)
50	0.349 (± 0.027)	0.375	0.189 ± (0.008)	0.204
100	0.554 (± 0.010)	0.526	0.306 ± (0.015)	0.286
150	0.615 (± 0.030)	0.677	0.389 ± (0.011)	0.366

Table 5.3. Actual (± 1 standard deviation) and predicted (using equations 5.1 and 5.2) dissolution rates of benzoic and salicylic acid compacts in the basket dissolution apparatus at 50, 100 and 150 rpm; dissolution data from the basket apparatus in 900 ml 0.1M HCl.

The data in Table 5.3 is illustrated graphically in Figure 5.25. A smaller increase in dissolution rate of benzoic acid at an agitation rate of 150 rpm from 100 rpm compared to the increase at 100 rpm from 50 rpm is evident in this graph. This suggests a non-linear increase in dissolution rate with the maximum velocity the dissolving surface is exposed to, as calculated using the method described in section 2.2.1.2, with higher agitation rates. The error bars on the data points which represent the predicted dissolution rate of benzoic acid in Figure 5.25, however, imply that when the error in the dissolution rate-velocity relationship is accounted for, equation 5.1 adequately predicts the dissolution rate of benzoic acid at the agitation rates examined. These error bars are calculated by using the values at the extremes of the 95% confidence interval of the intercept to predict the dissolution rate, rather than the value of 0.254 as detailed in equation 5.1. The error bars on the experimental dissolution rate data points represent 1 standard deviation. From Figure 5.25, the predicted dissolution rates using equations 5.1 and 5.2 are of acceptable accuracy, when the expected error of the predicted and experimental data is taken into account.

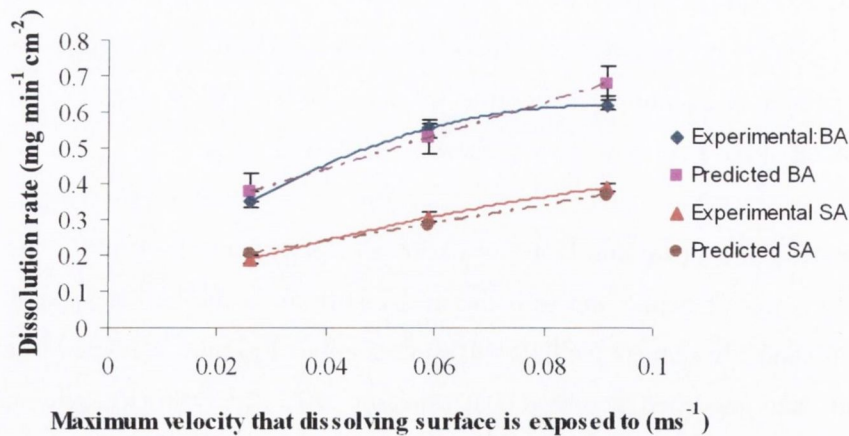


Figure 5.25. Predicted (equations 5.1 and 5.2) and experimentally observed dissolution rates (mg min⁻¹ cm⁻²) from compacts of benzoic (BA) and salicylic (SA) acid in the basket dissolution apparatus vs. maximum velocity (ms⁻¹) that the dissolving surface is exposed to.

The intercept value of 0.254 in equation 5.1 indicates a dissolution rate of $0.254 \text{ mg min}^{-1} \text{ cm}^{-2}$ for benzoic acid dissolving in the stagnant fluid. When a 95% confidence interval for the intercept of the line is calculated from the data in Figure 5.24, this interval gives a predicted range of $0.207 \text{ mg min}^{-1} \text{ cm}^{-2}$ to $0.300 \text{ mg min}^{-1} \text{ cm}^{-2}$ for the experimental value. This range does not take orientation into account.

5.6 Dissolution rates under conditions of natural convection.

Under natural convection conditions diffusion and the density difference between a saturated solution and pure dissolution medium are rate determining factors. Computation of diffusional flow in the case of a horizontally oriented cylinder has not yet been resolved, however equations have been presented for the case of cylindrical cavities (Krysa et al., 2000), and for a vertical plate by Levich (1962) who stated that the case of horizontal orientation of the reaction surface is considerably more complicated.

An estimate of the benzoic acid dissolution rate under natural convection conditions was made using the equation of Krysa et al., (2000), which quantified mass transfer to upward-facing cylindrical cavities by free convection:

$$Sh = 0.559(Pr \cdot Gr)^{0.265} \quad \text{Equation 5.3}$$

Where S_h is the dimensionless Sherwood number (KL_c/D), K is a mass transfer coefficient, D is the diffusivity of the solute in the solvent and L_c is the characteristic length. This length for a cylinder is defined as $(H + d/4)$ where H is the height of the cylinder (3 mm) and d is the diameter (13 mm) (Weber et al., 1984; Krysa et al., 2000). Pr is the Prandtl number, ν/D , and the Grashof number (G_r) is given by $gL_c^3\Delta\rho/\nu^2\rho$. D and L_c are defined above, g is gravitational acceleration, $\Delta\rho$ is the difference between the density of the saturated solution of the solute in the solvent and the density of the pure dissolution medium (bulk density), ρ is the bulk density and ν is the kinematic viscosity of the bulk. In the current work, the bulk density was determined to be $995.177 \text{ kg m}^{-3}$ (0.1M HCl) and the density of a saturated solution of benzoic acid was $997.163 \text{ kg m}^{-3}$. The density of a saturated solution of salicylic acid was taken to be $996.036 \text{ kg m}^{-3}$, as determined by Walsh (2006). Therefore, $\Delta\rho$ was determined to be 1.99 kg m^{-3} (benzoic acid) and 0.859 kg m^{-3} (salicylic acid). Values used for the saturated solubility, c_s , of benzoic and salicylic acid in 0.1M HCl, and values for the diffusion coefficient, D , of benzoic and salicylic acid were as described in section 2.2.1.4.2.

The previously determined value $7.043 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$ for ν was also used (Corrigan, 1973). Using these values with equation 5.3, the theoretical dissolution rate of benzoic acid was calculated to be $0.182 \text{ mg min}^{-1} \text{ cm}^{-2}$. The dissolution rate was calculated by multiplying the K value, (mass transfer coefficient (ms^{-1})), which was determined from S_h , by the saturated solubility, c_s .

Alternatively Levich described diffusional flow in natural convection at a vertical plate in a gravitational field as follows:

$$I/A = 0.9Pr^{1/4}G_r^{1/4}Dc_0/L_c \quad \text{Equation 5.4}$$

where (I) is the total diffusional flow to a plate of surface area (A), c_0 is the concentration far from the plate and L_c is the height of the vertical plate. In our case we are considering diffusional flow from a surface in natural convection, therefore the c_0 term is replaced with c_s , the saturated

solubility at the surface. The L_c value of $(H + d/4)$ was substituted for the height of the vertical plate, as was used in equation 5.3. Using equation 5.4 the dissolution rate of benzoic acid was calculated to be $0.236 \text{ mg min}^{-1} \text{ cm}^{-2}$. Given the approximations involved, these estimates of 0.182 (equation 5.3) and 0.236 (equation 5.4) $\text{mg min}^{-1} \text{ cm}^{-2}$ are of a similar order of magnitude to the experimental value of $0.254 \text{ mg min}^{-1} \text{ cm}^{-2}$, determined by extrapolation from Figure 5.24.

The orientation of the dissolving surface influences the dissolution rate under natural convection conditions (Patrick et al., 1977). The predictions of dissolution rate in 0.1M HCl of benzoic acid under conditions of natural convection from equations 5.1, 5.3 and 5.4, and of salicylic acid from equation 5.2, do not take the orientation of the dissolving surface into account, therefore they can only be approximate predictions of the contribution made by natural convection to an experimental dissolution rate. Consequently, dissolution of benzoic and salicylic acid from a number of different surface-orientation combinations was investigated. Details of the surface-orientation combinations are given in section 2.2.2.5. The dissolution rates (Fagan, 2006) from salicylic and benzoic acid from different surface-orientation combinations are given in Table 5.4. It is evident from the results in Table 5.4 that the dissolution rate is affected by orientation of the dissolving surface. The surfaces with a vertical orientation dissolve faster than the upward horizontal facing surface, and the downward facing benzoic acid surface dissolves fastest. That these vertical and downward facing surfaces dissolve faster than the upward facing surface is to be expected as the saturated solution at the dissolving surface is exposed to the effect of gravity. This saturated solution is denser than the surrounding dissolution media and will therefore move downwards away from the surface. As the curved side surface is located at the base of the jar, this saturated solution cannot move further downwards than the base of the compact. The concentration gradient at the base of the dissolving side surface will then be affected by the rate at which the saturated solution diffuses away from the dissolving surface. At the other vertically orientated dissolving surface, that of the top planar surface orientated vertically and located at the top of the jar, the saturated solution can freely move downwards away from the dissolving surface towards the base of the jar. The effect of the rate of diffusion of the more dense saturated solution away from the dissolving surface on the dissolution rate at this surface would be expected therefore to be less than at the curved side surface at the base of the jar, as convection would play a dominant role. This is evident in the dissolution rates from the top planar surface orientated vertically being significantly higher than the dissolution rates from the curved side surface.

	Benzoic Acid	Salicylic Acid
Surface/Orientation	Dissolution Rates (mg min ⁻¹ cm ⁻²)	
Top Planar Surface	0.065 (±0.0047)	0.029 (±0.0007)
Curved Side Surface	0.103 (±0.0097)	0.035 (±0.0008)
Bottom Planar Surface	0.134 (±0.0081)	0.081 (±0.0008)
Top Planar Surface orientated vertically	0.134 (±0.0055)	0.062 (±0.0047)

Table 5.4. Dissolution rates (mg min⁻¹ cm⁻²) of benzoic and salicylic acid from different surface-orientation combinations under conditions of natural convection (Data taken from Fagan, (2006)).

The dissolution rate with time data from these surface-orientation combinations are presented in Figure 5.26 (benzoic acid) and 5.27 (salicylic acid) (data taken from Fagan, (2006)).

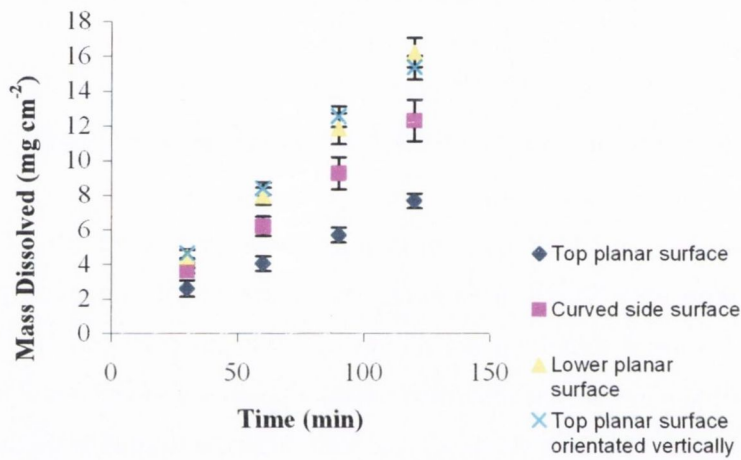


Figure 5.26. Mass of benzoic acid dissolved (mg cm⁻²) in 0.1M HCl vs. time (min) from different surface-orientation combinations under conditions of natural convection.

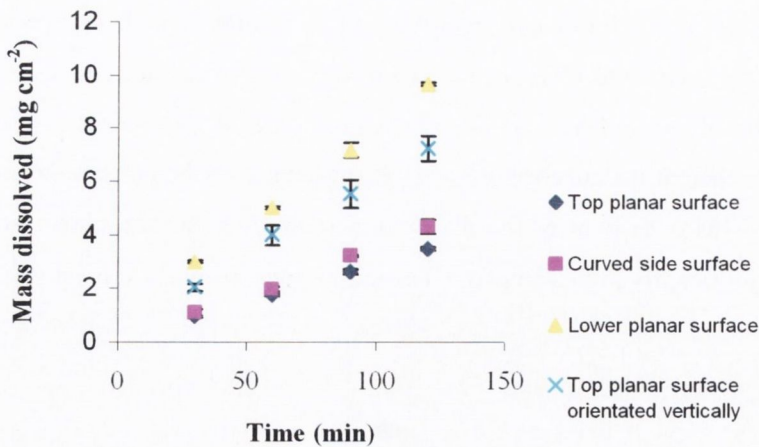


Figure 5.27. Mass of salicylic acid dissolved (mg cm⁻²) in 0.1M HCl vs. time (min) from different surface-orientation combinations under conditions of natural convection.

The effect of solubility of the dissolving substance is evident in Figures 5.26, 5.27 and from Table 5.4. As benzoic acid is more soluble than salicylic acid (as is evident from their saturated solubility values), dissolution rates are higher from dissolving surfaces of benzoic acid. The slowest dissolution rate from both compounds is from the surface facing upwards, (i.e. the top planar surface), and the dissolution rate is faster from the curved side surface. A solubility-related difference, however, is noticeable in the effect of orientation on dissolution rate from the lower planar surface and the top planar surface orientated vertically. There is no significant difference between the dissolution rate from these surface-orientation combinations for the more soluble substance, benzoic acid. On the other hand, dissolution from the top planar surface orientated vertically is lower than that from the lower planar surface of salicylic acid compacts. The saturated solution at the dissolving surface in both of these orientations is free to flow downwards under the effect of gravity. Therefore the higher dissolution rate from the lower planar surface of salicylic acid must be influenced by increased convective forces, resulting from a greater density difference between the saturated solution and the bulk solution at the lower planar surface than at the top planar surface orientated vertically. The greater solubility of benzoic acid results in a more dense saturated solution forming at the dissolving surface than at a dissolving salicylic acid surface. In the case of the top planar surface orientated vertically, the downward flow of this saturated solution will produce increased convection along the length of this dissolving surface compared to the convection at the salicylic acid surface. In contrast to the downward facing surface, this saturated solution formed at the top of the vertical surface will have to flow through some of this solution to leave the bottom of the surface. As the saturated solution from the salicylic acid is less dense, it is possible that there will be less resistance to this flow. Similarly, at the lower planar surface, all of the dissolving surface will be exposed to the already formed saturated solution to the same degree. Although the greater density difference between the saturated solution of benzoic acid and bulk dissolution media will drive the natural convective flow from the dissolving surface to a greater extent than the natural convective flow from the saturated solution of salicylic acid, the greater density and viscosity of the benzoic acid solution will inhibit the flow through this solution to a greater extent than the flow of the salicylic acid solution leaving the dissolving surface. Additionally, flow from the downward facing surface is complex (Patrick et al., 1977), and the type of flow formed dependent on the Rayleigh number (R_a , defined as $P_r.G_r$) with the possible formation of longitudinal vortices and ultimately boundary layer detachment. Some turbulence may additionally be introduced to the system. In other words, the density and viscosity of the saturated solution of benzoic acid will to some degree dampen the effect of increased convection produced by the density difference between the bulk medium and the density of the saturated solution of benzoic acid as compared with salicylic acid. This phenomenon is not apparent in the case of dissolution from the curved side surfaces, possibly due to the fact that the solution of both benzoic and salicylic acid may “pool” at the base of the jar near the compact surface. This will result in some resistance to flow from both compounds and

more importantly a broader concentration gradient which will slow the dissolution rate. The dominant factors influencing dissolution rate from this surface-orientation are therefore solubility and the density difference between the saturated solution and the bulk media.

Ratios of the dissolution rates for each compound from each surface-orientation combination are presented in Table 5.5. It is evident from the differences in these ratios between the two compounds that the effect of orientation on dissolution under conditions of natural convection is not a linear function of solubility.

	Benzoic Acid	Salicylic Acid
Ratios ($\text{mg min}^{-1} \text{cm}^{-2}$) of dissolution rates to dissolution from the top planar surface		
Curved side surface: Top planar surface	1.585	1.207
Lower planar surface: Top planar surface	2.062	2.800
Top planar surface orientated vertically: Top planar surface	2.062	2.138

Table 5.5. Ratios of dissolution rates ($\text{mg min}^{-1} \text{cm}^{-2}$) from the curved side surface, lower planar surface and the top planar surface orientated vertically, to the top planar surface (horizontal orientation) from compacts of benzoic and salicylic acid under conditions of natural convection.

Several equations have been developed to predict the rate of mass transfer under conditions of natural convection, taking the orientation of the dissolving surface into account (Nirdosh et al., 2003). Equation 5.3, describing mass transfer to an upward facing cylindrical cavity, was determined empirically using a method of cathodic copper deposition by a limiting diffusion current technique (Krysa et al., 2000). This method is analogous to heat transfer, with deposition of copper from the bulk medium to the cavity surface creating a less dense medium adjacent to the surface. This results in the development of natural convective flow due to a buoyancy effect between the bulk medium and the less dense solution at the surface where the mass transfer took place (Patrick et al., 1977). Mass transfer *from* a dissolving surface is the reverse of this process, i.e. a more dense solution is formed at the surface. As a result, equations derived empirically for a process of mass transfer from the bulk medium to a surface are interpreted as being applicable to situations where the opposite orientation of the surface is presented when investigating mass transfer from a surface. For example, mass transfer *to* an *upward* facing surface, where the more dense bulk medium will flow downwards to replace the less dense medium at the surface, is analogous to mass transfer *from* a *downward* facing surface, where the more dense medium at the surface flows downwards into the less dense bulk medium. The forces driving the mass transfer

are the same in each case, and for a vertical surface the same equation is applied whether mass transfer is to or from the surface. Equations such as equation 5.3, which are in the form: $S_h = a(P_r.G_r)^b$, can be modified to take the angle of inclination of the dissolving surface from the vertical, θ , into account by modifying the gravitational acceleration term (g) in the Grashof number. The term $g\cos\theta$ is inserted in place of g (Patrick et al., 1977).

The term $P_r.G_r$ is also known as the Rayleigh number, R_a . The mass transfer rate from the different surface-orientation combinations was predicted using an equation for each system, empirically derived from the limiting current cathodic copper deposition method. The equations used, together with the values for the coefficient, a , and the power to which $P_r.G_r$ is raised, b , for the different surface-orientation combinations is presented in Table 5.6.

Equation	a	b	Source
5.5	0.680	0.250	Patrick et al., 1977
5.6	0.166	0.330	Patrick et al., 1977
5.7	0.540	0.250	Lloyd and Moran, 1974
5.8	0.187	0.297	Sedahmed et al., 1995

Table 5.6. Equations derived from the limiting current cathodic copper deposition method used to predict the mass transfer rates from different surface-orientation combinations under conditions of natural convection. Equations are in the form $S_h = a(R_a)^b$

Equation 5.5 was used for prediction of mass transfer from vertically orientated surfaces, where $\cos \theta = 1$, as $\theta = 0^\circ$.

The predicted dissolution results are presented in Table 5.7, from the top planar surface orientated vertically, and from the curved side surfaces.

	R_a	Experimental Rate ($\text{mg min}^{-1} \text{cm}^{-2}$)	Predicted Rate ($\text{mg min}^{-1} \text{cm}^{-2}$)
Top planar surface orientated vertically			
Benzoic acid	49457415	0.134 (± 0.0055)	0.148
Salicylic acid	23310068	0.062 (± 0.0047)	0.067
Curved side surface			
Benzoic acid	607806	0.103 (± 0.0097)	0.214
Salicylic acid	286469	0.035 (± 0.0008)	0.096

Table 5.7. Experimental and predicted (from equation 5.5) rates of dissolution of benzoic and salicylic acid ($\text{mg min}^{-1} \text{cm}^{-2}$) under conditions of natural convection from the top planar surface orientated vertically and the curved side surface.

The characteristic length used in the equations is the length of the dissolving surface (Patrick et al., 1977). This was taken to be the diameter of the compact surface for the top planar surface orientated vertically, and the height of the curved side surface. Equation 5.5 is applicable to systems where $6 \times 10^4 < R_a < 3 \times 10^9$. The R_a numbers for the systems examined fall within this range. For the case of the curved side surfaces, the experimental rate is less than 50% of the predicted rate. This is possibly due to the dissolution rate of benzoic and salicylic acid being inhibited by the saturated solution pooling at the base of the jar near the dissolving surface, as described previously. Additionally, the equations were derived from experiments using flat surfaces, and the applicability of the equation, therefore, to a curved surface is questionable. The degree of curvature of the dissolving surface and effect of natural convection on and produced by a dissolving curved surface may differ from a flat surface.

A curvature parameter, χ , has been described by Ravoo et al. (1970) to quantify the effect of curvature on the Sherwood number under natural convection conditions. The parameter, χ , is defined as:

$$\chi \equiv \frac{z}{rR_a^{0.25}} \quad \text{Equation 5.9}$$

where z is the height of the cylinder, and r is the cylinder radius. It was found, however, that curvature had the effect of increasing the mass transfer rate, but that this effect was not significant for $\chi < 0.1$. Furthermore, for the side surfaces employed in the current work, χ was calculated to be 0.017 and 0.020 for salicylic and benzoic acid respectively. Therefore, according to Ravoo et al., (1970), an equation applicable to a flat vertical plate is applicable to compacts of the dimensions used in the current work. This suggests that the experimentally determined rate from the curved side surface was less than expected due to the location of the compact at the base of the jar, and consequent pooling of the solute inhibiting the formation of a steeper concentration gradient.

Although the characteristic length used has been described as the length of the dissolving surface (Patrick et al., 1977), it has also been defined as the (surface area of the dissolving surface)/(perimeter of the dissolving particle projected onto a horizontal plane) for nonspherical objects with high Rayleigh numbers (Weber et al., 1984). The dissolution rate was predicted from the lower planar surface, using the characteristic length defined as the length of the dissolving surface (L_{c1}) and as the (surface area of the dissolving surface)/(the perimeter of the dissolving surface) (L_{c2}). As the surface is orientated horizontally there is no requirement to project the perimeter onto a horizontal plane. The equations used were equation 5.6 and equation 5.7. The predicted dissolution results and the experimental results from the lower planar surface are presented in Table 5.8.

	R_a, L_{c1}	R_a, L_{c2}	Experimental Rate ($\text{mg min}^{-1} \text{cm}^{-2}$)	Predicted Rate ($\text{mg min}^{-1} \text{cm}^{-2}$) using L_{c1}	Predicted Rate ($\text{mg min}^{-1} \text{cm}^{-2}$) using L_{c2}
Equation 5.6					
Benzoic acid	49457415	772772	0.134 (± 0.0081)	0.150	0.152
Salicylic acid	23310068	364220	0.081 (± 0.0008)	0.063	0.064
Equation 5.7					
Benzoic acid	-	772772	0.134 (± 0.0081)	-	0.167
Salicylic acid	-	364220	0.081 (± 0.0008)	-	0.075

Table 5.8. Experimental and predicted (from equations 5.6 and 5.7) rates of dissolution of benzoic and salicylic acid ($\text{mg min}^{-1} \text{cm}^{-2}$) under conditions of natural convection from the lower planar surface. Characteristic lengths used were diameter of the dissolving surface (L_{c1}) and (surface area/perimeter) of the dissolving surface, L_{c2} .

The predicted results from equation 5.6 using L_{c1} and L_{c2} are very similar, although the predictions for benzoic acid are slightly higher than the experimental results, and those for salicylic acid are slightly lower than the experimental results. The equation is applicable to systems where $10^7 < R_a < 4 \times 10^{10}$. Although the R_a number calculated using L_{c2} is outside this range, the equation was derived using the length of the dissolving surface as the characteristic length. It is therefore applicable to the R_a number calculated from L_{c1} . Lloyd and Moran, 1974, derived an equation (equation 5.7) where the characteristic length is calculated as the (surface area)/(the perimeter of the transfer surface), i.e. the method used to calculate L_{c2} (Patrick et al., 1977). This equation is applicable to systems where $2.6 \times 10^4 < R_a < 8 \times 10^6$, a range in which the R_a values calculated using L_{c2} fall. Equation 5.7 was therefore used to predict dissolution rates from the lower planar surface using L_{c2} as the characteristic length.

As is evident from Table 5.8, equation 5.7 predicts a slightly higher rate of dissolution from the lower planar surface than equation 5.6. The predictions, therefore, are closer to the experimental values for salicylic acid, but a little higher again than predictions from equation 5.6 for benzoic acid.

The Sherwood number was determined to be lowest for surfaces in the horizontal downward facing position (Patrick et al., 1977), using the limiting current cathodic copper deposition method. This is analogous to the Sherwood number being lowest at the horizontal upward facing orientation in the current work, as is evidently the case from Table 5.4. Prediction of mass

transfer from this surface-orientation combination is not as straightforward as that from the other surface-orientation combinations investigated. The complexity using the limiting current technique resulting from upward buoyancy force at the downward facing surface and the resulting natural convection is thought to be influenced by the surface geometry and its bounding walls (Patrick et al., 1977). Rather than employing an equation to predict mass transfer from the top planar surface similar to equations 5.5-5.7, mass transfer from the top planar surface was predicted by calculating the predicted mass transfer from a downward facing cylindrical cavity, analogous to mass transfer from an upward facing cylindrical cavity (Sedahmed et al., 1995). The experimentally determined mass transfer rates from the curved side surface could then be subtracted from this predicted rate from an upward facing cylindrical cavity, leaving a predicted rate from the top planar surface alone. The equation used, equation 5.8, employed the value from the (surface area)/(perimeter projected onto a horizontal plane) as L_c . In the case of a cylindrical cavity, L_c calculated in this way is the same as that calculated for equation 5.3, i.e. $L_c = (H + d/4)$. The results for the dissolution rate from the top planar surface predicted in this manner are presented in Table 5.9.

	R_a (top and sides)	Predicted Rate top and sides ($\text{mg min}^{-1} \text{cm}^{-2}$)	Experimental Rate curved side surface ($\text{mg min}^{-1} \text{cm}^{-2}$)	Predicted Rate top planar surface ($\text{mg min}^{-1} \text{cm}^{-2}$)	Experimental Rate top planar surface ($\text{mg min}^{-1} \text{cm}^{-2}$)
Benzoic acid	5495933	0.102	0.103 (± 0.0097)	0.100	0.065 (± 0.0047)
Salicylic acid	2590321	0.044	0.035 (± 0.0008)	0.053	0.029 (± 0.0007)

Table 5.9. Experimental dissolution rates from the curved side surface and top planar surface and predicted (from equation 5.8) rates of dissolution of benzoic and salicylic acid ($\text{mg min}^{-1} \text{cm}^{-2}$) under conditions of natural convection from the top planar and curved side surfaces combined, and from the top planar surface alone by subtraction of the experimental rate of dissolution from the curved side surface from the predicted rate for combined top and side surfaces.

The predicted dissolution rates from the top planar surface alone are much higher than the experimental rates. Possible reasons for this include the fact that the contribution to the predicted rate from a cylindrical cavity which was from the curved side surfaces, may have been higher than the experimentally determined rate from the curved side surface. This might be expected from the experimental and predicted curved side surface dissolution rates detailed in Table 5.7. An additional issue is the fact that equation 5.8 was applicable to systems where R_a was in the range $1 \times 10^8 < R_a < 1.3 \times 10^{10}$, a range which is obviously higher than the R_a numbers presented in Table 5.9. Furthermore, the largest aspect ratio (cylinder height/diameter) studied in the derivation of

equation 5.8 was 1.74 (Sedahmed et al., 1995), whereas that used in the current work was 2.31. The experimental technique used by (Sedahmed et al., 1995) has been criticised (Krysa et al., 2000) due to the fact that an anode was placed in the cavity disrupting open cavity convective behaviour. Possibly the most important factor influencing the predicted result for mass transfer from the top planar surface in Table 5.9 is the question of whether dissolution under conditions of natural convection is additive for combinations of different surfaces. By subtracting the experimentally determined rate for the curved side surface from the predicted rate from a cylindrical cavity surface (i.e., a combination of the top planar and curved side surface) to determine the rate from the top planar surface alone, it is assumed that the rates from each surface are additive. This approach has been suggested in predictions of rates from inclined surfaces with active ends (Nirdosh and Sedahmed, 2003), however the accuracy of predictions using the sum of the predictions from separate surfaces was found to decrease with more dilute bulk medium of acidic copper sulphate solution. This implies that a less steep concentration gradient at the surface decreases the accuracy of summative predictions. Previous investigations into the difference between the summed mass transfer rates to separate sides of vertical cylinders and the total mass transfer rate from the cylinder found that the actual rate was lower than the predicted rate from the summation of the separate surface rates (Krysa and Wragg, 1992). The effect of the surface combinations is dependent on the height and aspect ratio of the cylinders. It was postulated that the fact that at a combination of horizontal and vertical dissolving surfaces, the solution formed at the surface will be interacting with solution in which there will already be some dissolved solute. Experimental work using the limiting current technique suggested that currents at the surface will be influenced by surrounding medium already depleted of copper ions, which will lead to a decreased mass transfer rate to this surface. A decrease in dissolution rate might therefore be expected from a combination of dissolving surfaces. Despite these limitations, addition of mass transfer rates from separate surfaces should give a good approximate estimation of mass transfer rates from a system where these surfaces are combined.

Although the equations 5.5-5.8 are empirically derived from an experimental method which involves mass transfer *to* a surface, mimicking heat transfer phenomena, the predicted mass transfer rates for the lower planar surface and top planar surface orientated vertically give a reasonable estimate of the experimental results, in some cases within the 1 standard deviation error bars of the experimental data. The choice of characteristic length, L_{c1} or L_{c2} , does not have a great influence on the predicted rate from the lower planar surface using either equation 5.6 or 5.7. In the case of the curved side surfaces, although the experimental rates are less than 50% of the predicted rates in each case, it can be concluded that this is due to the saturated solution pooling at the base of the jar where the compact was located rather than an inaccuracy in equation used, equation 5.5.

5.7 **Determination of the maximum possible contribution from dissolution under natural convection conditions to dissolution under forced convection in areas of low velocity in the paddle and basket apparatuses.**

In a horn-shaped dissolution cell where there was laminar upward flow of solvent, a downward flow of more concentrated solution was observed at a vertical dissolving surface at low Re numbers (Fee et al., 1976). The mean linear velocity at the Re below which this downward flow was noticed was 0.0079 ms^{-1} . Above this flow rate, the flow at the vertical surface was noted, through flow visualisation studies, to leave the surface at right angles and change direction to flow upwards a few millimetres from the surface. The effect of natural convection on the dissolution rate against a background of forced convection was also evident in terms of the calculated (from experimental dissolution rate data) diffusion boundary layer thickness. At lower Reynolds numbers the thickness of this layer was less than that expected from the physical constants of the system, considering forced convection only. This discrepancy was attributed to the effect of natural convection on the diffusion boundary layer, suggesting that the contribution from natural convection to the dissolution rate becomes increasingly important at lower flow rates (Fee et al., 1976). It is conceivable, therefore, that in areas of low velocity in the paddle and basket apparatuses there will be a contribution to the dissolution rate from natural convection. The lower surface of the tablet located within the basket of the basket apparatus is one such area. Although the surface of the tablet will be subject to a relatively high tangential velocity, as the tablet itself is rotating, the magnitude of the positive axial flow beneath the basket is low, in the region of 0.005 to 0.01 ms^{-1} . The tangential rotation of the tablet would not prevent its exposure to gravitational forces, and the saturated solution formed at the surface will flow downward, maintaining a narrow concentration gradient at the surface. The dissolution rate under natural convection conditions as percentage of the dissolution rate from the whole compact within the basket at 50 rpm is presented in Table 5.10. In this case the dissolution is expressed as $\text{mg min}^{-1} \text{ cm}^{-2}$. This is equivalent to approximately 14% of the total dissolution rate (mg min^{-1}) from a compact of benzoic or salicylic acid within the basket apparatus at 50 rpm.

	Benzoic acid	Salicylic acid
	Dissolution rate ($\text{mg min}^{-1} \text{cm}^{-2}$)	
Basket apparatus, 50 rpm	0.349 (± 0.0267)	0.189 (± 0.0085)
Natural convection conditions, lower planar surface	0.134 (± 0.0081)	0.081 (± 0.0008)
Natural convection dissolution rate from the lower planar surface as % dissolution rate in the basket apparatus	38.4%	42.9%

Table 5.10. Comparison of dissolution rate under conditions of natural convection from the lower planar surface with total dissolution rate from whole compacts of benzoic and salicylic acid in the basket dissolution apparatus at 50 rpm, in 900 ml 0.1M HCl.

There is potential for the upward axial flow beneath the basket to inhibit the downward flow of the more dense saturated solution which would decrease the natural convection influence on the dissolution rate from this surface. Furthermore, the upward axial convection and rotational motion of the compact could serve to add further complexity to the already complex natural convection at this downward facing surface (Patrick et al., 1977). It is impossible, from the data presented in the current work, to determine exactly the contribution of dissolution from natural convection at this surface, suffice to say that the potential for a significant contribution should be accounted for when relating dissolution rate data to forced convection velocities.

A second situation which presents an area of low very low velocity in which natural convection rates may significantly contribute to the overall dissolution rate is the top planar surface of a compact located in the centre of the base of the paddle apparatus. As has been described in section 3.2.2.2, the dissolution rate from this surface in this position is much lower than either the compact sides in the central position or any of the compact surfaces in the off-centre position. The dissolution rate ($\text{mg min}^{-1} \text{cm}^{-2}$) from the top planar surface under natural convection conditions is 14.46% of the rate determined from the same surface at 50 rpm at the centre of the base of the paddle apparatus. As detailed in Chapter 3 (Figure 3.6, Figure 3.7.d) there is some fluid motion at the outer region of this dissolving surface, however approximately 50% of the surface area is exposed to little or no fluid movement. The method described in Chapter 4 uses the experimental dissolution rate data from the central side surface to determine the “cut-off” point representing the “edge” of the hydrodynamic boundary layer. This method therefore incorporated any contribution to dissolution from natural convection from this side surface. The simulation of diffusion of the saturated solution from the dissolving surface in Chapter 4 did not incorporate a density difference between the saturated solution and the bulk. For the off-centre surfaces and the central side surface the forced velocity component was higher than at the central top planar surface, and possibly rendered any density gradient-induced natural convection

insignificant. At the central top planar surface, however, the density difference would have induced a downward flow of the saturated solution at the compact surface, diminishing the height of the central “peak” depicted in Figure 4.3.

The experimentally determined natural convection dissolution rate is added to the dissolution rate predictions using the simulated diffusion boundary layer from the top planar surface surface, detailed in section 4.2, to account for the lack of density difference in the simulations of diffusion of saturated solution at this surface. The predicted dissolution rate including the natural convection component is presented in Table 5.11.

	Dissolution rate (mg min ⁻¹ cm ⁻²)
Predicted dissolution rate	0.2775
Natural convection dissolution rate	0.065 ± 0.0048
Predicted dissolution rate including natural convection contribution	0.3425
Experimental dissolution rate at 50 rpm	0.4495 ± 0.0153

Table 5.11. Dissolution rate prediction from the top planar surface of the benzoic acid compact at the centre of the base of the paddle apparatus using the results presented in section 4.2, from CFD simulations of the diffusion boundary layer, with the addition of the contribution to dissolution from natural convection.

Although the incorporation of the contribution to dissolution from natural convection results in a predicted dissolution rate that is closer to the experimental value from the top planar surface in the central position, the predicted dissolution rate is approximately 20% less than the experimental rate. This may be due to the “dynamic vortex” concept, as discussed in section 4.2.2, which is not captured in the time averaged CFD solution. The resulting overestimation of the diffusion boundary layer thickness at the centre of the surface results in an underprediction of the dissolution rate, despite incorporation of the contribution from natural convection. Additionally, a more complex interaction between the natural and forced convection is possible, which could result in a higher than predicted dissolution rate.

Dissolution rate predictions using shear rate data from the CFD simulations of compacts in the central and off-centre positions was also presented in section 4.3.3 The predicted dissolution rates from the curved side surfaces of the compacts were lower than the experimental rates, suggesting that the model used was not appropriate for the dissolution systems examined. The dissolution rates under natural convection conditions for the top planar surface and curved side surface were added to the dissolution rate predictions using the shear rate data, and are presented in Figures 5.28 (top planar surface) and 5.29 (curved side surface).

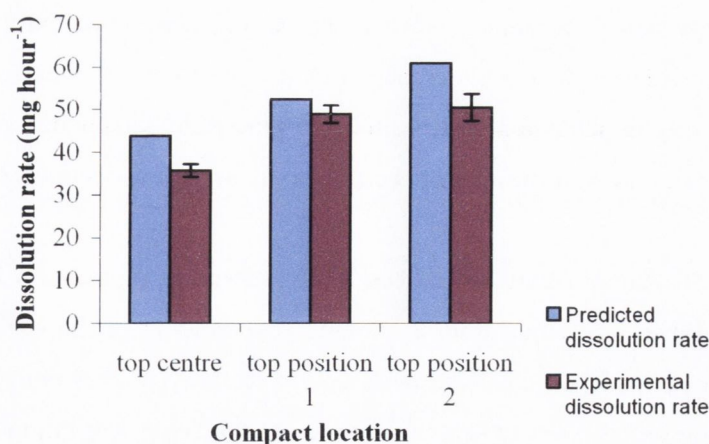


Figure 5.28. Predicted (using CFD-generated shear rate data and natural convection dissolution rates) and experimental dissolution rates from the top planar surfaces of benzoic acid compacts in the central position, position 1 and position 2; in 900 ml 0.1M HCl in the paddle dissolution apparatus at 50 rpm.

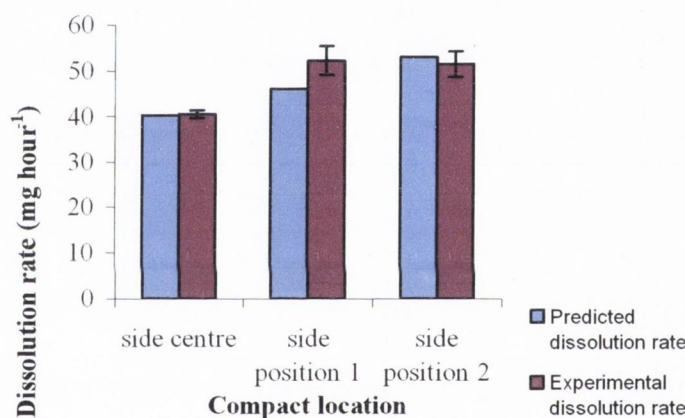


Figure 5.29. Predicted (using CFD-generated shear rate data and natural convection dissolution rates) and experimental dissolution rates from the curved side surfaces of benzoic acid compacts in the central position, position 1 and position 2; in 900 ml 0.1M HCl in the paddle apparatus at 50 rpm.

The predicted dissolution rates from the curved side surfaces are closer to the experimental results than those presented in Figure 4.20, which did not include the contribution from natural convection. The predicted dissolution rates from the top planar surface, however, are greater than the experimental rate. This suggests that natural convection contributes to the rate of shear at the curved side surfaces to a significant extent, and the contribution of natural convection to the dissolution rate should be accounted for when using models based on shear rates at vertical surfaces. The dissolution rate predictions from the top planar surface, however, were in reasonable agreement with the experimental rates as presented in Figure 4.18. Incorporating the contribution from natural convection to these surfaces results in an over-prediction of the dissolution rate, as shown in Figure 5.28. It is possible, therefore, that natural convection at

upward facing surfaces does not contribute significantly to the rate of shear introduced through forced convection. It should be noted also that the natural convection rates used were those experimentally determined for the top planar and curved side surfaces of a horizontally orientated compact. The compacts in position 1 and position 2 in the paddle apparatus were slightly at an angle to the horizontal, which would affect the degree of natural convection occurring at these surfaces.

The contribution to dissolution from natural convection offers an explanation for the apparently higher than expected dissolution rate from a salicylic acid tablet at the base of the vessel of the basket apparatus (Mori-hara et al., 2002), as described in section 5.5. For more soluble drugs the natural convection contribution would be greater because of a larger density gradient contribution. In the case of dissolving salicylic acid tablets at the base of the vessel of the basket apparatus in a medium of pH 7.4 phosphate buffer, dissolution rates at 100 rpm were observed to be equivalent to dissolution rates from a salicylic acid tablet within the basket at 50 rpm in the same medium (Mori-hara et al., 2002). It is likely that natural convection significantly influences the dissolution rate, as CFD simulated forced convection velocities were very low at the base of the vessel at 100 rpm, and much lower than the velocities within the basket at 50 rpm.

5.8 Conclusions

Results of the present study indicate that CFD gives both a good qualitative and quantitative representation of the hydrodynamics present in the basket dissolution apparatus. The CFD model allows a visualisation of flow patterns within the basket itself and indicates that fluid enters axially at the base, flows upwards and exits at the sides. At the same rotation speed, the velocities present inside the basket are of a similar magnitude to those at the base of the vessel of the paddle apparatus, although slightly lower.

Calculated fluid velocities, relative to the velocity of the rotating compact within the basket, can be used to predict dissolution from a compact within the basket with reasonable accuracy. This prediction uses the relationship between dissolution rate and CFD generated fluid velocity data from both the paddle and basket apparatus in the vicinity of the dissolving surface. It can be concluded that the relationship between CFD generated fluid velocity values and dissolution rate holds for data from both the paddle and basket apparatuses, from dissolving surfaces in several locations and exposed to different agitation rates.

The dissolution rate - CFD-generated velocity data relationship implies a significant contribution from natural convection to the dissolution rate. The dissolution rate under conditions of natural convection can be predicted from equations derived from mass transfer to a surface using a limiting current technique. The accuracy of these predictions decreases when a surface is located at the base of a dissolution vessel, suggesting that the boundary effect imposed on the system by the base interferes with the gravitational contribution to the development of natural convection. The resulting pooling of saturated solution at the base of the dissolution chamber before diffusion into the medium causes a wide concentration gradient to develop and the dissolution rate is therefore inhibited. The dissolution rate under natural convection conditions is therefore influenced by solubility, orientation and proximity to the bounding walls of the system being investigated, and the density and viscosity differences between the saturated solution and the bulk. The analysis of dissolution rate data for compacts situated at the base of the vessel of the basket apparatus (Moriwaka et al., 2002) suggests a significant contribution from free convection dissolution. It is possible, from CFD simulations of hydrodynamics within the paddle and basket dissolution apparatuses, to identify areas of low velocity where natural convection might have a significant contribution to the overall dissolution rate. The magnitude of this contribution requires further investigation.

The basket apparatus is a common method for measuring the dissolution rate of solid dosage forms. It consists of a basket containing the dosage form, which is immersed in a dissolution medium. The dissolution medium is stirred by a magnetic bar, and the temperature is controlled by a water jacket. The dissolution rate is determined by measuring the amount of drug that dissolves over a period of time. The basket apparatus is used to study the effect of various factors on the dissolution rate, such as the size of the dosage form, the composition of the dissolution medium, and the stirring rate. The basket apparatus is also used to study the effect of natural convection on the dissolution rate. Natural convection is the flow of fluid that occurs due to differences in density caused by temperature gradients. In the basket apparatus, natural convection can occur in the dissolution medium, and this can affect the dissolution rate. The basket apparatus is a simple and reliable method for measuring the dissolution rate of solid dosage forms, and it is widely used in pharmaceutical research and development.

6.0

Simulation of hydrodynamics in the Levy beaker dissolution apparatus and the relationship between hydrodynamics and dissolution rate, *in vitro* and *in vivo*.

6.1 Introduction.

The Levy beaker dissolution apparatus is one of the earliest apparatuses to be used in dissolution studies where the importance of hydrodynamic effects was recognised. There are a number publications which examined the effect on dissolution rate of altering various operational and geometrical parameters of the apparatus. These included using a round-bottomed beaker (Bolhuis et al., 1973; Lerk and Lagas, 1977), altering the volume of the beaker (Corrigan and Timoney, 1978; Lerk and Lagas, 1977) altering the position of the dosage form at the base of the beaker and altering the rotational direction and blade angle of the stirrer (Lerk and Lagas, 1977). In several instances, dissolution rates were compared to those from other dissolution apparatuses (Bolhuis et al., 1973; Lerk and Lagas, 1977; Withey, 1971; Needham and Luzzi, 1974). The Levy beaker dissolution apparatus was used to investigate dissolution rates of different aspirin formulations and to propose a relationship between *in vitro* dissolution rate and *in vivo* absorption (Levy and Hayes, 1960). Following this a modification of the apparatus was employed involving the use of a rotating tablet holder in place of the stirrer to determine dissolution rates of aluminium salicylate and acetylsalicylic acid (Levy and Sahli, 1962). These dissolution rates were compared to *in vivo* absorption and excretion rates, and although the increased dissolution rate of the acetylsalicylic acid corresponded with an increase in the *in vivo* absorption rate, no IVIVC was established. The original Levy beaker dissolution apparatus with the 3-bladed stirrer was again engaged in dissolution studies which related absorption of aspirin tablets with *in vitro* dissolution rates. Data was only included from those tablets which formed a mound in the centre of the beaker base rather than at the edge. A quantitative correlation between *in vitro* dissolution rates and *in vivo* absorption rates was obtained for a particular aspirin formulation (Levy and Hollister, 1964) and several different aspirin formulations (Levy et al., 1965). The quantitative correlation is not the same in each case and seems to be highly dependent on agitation rate (Levy et al., 1965). Intersubject variability was high, especially in the earlier stages of absorption, in both studies. Additionally, both correlations involved dividing the *in vitro* dissolution rate by an “intensity factor” which was a ratio of the rate constant for dissolution: rate constant for absorption. The fact that the *in vitro* dissolution generally proceeded faster than the *in vivo* absorption suggests that the *in vivo* hydrodynamics are of a much lower magnitude than those present in the Levy beaker dissolution apparatus. Frequent attempts have been made since this time to relate *in vivo* data to *in vitro* dissolution data in various dissolution apparatuses. The objectives of this chapter are

- to simulate and validate a model of the Levy beaker dissolution apparatus at 20, 50, 59, 100 and 174 rpm, and a modified version of the apparatus containing 550 ml dissolution medium in a larger beaker at 20, 59, 100 and 174 rpm;
- to explore the hydrodynamic characteristics of the apparatus;

- to determine the effect of agitation rates on velocities in the lower region of the vessel and on dissolution rates from the apparatus;
- to compare the magnitudes of velocities in the lower region of the apparatus where a dosage form would be located to functions of dissolution rate used in *IVIVC* studies, and velocities used in other apparatuses involved in similar *IVIVC* experiments. This concept is extended to comparisons of *in vivo* pressure data and pressure data within corresponding dissolution apparatuses.

6.2 Convergence and validation.

6.2.1 Solution convergence.

As all of the models were examined for convergence using the same method, a sample of the simulations will be discussed in terms of determination of convergence. In Figures 6.1 and 6.2 the levelling of the residuals and surface forces, respectively, are apparent. The locations of the surface forces examined are described in Table 2.4, section 2.2.1.3. The number of iterations on the x-axis in Figure 6.2 represents the number of iterations following the increase from 20 rpm to 59 rpm. The number of iterations in Figure 6.1 represents the total number of iterations including those used to reach a solution at 20 rpm. The 20 rpm solution was then used as initial data in the 59 rpm solution, and this was then run to convergence. Although the residuals continue to decrease at the point where the 20 rpm solution was accepted, the surface forces remained level from this point (16,000 iterations) until 20,000 iterations as is evident in Figure 6.3.

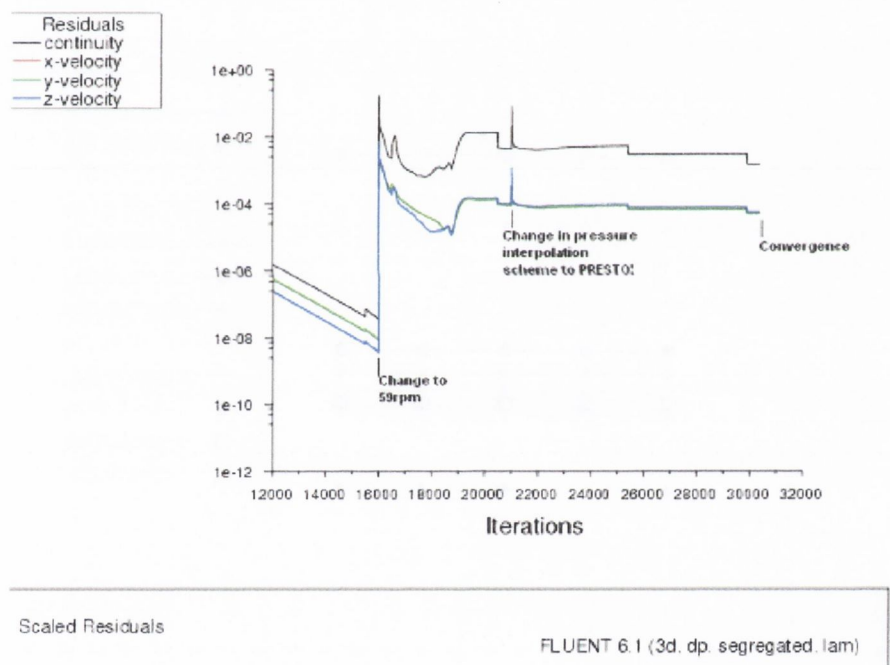


Figure 6.1. Change in residual magnitude with iteration in the convergence of the 59 rpm 350 ml CFD simulation of the flow field in the Levy beaker apparatus. The point at which the change from 20 rpm to 59 rpm was made can be seen.

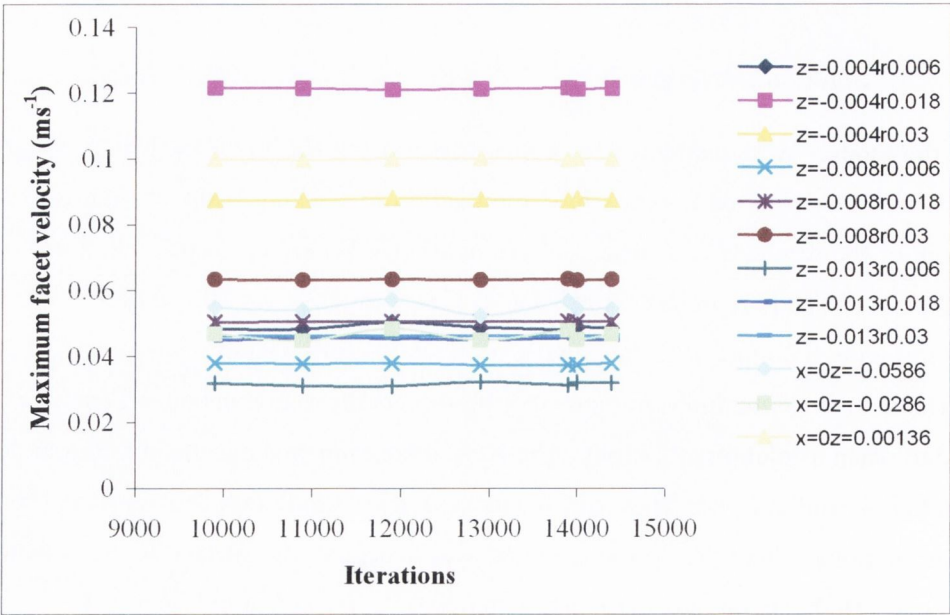


Figure 6.2. Maximum CFD-generated facet velocity vs. iterations when the solving flow field for the 350 ml volume simulation in the Levy beaker apparatus, at 59 rpm.

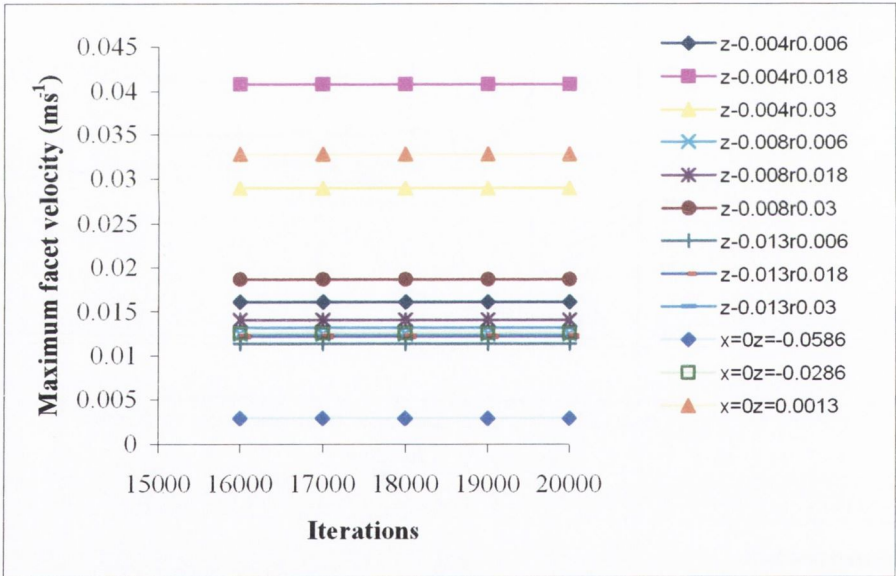


Figure 6.3. CFD-generated facet velocity vs. iterations when solving the flow field for the 350 ml volume simulation in the Levy beaker apparatus, at 20 rpm.

The increasing difficulty in obtaining a solution at a higher rpm is demonstrated in Figures 6.4 and 6.5. The residuals do not reach a steady level but rather fluctuate about a magnitude. For example, the continuity residual is fluctuating at about 10^{-3} in Figure 6.4. In contrast, it can be seen from Figure 6.5 that the surface forces levelled at approximately 18,000 iterations having been quite unsteady prior to this.

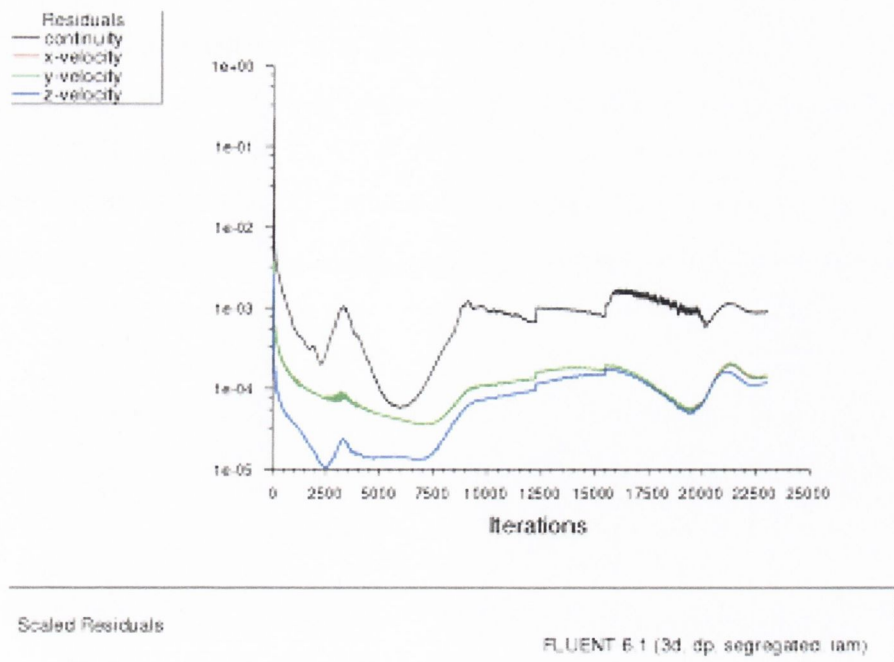


Figure 6.4. Change in residual magnitude with iteration in the convergence of the 174 rpm 350 ml CFD simulation of the flow field in the Levy beaker apparatus.

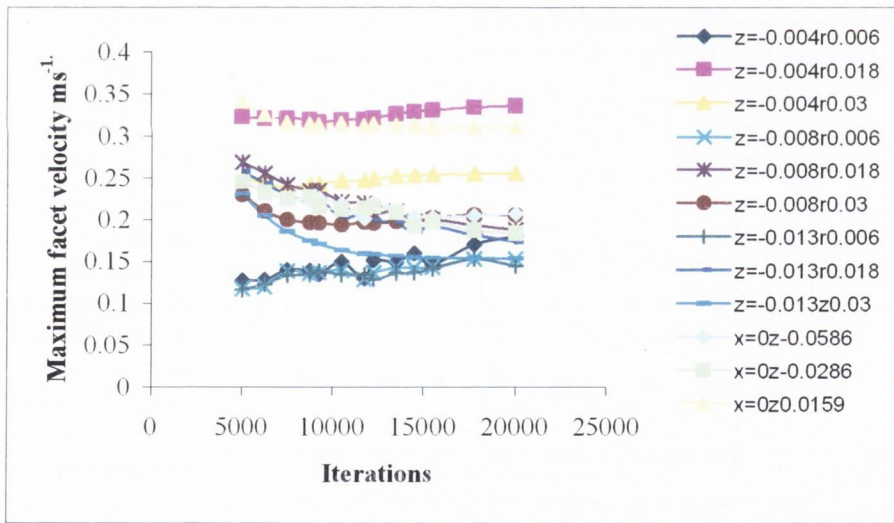


Figure 6.5. CFD-generated facet velocity vs. iterations when solving the flow field for the 350ml volume simulation in the Levy beaker apparatus, at 174 rpm.

Figures 6.6 and 6.7 are an example of how a solution appears to have converged according to the surface forces, despite the continuing decrease in residuals. The residuals finally level off in Figure 6.6 at magnitudes in the range of 10^{-15} to 10^{-16} , in the final 5,000 iterations. However, the surface forces in Figure 6.7 are level for over 20,000 iterations. This is similar to the situation encountered in the simulation at 20 rpm of the 350 ml volume. It illustrates how further convergence of residuals until the residuals reach a plateau, when residuals are already of

magnitudes in the approximate range of 10^{-8} to 10^{-12} , does not noticeably affect the velocity values. Again, the number of iterations on the x-axis in Figure 6.7 reflects the iterations for the simulation at 59 rpm, whereas the iterations on the x-axis in Figure 6.6 reflect the number of iterations from the beginning of the simulation modelling. This would include, in this case, the residuals from the initial 20 rpm solution.

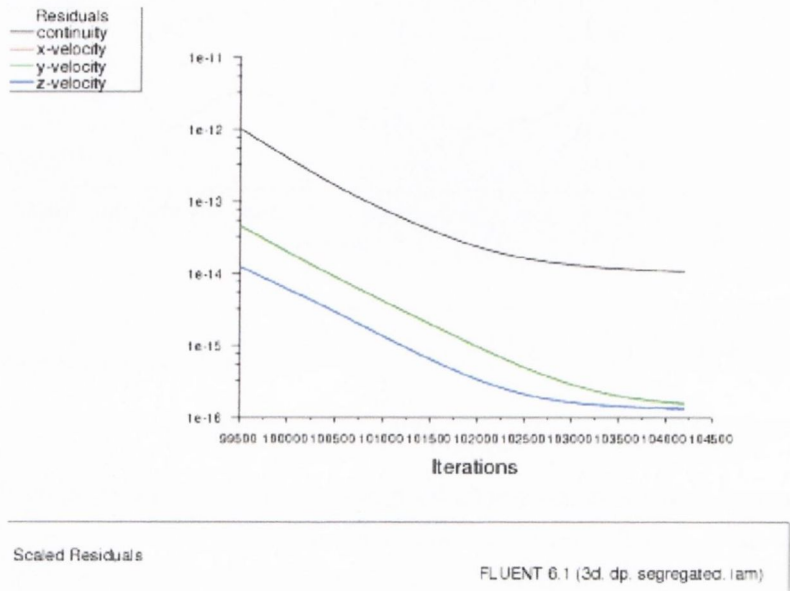


Figure 6.6. Change in residual magnitude with iteration in the convergence of the 59 rpm 550 ml CFD simulation of the flow field in the Levy beaker apparatus.

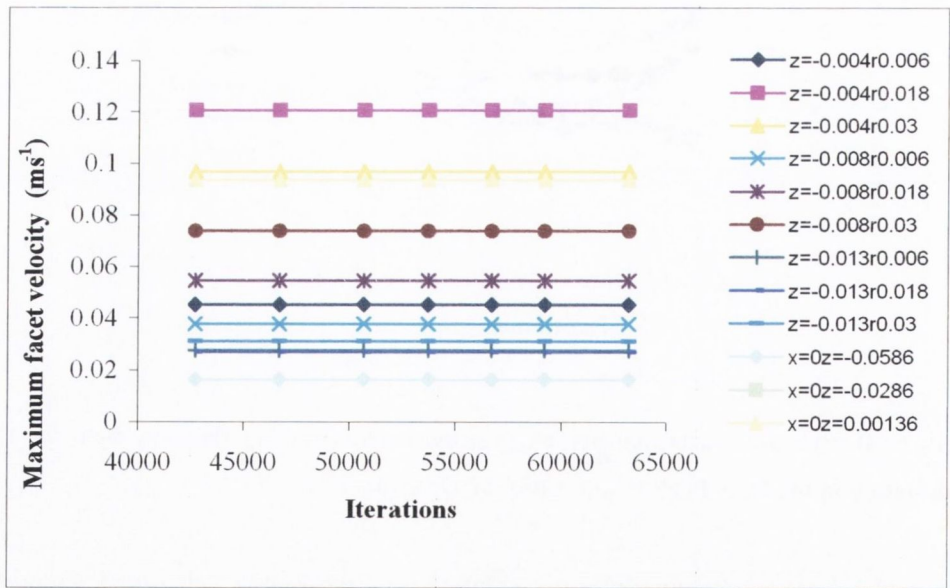


Figure 6.7. CFD-generated facet velocity vs. iterations when solving the flow field for the 550 ml volume simulation in the Levy beaker apparatus, at 59 rpm.

Figures 6.8 and 6.9 illustrate the convergence monitoring of the 550 ml 174 rpm simulation. The residuals are level for about 5,000 iterations in Figure 6.8. The surface forces are depicted as they

increase/decrease then level off over approximately 10,000 iterations in Figure 6.9. The continuity residual in Figure 6.8 does not decrease to a magnitude of less than approximately 3×10^{-3} . This is due to the difficulty of obtaining a solution with a complex rotating flow at a relatively high speed such as 174 rpm in this apparatus. In comparison, the residual for the continuity variable at 174 rpm in the 350 ml simulation fluctuates about a value of approximately 1×10^{-3} . In both the 350 ml and 550 ml simulations the x, y and z residuals are in the range of 10^{-4} to 10^{-5} . This implies that there was a difficulty with both the 350 ml and 550 ml volume simulations in achieving a similar decrease in residual values when solving the flow field at 174 rpm.

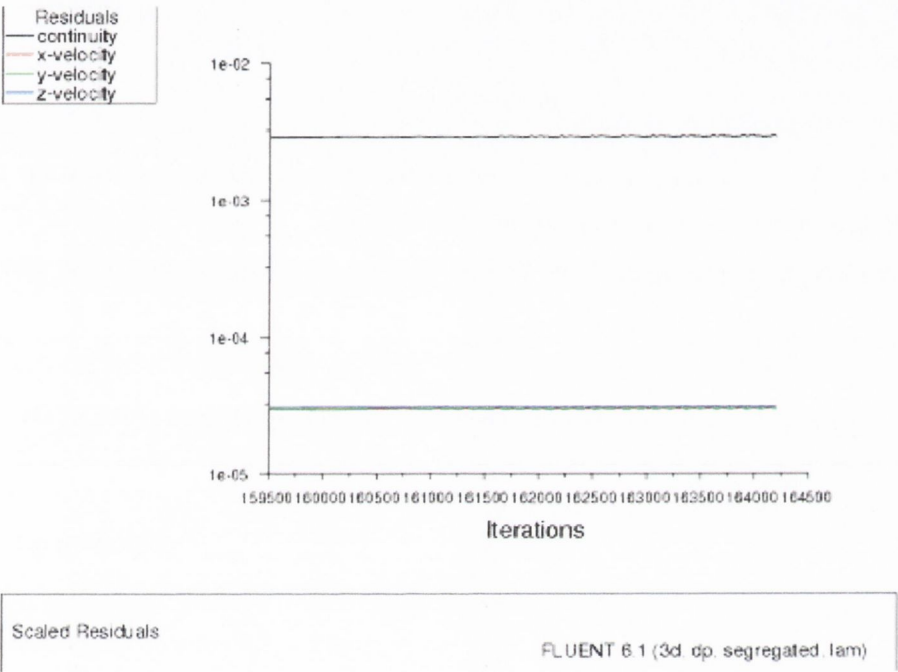


Figure 6.8. Change in residual magnitude with iteration in the convergence of the 174 rpm 550 ml CFD simulation of the flow field in the Levy beaker apparatus.

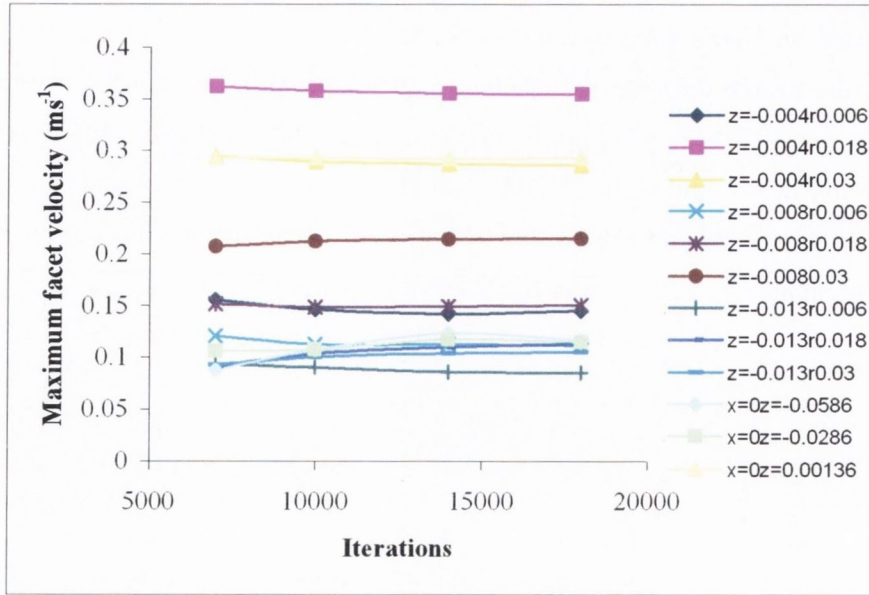


Figure 6.9. CFD-generated facet velocity vs. iterations when solving the flow field for the 550 ml volume simulation in the Levy beaker apparatus, at 174 rpm.

In an attempt to increase convergence, the PRESTO! pressure interpolation scheme was employed at this point in the 550 ml 174 rpm solution.

Use of the pressure interpolation scheme, Pressure Staggering Option (PRESTO).

The mass flux through a face f , J_f , can be written as

$$J_f = \hat{J}_f + d_f (p_{ca} - p_{cb}) \quad \text{Equation 6.1}$$

The term d_f is a function of the momentum equation coefficients for cells on either side of the face f , and p_{ca} and p_{cb} are pressures within the two cells (ca and cb) on either side of face f . The effect of velocities in the cells adjacent to face f is contained in the $\hat{J}_f$ term.

Discretised momentum equations need pressure fields and mass fluxes to solve the velocity field. These are not known *a priori* and therefore need to be solved along with the momentum equations. The pressure values in FluentTM are held at the cell centre, however the values at the face between cells ca and cb are needed to solve the momentum equations. To calculate the values of pressure at face f from the centres of cells ca and cb , a pressure interpolation scheme is used. The default (standard) pressure interpolation scheme is sufficient for many cases where the pressure variation between cells is smooth and momentum gradients are not large. If the standard scheme is used in situations where there is a high pressure gradient at the cell face, the solution to the cell velocity will be inaccurate. In a strongly swirling flow it is envisaged that the standard scheme may have difficulty due to high radial pressure gradients. A refined mesh in these areas assists in obtaining accurate pressure interpolations. Additionally, the standard scheme assumes that there is a normal pressure gradient of zero at the wall. Although this is the case within a

boundary layer, with curved walls this is not always a valid assumption. Incorrect pressure at the walls can manifest itself in vectors pointing into/out of walls.

The PRESTO scheme is an alternative to the standard scheme. It is recommended for use in high-speed rotating flows, flows in strongly curved domains and flows with high swirl numbers (Fluent™ User’s Guide, 2003). It uses the discrete balance in continuity between cells to compute a “staggered” pressure about the face of interest.

As is evident in Figure 6.10, use of the PRESTO! scheme resulted in a very slight decrease in residuals (approximately 2.8×10^{-3} for the continuity equation). The impact of this change in pressure interpolation scheme was a minor change in surface forces which then remained level between 2,000 and 4,000 iterations following the change to PRESTO!. This can be seen in Figure 6.11.

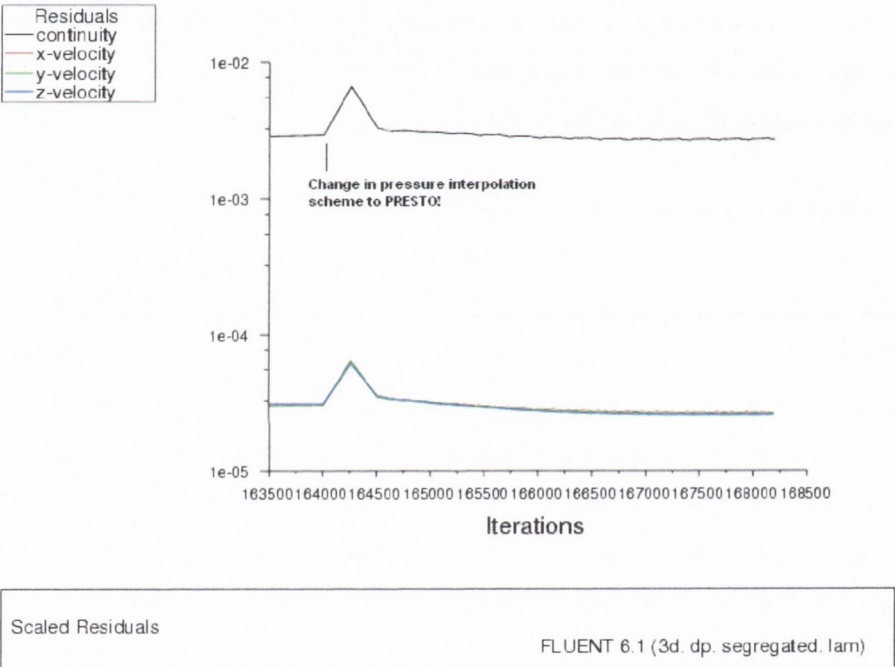


Figure 6.10. Change in residual magnitude with iteration in the convergence of the 174 rpm 550 ml CFD simulation of the flow field in the Levy beaker apparatus, following application of the PRESTO! pressure interpolation scheme.

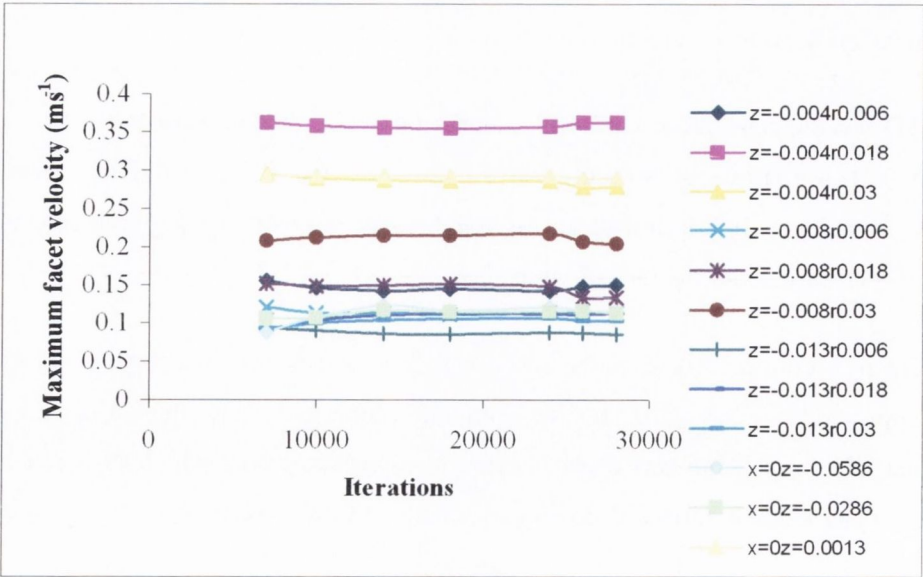


Figure 6.11. CFD-generated facet velocity vs. iterations when solving the flow field for the 550 ml volume simulation in the Levy beaker apparatus, at 174 rpm. The final 2 data points in each series are recorded following the change to PRESTO!

The 350 ml volume has a smaller diameter and therefore a higher wall-curvature than the 550 ml volume. The smaller volume could also result in a higher degree of “swirl” than the larger volume at the same rpm. The effect of changing from the standard scheme to the PRESTO! scheme is visible in Figure 6.1, at approximately 21,000 iterations. After an initial increase the residuals levelled. Overall, therefore, there was little effect on convergence from using the PRESTO! scheme with this model. It is possible that this may be attributable to the unstructured mesh. The PRESTO! scheme was also used in solving the 350 ml models at 50, 59, 100 and 174 rpm. A satisfactory convergence was attained with 550 ml model using the standard scheme, with the exception of the 174 rpm simulation. The lesser degree of curvature and greater fluid volume are likely to incur fewer wall and pressure-gradient effects. Application of the PRESTO! scheme to the 174 rpm model resulted in a slight decrease in residuals which had reached a level that, although consistent, were relatively large in magnitude using the standard scheme.

6.2.2 Validation.

6.2.2.1 Qualitative validation.

The 59 rpm 350 ml simulation was qualitatively validated through comparison with descriptions of fluid flow in the same apparatus at 60 rpm. The flow in the Levy beaker was described (Withey and Bowker, 1971) as having a central core of vortical fluid, surrounded by a slower moving region, which was visualised through the photographic recording of tracks of light-reflecting particles (particle image velocimetry (PIV)). This flow feature was common to several apparatuses investigated by the authors. One of the apparatuses investigated in addition to the Levy beaker was the Levy stirrer in 900 ml of solvent in a “resin kettle” 1 litre vessel. This vessel was cylindrical in shape with a slightly concave bottom similar to that in the USP 1970/1975. A photograph depicting this central vortical core surrounded by the slower region is shown in Figure 6.12. This can be compared to CFD images of velocity vectors from the 350 ml Levy vessel at 59 rpm in Figure 6.13. A similar feature of a central vortex within a higher velocity region surrounded by a lower velocity region is obvious from this image, confirming that the major flow patterns in the vessel generated by the CFD are the same as that visualised in the physical set-up at this rotation speed.

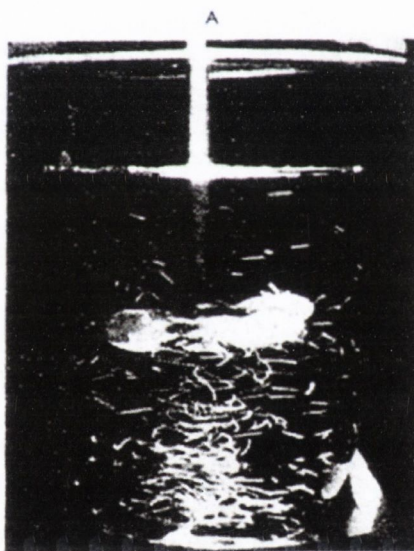


Figure 6.12. Photograph using PIV of flow under a Levy apparatus stirrer in a concave-based vessel. The central vertical core feature was also reported for the Levy beaker apparatus.

Taken from Withey and Bowker (1971).

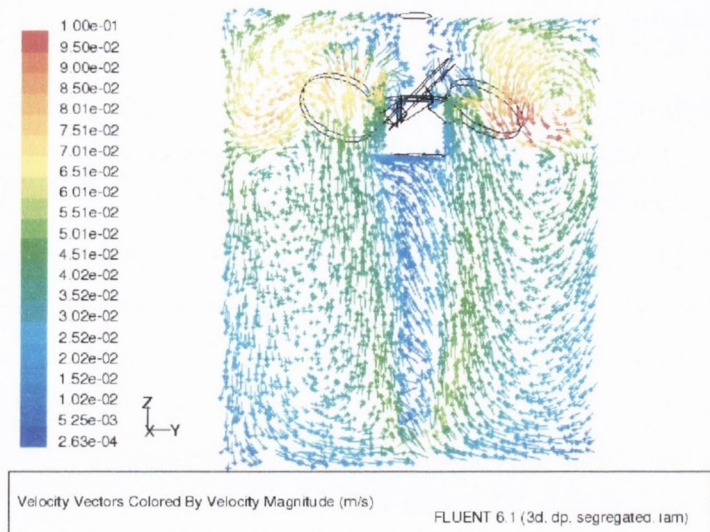


Figure 6.13. CFD-generated vectors coloured by velocity magnitude on the vertical $x=0$ plane through the flow field solution of the 350 ml volume at 59 rpm. Only 1 vector in 11 is shown for clarity.

6.2.2.2 Indirect quantitative validation.

The indirect quantitative validation results are presented in Figures 6.14. The method used is described in section 2.2.1.3.

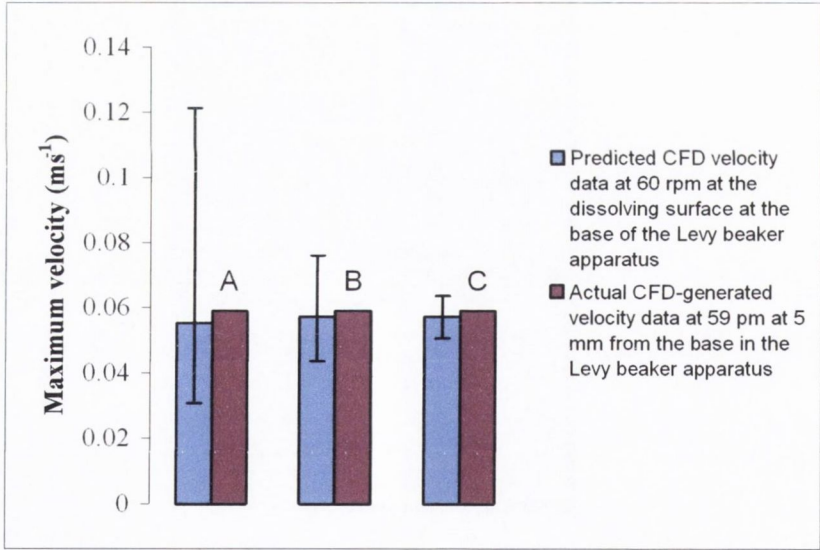


Figure 6.14. Predicted and CFD-generated velocity in the vicinity of the dissolving surface in the Levy apparatus in 350 ml at 59 rpm, using the relationship between dissolution rate in the Levy apparatus and the rotating basket apparatus and CFD-generated velocity data from the USP basket apparatus.

Error bars are calculated from A) variability in dissolution rate data from both the Levy beaker dissolution apparatus and the basket dissolution apparatus; B) variability in dissolution rate data from both the Levy beaker dissolution apparatus and the basket dissolution apparatus, excluding outlying points; C) variability in dissolution rate data from the Levy beaker dissolution apparatus only.

The error bars in the first set of columns in Figure 6.14 (Figure 6.14 (A)) are obviously extremely wide, and the major component of this error stems from the error in the dissolution rate data from the basket apparatus. To calculate these error bars, standard deviations from dissolution rate data from both the basket and Levy beaker dissolution apparatus were used in combination, to calculate the smallest and greatest possible ratio of dissolution rates between the basket and Levy beaker dissolution apparatuses, in addition to the average ratio.

Of the 5 replicates presented for the basket dissolution rate data (Withey, 1971), 2 outlying points differ by approximately 35% and 74% from the mean. The other 3 rate values are within 25% of the mean. Using these 3 dissolution rate values, a predicted velocity similar to that in Figure 6.14 (A) is calculated, but the RSD% value for the data is reduced from almost 50% to approximately 16%. The RSD% value for the Levy beaker dissolution apparatus dissolution rate data is approximately 11%. This actual and predicted velocity in the Levy beaker dissolution apparatus, with error bars calculated from a combination of variability in the beaker apparatus data and the basket apparatus data (excluding outliers) is presented in Figure 6.14 (B).

In Figure 6.14 (C) it can be seen that the error from the Levy beaker dissolution apparatus alone results in much narrower error bars.

The predicted maximum velocity value that the dissolving surface of a 1 cm^3 NaCl cube would be exposed to in the Levy beaker dissolution apparatus at 60 rpm (Withey, 1971) is in quantitative agreement with the maximum CFD-generated velocity at 0.005 m from the beaker base at 59 rpm. Neither this velocity value, nor that from the basket apparatus used in the prediction, accounts for the manner in which fluid flow is disturbed by the presence of a 1 cm^3 cube, which is diminishing in size over the period of the dissolution. The close agreement, however, of the predicted velocity with the CFD-generated velocity value suggests that the velocities in the CFD simulation of fluid flow in the Levy beaker dissolution apparatus at 59 rpm are of a realistic magnitude, suitable for general investigation of dissolution behaviour in the apparatus. Thus, the simulation can be said to be validated quantitatively.

The older USP basket dissolution apparatus vessel used by Withey (1971) had a slightly concave bottom, as described above. It has been shown that, provided the dissolving surface remains within the basket, as opposed to disintegrating and passing through the mesh, there is no significant difference in dissolution rate from a dosage form in the basket in a flat-bottomed vessel or in the older USP “slightly concave” vessel (Rees et al., 1978). The CFD simulations of fluid flow in the USP basket apparatus are modelled in the current USP vessel which incorporates a hemispherical base, rather than a flat or “slightly concave” base. Velocities from these simulations were used in the validation of the Levy beaker apparatus. However, it has also been demonstrated that for dosage forms remaining within the basket, there is no difference in dissolution rate between a flat bottomed vessel and one with a hemispherical base (Smith et al.,

1985). Therefore it is considered that velocities and dissolution rate data within the baskets in these three vessel configurations are of a comparable magnitude.

6.3 Investigation of flow field velocities and hydrodynamic characteristics in the Levy beaker dissolution apparatus at different agitation rates and fluid volumes.

6.3.1 Flow field velocities.

Contours of velocity magnitude on a vertical plane at $x=0$ are presented in Figures 6.15.a-d (350 ml) and 6.16.a-d (550 ml).

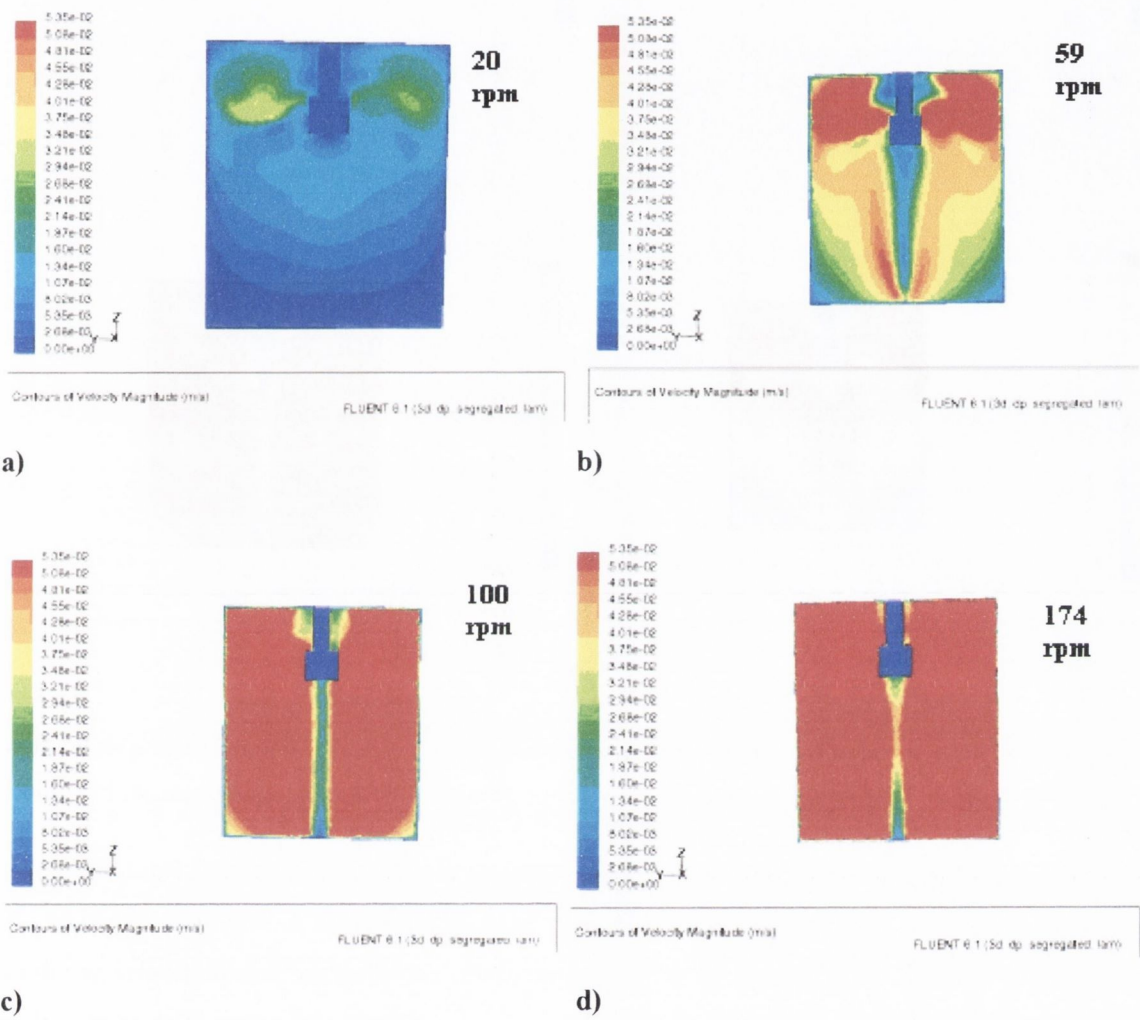


Figure 6.15. CFD-generated velocity magnitude contours on the vertical $x=0$ plane from a simulation of 350 ml in the Levy beaker dissolution apparatus at a) 20 rpm, b) 59 rpm, c) 100 rpm, d) 174 rpm.

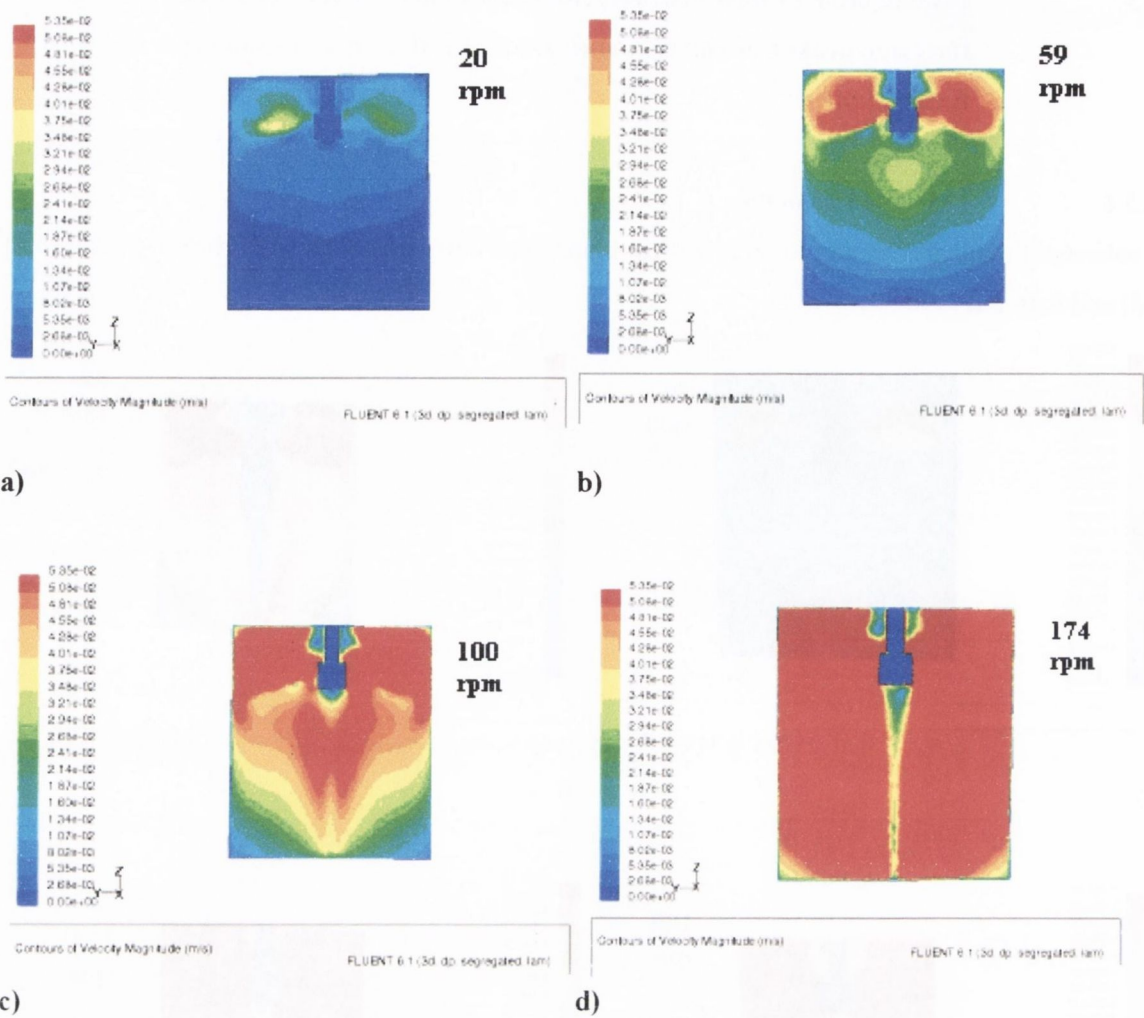


Figure 6.16. CFD-generated velocity magnitude contours on the vertical $x=0$ plane from a simulation of 550 ml in the Levy beaker dissolution apparatus at a) 20 rpm, b) 59 rpm, c) 100 rpm, d) 174 rpm.

For simulations involving both 350 and 550 ml volumes, the increase in overall fluid velocities within the vessels can be seen to increase with increasing agitation rate, as would be expected. It is of interest, however, to compare the velocity contours in each volume at a particular agitation rate. The 20 rpm, 59 rpm and 100 rpm simulations reveal a greater proportion of fluid at higher velocity values in the 350 ml volume compared to the 550 ml volume. In each case, the area in the upper part of the beaker near the propeller is comparable for both volumes. The lower part of the vessel, where velocities are more relevant to dissolution of a dosage form on the base of the vessel, is generally slower for the 550 ml volume. This can be attributed to the fact that the same size stirrer has to agitate a greater volume of fluid. On the scale presented in Figures 6.15 and 6.16, it is difficult to distinguish between the 350 ml and 550 ml volume at 174 rpm, as all velocities above 0.0535 ms^{-1} are coloured in red. Quantitative comparisons of velocity values within the flow fields of both volumes can be made by examining Figures 6.5 and 6.9. In general, the velocities are of a similar magnitude throughout both volumes, except in the lower part of the vessel where the maximum velocity recorded at the $z=-0.0586$ and $z=-0.0286$ points on the $x=0$

vertical plane is slightly higher for the 350 ml volume compared to the 550 ml volume. It should be noted at this point how the cut off value at the top end of the scale, in Figures 6.15 and 6.16, of 0.0535 ms^{-1} compares to velocities in the paddle apparatus. At 50 rpm in the paddle apparatus, the maximum facet velocities at the top and sides of the compact in the central position were 0.049 and 0.076 ms^{-1} , respectively. The velocities at the tops and sides of the compacts in positions 1 and 2 ranged from 0.085 to 0.090 ms^{-1} . Velocities in the region of 0.1 ms^{-1} are reached in the lower part of the Levy beaker dissolution vessel at 174 rpm, as can be seen from Figures 6.5 and 6.9 (the base of the Levy beaker dissolution vessel has an axial co-ordinate value of $z=-0.068641$, and the zero axial co-ordinate value is at the centre of the stirrer blades). For comparative purposes, velocities that a dissolving surface would be exposed to within the basket of the basket apparatus were calculated to be approximately 0.026 ms^{-1} at 50 rpm and 0.059 ms^{-1} at 100 rpm. Velocities within the paddle, basket and Levy beaker dissolution apparatuses are compared further in Chapter 7.

As the contours shown in Figures 6.15 and 6.16 are from the vertical plane $x=0$, it is of interest to demonstrate that the contours are similar for a surface rotated through 120° and 240° . These are shown in Figure 6.17, and are at the same angle to and distance from the nearest stirrer blade as the $x=0$ plane, illustrating the consistent nature of the flow field solution. Obviously, as it is a time-averaged simulation, no time-dependent features will be modelled.

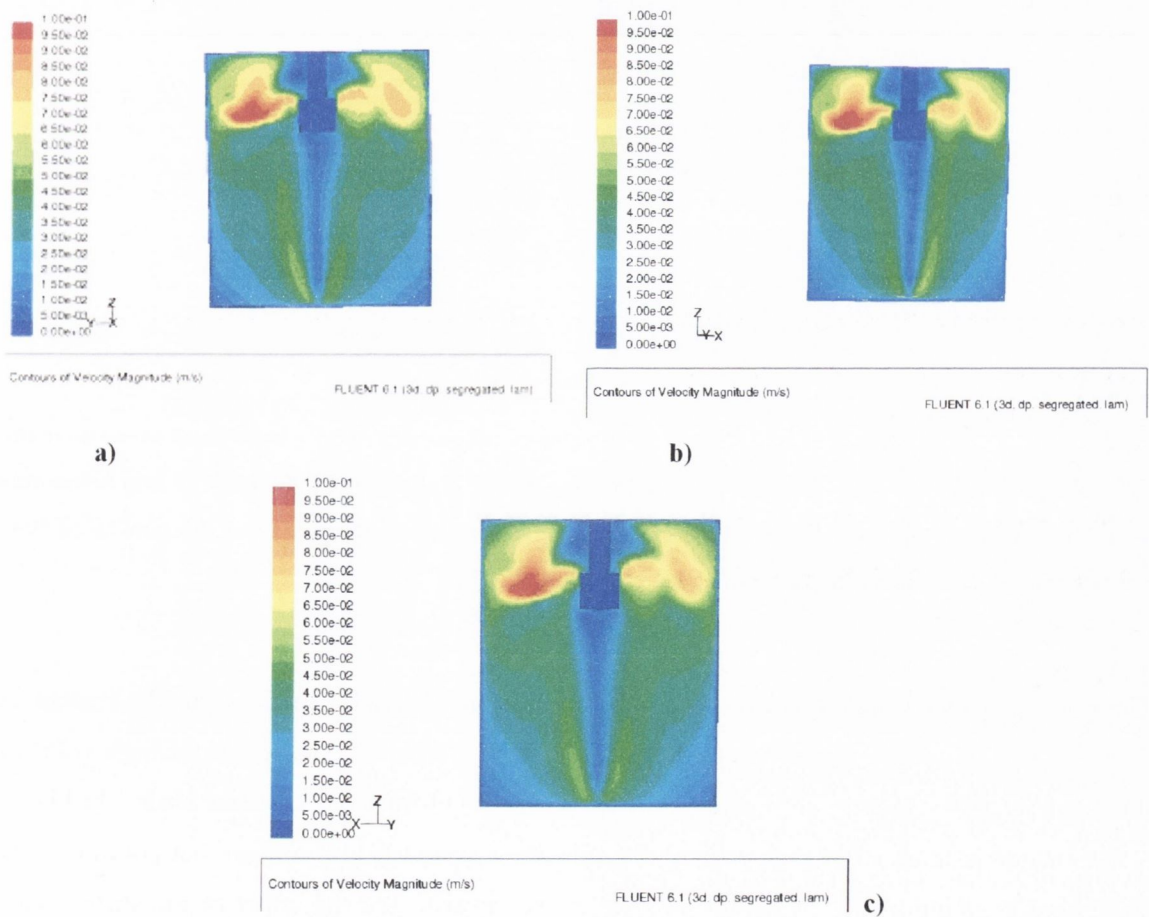


Figure 6.17. CFD-generated contours of velocity magnitude from simulations of the 350 ml flow field in the Levy beaker apparatus at 59 rpm on a) plane $x=0$, b) $x=0$ rotated 120° and c) $x=0$ rotated 240° .

6.3.2 Hydrodynamic characteristics.

The hydrodynamics of the 59 rpm 350 ml volume was investigated as an example of hydrodynamic characteristics in the Levy beaker dissolution apparatus as this is the validated model. Comparisons of the hydrodynamics in the apparatus at this rpm and at other agitation rates and with the 550 ml volume were made. Velocity vectors on three different planes in the region of the stirrer blades are shown in Figure 6.18.

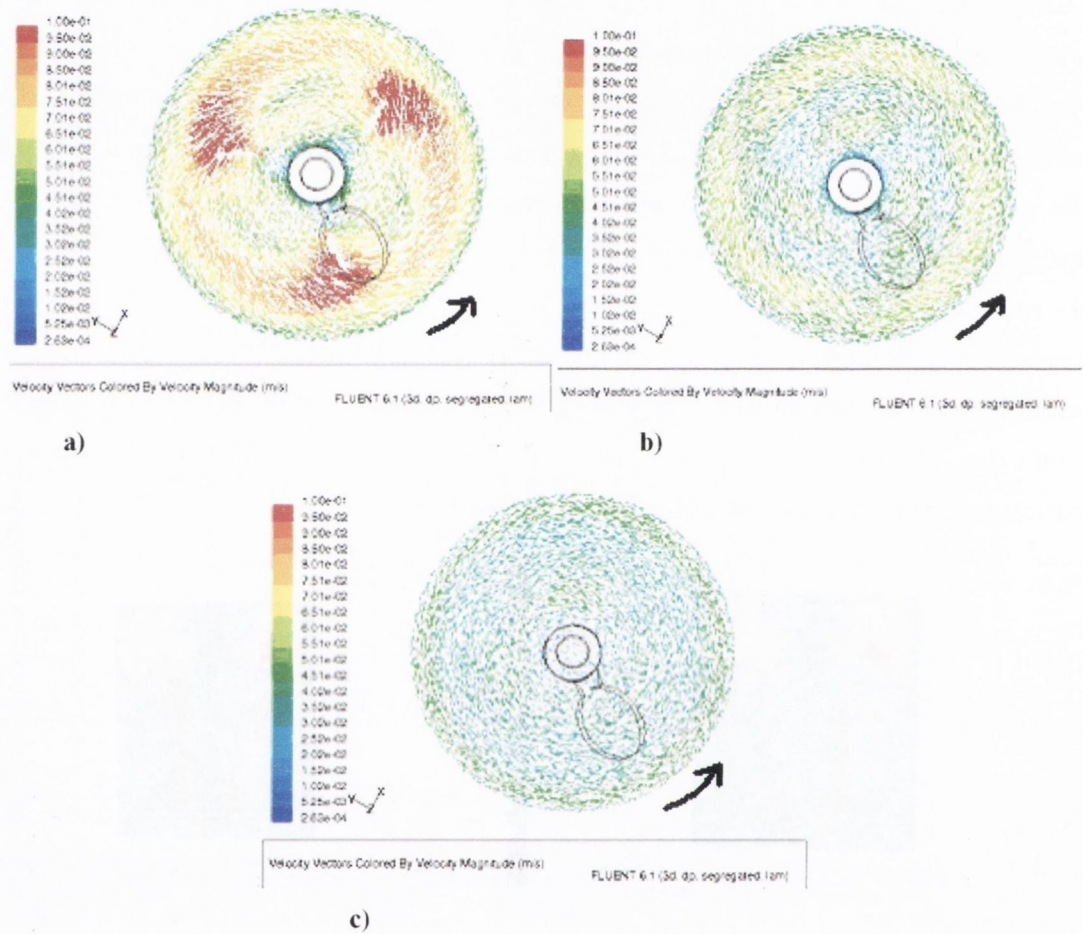


Figure 6.18. CFD-generated vectors coloured by velocity magnitude on a) a horizontal plane near the base of the stirrer blades ($z=-0.004$), b) just below the stirrer blades ($z=-0.008$) and c) 5 mm below this again ($z=-0.013$). Only one stirrer blade is shown for clarity in each case; from the simulated flow field of 350 ml in the Levy beaker apparatus at 59 rpm.

There is a region of high velocity trailing behind the stirrer blade which is clearly evident in Figure 6.18.a, however, slightly below this level in Figure 6.18.b, the region of high velocity (although overall velocities are lower below the stirrer) is in front of the stirrer blade. In Figure 6.18.c, which is further below the stirrer, the velocities are much lower again, but not uniformly distributed over the plane. It is still possible at this level to see the effect of the stirrer blade operating above it, and the higher velocity region is visible at a point corresponding horizontally to the region in front of the stirrer blade rather than behind it. As these regions of high velocity

vary depending on the axial position of the plane investigated, it can be assumed that there are secondary flow patterns in axial and radial directions in addition to the main tangential flow.

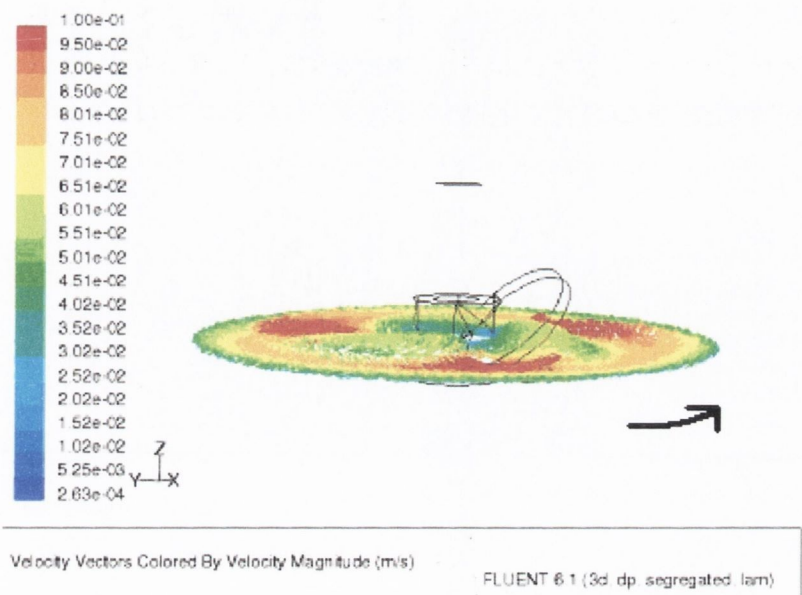


Figure 6.19. CFD-generated vectors coloured by velocity magnitude on a horizontal plane in the region of the stirrer blade. ($z=-0.004$); from the simulated flow field of 350 ml in the Levy beaker apparatus at 59 rpm.

The velocity vectors in Figure 6.19 appear to show a region of fluid being “pushed” upwards by the stirrer blade, with the fluid being pulled in its wake resulting in the high velocity region seen in Figure 6.18.a. The vectors, however, represent finite elements of fluid on the same horizontal plane, with the vectors displayed as arrows whose direction correspond to the vectors’ values. Therefore, the vectors in front of the stirrer blade represent fluid elements towards the base of the blade which are moving (essentially being pushed) in a forward-and-upward direction. The angle of the stirrer blade and the direction of rotation of the stirrer have previously been demonstrated to be of importance, as the stirrer direction determines whether a “pushing” or “pulling” action is produced (Lerk and Lagas, 1977). In terms of effect on dissolution rates, when rates for KCl disks in distilled water were obtained from different positions along the base of the beaker, the rates increased with distance from the centre then decreased again (Lerk and Lagas, 1977). The profile of the variation of rate with distance was dependent on the direction of rotation and angle of the stirrer blade. The apparatus geometry and volumes of dissolution medium used were slightly different to the current work.

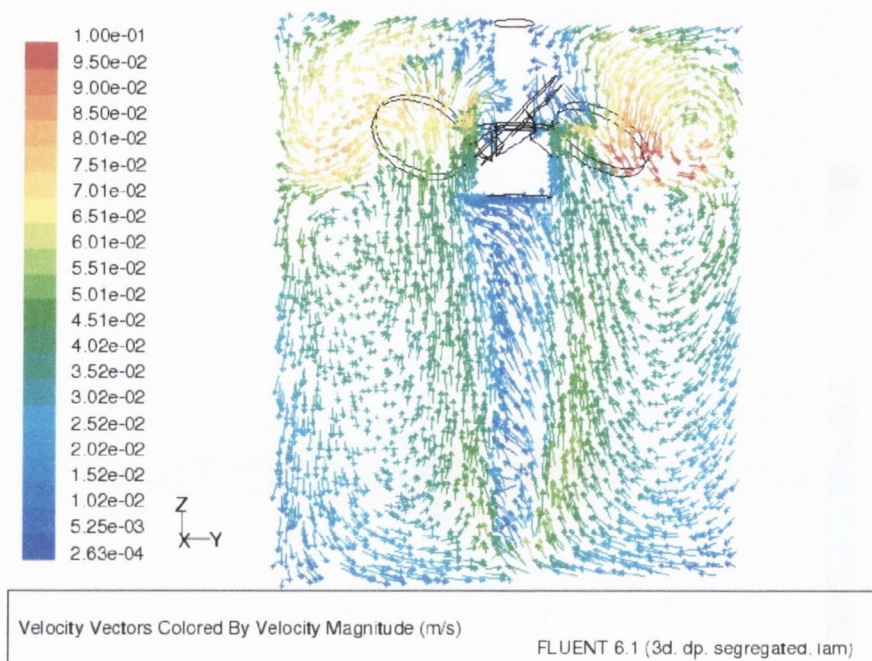


Figure 6.20. CFD-generated vectors coloured by velocity magnitude on the vertical $x=0$ plane through the flow field solution of the 350 ml volume at 59 rpm. Only 1 vector in 11 is shown for clarity.

Some of the secondary flow characteristics are apparent in Figure 6.13, which is reproduced as Figure 6.20, in particular regions of axial circulation near the stirrer blades and inward radial flow at the base of the vessel. This radial flow is also evident in Figure 6.21.a, where the vectors are coloured according to the radial velocity magnitude. The darker blue colour at the base of the vessel is indicative of negative (inward) radial flow, with most of the positive (outward) radial flow occurring in the upper region of the vessel near the stirrer blades (Figure 6.21.b). This is especially of importance when considering dosage forms which may be subject to these hydrodynamic forces at the base of the beaker. Disintegrating and dissolving particles are likely to be pulled inwards towards the centre of the vessel, unless the original dosage form falls in the outer region/perimeter of the vessel base. This is consistent with observations from earlier work with the Levy beaker dissolution apparatus (Levy and Hollister, 1964), where it is stated that “data for tablets which formed a “mound” at the edge rather than in the centre of the bottom of the beaker were excluded”. This suggests that the dissolving dosage forms produced disintegrated particles which were either swept in to the centre or remained at the outer edge. Vectors at the edge of the beaker base in Figure 6.21.b show radial velocity magnitudes close to neutral, which would support the concept of a “mound” which formed at the edge of the beaker base remaining undisturbed at this edge.

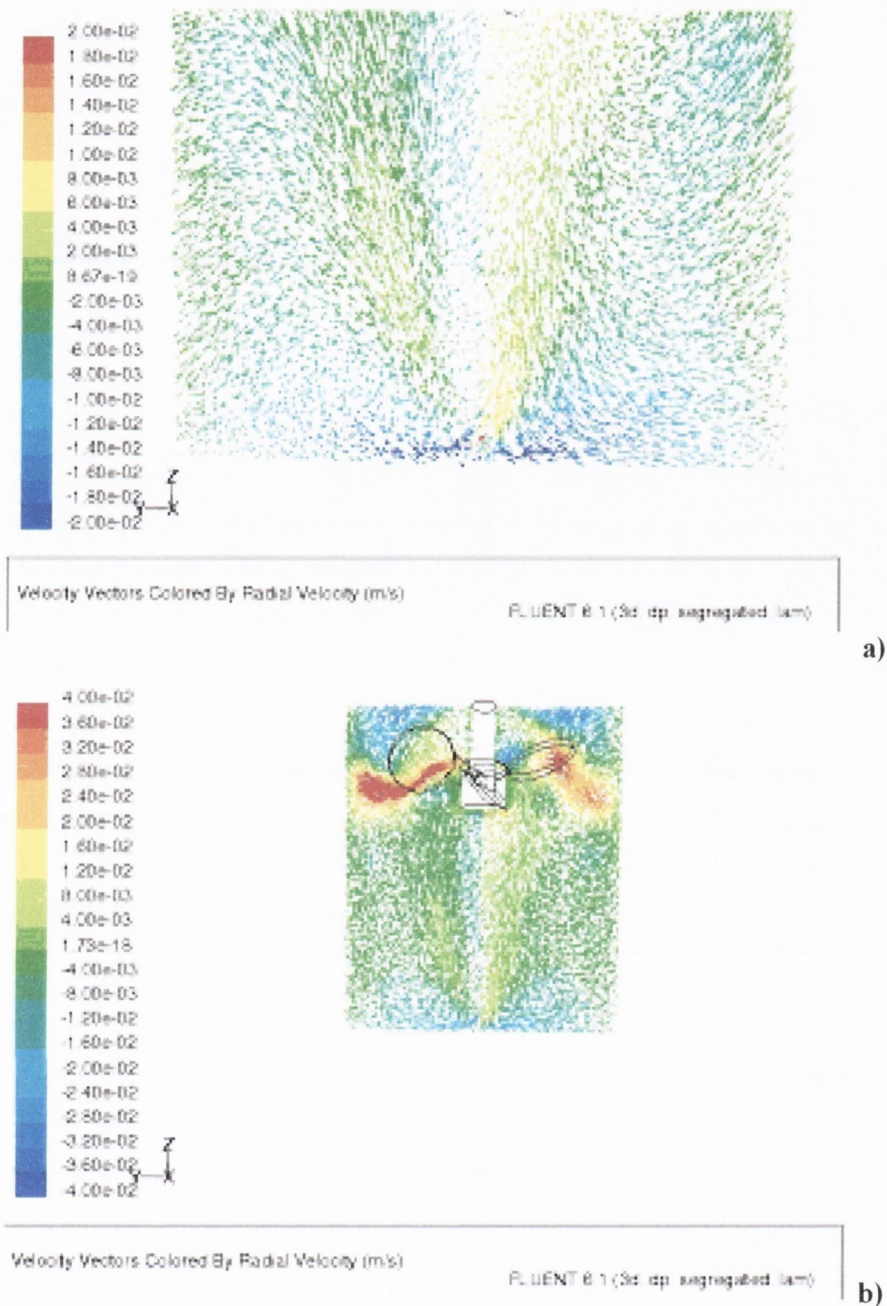


Figure 6.21. CFD-generated vectors coloured by radial velocity on the vertical $x=0$ plane, in a) the lower region of the beaker and b) in the whole beaker; from simulations of the flow field of 350 ml in the Levy beaker apparatus at 59 rpm.

The hydrodynamics within the 350 ml fluid volume at 59 rpm are compared to those within the same fluid domain at an agitation rate of 174 rpm.

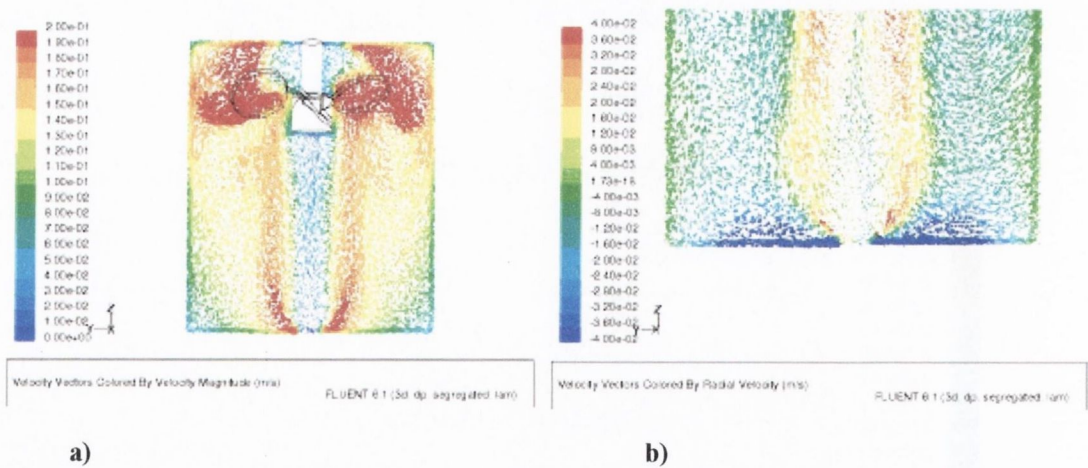


Figure 6.22. CFD-generated vectors on the $x=0$ plane coloured by a) velocity magnitude and b) radial velocity; from simulations of the flow field of 350 ml in the Levy beaker apparatus at 174 rpm.

Although the velocity scale is different, the hydrodynamic characteristics of Figure 6.22.a are similar to those in Figure 6.20, consisting of a central low velocity vortex region surrounded by a higher velocity region, and lower velocities again towards the outer regions of the vessel. The sharp radial inflow at the base of the vessel in 6.22.b is similar (but of greater magnitude) to that present at 59 rpm in Figure 6.21.a. At 174 rpm, however, there is a much greater degree of outward radial flow in the lower portion of the vessel at the edge of the vortex region than at 59 rpm.

Comparison of hydrodynamics in 350 ml simulation and 550 ml simulation at 59 rpm.

The hydrodynamics in the 350 ml volume at 59 rpm can also be compared with those at 59 rpm in the 550 ml volume. Similar regions of high velocity behind the stirrer blades can be seen in Figure 6.23.a, and the fluid also appears to be pushed upwards in front of the blade at this level in Figure 6.23.c. Figure 6.23.b, however, shows little or no evidence, with the velocity scale presented, on the horizontal plane $z=-0.013$ of any periodic effect from the stirrer blades above. This is in contrast to the effect apparent in Figure 6.18.c. Presumably, the greater vessel diameter, fluid volume and distance from the stirrer to the base in the 550 ml model enables these secondary flow effects from the stirrer blades to have dissipated at several millimetres below the bottom of the blade.

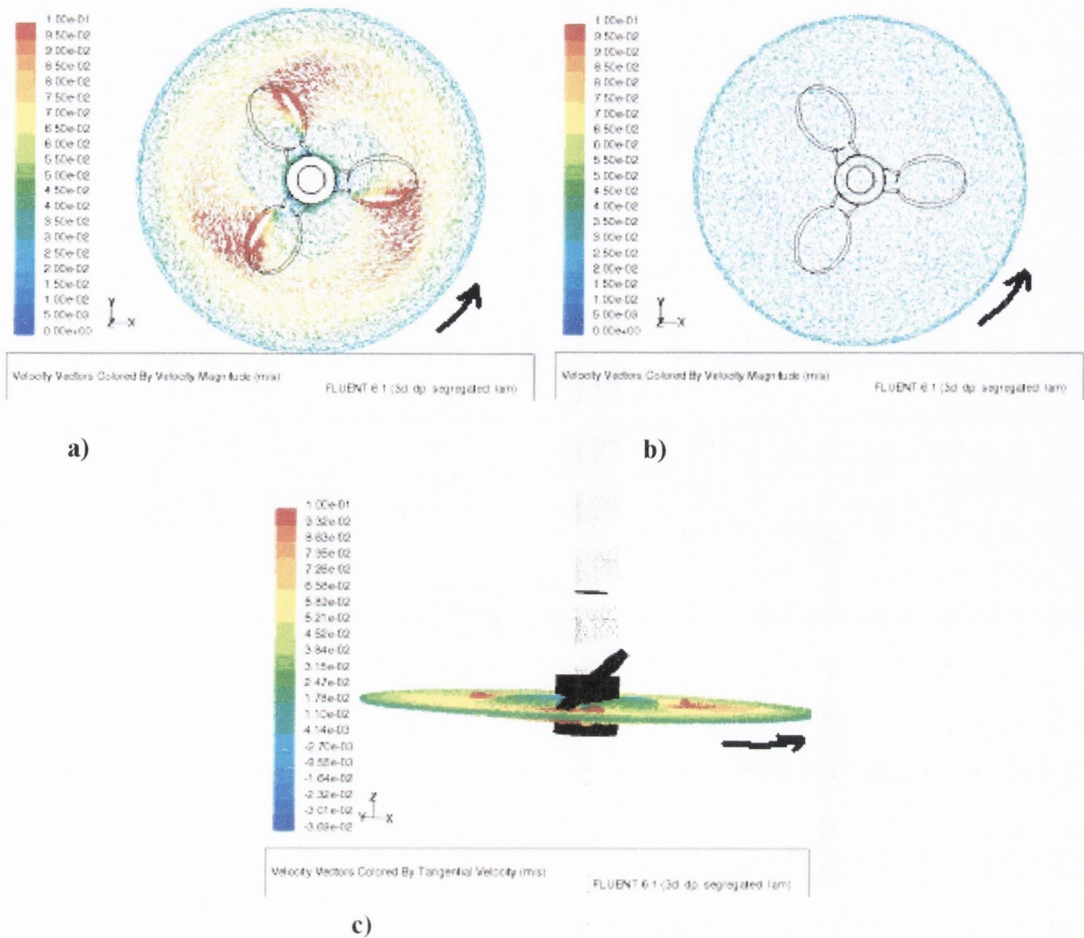


Figure 6.23. CFD-generated vectors coloured by velocity magnitude on a) and c) horizontal plane $z=-0.004$ and b) and $z=-0.013$; from simulations of the flow field of 550 ml volume in the Levy beaker apparatus at 59 rpm.

The effect of the greater volume and distance of the stirrer from the vessel base is especially evident on the $x=0$ vertical plane. Although the hydrodynamics in the region of the blade are similar to those in the 350 ml volume, in the lower region of the vessel the fluid velocities are very low. There are no obvious characteristics to the fluid flow in the lower regions of the vessel (Figure 6.24), with the exception of a slight axial circulation as seen in Figure 6.24.c. There is some positive (upward) axial flow in the central region of the beaker, with some negative (downward) flow at the edge of the beaker. The velocity magnitudes involved in this, however, are low.

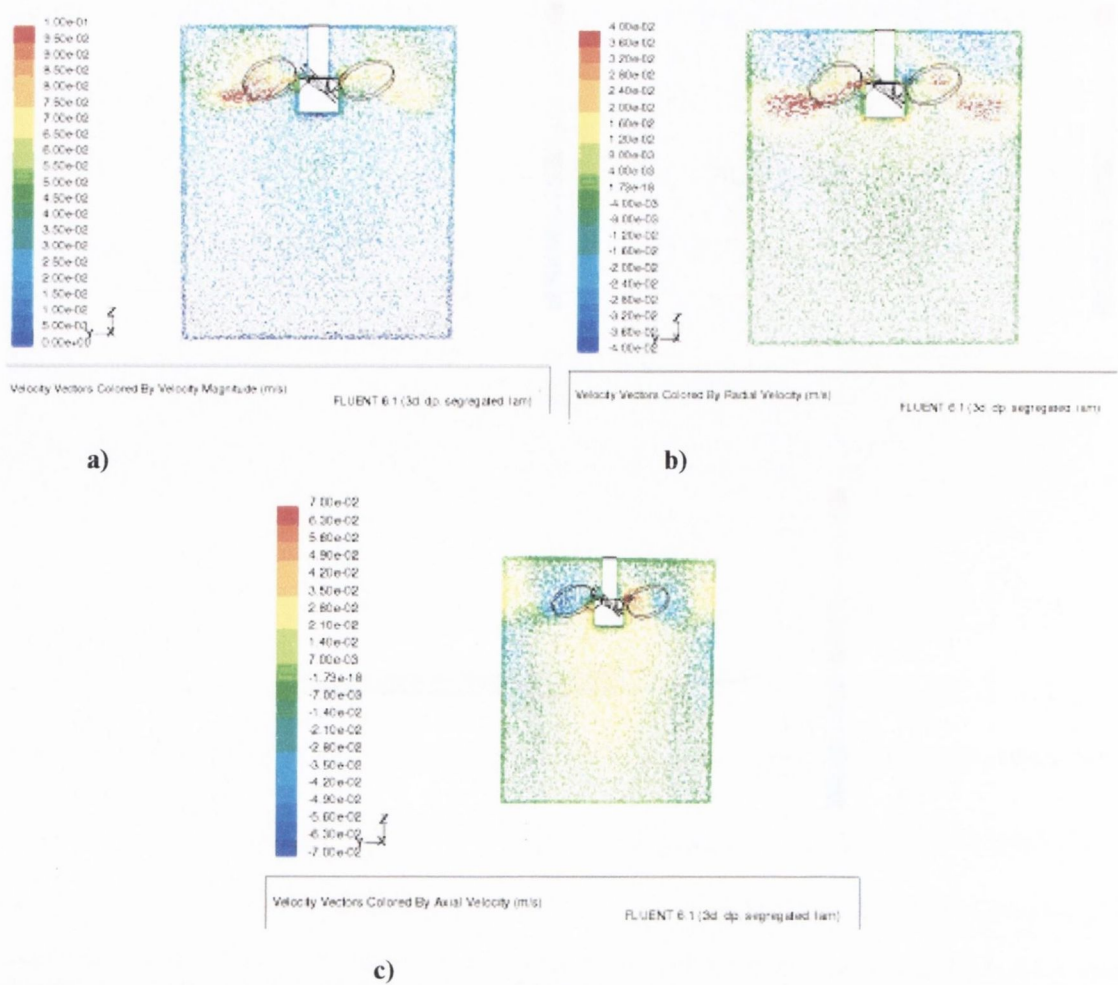


Figure 6.24. CFD-generated vectors on the $x=0$ plane coloured by a) velocity magnitude, b) radial velocity and c) axial velocity; from simulations of the flow field of 550 ml in the Levy beaker apparatus at 59 rpm.

Comparison of hydrodynamics in the 550 ml and 350 ml volume simulation at 174 rpm.

When the agitation rate is increased in the 550 ml volume to 174 rpm (Figure 6.25), the same hydrodynamic characteristics that are present in the 350 ml volume return. The central low velocity vortex surrounded by the higher velocity region is once again evident in Figure 6.25.a, and the radial inflow at the base of the vessel is evident in Figure 6.25.b.

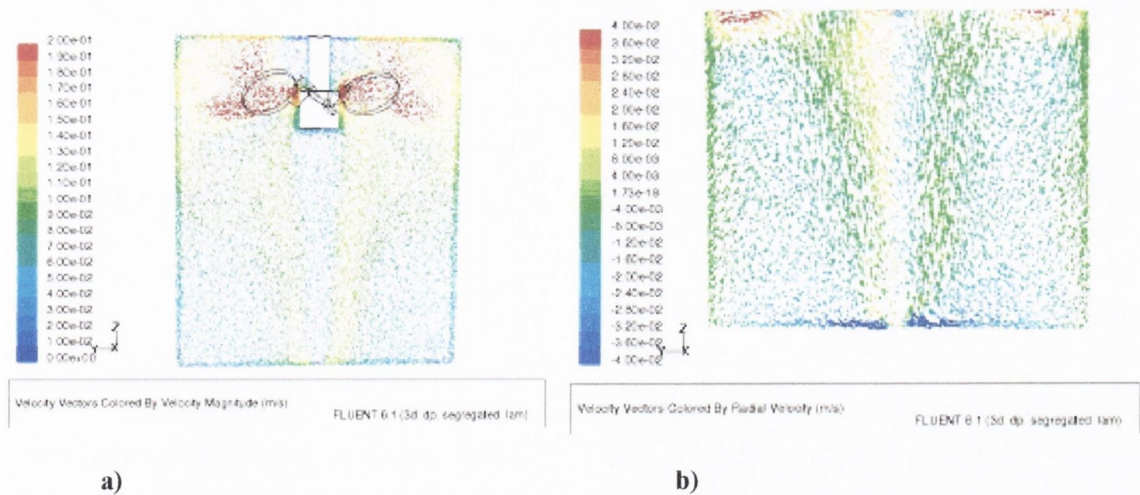


Figure 6.25. CFD-generated vectors on the $x=0$ plane coloured by a) velocity magnitude and b) radial velocity; from simulations of the flow field of 550 ml in the Levy beaker apparatus at 174 rpm.

From this investigation into the hydrodynamics of the Levy beaker dissolution apparatus, it would appear that the hydrodynamic characteristics within the 350 ml volume remain consistent following an increase in agitation rate, although the velocity magnitudes will increase. An increase in the diameter, depth and therefore volume of the fluid domain, however, requires a higher agitation rate to produce the same characteristics that are seen in the smaller volume. At lower agitation rates, there are very low fluid velocities in the lower part of the 550 ml vessel.

6.4 Relationship between fluid velocities in the Levy beaker dissolution apparatus and dissolution rates.

6.4.1 Determination of appropriate location of data extraction from CFD flow-field simulations.

In order to compare dissolution rates and hydrodynamic characteristics within the Levy beaker dissolution apparatus at different agitation rates, vessel geometries and dissolution media volumes, an appropriate location for data extraction from the flow-field simulations must be determined. As the flow field simulations do not contain a compact, flow around a compact is not simulated. The approach taken, therefore, was to identify a region above the base of the paddle apparatus, containing no compact, which would have a similar velocity distribution as a region directly above a compact (of 13 mm diameter and 3 mm height) at the centre of the base of the paddle apparatus. Figure 6.26 illustrates the maximum, minimum and average velocity distributions at four different locations.

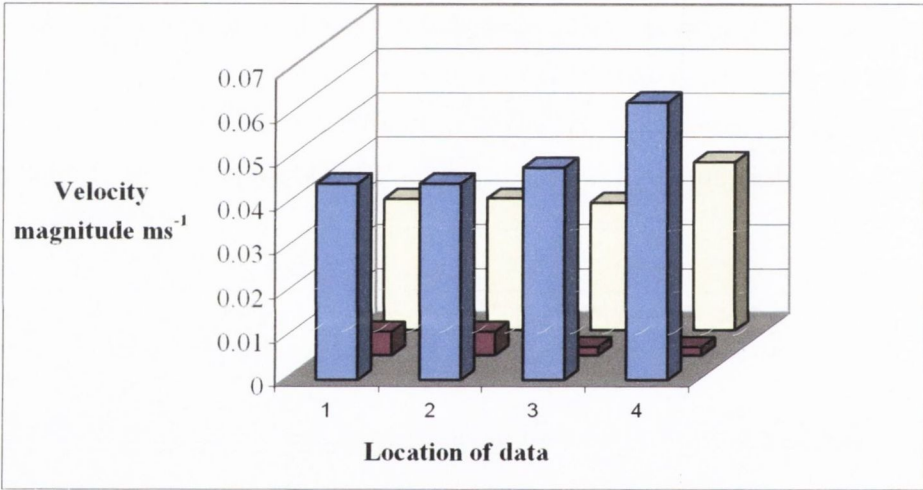


Figure 6.26. Maximum (■), minimum (■) and average (■) CFD-generated velocity magnitudes in the paddle apparatus at 1) 1 mm above the compact surface in the central position – 13 mm diameter plane; 2) 2 mm above the compact surface in the central position – 13 mm diameter plane; 3) 2 mm above the centre of the base of the vessel containing no compact – 10 mm diameter plane; 4) 2 mm above the centre of the base of the vessel containing no compact – 13 mm diameter plane.

Several observations may be made from Figure 6.26. Firstly, there is little difference in velocity data taken either 1 or 2 mm above the surface of the compact in the central position (locations 1 and 2, respectively). Secondly, although the compact was 13 mm in diameter, and therefore the planes above the compact surface in locations 1 and 2 were defined as 13 mm in diameter, a plane of 10 mm diameter, 2 mm from the base of the vessel containing no compact (location 3), contained a similar distribution of velocity values to the planes in locations 1 and 2. Thirdly, a plane of 13 mm diameter 2 mm from the base of the vessel (location 4) contained velocities that were generally of a higher magnitude than those above the compact in the central position

(locations 1 and 2). Therefore, a plane of 10 mm diameter and 2 mm from the vessel base was considered, from hydrodynamic simulations in the paddle apparatus containing no compact, to contain velocity data of a magnitude relevant to the interpretation of dissolution rate data from the paddle apparatus containing a compact at the centre of the vessel base. A 10 mm diameter plane located 2 mm from the vessel base was also used in the extraction of data from the Levy vessel dissolution apparatus. It should be noted that a compact which did not fall directly in the centre of the vessel in either the paddle or Levy apparatus would be exposed to a different range of velocities. These would be slightly higher for the paddle apparatus (illustrated by the higher velocities on the wider diameter plane in location 4, Figure 6.26) and possibly slightly lower within the Levy vessel once a compact was far enough off centre that it was not exposed to the higher velocity area around the central vortex region.

6.4.2 **Hydrodynamics and dissolution rates in the Levy beaker dissolution apparatus.**

The dissolution rates of the ASA and HFMI disks are presented in Table 6.1 (Corrigan, 1973).

Dissolution rate mg hour ⁻¹ cm ²				
350ml	20 rpm	59 rpm	100 rpm	174 rpm
HFMI	1.87	3.22	4.61	6.18
ASA	17.40	31.16	44.35	61.55
550ml				
HFMI	1.68	3.70	4.70	6.65
ASA	17.13	30.99	47.27	71.23

Table 6.1 Dissolution rates (mg hour⁻¹ cm²) of HFMI and ASA compacts in the Levy beaker dissolution apparatus under agitation/fluid volume conditions consistent with those simulated.

The relationship between agitation rate and dissolution rate for HFMI and ASA disks can be seen in Figure 6.27.

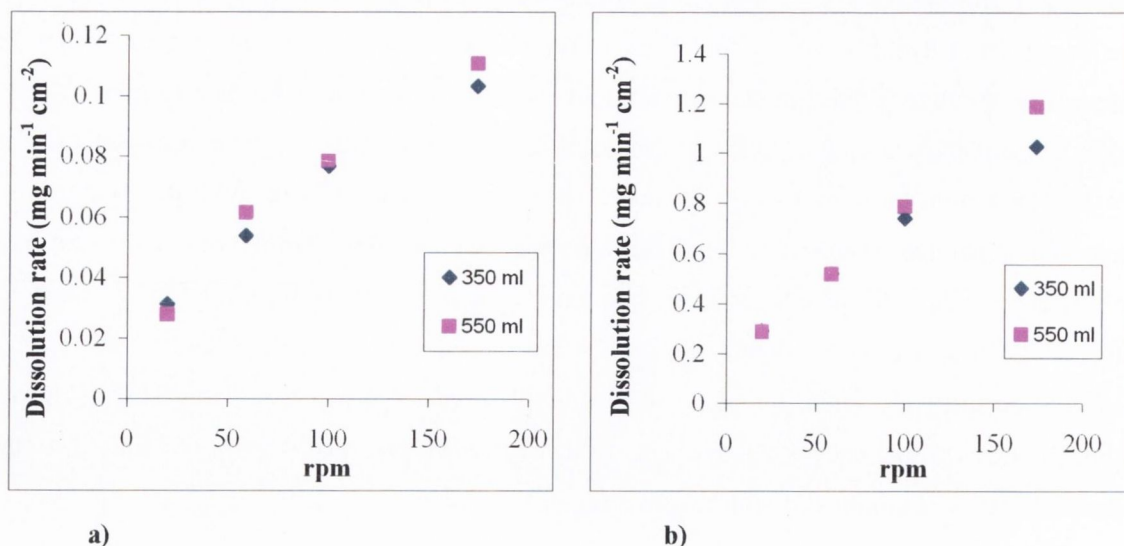


Figure 6.27. Dissolution rates ($\text{mg min}^{-1} \text{cm}^{-2}$) vs. agitation rate in 350 ml and 550 ml volumes in the Levy beaker dissolution apparatus for a) HFMI and b) ASA.

It is evident that for both compounds the dissolution rate at the highest agitation speed (174 rpm) is greater in the 550 ml volume than the 350 ml volume. There is a discrepancy between the effect of rotation speed at the intermediate agitation rates on dissolution rate in the 350 ml and 550 ml volumes. The ASA results seem to show a slight deviation in favour of a higher dissolution rate in the 550 ml volume at the 100 rpm agitation speed, however the HFMI results show an increased dissolution rate in 550 ml at 59 rpm, but no increase at 100 rpm. There is an approximately linear relationship in each case between dissolution rate and agitation rate. When dissolution rates are plotted against the maximum velocity at 2 mm from the vessel base, the result is an approximately linear relationship for both compounds in 350 ml, but a 2nd order polynomial relationship with velocity values from the 550 ml simulation, as shown in Figure 6.28. This curve relating local maximum velocity values to dissolution rate in the 550 ml volume suggests that the increase in agitation rate will have a greater effect on dissolution rate at lower agitation speeds.

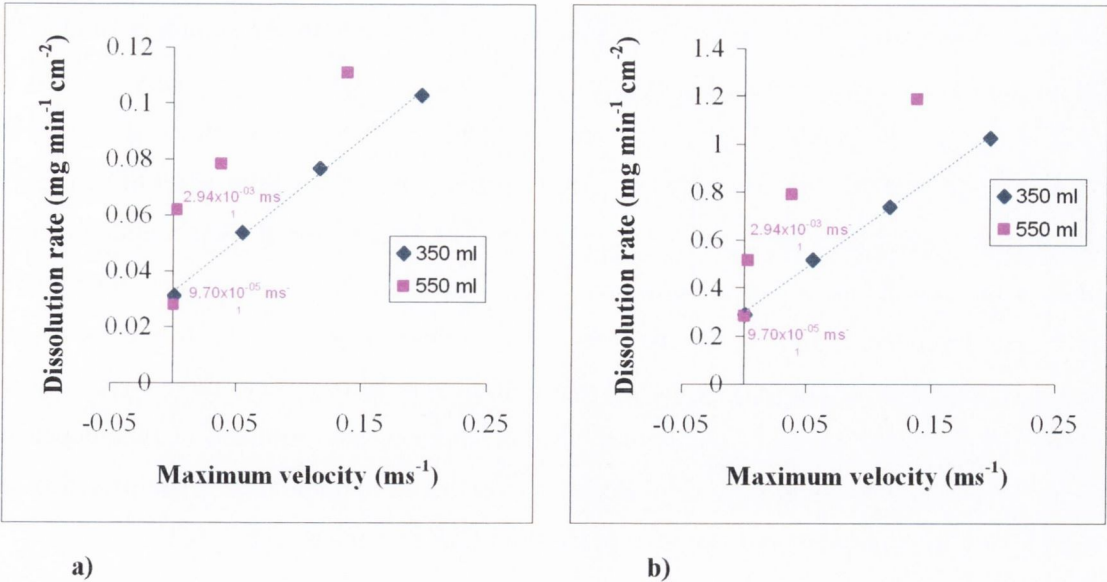


Figure 6.28. Dissolution rates (mg min⁻¹ cm⁻²) vs. maximum CFD generated velocity on a 10 mm diameter plane 2 mm from the beaker base in 350 ml and 550 ml volumes in the Levy beaker dissolution apparatus for a) HFMI and b) ASA.

When relating dissolution rate to maximum velocity in 550 ml, it can be seen from Figure 6.28 that there is an increase in dissolution rate from 20 to 59 rpm with a very minor increase in velocity (0.003 ms⁻¹), and the higher dissolution rate at 174 rpm corresponds to a lower maximum velocity than in the 350 ml volume. An explanation for this could be that although the maximum velocity has not increased by any significant amount, there may be an increase in the amount of fluid in the area examined which has reached this maximum velocity. In Figure 6.29 the relationship between dissolution rate and average velocity in the region is examined.

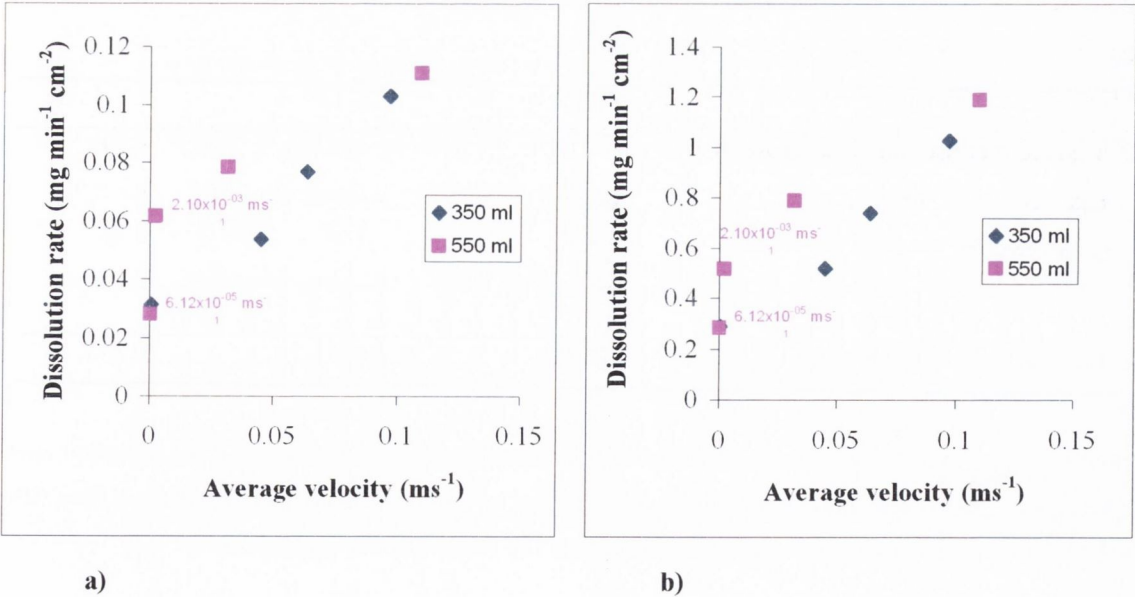


Figure 6.29. Dissolution rate (mg min⁻¹ cm⁻²) vs. average CFD-generated velocity on a 10 mm diameter plane 2 mm from the beaker base in 350 ml and 550 ml volumes in the Levy beaker dissolution apparatus for a) HFMI and b) ASA.

The relationship between dissolution rate and average velocity for both compounds is similar, and at 20 rpm and 174 rpm the relationship between dissolution rate and average velocity for both 350 ml and 550 ml is comparable. The lower average velocities in the 550 ml volume at 59 rpm and 100 rpm indicate that the variable ‘average velocity’, although reflecting the effect of velocity on dissolution rate better than maximum velocity, is not very informative at these agitation speeds. Further factors which may affect velocity-dissolution rate relationships are the lack of simulation of any time-dependent features, and the effect of experimental error. The former is perhaps particularly important in the case of the 59 rpm 550 ml simulation, where there were very low velocities in the lower region of the vessel. In this situation, any turbulent or time-dependent hydrodynamic features would have a greater effect on the dissolution rates. The presence of a dissolving disk in the fluid would also disrupt the fluid flow to some extent.

To determine a general relationship between local velocity values and dissolution rate, the dissolution rate data for both HFMI and ASA were combined. This was achieved by dividing the dissolution rate by the saturated solubility (HFMI: 0.605 mg ml⁻¹; ASA 5.756 mg ml⁻¹ (Corrigan, 1973)). The resulting value was “K”, the mass transfer coefficient. In this case, the surface area of the dissolving surface was not taken into account, as it was identical for each dissolving disk. Log-log plots were constructed, and the relationships between log K and log agitation rate (LK-LAR), log K and log maximum CFD-generated local velocity (LK-LV) and log maximum CFD generated local velocity and log agitation rate were determined (LV-LAR). The slope of these graphs for both 350 ml and 550 ml could be compared to numerically assess the difference in the relationships.

	LK-LAR	LK-LV	LV-LAR
Average (HFMI and ASA) slope (350 ml)	0.572	0.191	2.701
	Average R ² : 0.997	Average R ² : 0.888	R ² : 0.912
Average (HFMI and ASA) slope (550 ml)	0.645	0.185	3.456
	Average R ² : 0.992	Average R ² : 0.980	R ² : 0.990
Ratio of slopes (350:550)	0.886	1.032	0.782

Table 6.2. Slopes of log-log plots determining relationships between log K (LK), log agitation speed (LAR) and log local maximum CFD generated velocity (LV) in the 350 ml and 550 ml fluid flow fields in the Levy beaker dissolution apparatus, where K is the mass transfer coefficient.

The conclusions that can be drawn from the information presented in Table 6.2 is that the dissolution rates in the 550 ml vessel are dependent on the agitation rate to a higher fractional power than in the 350 ml vessel, implying more turbulent flow in the 550 ml vessel (Grijseels et al., 1981). Similarly, an increase in local CFD-generated velocity is dependent on the agitation

rate to a higher power in the 550 ml vessel than in the 350 ml vessel. This supports the observation of dissolution rate dependency on agitation rate, as the local velocity near the dissolving surface should have the same effect on dissolution rate regardless of overall vessel shape/size, provided sink conditions are maintained. That a lesser increase in agitation rate is required in the 550 ml volume to induce the same increase in local velocity as in the 350 ml volume, implies that the agitator rotation does not result in smooth laminar fluid flow in the 550 ml volume. The local velocity is therefore partially dependent on secondary hydrodynamics rather than the tangential movement induced by the stirrer. The ratio of the slopes for the LK-LV plots is near unity. This would be expected, as the dependency of the dissolution rate on the local velocity value should be similar regardless of the vessel size or geometry. The slopes of the LK-LV plots, however, are much lower, at an overall average of 0.188, than the slopes of the LK-LAR plots. This implies that a greater relative increase in local maximum velocity value is needed to produce an increase in dissolution rate than the relative increase in agitation rate (rpm) required to produce an increase in dissolution rate. It is possible that this phenomenon is related to the fact that the CFD-generated maximum velocity is the maximum velocity at one point on the plane investigated. A slight increase in maximum velocity does not imply that the overall velocities that a dosage form is exposed to have increased significantly. Despite the fact that a larger increase in maximum velocity value in the region of the dosage form is needed to provide an increase in dissolution rate compared to the dissolution rate increase induced by an agitation rate increase, according to the LV-LAR plot data in Table 6.2 the CFD-generated maximum velocity will increase rapidly with a small increase in agitation rate. Additionally, the CFD generated data does not account for the effect of a dosage form present in the region of interest on the local maximum velocity values.

The effect of using a greater 550 ml volume in a 600 ml beaker as opposed to a 350 ml volume in a 400 ml beaker is complex. The resulting 550 ml system contains both a wider diameter beaker and additionally the distance from the stirrer to the vessel base is increased (as the stirrer depth below the fluid surface was kept constant). To maintain the same stirrer dimensions but increase the fluid volume could be compared to a situation where the fluid volume is maintained but the stirrer dimensions are altered. The effect of changing from a 2 cm diameter stirrer to a 4.3 cm diameter stirrer, while maintaining constant dissolution medium volume, was examined in dissolution studies on capsules (Lin et al., 1970). Various methods were investigated to ensure that the capsule remained at the base of the beaker, which in this case did not have a flat bottom. Other geometrical specifications of the systems examined differed from the current work also, however in each case the increased stirrer size resulted in an increase in dissolution rate. The effect of stirrer height from the base of the vessel on the dissolution rate of spherical particles of benzoic acid in vessels with concave/flat/convex bases and of differing diameters was also examined (Underwood and Cadwallader, 1976). The effect of propeller height varied with shape

of base and vessel diameter, implying complex interactions between these geometrical features leading to unpredictable hydrodynamic characteristics affecting the dissolution rate.

As the Levy beaker dissolution apparatus was a predecessor of the current compendial paddle apparatus, it is of interest to compare the relationship between dissolution rate and agitation rate in both apparatuses. Morihara et al. (2002) presented data from dissolution of salicylic acid tablets in the paddle apparatus, at six different rpm values. The dissolution data is presented as a k_d (dissolution constant) value, in % dissolved per minute. A plot of $\log k_d$ vs. $\log \text{rpm}$ is shown in Figure 6.30.

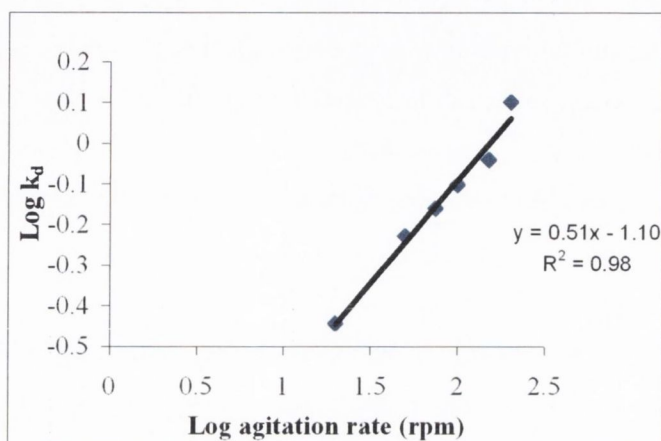


Figure 6.30. Log of k_d vs. Log agitation rate (rpm) from dissolution data (0-30 minutes) of salicylic acid in pH 7.4 phosphate buffer, taken from data presented in Morihara et al. (2002).

The slope of 0.51 suggests a dependency of dissolution rate on the stirring speed which is consistent with the rotating disk theory where dissolution rate is proportional to the angular velocity^{0.5} (Levich, 1962). The agitation rate to the power of 0.66 was related to the erosion rate constant (a measure of a change in mass dissolved with time) for benzoic acid dissolution in phosphate buffer at pH 7.4 in the paddle dissolution apparatus (Kavanagh, 2000). The solubility of both salicylic acid and benzoic acid is of a similar order of magnitude at pH 7.4 (Kavanagh, 2002; Ramtoola and Corrigan, 1987). The latter value of 0.66 was from a system containing 1000 ml of fluid, whereas the former value of 0.51 was for 900 ml. It is unlikely that the discrepancy between the values of 0.51 from Morihara et al. (2002) and that of 0.66 from Kavanagh (2000) is entirely due to an increase in volume of dissolution media. The coefficient describing dissolution rate is related to the cube-root of a change in mass from a cylindrical (rather than spherical) compact in Kavanagh (2000) which may alter the relationship with agitation rate. Additionally, the dissolving salicylic acid (Morihara et al., 2002) and benzoic acid (Kavanagh, 2000) would have created a microenvironment, with the viscosity influenced by the amount of salicylic or benzoic acid dissolved and a pH different to the bulk pH of 7.4. This creation of the microenvironment may have been affected by changing boundary layer thickness with variation in agitation rate, which in turn may have affected the dissolution rate and the exponent to which the agitation rate is raised. However that the volume increase would contribute to some extent to an

increase in the exponent would be expected. In summary, dissolution rate data from a non-disintegrating dosage form in either the paddle apparatus or the Levy beaker dissolution apparatus may be expected to be approximately related to the agitation rate to the power of 0.5-0.66, at the agitation rates investigated.

6.5 Conclusions regarding simulation of hydrodynamics within the Levy beaker dissolution apparatus.

When investigating the strategy used to achieve convergence in this simulation, it is evident that to monitor both residuals and some surface forces is beneficial in deciding whether a solution has reached an acceptable degree of convergence. It has also been shown that in some cases surface forces do not change significantly while residuals are still decreasing by a small magnitude. This fact is worth noting when analysing solutions which are time- and resource-consuming. Attempting to achieve a “levelling” of residuals may not always be necessary for the solution to be of use. Simulations with more complex hydrodynamics in this work, especially at the 174 rpm agitation rates, were difficult to converge to a level similar to those at lower agitation rates, however the resulting solutions were informative nevertheless in terms of analysis of the overall velocity magnitudes which developed at higher agitation rates.

Comparisons of dissolution rates from within the basket dissolution apparatus and the Levy beaker dissolution apparatus enabled accurate predictions of velocity magnitudes to be made for the simulation of the Levy beaker dissolution apparatus at 59 rpm in a 350 ml volume using velocity data from corresponding simulations of the basket dissolution apparatus. This resulted in this solution being validated, and velocities within the apparatus at different agitation rates and different volumes could be examined. The hydrodynamic characteristics of the apparatus generally involved a central vortex of low velocity, surrounded by a higher velocity region with the velocity decreasing again in the outer region of the beaker. There is evidence of secondary recirculation patterns around the stirrer blades, and of radial inflow at the centre of the vessel base. These characteristics, although of different velocity magnitudes, were similar in both the 350 ml and 550 ml volumes, when the agitation rate was sufficient to generate significant flow in the lower region of the vessel. The velocities at the centre of the vessel base were used to establish a relationship between dissolution rates and average and maximum velocity values. The relationship between dissolution rate and velocity was more complex for the 550 ml volume than the 350 ml volume which was linear, however log-log plots of mass transfer coefficient vs. local velocity maximum revealed a similar dependency on local CFD-generated velocity values of dissolution rate within both vessels. Log-log plots of mass transfer coefficient vs. agitation rate revealed a lower dependency of the dissolution rate on agitation rate in the 550 ml volume than the 350 ml volume, implying a partial dependency on secondary flow velocities and therefore a degree of turbulence within the larger volume. The exponent in each case relating mass transfer coefficient to agitation rate of the stirrer, however, was between 0.5 and 0.65, which is in the range describing mainly laminar flow. Dissolution rates from different compounds within the paddle apparatus at varying agitation rates provide an exponent in a similar range of 0.51 to 0.66, with the higher exponent resulting partially from an increase in volume of dissolution medium. Therefore the hydrodynamics relevant to a dissolving compact within the Levy beaker dissolution apparatus generate near-laminar flow in a similar manner to those in the paddle dissolution

apparatus. The contribution of dissolution from natural convection, which may be especially prevalent in for example the 550 ml volume 59 rpm system which contains very low velocities in the lower region of the vessel, should be considered.

6.6 *In vitro in vivo* relationships.

6.6.1 Determining the hydrodynamics relevant to *in vitro* dissolution rate and *in vivo* data used in IVIVC correlations.

6.6.1.1 The Levy beaker dissolution apparatus.

The absorption rate of 975 mg aspirin (3 x 325 mg tablets) in two separate tests in 15 volunteers was found to correlate with the *in vitro* dissolution rate in 350 ml of 0.1M HCl, in the Levy beaker dissolution apparatus at 59 rpm (Levy and Hollister, 1964). The first-order rate constant for *in vitro* dissolution was 8.5 times faster than the first order rate constant for *in vivo* absorption. A plot of % absorbed at time, t , vs. % dissolved at time, t , divided by 8.5, yielded a linear relationship with a slope of unity. The divisor of t , 8.5 in this case, is termed the intensity factor, as it relates intensities of the *in vivo* rate constant and the *in vitro* rate constant.

From the CFD simulation of 350 ml in the Levy beaker dissolution apparatus at 59 rpm, the maximum velocity 2 mm from base of the beaker within a 5 mm radius of the centre (i.e. the location described in section 6.4.1) was 0.055 ms^{-1} . This value divided by 8.5 is 0.0065 ms^{-1} , which should reflect the magnitude of the hydrodynamics to which the aspirin tablets used in the study were exposed to *in vivo*. As aspirin is rapidly and completely absorbed in the gastro-intestinal tract, its absorption is considered to be dissolution rate-limited (Levy and Hollister, 1964). Salicylates can be absorbed from the stomach, therefore this fluid - velocity magnitude obtained through the relationship between *in vitro* dissolution and *in vivo* absorption could be considered to be indicative of gastric or intestinal hydrodynamic magnitudes. The correlating relationship, however, consisted of only four data points (Levy and Hollister, 1964). Additionally, the population sample had a high level of both inter- and intra- subject variability. This CFD-derived velocity value divided by the intensity factor will be referred to as the apparent gastro-intestinal velocity (AGV). The AGV values calculated in this section assume a linear relationship, through the origin, between fluid velocity and dissolution rate, without accounting for dissolution under natural convection conditions *in vivo*.

Subsequent to the study by Levy and Hollister (1964), a second relationship was determined between *in vivo* absorption and *in vitro* dissolution (Levy et al., 1965) in a study using 12 subjects, each receiving the same dose of aspirin. In this case, however, several different aspirin formulations were examined: disintegrating tablets prepared using a microencapsulation technique, disintegrating "plain" tablets and disintegrating tablets containing aspirin and alkaline additives. An intensity factor of 5.35 was found to relate *in vitro* dissolution rate in 350 ml 0.1M HCl at 60 rpm in the Levy beaker dissolution apparatus to the *in vivo* absorption rate of the disintegrating plain tablets and the disintegrating tablets with the aspirin and alkaline additives, with the regression line slope of near unity. The tablet containing the microencapsulated particles did not fit this regression line however. These tablets had the longest absorption half life (around

80 minutes), implying significant absorption from the small intestine as the gastric absorption half life of aspirin is approximately 30 minutes (Levy et al., 1965). Furthermore, as the subjects were fasting it would be expected that the tablets would have left the stomach within 1 hour of administration. A study of transit of dosage forms in 12 subjects found that 7 out of 12 capsules administered to fasting subjects were located in the small intestine 1 hour after administration (Schiller et al., 2005), with 5 capsules still in the stomach.

This intensity factor of 5.35 results in an estimated AGV of 0.0103 ms^{-1} from the CFD velocity data of the Levy beaker dissolution apparatus at 59 rpm. The fact that this intensity factor is less than the previously determined value of 8.5 (Levy and Hollister, 1964) demonstrates the variability associated with such relationships. This may be influenced by the smaller patient population and the inclusion of some female subjects (Levy et al., 1965). In order to produce an *in vitro in vivo* relationship where the *in vivo* absorption of the microencapsulated particles was reflected in the *in vitro* dissolution characteristics in a manner similar to the other two dosage forms investigated, the agitation rate producing the same ratio of dissolution rates for the plain tablets and the microencapsulated particles as the *in vivo* absorption ratios was determined. This agitation rate was 50 rpm, and the intensity factor was 2. A successful correlation between *in vitro* dissolution and *in vivo* absorption was found for the combined data from all three dosage forms investigated at this agitation rate and intensity factor. The hydrodynamics in the Levy beaker apparatus at 50 rpm were therefore also simulated using CFD. The resulting CFD-generated velocity data, from the simulation of 350 ml in the Levy beaker dissolution apparatus at 50 rpm, revealed a maximum velocity 2 mm from base of the beaker within a 5 mm radius of the centre to be 0.044 ms^{-1} . This velocity divided by an intensity factor of 2 results in an apparent AGV of 0.0220 ms^{-1} . This is obviously greater than either of the AGV magnitudes described above, however the plain tablets are more sensitive to *in vitro* stirring rate than the tablets incorporating the microencapsulated particles and the *in vivo* data is highly variable (Levy et al., 1965). The derived intensity factors, therefore, could be considered as representative of an approximate gastro-intestinal velocity magnitude. Additionally, as a significant proportion of the microencapsulated particles were probably absorbed in the small intestine, the representative velocity magnitude has to reflect such diverse forces as gastric emptying and intestinal peristalsis, in addition to dissolution under natural convection conditions. As the stirring rate of 50 rpm was appropriate for the three formulations investigated in a small sample of only 12 subjects, its use may not be appropriate with different formulations and larger population samples.

A summary of the CFD-derived AGV values and the sources of the data are shown in Table 6.3.

Source	Agitation rate	Intensity factor	CFD derived AGV (ms ⁻¹)	Formulations
(Levy and Hollister, 1964)	59 rpm	8.5	0.0065	325 mg "compressed aspirin tablets"
(Levy et al., 1965)	60 rpm	5.35	0.0103	Rapidly disintegrating tablets containing a) 325 mg aspirin and b) 325 mg aspirin and alkaline additives
(Levy et al., 1965)	50 rpm	2	0.0220	Rapidly disintegrating tablets containing a) 325 mg aspirin, b) 325 mg aspirin and alkaline additives and c) 650 mg microencapsulated particles

Table 6.3. Agitation rates and intensity factors derived from (Levy and Hollister, 1964) and (Levy et al., 1965) and Apparent Gastrointestinal Velocity (AGV) values derived from CFD simulations of hydrodynamics of 350 ml in the Levy beaker dissolution apparatus.

An obvious issue with the extraction of relevant velocity data from the CFD simulations is that of location within the beaker. The data above were all taken from a 5 mm radius in the centre of the beaker, 2 mm from the base of the Levy beaker apparatus, which has been demonstrated to be an appropriate diameter and distance from the base of the paddle apparatus (Figure 6.26). The published dissolution rate data were all stated to be taken from dissolution studies where the tablets formed a mound at the centre of the base of the vessel, but a definite diameter for this mound was not stated. Additionally, the presence of the tablets in the beaker in the *in vitro* studies would have altered the hydrodynamics in the vicinity of the tablets.

6.6.1.2 The paddle dissolution apparatus.

There are many instances of published data relating *in vitro* dissolution rate to *in vivo* parameters (e.g. Levy et al., 1965; Parojcic et al., 2006; Hougaard Sunesen et al., 2005; Katori et al., 1995). It is of interest to investigate *in vitro in vivo* relationships within the paddle dissolution apparatus in order to compare any AGV value determined from CFD simulations of hydrodynamics in the paddle apparatus with the hydrodynamic magnitudes determined using CFD data from the Levy beaker dissolution apparatus. Figure 6.31 shows the relationship between rpm and velocity magnitude (ms^{-1}) from CFD simulations of the paddle dissolution apparatus.

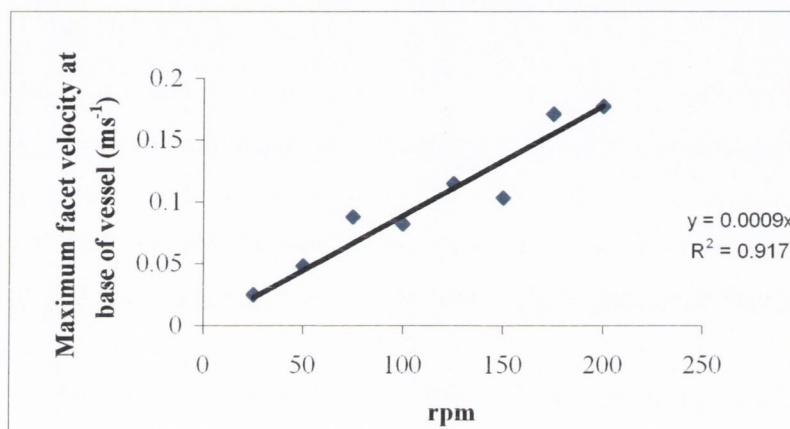


Figure 6.31. Maximum facet velocity (ms^{-1}) from CFD simulations of 900 ml in the paddle dissolution apparatus on a horizontal circular plane 2 mm from the base of the vessel and 10 mm in diameter vs. agitation rate (rpm).

Parojcic et al. (2006) reported dissolution rates of ibuprofen in the presence of magnesium hydroxide in 900 ml of USP phosphate buffer pH 6.8 in the paddle dissolution apparatus. The agitation rate was 50 rpm. A time scaled approach was used to relate the *in vitro* dissolution data to the fraction absorbed, calculated from published *in vivo* data, to determine a level A IVIVC. The time scaling involved an *in vivo* lag time of 30 minutes and an intensity factor of 3. A correlation was established with a regression line close to unity. At 50 rpm, the CFD determined velocity value as shown in Figure 6.31 was 0.045 ms^{-1} . This value divided by an intensity factor of 3 results in a calculated AGV of 0.015 ms^{-1} .

Katori et al. (1995) obtained dissolution profiles from two different tablet formulations of acetaminophen whose side walls were coated to obtain a zero order release profile. The dissolution profiles from the first tablet (tablet 1) were super-imposable on *in vivo* profiles for the first 2 hours of dissolution. The paddle rotation rate was 10 rpm, however the volume used is not clear, as between 900-2,000 ml were used in several different test apparatuses in the study (Katori et al., 1995). The tablet also contained fumarate and tryptophan to control the dissolution rate, and hydroxypropylcellulose (HPC) (2%). The velocity value at 10 rpm in 900 ml in the paddle apparatus can be calculated from Figure 6.31 to be 0.009 ms^{-1} . A second tablet, tablet 2,

containing 1% w/w magnesium stearate and 1.3% w/w corn starch in place of HPC, had a higher *in vivo* rate after 2 hours than that achieved at 10 rpm in the paddle apparatus, illustrating the importance of formulation in determining relevant AGV values. According to the published dissolution profiles (Katori et al., 1995) the *in vivo* profiles were similar to the *in vitro* profiles obtained in the paddle apparatus at 50 rpm. The corresponding CFD-determined velocity of 0.045 ms^{-1} at 50 rpm is much higher than any of the AGV values calculated thus far, and supports the postulation that this dosage form was more susceptible to destructive forces than flow rates. The increased pressures at 50 rpm in the paddle apparatus may have contributed to the dissolution. The effect of pressure will be discussed in section 6.6.3.

Soon Yong et al. (2005) developed a novel oral delivery system using diethanolamine as solubiliser and PEG 400 as a base for aceclofenac (100 mg) in a soft capsule. Using 900 ml of dissolution medium in the paddle apparatus at 50 rpm, the data presented suggest 100% dissolution of aceclofenac was achieved after approximately 15 minutes (Soon Yong et al., 2005). *In vivo* studies revealed that the average time to peak concentration in 14 fasting male human subjects was 30 minutes. The *in vivo* data was not presented as deconvoluted absorption data, however the elimination rate constant was 0.18 hour^{-1} (Soon Yong et al., 2005). Furthermore, the slope of the concentration-time curve decreased sharply after peak concentration levels were achieved. Therefore it was considered that the time to peak was a reasonable variable to compare with time to 100% dissolution, although in reality some *in vivo* dissolution would occur after this point. This data yields an intensity factor of 2, resulting in an AGV of 0.0225 ms^{-1} .

The calculated AGV values from *in vivo in vitro* relationships using the paddle dissolution apparatus and human subjects can be compared in Table 6.4

Source	Agitation rate	Intensity factor	CFD derived AGV (ms^{-1})	Formulations
Parojcic et al., 2006	50 rpm	3	0.015	Ibuprofen sugar-coated tablets, antacid added to medium.
Katori et al., 1995	10 rpm	-	0.009	Acetaminophen 100 mg, tryptophan, fumarate, HPC 2%.
Soon Yong et al., 2005	50 rpm	2	0.0225	Acetoclofenac 100 mg soft capsule, also containing diethanolamine 7 mg, PEG 400 246 mg.

Table 6.4. Agitation rates and intensity factors derived from Parojcic et al., (2006), Katori et al., (1995) and Soon Yong et al., (2005), and Apparent Gastrointestinal Velocities (AGV) values derived from CFD simulations of hydrodynamics of 900 ml in the paddle dissolution apparatus.

From the information in Tables 6.3 and 6.4, velocities in the region of 0.009 to 0.025 ms^{-1} would seem to be representative of the forces experienced by a dosage form in the GI tract.

Animal models are frequently used to study formulation effects, and the nature of gastrointestinal hydrodynamics in dogs has been investigated and used to interpret *in vivo* absorption data of micronised and coarse grade felodipine powders (Scholz et al., 2003). It was found that the ratio of *in vivo* absorption rates in the fed and fasted states (representing different hydrodynamic conditions), corresponded to the ratio of *in vitro* dissolution rates at 125 (fed) and 75 (fasted) rpm, respectively (Scholz et al., 2003). In this study, 500 ml of bio-relevant dissolution media (imitating canine chyme) was used. These agitation rates of 75 and 125 rpm are predicted to produce velocities in the dissolution apparatus of 0.0675 ms^{-1} and 0.1125 ms^{-1} in 900 ml of dissolution media, (from Figure 6.31) and higher velocities would be expected in a smaller volume. Although there is no intensity factor described in the study, the AGV values and therefore gastro-intestinal agitation in dog models appear much greater than the corresponding human gastro-intestinal agitation. Katori et al. (1995) found that the *in vitro* dissolution profile at 100 rpm of the acetaminophen tablet (tablet 1) described in Table 6.4, was similar to the *in vivo* release rate in the beagle dog, over the first hour. From Figure 6.31 this yields an AGV of 0.09 ms^{-1} . Consequently, *in vitro in vivo* relationships involving canine models should be interpreted with care as the hydrodynamics present in the canine GI tract are of a greater apparent magnitude than in human subjects, according to the AGV values presented.

Scholz et al., (2003) found that the hydrodynamic conditions did not affect the dissolution rate of micronised powder at agitation rates greater than 75 rpm, indicating the relevance of particle size when interpreting *in vitro* dissolution results.

6.6.2 *In vivo* gastro-intestinal hydrodynamics.

The unstirred water layer (UWL) is a layer of water, mucus and other components adjacent to the intestinal wall across which a solute must diffuse to present itself to the intestinal membrane for systemic absorption (Lennernäs, 1998). This thickness of this layer has been estimated to be 30 to 100 μm (Lennernäs, 1998). From this, it is reasonable to assume that the diffusion boundary layer, h , at the surface of a dosage form located in the intestine, and therefore subject to the same hydrodynamic conditions as the intestine wall, would have a thickness of the same order as the UWL. Regardless of the composition of the luminal contents, the hydrodynamic conditions *in vitro* producing the same thickness of h as is produced *in vivo* should result in a similar *in vitro* dissolution rate as is produced *in vivo*, provided the dissolution is diffusion rate limited and D is not significantly different *in vivo* and *in vitro*. Equation 4.1 was used to estimate a value of h , in the system used by Levy et al. (1965) to obtain an *in vitro in vivo* correlation with different aspirin formulations, as presented in Table 6.3. (i.e. an agitation rate of 50 rpm). The maximum CFD-generated tangential velocity value on a 10 mm diameter plane, 2 mm above the base of the beaker in the Levy beaker apparatus, was used to calculate the angular velocity value, used in equation 4.1, by dividing this tangential velocity by the radius of the plane, 5 mm. This velocity value was then divided by 2 as this was the intensity factor reported by Levy et al., (1965) (Table 6.3). Using $1.04 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ as the value for D for ASA (aspirin), (Corrigan, 1973), the *in vitro* value of h was calculated to be 77.7 μm . Thus the hydrodynamic conditions produced at the base of the Levy beaker at 50 rpm with 350 ml 0.1M HCl, using an intensity factor of 2, can be considered to be of a similar magnitude to those produced *in vivo*.

Actual *in vivo* hydrodynamics are difficult to quantify due to variation along the GI tract and inconstant motion. Early attempts (Dillard et al., 1965) to quantify flow rates in the small intestine involved the use of a triple lumen tube being inserted into human subjects. Dye was released into the small intestine and then collected at a sampling point further along the tube. The average transit time along a 100 cm segment of jejunum was recorded in a single subject was observed to be 23.9 (± 2) minutes, or 0.0007 ms^{-1} . This experimental set up, however, involved a constant infusion of isotonic solution proximal to the dye injection point which, along with the presence of the tube in the intestinal lumen, would influence recorded dye transit times. More recent studies on transit of dosage forms within the intestine using magnetic resonance imaging (MRI), has concluded that there is an inhomogenous distribution of fluid along the intestinal tract (Schiller et al., 2005). Fluid volumes in the small intestine were found to be highly variable after a meal (20-156 ml), and distributed into separate fluid-filled pockets. Capsules located in the stomach, however, were surrounded by liquid in both fasted and fed state. The authors conclude

that *in vitro* dissolution tests are not suitable to predict *in vivo* release, due to the distribution of fluid in the intestine being inhomogenous, and the finding that 27% of capsules in the small intestine were not in contact with any fluid pockets. As a result it may be more appropriate to consider *in vivo* hydrodynamics in terms of the mixing patterns and fluid velocities that are present in the stomach and small intestine regardless of flow direction or transit time. Flow back into the stomach at the pylorus is termed retrograde flow. Retrograde and radial flow in addition to antegrade flow are features of peristaltic movements, and at any one time in the human stomach there are 2-3 contractions involving separate sections of the stomach (Schulze, 2006). A recent numerical simulation of gastric flow and mixing in the human stomach (using data from MRI scans after ingestion of 330 ml of a nutrient meal), calculated velocities of up to 0.0075 ms^{-1} in retropulsive jets (Pal et al., 2004). Recirculating flow patterns creating eddies within the stomach were also a notable feature, with velocities of 0.002 ms^{-1} . Some approximations employed in this numerical model were that it was a 2-D rather than 3-D simulation, and the value used for density of the stomach contents was 1 g cm^{-3} . Although the retropulsive jet velocities are generally slightly lower than the AGV values calculated in Tables 6.3 and 6.4, it has been recognised that there is a contribution from pressure forces, shear stresses, flow reversals and vertical flow to the dispersion of particles in the stomach, but these forces have not yet been quantified (Schulze, 2006). These are forces in addition to fluid velocity within the gastrointestinal tract which would contribute to dissolution.

Additionally, peristaltic contractions in the stomach between the incisura and sinus region have been likened to the action of a mortar and pestle. In view of these observations, pressure magnitudes within the CFD simulated dissolution apparatus have been investigated.

6.6.3 Relating CFD-generated pressure data to *in vivo* drug release.

6.6.3.1 The effect of destructive forces on drug release mechanisms.

Drug dissolution and release from a dosage form can be influenced by factors other than the thickness of the diffusion boundary layer affecting dissolution rate. If a tablet is designed to disintegrate, for example, the degree of agitation and shearing stresses on the surface of the tablet will influence the rate of disintegration. Many sustained release tablets are formulated as hydrophilic matrices which release the active constituent through a complex process of swelling and gel formation, diffusion of drug through gel layer and erosion of the polymeric matrix. In general, less soluble drugs are released through erosion of the matrix rather than diffusion through the hydrated gel layer, and release of more soluble drugs is dependent on the diffusional path length through the hydrated gel layer rather than erosion. The degree to which this type of matrix tablet is influenced by *in vivo* gastrointestinal motility patterns and hydrodynamics is very much formulation dependent. Although pH, ionic strength and surfactant concentration altered erosion rates to a minor extent, the stirring rate of a modified USP paddle apparatus was the main factor influencing erosion rate for a matrix tablet containing hydroxypropylmethylcellulose (HPMC), ethylcellulose and carboxypolymethylene (Abrahamsson et al., 1999). This matrix tablet was also eroded faster *in vivo* postprandially than under fasting conditions. In contrast to this, a second tablet, containing HPMC alone as the matrix excipient, was less affected by fed/fasting conditions or by agitation rate, demonstrating the importance of formulation in determining sensitivity to erosive conditions. It has been found that low molecular weight HPMC matrix tablets are more susceptible to erosion, however the effect of agitation rate on the erosion rate is more evident in higher molecular weight grades of HPMC (Kavanagh and Corrigan, 2004). This evidence of *in vitro* sensitivity of polymer erosion to hydrodynamic forces is consistent with observations in dogs that *in vivo* release rates from some HPMC tablets are faster than *in vitro* using a paddle speed of 100 rpm, however, the use of beads in the paddle apparatus to increase frictional forces *in vitro* resulted in a better *in vitro* *in vivo* relationship (Aoki et al., 1992). Drug release from matrix tablets *in vivo* is often biphasic (Shameem et al., 1995; Wingstrand et al., 1990), with a lower release rate corresponding to the conditions in the colon where there is less available water and less motility. To complicate matters further, *in vivo* release from this type of hydrophilic matrix tablet can be highly variable, with one study revealing that the drug release under fasting conditions was, in the subject with the fastest release, similar to *in vitro* release rates from the basket apparatus at 150 rpm, and in the subject with the slowest release, less than the *in vitro* release from the paddle apparatus at 10 rpm (Shameem et al., 1995). It is of interest, however, to note the high *in vitro* agitation speeds used in *in vitro* *in vivo* comparisons when matrix tablets are being investigated. The mechanical destructive forces of the dosage form against the side of the basket and the edge of the vessel of the paddle apparatus may contribute to observed *in vitro* erosion in these studies. Destructive forces have also been noted to play a role *in vitro* drug

release from matrices of xanthan and karaya gums (Munday and Cox, 2000), resulting in increased rates of erosion, and in tablets containing corn starch and magnesium stearate (tablet 2, described in section 6.6.2.1) (Katori et al., 1995). In this case, only one surface was exposed for dissolution, and the *in vitro* dissolution rate profile at 50 rpm in the paddle apparatus was similar to the *in vivo* rate profile over the first 4 hours (Katori et al., 1995). The *in vitro* hydrodynamics may have provided the adequate shearing forces at the tablet surface to promote a degree of tablet disintegration consistent with *in vivo* forces. Finally, the contribution of mechanical destructive forces, such as high shear forces, to other dosage forms and release mechanisms should not be overlooked. For example, deformation and spreading patterns of melting suppositories investigated in the basket and paddle apparatuses were influenced by the different hydrodynamics in the apparatuses (Gjellan and Graffner, 1994).

6.6.3.2 Pressure gradients in the CFD simulations of hydrodynamics in the dissolution apparatuses studied.

The pressure distribution within the paddle apparatus at 50 rpm on the $y=0$ plane, the basket apparatus at 100 rpm on the $x=0$ plane, and the Levy beaker apparatus at 59 rpm (350 ml) on the $x=0$ plane can be seen in Figure 6.32, and within the Levy beaker at 59 rpm (350 ml) on the horizontal $z=-0.066$ plane (2 mm from the base) in Figure 6.33.

In each apparatus, pressures tended to increase with increasing distance from the centre of the apparatus. This feature was common to all of the apparatuses examined as they all contained rotating flow. It would be expected that the pressure would increase radially as the fluid velocity decreased towards the wall of the vessel. This complies with Bernoulli's theorem that from a region of higher to lower fluid velocity, the pressure of the fluid changes in the opposite direction (Levich, 1962). In the low velocity region of the flow field, under the stirrer in the paddle and Levy apparatuses, the swirling flow promotes the development of a free vortex flow. An ideal free vortex flow is represented by

$$\frac{\partial p}{\partial r} = \frac{\rho v_c^2}{r} \quad \text{Equation 6.2}$$

where v_c is circumferential velocity, ρ is density, r is the radial coordinate and p is pressure (FluentTM User's Guide, 2003). This creates a highly non - uniform pressure distribution and in a real (non-ideal) scenario the generation of axial and radial secondary flows to compensate for the steep radial pressure gradients. Therefore, in addition to a high pressure gradient in the low velocity region near the wall in accordance with Bernoulli's theorem, the pressure would also be expected to change with the square of circumferential velocity in the central vortex region. Pressure increases were marginal within the basket apparatus, with the exception of the point at which the cylindrical part of the vessel met the hemispherical portion.

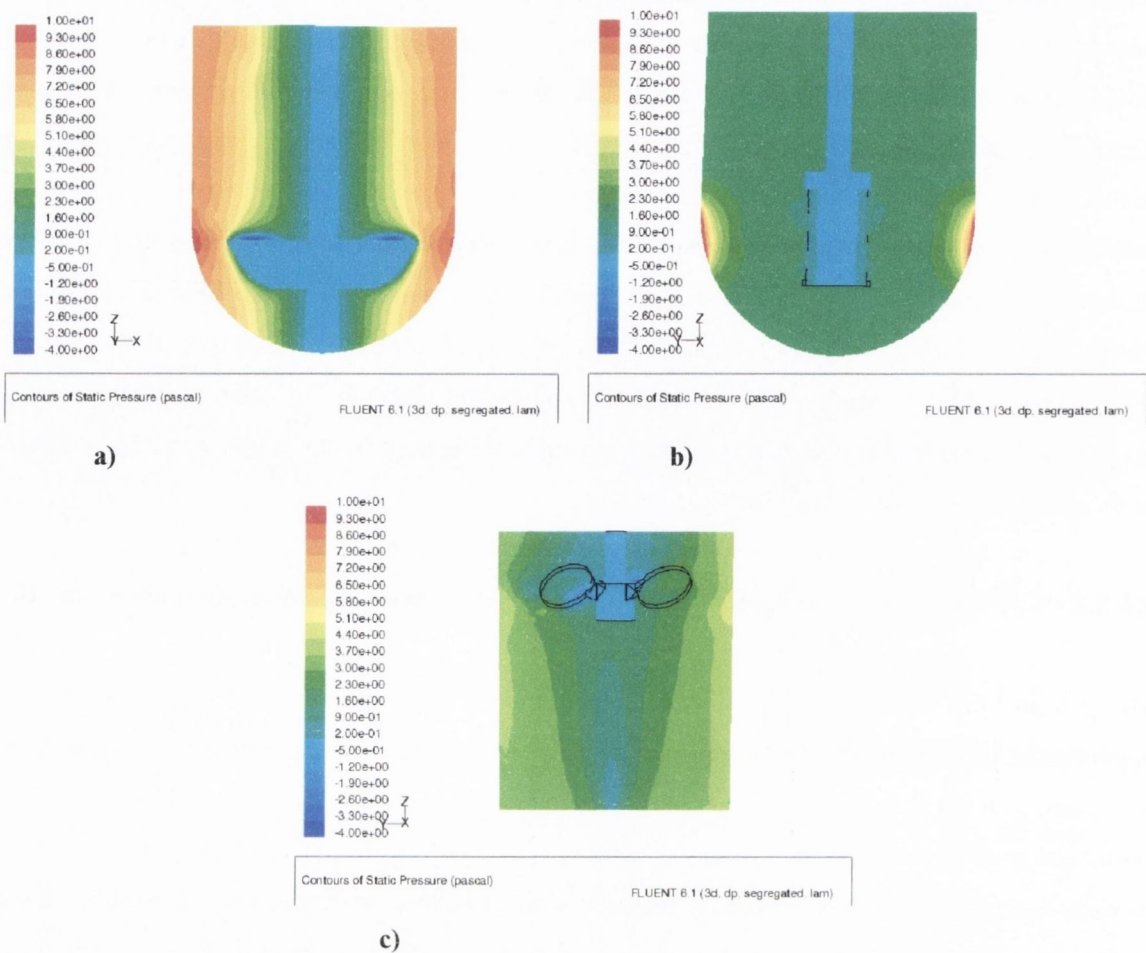


Figure 6.32. CFD-generated contours of static pressure on a) the y=0 plane within the paddle apparatus at 50 rpm (900 ml), b) the x=0 plane within the basket apparatus at 100 rpm (900 ml), and c) the x=0 plane within the Levy apparatus at 59 rpm (350 ml).

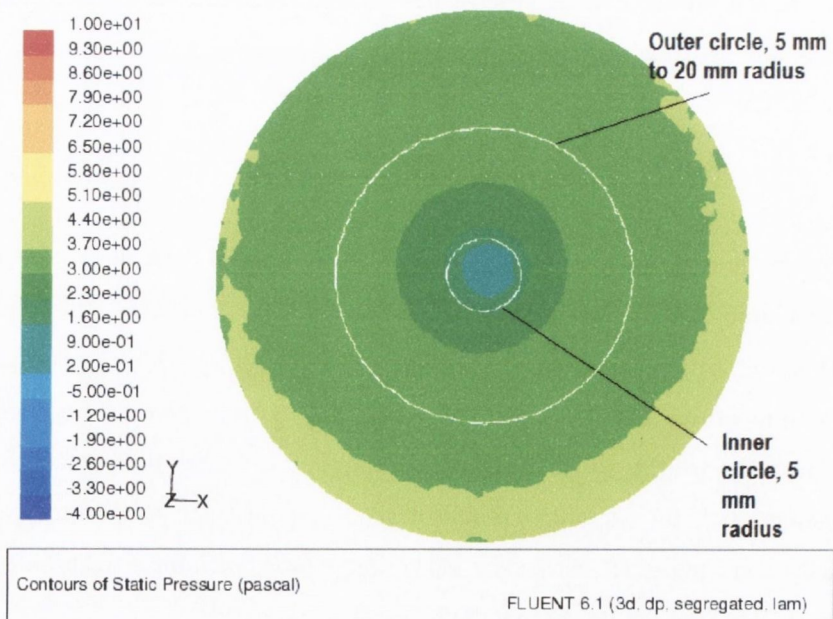


Figure 6.33. CFD-generated contours of static pressure within the Levy beaker dissolution apparatus at 59 rpm (350 ml) on the horizontal z=-0.066 plane.

It can be seen from both Figures 6.32 and 6.33 that there is a sharp radial pressure gradient. The white circles in Figure 6.33 describe the area where data is taken from the centre (10 mm diameter) of the vessel (inner circle), and from the area in the central region outside the central 10 mm plane with an outer diameter of 40 mm (outer circle).

6.6.3.3 Values of static pressure within the dissolution apparatuses investigated.

The static pressure is the gauge pressure expressed relative to the operating pressure (Fluent™ User’s Guide, 2003). The variation of pressure at the base of the paddle apparatus with rpm is shown in Figure 6.34, and at the base of the Levy beaker dissolution apparatus in Figure 6.35. It is clear that there is an exponential rather than linear increase in pressure with increasing agitation rate, particularly beyond the central region (10 mm diameter) of the Levy beaker dissolution apparatus described in Figure 6.33. These sharp increases in pressure within the apparatuses may be informative in interpreting dissolution data from dosage forms which seem to be susceptible to destructive forces at higher agitation rates.

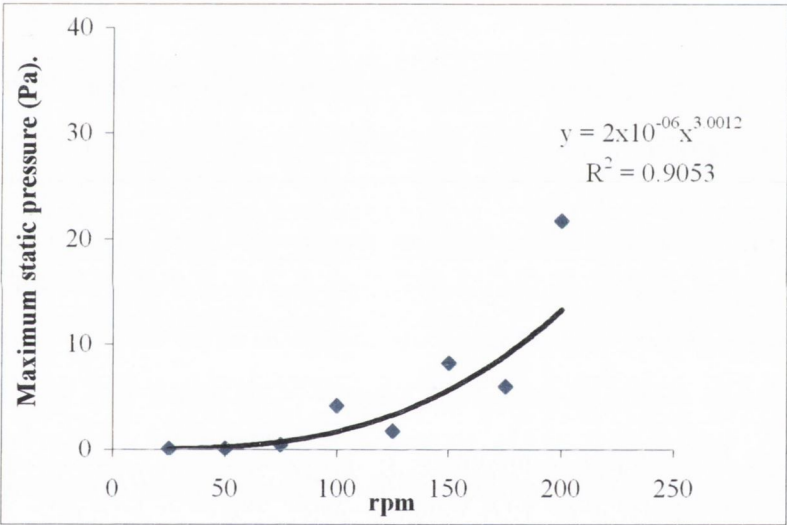


Figure 6.34. Maximum CFD-generated static pressure vs. rpm from simulations of 900 ml in the paddle dissolution apparatus. Data taken from a circular horizontal plane 2 mm from the base of the centre of the vessel, 10 mm in diameter.

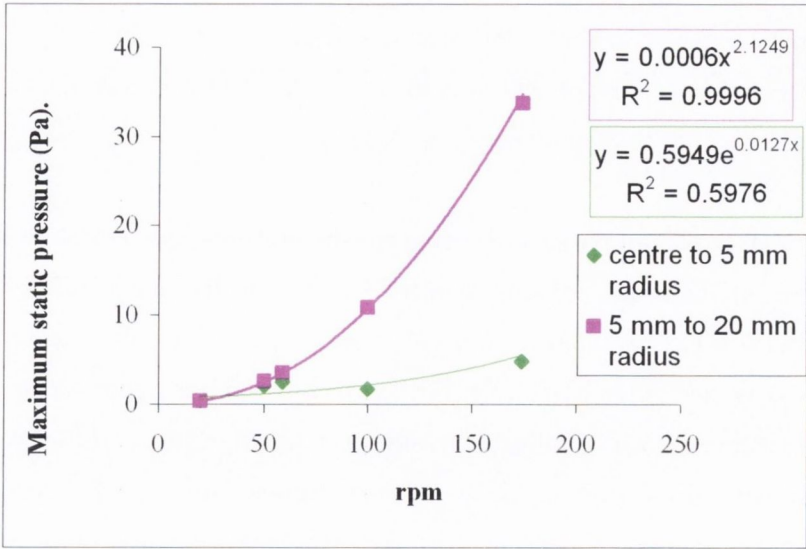


Figure 6.35. Maximum CFD-generated static pressure vs. rpm from simulations of 350 ml in the Levy beaker dissolution apparatus. Pressure data taken a circular horizontal plane region 2 mm from the base of the beaker, within a radius of 5 mm from the centre, or between 5 mm and 20 mm from the centre.

The difference in pressure variation in the Levy apparatus with rpm within a 5 mm radius of the centre and from a 5 mm to 20 mm radius is of interest, as the maximum pressures within 5 mm and 20 mm of the centre in the Levy beaker dissolution apparatus are of a similar magnitude to those present in the paddle dissolution apparatus, as is evident from Figure 6.36. The velocities investigated in the Levy beaker dissolution apparatus, described in section 6.4.1, are taken from within a 5 mm radius of the centre. However, the magnitude of the decrease in velocity from this region to the adjacent region within a 20 mm radius is not as great as the magnitude of the pressure increase. For example, in the 50 rpm simulation of the 350 ml volume in the Levy apparatus, the maximum velocity within 5 mm of the centre is 0.045 ms^{-1} , while the maximum velocity within a 5 mm to 20 mm radius of the centre is 0.041 ms^{-1} . The corresponding pressures within these two regions are 1.99 Pa and 2.57 Pa, respectively. Therefore, the outer radial limit of the central region used to report velocity data may not be as critical as that used to report pressure data.

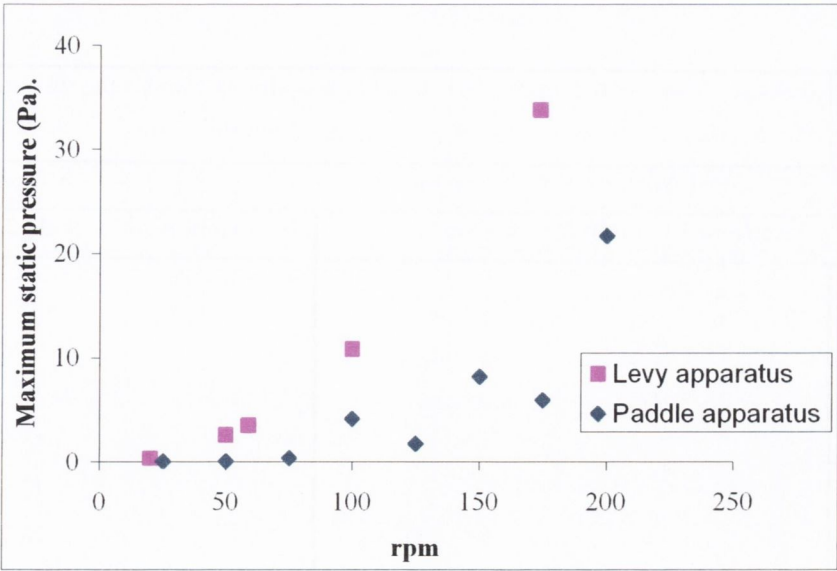


Figure 6.36. Maximum CFD-generated static pressure vs. rpm in the Levy apparatus (350 ml simulation) from a region 2 mm from the vessel base and within 5 mm to 20 mm radius of the centre of the vessel, and the paddle apparatus (2 mm from the vessel base and 10 mm diameter, 900 ml simulation).

Kamba et al. (2003) measured fluid resistance on a 8 mm x 8 mm baffle at various locations within the paddle apparatus at different rotation speeds. The fluid resistance was presented as Newtons (N) on the baffle plate. As the surface area of the baffle plate is known, the data can be converted to Nm^{-2} (i.e. Pascals). This can then be compared to the static pressure values from the CFD solutions of the paddle apparatus. Data from Kamba et al. (2003) measured at 4 mm from the centre of the vessel base can be compared to the CFD data using the equation on the graph in Figure 6.33, which is from the curve fitted to data taken from within a 5 mm radius from the centre of the vessel base at different agitation rates. This equation is presented here as equation 6.3.

Maximum static pressure = $2 \times 10^{-6} (\text{agitation rate})^{3.0012}$

Equation 6.3.

Pressure data from 20 mm and 28 mm from the centre of the vessel base can be compared to pressure data adjacent to the compacts in position 1 and position 2, respectively, at 50 rpm. This data is presented in Table 6.5.

Agitation rate (rpm)	Distance from centre (mm). For data from positions 1 and 2 the distance refers to the distance of the outer edge of the compact from the centre.				
	5	18.3 (position 1)	28.9 (position 2)	4	20 28
	Data from CFD simulations (Nm ⁻²)			Data from Kamba et al., 2003 (Nm ⁻²)	
25	0.03			undetectable	0.47 0.63
50	0.25	4.55 (side) 2.68 (top)	6.67 (side) 5.35 (top)	0.47	3.75 5.47
75	0.85			3.91	8.75 12.50
100	2.01			4.69	17.50 23.75
125	3.93			9.22	28.75 37.66
150	6.79			13.44	40.16 102.03

Table 6.5. Pressure data from CFD simulations of the paddle dissolution apparatus and from fluid resistance data measured by Kamba et al., 2003. Data from the CFD simulations are calculated using equation 6.3, which was generated data taken from a horizontal plane 2 mm above the centre of the vessel base and 10 mm in diameter. The data from positions 1 and 2 are taken at 1 mm from either the side or the top of the compact.

It can be seen from Table 6.5 that the magnitudes of the CFD generated pressure values from the central region at the base of the vessel are comparable to the values measured by Kamba et al. (2003). The lower overall CFD-generated static pressure values may be due to the horizontal plane that the data was taken from lying within the low pressure vortex region. The diameter of this vortex region may have been overestimated in the CFD simulation, particularly as this diameter may have changed with both time and agitation rate, as discussed in section 3.4.2. The off-centre (20 and 28 mm from centre) pressure values determined by Kamba et al. (2003) at 50 rpm fall within the CFD generated values from the top and sides of the compact at positions 1 and 2. In addition to demonstrating that the CFD generated pressure values are of a similar magnitude to the experimentally determined values of Kamba et al. (2003), Table 6.5 also illustrates the increase in pressure data with increased radial location.

The maximum pressure values extracted from the central region of the Levy apparatus within a 5 mm radius of the centre of the vessel, although of a much lower magnitude than those in the paddle apparatus, are, however, of a similar magnitude to those present in the basket apparatus as illustrated in Figure 6.37. Data from the basket apparatus is calculated as the average of the maximum static pressure data reported from a series of rings defined at radii 0.0065 to 0.01 m from the centre of the basket, 3 mm from the basket base. These are the same rings that were used to report the relative velocity data as described in section 2.2.1.2.

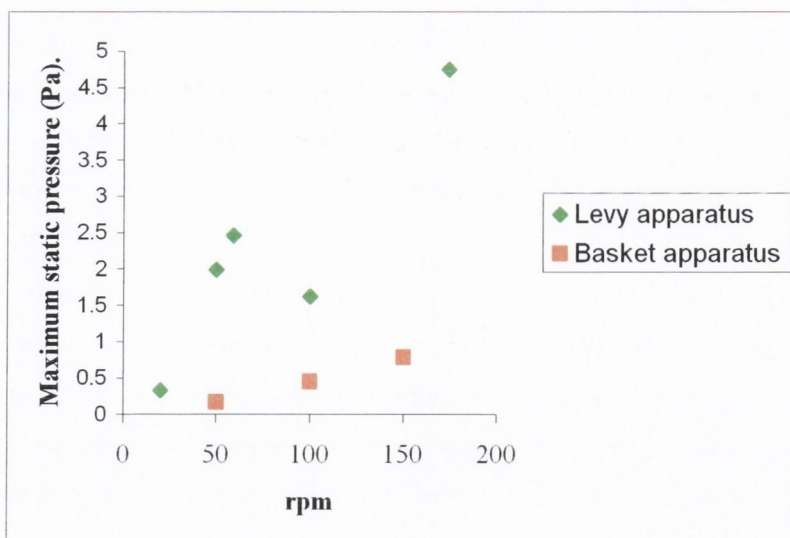


Figure 6.37. Maximum CFD-generated static pressure vs. rpm in the basket apparatus (average pressure data from 6.5 to 10 mm radius, 3 mm from bottom of basket mesh) and Levy beaker apparatus from a horizontal plane 2 mm from the centre of the beaker base and 10 mm in diameter.

Although the static pressure magnitudes are much lower in the basket than the paddle apparatus, the presence of the basket side and bottom mesh shearing and/or eroding a dosage form would contribute to the mechanical destructive forces that the dosage form would be subject to.

6.6.4 Comparison of *in vitro* and *in vivo* pressure values.

Kamba et al. (2000) measured the crushing strength of the stomach and small intestine (Kamba et al., 2002) through the use of a unique dosage form developed for this purpose. The dosage form would not release the active drug content until an outer Teflon layer was crushed, with the strength of this layer regulated through use of compression forces and the grade of Teflon powder used. Additionally, an outer coating was used which was developed to dissolve either in gastric pH (Kamba et al., 2000) or an enteric coating which would only dissolve in an environment above pH 5.5, thus preventing dissolution prior to reaching the small intestine (Kamba et al., 2002). The stomach was able to crush tablets with a crushing strength of 1.89 N under fed conditions and 1.5 N under fasting conditions. Interestingly, the forces present in the paddle dissolution apparatus containing 900 ml and agitated at 50 rpm were not sufficient to crush any of these tablets. This indicated that the pressures present in the paddle dissolution apparatus at 50 rpm are less than those present in the stomach in either the fed or fasted condition. The use of higher agitation speeds to investigate *in vitro in vivo* relationships for swelling/disintegrating dosage forms which may be more susceptible to destructive forces may therefore be warranted. The small intestine was able to crush tablets having a crushing strength of 1.2 N, implying the highest destructive forces are present in the stomach in humans (Kamba et al., 2002).

In vivo gastrointestinal manometry, or pressure recording, has often been carried out using some form of catheter inserted in to the gastrointestinal tract, with the catheter being perfused with

water and pressure changes recorded using pressure transducers. Values in the region of 45 mmHg or greater of duodenal intraluminal pressure have been recorded in this manner during duodenal monophasic wave contractions (Friedman et al., 1965). Similarly, values of 30-60 mmHg have been recorded during pressure waves in the jejunum (Beck et al., 1965).

A more recent study used high-resolution high-accuracy manometry and antropyloroduodenal anatomy with 3-dimensional MRI to investigate contributions of pressure to gastric emptying (Indireshkumar et al., 2000). Pressure magnitudes within the antrum of the stomach and the duodenum reached approximately 40 to 60 mmHg. Antral pressures were described relative to baseline duodenal pressures as the pressure difference between the cavities of the distal antrum and proximal duodenum was the dominating mechanical factor influencing gastric emptying. The baseline pressure in the antrum was higher than that in the duodenum. To use these relative pressure values for *in vivo* pressure comparisons is possibly more appropriate than values relative to atmospheric pressure (as in the *in vitro* paddle apparatus) as a dosage form *in vivo* would also be subject to pressure differences in the gastrointestinal lumen. Nevertheless, during periods of high pressure activity antral pressure increases (relative to basal antral pressures) were between 5 and 12 mmHg (667-1600 Pa) in all of the 7 subjects studied.

As the magnitude of erosive/destructive forces that a dosage form would undergo from contact with the sides of the basket in the basket apparatus cannot be quantified from the CFD simulations presented here, pressures within the paddle apparatus are compared to those experienced *in vivo*. Figure 6.38 is the same data as that in Figure 6.33 with the pressures presented as mmHg instead of Pa. It can be seen from this graph that the pressures present in the paddle dissolution apparatus are much less than those recorded *in vivo*, including increased antral pressure values relative to basal antral pressures (Indireshkumar et al., 2000). The highest pressure value from fluid resistance measurements as determined by Kamba et al., (2003), from Table 6.5 was 102 Pa at 150 rpm. This was located at 28 mm from the centre of the vessel, and is comparable to the outer edge of a compact in position 2 which lies at 28.9 mm from the centre of the vessel. The pressure value in Pa at this location is equivalent to 0.765 mmHg. Although this value is higher than CFD-generated values from the centre of the vessel in Figure 6.38, it is still less than recorded *in vivo* pressure values.

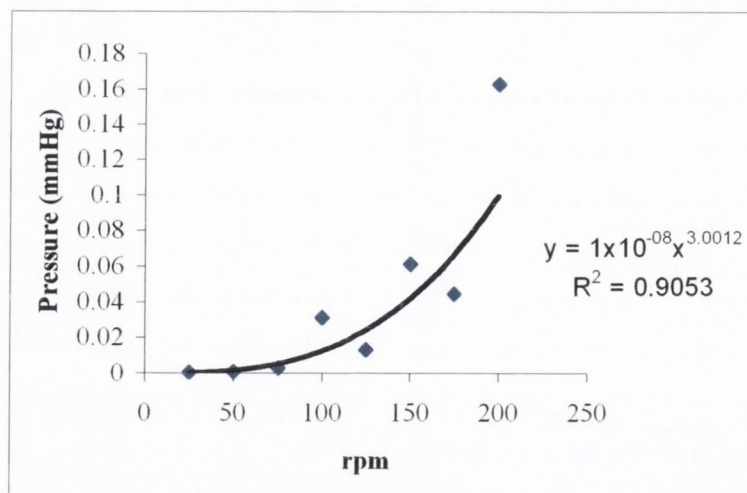


Figure 6.38. Pressure (mmHg) vs. rpm from CFD simulations of hydrodynamics of 900 ml in the paddle apparatus. Data taken from a horizontal circular plane 2 mm from the centre of the base of the vessel, 10 mm in diameter.

The measurement uncertainty determined using high resolution manometry was 0.5 mmHg, implying that the data from the paddle apparatus in Figure 6.38 would be within the background “noise” levels *in vivo* (Indireskumar et al., 2000). Data from numerically simulated gastric flow and mixing, however, revealed a maximum pressure value (relative to duodenal pressure) of approximately 0.1 mmHg near the pylorus (Pal et al., 2004), with much of the predicted gastric pressure below this value. This is consistent with pressure values (relative to atmospheric pressure) in the region of the base of the paddle apparatus at higher agitation speeds. From the equation in Figure 6.38, a rotation speed of approximately 215 rpm would create a pressure of 0.1 mmHg on the plane investigated. This would only be relevant for a dosage form falling within 5 mm of the centre of the base of the vessel, and being exposed to the maximum pressure within this region. The pressures from the CFD simulations of the dissolution apparatuses, and the numerical simulations of gastric flow result from fluid pressures alone and not contact pressures. These fluid values are more consistent with the mean transpyloric pressure difference during antral quiescent periods (0.3 mmHg cm⁻¹) than the larger pressures recorded through direct contact between the luminal wall and the manometer catheter (Indireskumar et al., 2000).

The pressure present at the centre of the base of the paddle apparatus at 50 rpm would be in the region of 0.0013 mmHg, which is much lower than the simulated *in vivo* magnitudes, consistent with the results from Kamba et al. (2000) demonstrating that tablets crushed in the stomach did not disintegrate in the paddle apparatus at 50 rpm. It should be taken into consideration that a dosage form in the stomach *in vivo* would not be continuously exposed to this pressure magnitude, but rather intermittently. This has implications for the use of *in vitro* continuous pressure data in an *in vitro in vivo* temporal relationship.

6.7 Conclusions regarding use of hydrodynamic data in IVIVC.

Although the AGV values presented in this section vary both within and between each apparatus investigated, it can be concluded that for *in vitro in vivo* correlations lower velocities than are present in current common operating conditions (e.g. 50 rpm in the paddle apparatus or 100 rpm in the basket apparatus) are representative of GI tract velocities. The rotational flow present in the basket and paddle apparatus may be more representative of *in vivo* gastric conditions than unidirectional flow, as the antegrade, retrograde and recirculating flow are characteristic of the flow patterns in the stomach (Schulze, 2006; Pal et al., 2004).

Dosage forms which are more susceptible to mechanical destructive forces than fluid shear forces may require higher dissolution apparatus velocities to develop *in vitro in vivo* correlations. These higher *in vitro* velocities may be more representative of fluid pressures *in vivo*, but not contact pressures unless some frictional force is introduced. This frictional force could be produced by contact with the basket sides, or for example the introduction of beads, as demonstrated by Aoki et al. (1992). Although contact with the side of the basket/vessel can contribute to erosion, this effect is difficult to quantify or reproduce. As a result, modelling of the contribution to erosion through contact with the basket/vessel sides through CFD is not readily achievable.

In general, the inconstant, inhomogenous nature of the gastrointestinal flow, combined with other destructive forces, should promote an approach to IVIVC using different/alternating velocities, intermittent pressure forces, and biorelevant dissolution media. The relative importance of these contributing factors will be formulation dependent. The current approach of using an *in vitro* dissolution test where the environment is so different to the *in vivo* environment will be informative in terms of relative importance of different factors for a particular formulation. However, from a hydrodynamic perspective, this is a trial and error approach to get IVIVC rather than a test designed to mimic *in vivo* conditions.

7.0

General Discussion

7.1 Simulation of hydrodynamics in commonly used dissolution apparatuses.

The hydrodynamics of three basic models were successfully simulated using CFD in this work, the USP basket apparatus (Apparatus 1), the USP paddle apparatus (Apparatus 2) and the Levy beaker dissolution apparatus. Variations on the models included changing the agitation rate and the media volume. Vessel dimensions were also varied in the Levy beaker dissolution apparatus. Within each apparatus simulated, the presence of certain flow characteristics remained constant with a change in agitation rate, although the nature of the characteristics tended to vary. Examples of such characteristics include the presence of a vortex region under the paddle in the paddle apparatus, and radial emanations from the sides of the basket in the basket apparatus. In the Levy apparatus, a higher agitation rate was required in the larger volume (550 ml) simulation, to promote the development of the central vortex region, than in the smaller volume (350 ml) apparatus. The effect of stirrer size and shape (Wu et al., 2004), blade angle and rotation direction (Röst and Quist, 2003) on dissolution rates has been previously demonstrated. In this work the effect on hydrodynamics of a constant stirrer size in a varying media volume and dimension is demonstrated. Although the size of the stirrer in each volume did not vary, the effect of changing the ratio of the stirrer: vessel dimensions was investigated, through comparisons of hydrodynamics in the larger beaker (600 ml) containing 550 ml of dissolution media with hydrodynamics in the 400 ml beaker containing 350 ml of dissolution media.

The secondary flow features have been previously investigated in the paddle dissolution apparatus (McCarthy et al., 2004), and in this work, secondary flow features within the basket and Levy beaker dissolution apparatuses are presented. Radial inflow at the base of the central vortex in the Levy beaker is particularly relevant, as this would influence the likelihood of a disintegrating dosage form being located within this region. The formation of a “central mound” on disintegration of some dosage forms has been previously noted (Levy and Hollister, 1964). The secondary flow characteristics around the stirrer blades are also of interest, in particular the pushing upwards and outwards of the fluid demonstrated in the 350 ml volume at 59 rpm (Figure 6.19). From a range of blade angles investigated in the paddle apparatus with a modified adjustable paddle (Röst and Quist, 2003), the fastest dissolution rate was found with paddle blades angles at 15-45° downward. It is emphasised, however, that this finding cannot be applied to a marine-type stirrer with skewed blades (such as that in the Levy apparatus). As CFD has enabled visualisation of the flow around the angled stirrer blades in the Levy apparatus, it may be of interest to model the hydrodynamics around angled paddle blades in the paddle apparatus in order to elucidate the hydrodynamics relevant to the effect which this geometrical alteration had on the dissolution rate.

In both the paddle apparatus and the Levy vessel dissolution apparatus a low velocity vortex was noted to form beneath the stirrer. This did not occur beneath the basket in the basket apparatus, where low velocity upward axial flow was generated under the basket. There is a typical

relationship between circumferential velocity and radial location in a free vortex, which is illustrated in Figure 7.1.

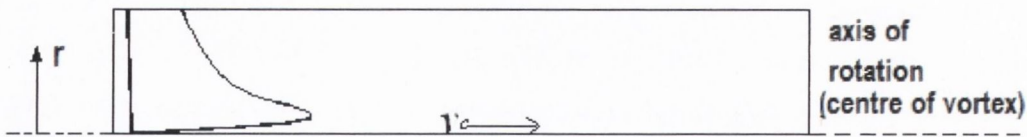


Figure 7.1. Distribution of circumferential velocity with radial location (r) in a free vortex – adapted from FluentTM User’s Guide, (2003).

It is clear from the distribution of the velocity in the vortex in Figure 7.1 that there is a sharp increase in velocity from the centre of the vortex until it reaches a maximum, then the velocity decreases with increasing radial location. The variation in tangential velocity with radius from the centre of the vessel can be seen in Figure 7.2 for both the paddle and Levy apparatuses. It is evident from this that the velocity distribution in the Levy apparatus at this rotation speed follows that of a typical free vortex, with a sharp increase in velocity followed by a decrease. This is not the case in the paddle apparatus, where the velocity continues to increase with radial location until it is influenced either by the boundary layer at the vessel wall or the secondary flow nearer the paddle blades. It can be assumed, therefore, that the vortex formed over a hemispherical surface is not the same as that of a typical free vortex found over a flat surface.

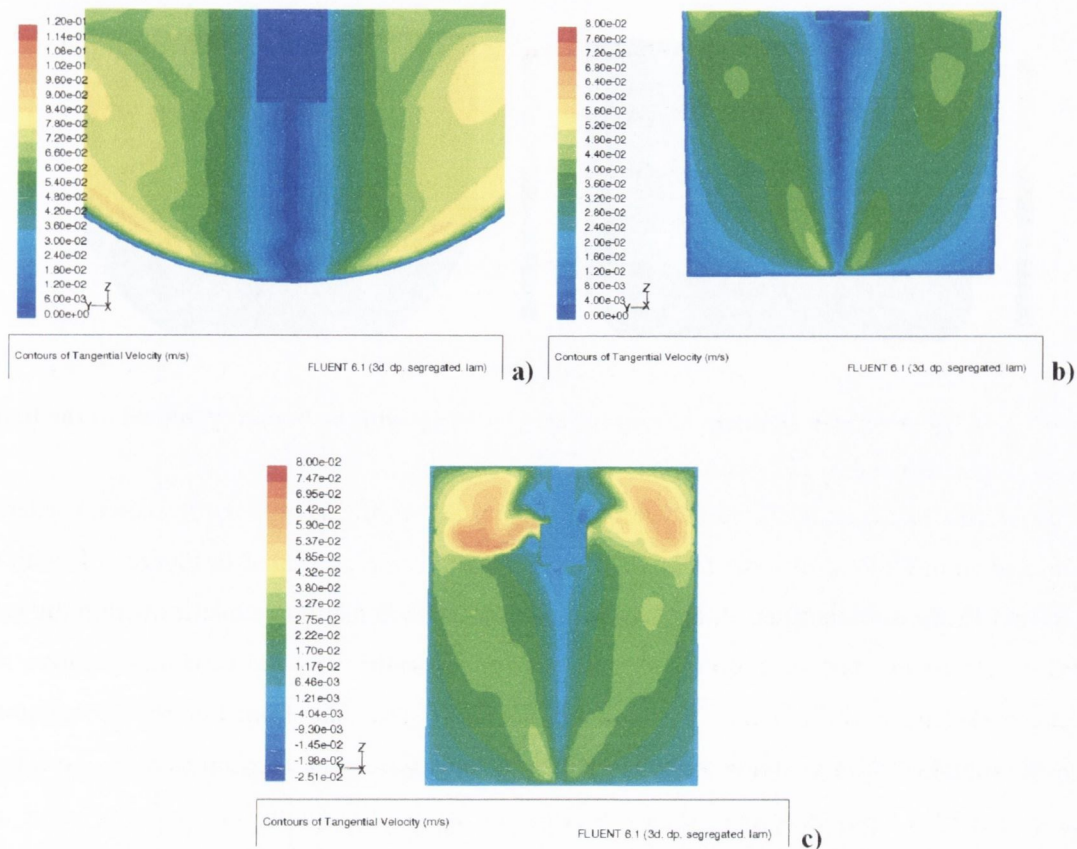


Figure 7.2. CFD-generated contours of tangential velocity in the region of the central vortex at the base of the vessel in a) the paddle apparatus at 50 rpm (900 ml) and the Levy apparatus at b) 59 rpm and c) 50 rpm (350 ml).

The formation of a vortex is visible in the simulations of all rotation speeds for the paddle apparatus, as can be seen in Figure 3.28. The formation and nature of a vortex in the Levy beaker dissolution apparatus is dependent on stirring speed and beaker volume, as is evident from Figures 6.15 and 6.16., with a vortex first apparent in the 59 rpm simulation in the 350 ml volume in Figure 6.15, and in the 100 rpm simulation of the 550 ml volume. It is clear, however, from Figure 7.2 that there is also a central low-velocity region in the Levy apparatus at 50 rpm in 350 ml. Examination of tangential velocity contours (not shown) in the 20 rpm (350 ml) and 59 rpm (550 ml) simulations reveals an area of low tangential velocity under the stirrer, with tangential velocity increasing in the radial direction implying the formation of a vortex. In these simulations, however, the increase in tangential velocity around the vortex does not extend as far as the base of the vessel.

Although the basket is the “stirrer” in the basket apparatus, there is no vortex below the basket itself due to the upwards axial flow illustrated in Figure 5.15. However, if the tangential velocity distribution within the basket is examined, it can be seen that the tangential velocity increases with radial location until the edge of the basket is reached. This is illustrated in Figure 7.3 at 100 and 150 rpm. In this situation, the lid of the basket could be considered to be the stirrer, as fluid can move through the grid of the basket side.

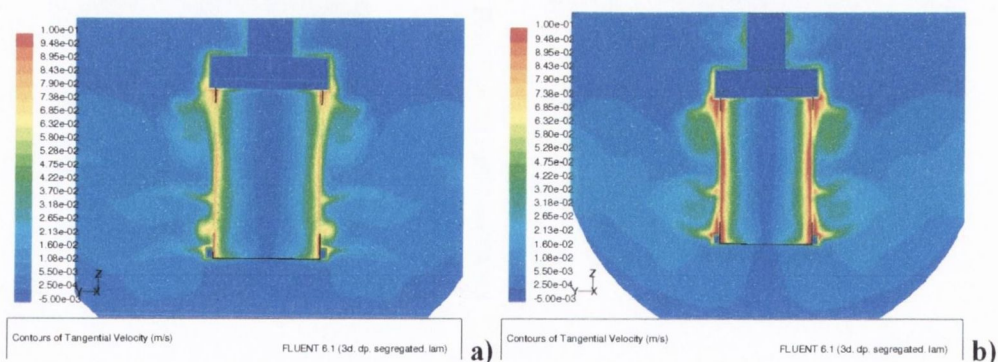


Figure 7.3. CFD-generated contours of tangential velocity around the basket in 900 ml in the basket apparatus at a) 100 and b) 150 rpm.

It is of interest to compare the fluid velocity magnitudes within the apparatuses investigated as determined from CFD solutions. Data from each apparatus are presented in Figure 7.4, with the line of best fit for each data set. It is clear from this set of data that the velocities within the Levy beaker (350 ml) are fastest, followed by the paddle apparatus, and the velocities relative to a rotating tablet are slowest within the basket apparatus. The data from the paddle apparatus, however, are taken from a 10 mm diameter plane located 2 mm from the centre of the vessel base. Also presented in Figure 7.4 are 2 data points indicating the maximum fluid velocity value at 1 mm from the surface of the side of the compact in the central position and position 1. These data points, both obtained at 50 rpm, are higher than the fluid velocities on the plane examined in the Levy beaker apparatus at 59 rpm. The data in Figure 7.4 indicate that dissolution rate data from one dissolution apparatus could be reproduced in a different apparatus providing the appropriate hydrodynamic conditions were achieved. The increased velocities at the compact sides in the paddle apparatus compared to the velocity from the 10 mm central plane, however, illustrate the need to ascertain the location within an apparatus where dissolution rate data was obtained. To produce similar dissolution rate data from a different apparatus would require replication of the hydrodynamic conditions at a particular location. Additionally, the effect of agitation rate on the fluid velocity value at the location examined presented in Figure 7.4 suggests that there is a greater increase in maximum fluid velocity value with agitation rate in the Levy apparatus compared to in the paddle apparatus. Attempts to reproduce hydrodynamic conditions from one apparatus in a second apparatus, therefore, should not assume a similar relationship between agitation rate and local hydrodynamics at a specific location in each apparatus. In Figure 7.4 maximum fluid velocity data are presented. Further information on minimum fluid velocity values and the area of the dosage form exposed to specific ranges of fluid velocities could be derived from CFD simulations. Operating conditions and dosage form location in a different apparatus which best matched these hydrodynamic conditions could then be specified in order to attempt to replicate dissolution rate data between different dissolution rate apparatuses.

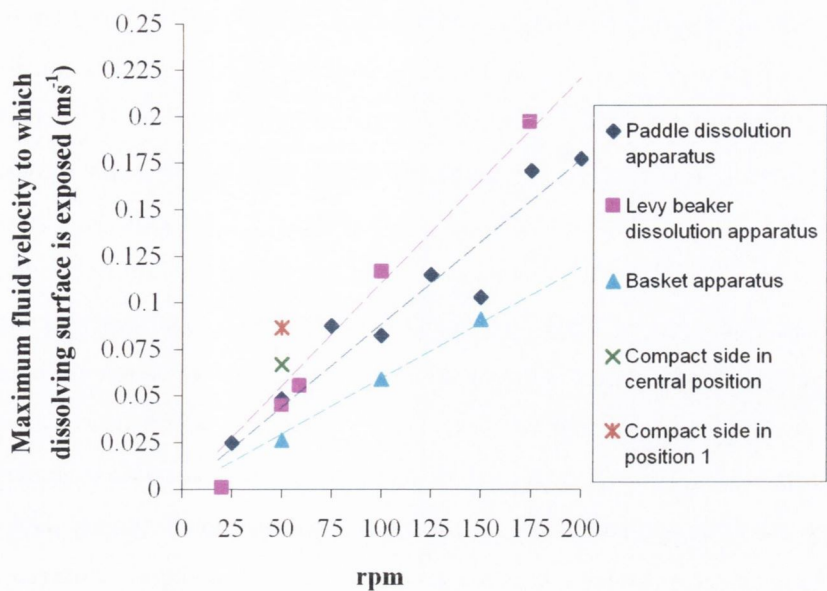


Figure 7.4. Comparison of CFD-generated velocity values within each apparatus investigated at different rotation rates. Data from the paddle apparatus is taken from a 10 mm diameter horizontal plane located at 2 mm from the vessel base, in 900 ml. Data from the compact sides in the central position and position 1 is taken at 1 mm from the surface, in 900 ml in the paddle apparatus at 50 rpm. Data from the Levy beaker dissolution apparatus (350 ml simulation) is taken from a 10 mm horizontal plane, 2 mm from the vessel base. Data from the basket apparatus (in 900 ml) is taken from Table 5.2.

A database of CFD solutions of common dissolution apparatuses at different rotation speeds would therefore facilitate dissolution rate investigations.

All three apparatuses modelled in this work were examples of rotating flow. It would be of interest to consider use of CFD to simulate other relevant flow types. The flow-through dissolution apparatus (USP apparatus 4) consists of pulsed unidirectional flow through a dissolution cell. As this apparatus is being used increasingly in *IVIVC* (Hougaard Sunesen et al., 2005; Katori et al., 1995) the hydrodynamics within the cell and their impact on dissolution rates should be investigated. As *in vivo* flow is not constant in nature, simulation of peristaltic flow and its influence on dosage form dissolution should also be investigated. The mechanics of peristaltic flow in terms of non-newtonian physiological fluids have frequently been examined (El Hakeem et al., 2006), including a mathematical model of peristaltic carrying and mixing of chyme in the small intestine (Lew et al., 1971). Application of such models to numerical analysis of peristaltic flow around a dissolving dosage form and comparison with physical models has potential to be of more relevance to a temporal *in vitro in vivo* correlation than constant rotational or unidirectional flow.

7.2 Solution convergence

Several methods to determine solution convergence have been explored in this work. The simulation of fluid flow in the paddle apparatus containing no compact was considered converged when the magnitude of the scaled residuals decreased by a factor of 10^3 , which is the default convergence criterion in FluentTM. For many problems, these convergence criteria are sufficient, but in some situations they may not be appropriate (FluentTM User's Guide, 2003). For example, if the initial guess to the flow field solution is good, the initial continuity residual may be small leading to a small decrease in scaled residual. It is advisable, therefore, to consider alternative methods for judging convergence. Various under-relaxation factors were employed in running the solution to convergence according to these convergence criteria (a decrease in magnitude of residuals by a factor of 10^3), as described in section 2.2.1.1.1, in order to generate a flow field solution which could be optimally validated using the laser Doppler velocity data of Bocanegra et al. (1990). As each set of under-relaxation factors resulted in a slightly different solution, it can be concluded that the solutions investigated may not actually have fully converged when the residuals had reached a magnitude 10^{-3} times that of their initial value. Altering under-relaxation values may alter the number of iterations needed to reach solution convergence, but should not necessarily alter the solution itself. For this reason, when solving the flow fields for the vessels containing the off-centre compacts, the convergence criteria in FluentTM were switched off, i.e. the solver did not cease to iterate on reaching a predetermined decrease in residual magnitude. The solution was considered to have reached convergence when the residuals levelled. The effect of altering under-relaxation values on solution convergence is illustrated in Figure 7.5. Figure 7.5.a shows normalised tangential velocities using the co-ordinate system of Bocanegra et al. (1990) (Appendix 1), just below the paddle tips, from a simulation of the paddle apparatus at 50 rpm where the compact volume in position 2 is defined as fluid. The data is taken from a solution after 5,500 iterations, with under-relaxation values of 0.3 for pressure and 0.525 for momentum. Figure 7.5.b shows data from the same model, after 7,000 iterations, with under-relaxation values of 0.5 for pressure and 0.4 for momentum. It is clear that there is little difference between the final solutions from these graphs despite the difference in time to reach the solution (number of iterations). The graphs can be compared to the laser-Doppler determined velocity values (Bocanegra et al., 1990) used in the validation of these solutions in Appendix 6.

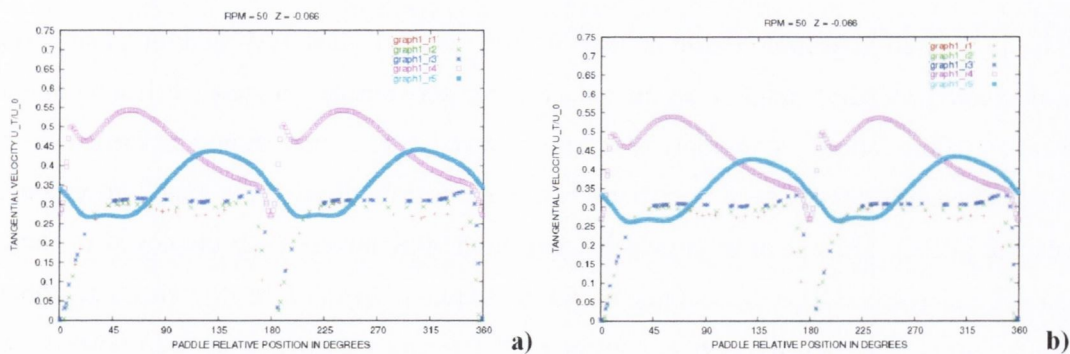


Figure 7.5. Normalised CFD-generated tangential velocity values using the Bocanegra coordinate system just above the paddle tips, from a model of the paddle apparatus at 50 rpm with the volume of the compact in position 2 defined as fluid. The data is taken from a simulation with under relaxation factors of (a) 0.3 for pressure and 0.525 for momentum after 5,500 iterations, and (b) 0.5 for pressure and 0.4 for momentum after 7,000 iterations; from simulations of 900 ml in the paddle apparatus at 50 rpm, with the compact volume in position 2 defined as fluid.

A third approach was taken when solving the fluid flow within the basket apparatus. As illustrated in section 5.2, velocities at specific locations within the flow field continued to either increase or decrease after the residuals had levelled. The solutions were considered to be converged when the velocity values at a particular location stopped changing in one direction, i.e. ceased to consistently increase or decrease with each iteration. In some cases, particularly at higher agitation rates, the velocity values did not cease to change with iteration, but fluctuated around a particular magnitude, as illustrated in Figure 5.6. It could be concluded from this that a greater assurance of convergence is achieved if iteration through a flow field is continued until the residuals level and the velocity values at pre-defined locations cease to consistently change in a particular direction. When solving the flow field at 20 rpm within the Levy 350 ml beaker dissolution apparatus, however, it was found that in some cases the velocity values at specified locations ceased to change while the residuals continued to decrease. Although the residuals were still decreasing having reached approximately 10^{-7} times their initial value (Figure 6.1), the maximum facet velocity values remained level (Figure 6.3). Therefore, in such a situation, it may have been appropriate to define convergence criteria as, for example, a 10^6 decrease in residual values with no requirement to monitor surface forces. The difference between the residual value at 10^{-6} times its original value and 10^{-7} times its original value is obviously so minimal in this case that the fluid velocities generated are not noticeably different. To define a decrease in residual value to 10^{-6} times its original value as convergence criteria for a case such as this would result in a saving of time and computational resources. The lack of an effect of decreasing residual values beyond a certain level on velocity values is also evident in Figures 6.6 and 6.7, in the 550 ml solution. On increasing the agitation rate to 174 rpm, however, in the 350 ml volume, the residuals fluctuate about a certain magnitude while the surface forces continue to change as illustrated in Figures 6.4 and 6.5. Therefore in this situation, convergence criteria of a predefined

decrease in residual magnitude would not be suitable. It can be deduced, therefore, that defining solution convergence is dependent on the nature of the convergence process. It is advisable that preliminary investigations on appropriate solution convergence criteria should be carried out on a basic model when solving a new flow field, before modifications of, for example, insertion of a tablet or a baffle. The extent to which different numerical methods are employed to increase convergence also depends on the required use of the solution. In all of the flow fields described in this work, a time-averaged solution was generated. Therefore, by the nature of a time-averaged solution, it must be assumed that the solution data contain some approximations. Furthermore, application of periodic boundary conditions or wall/symmetry conditions at the air-water interface lead to further approximations in the flow field solution. Therefore, velocity data generated must be considered as average values over time, with no accurate simulation of turbulent time-dependent features. The nature of the velocity data should be considered in its employment, and it should not, for example, be used to predict exact events at a specific time, but rather a general effect over time.

7.3 Effect of hydrodynamic parameters on mass transfer rates.

The dissolution rate from benzoic acid compacts located at the centre of the vessel base was significantly different to the rate from a compact located off-centre directly adjacent to the central location (position 1), and adjacent to this again (position 2). There was no significant difference in dissolution rates from compacts located in position 1 and position 2. Dissolution rates from the top planar surfaces alone and the curved side surfaces alone were also significantly higher when the compact was located in either position 1 or 2 compared to the central position, but the rates from either of the off-centre locations were again not significantly different from each other. When the compact was located in the central position, the dissolution rate per unit surface area (cm^2) from the top planar surface was less than that from the curved side surface. These observations are consistent with the presence of a low velocity region in the centre of the vessel, and higher fluid velocities with increased radial distance from the centre, as is evident from hydrodynamic simulations of the paddle apparatus. The fluid flow within the paddle apparatus containing a compact at each of these locations was successfully simulated. These simulations revealed complex flow patterns around the compact surfaces, including differences in velocity gradient at the surface within the hydrodynamic boundary layer. In general, the thickness of the hydrodynamic boundary layer was in the region of 1 mm, but was noted to vary between different regions of the compact surface. For example, the velocity near the compact side surface in the y-positive direction in position 1 reaches the bulk velocity value at a distance of approximately 750 μm from the surface. In contrast, for the lines profiled along the x axis towards the centre of the compact surface in positions 1 and 2, the distance from the top planar surface to the point where the velocity levelled with bulk velocity was approximately 1500 μm , although there was little change in velocity with distance from the surface at 1 mm from the surface (Figure 3.19). The actual value, however, of the bulk velocity at the edge of the hydrodynamic boundary layer varies with each region investigated, with bulk velocities in the region of 0.09 ms^{-1} at the top planar surfaces, and bulk velocities in the region of $0.06 - 0.07 \text{ ms}^{-1}$ being observed at the curved side surfaces. The experimental dissolution rates were, therefore, influenced by both the thickness of the hydrodynamic boundary layer and the velocity gradient within the layer. The shape of each compact, after being exposed to dissolution conditions for 1 hour in each position, was examined. In the off-centre positions, a sloped edge was noted to have formed in the region of the curved side surface which faced into the fluid flow on the 3 mm compacts. Grooves were noted to have formed around the sides of the 8.5 mm compact in position 1, along with a hump on the region of the top planar surface which faced into the fluid flow. These changes in shape from the original cylindrical shape of the compacts were consistent with velocity gradients noted in the simulations of hydrodynamics around each compact. Regions of lower velocity corresponded with regions of the compact where there was less dissolution, and adjacent regions of increased velocity corresponded with regions of increased dissolution, resulting in a slope or groove forming on the compact surface. It is possible, therefore, that CFD could be used to anticipate changes in the

shape of a dosage form when subject to specific hydrodynamic conditions. The time required under these conditions for a shape-change to be visible on a dosage form, however, would need to be determined for each particular combination of dosage form-hydrodynamic conditions. For example, a central hump was not visible on the top planar surface of the compact in the central position after 1 hour of dissolution, but the CFD generated hydrodynamics would suggest that due to the lower velocity at the centre of this surface, and increased velocity towards the outer edge, less dissolution would occur at this central point and in time a central hump would form. After dissolution for 5 hours in the central position, a hump was noted to form on this surface. Therefore, the relative difference between velocity magnitudes in adjacent regions, as well as the actual velocity magnitudes, are likely to influence any change in shape, and therefore the surface area, of a dosage form over the course of its dissolution.

The dissolution from the top planar surface of the compact in the central position appeared to follow linear (zero order) kinetics for the duration of the dissolution study (1 hour). As the longer dissolution study revealed the formation of a hump in the centre of this surface, the dissolution at the centre of the top planar surface must occur at a lower rate than at the outer edges of the top planar surface. It is possible, therefore, that the rate of dissolution from this surface changes over time, as the surface area of the resulting “humped” surface differed from the original planar surface. A CFD simulation of hydrodynamics around a dosage form, therefore, could be employed to anticipate regions of the dosage form where the rate of dissolution or drug release may change with time, depending on the interaction between the dosage form and the surrounding hydrodynamics.

When the relationship between dissolution from different surfaces of the compacts in the different positions with the local Re was investigated, the results suggested that the flow around the sides of the compacts in position 1 and position 2 was not entirely laminar. A critical Re number of approximately 800 was determined for the systems investigated. The critical Re is the Re above which there is a transition from laminar to turbulent flow. Turbulence generally involves unpredictable time-dependent flow features such as eddies, and cannot as such be accurately captured in a time-averaged simulation, but the presence of turbulence can be suggested in a time-averaged simulation through the existence of regions of complex swirling flows and eddies. Such time-dependent features in a moving liquid are indicative of the presence of a chaotic or non-linear dynamical system governing the hydrodynamics. The concept of chaos, in the mathematical sense, relates to the non-linearity of the equations controlling the system. In a chaotic system, the sensitivity to initial conditions implies that an infinitesimal change in an initial condition at a particular point in time can evolve unpredictably with time as the magnitude of the initial change cannot be accurately determined (Dokoumetzidis et al., 2001). For this reason chaotic activity can often be mistaken for random variation. In the field of hydrodynamics the point at which a system is driven further from equilibrium such that nonlinearities can no longer

be neglected, opening the possibility of bifurcations where regimes can coexist and compete, is recognised as the transition from laminar and turbulent flow (Manneville, 2004).

The use of the concept of chaos to interpret behaviour has been frequently applied to the life-sciences, including characterisation of pharmacodynamic phenomena (Dokoumetzidis et al., 2001) and use of fractal analysis to explain non-linear Hixson-Crowell dissolution plots on the basis of surface irregularity (Valsami and Macheras, 1995).

It was attempted to relate the local angular velocity, ω , to the dissolution rate from the top planar and curved side surfaces of compacts in the central and off-centre positions. Although the dissolution rate of a rotating disk has been related to angular velocity at the disk surface (Levich, 1962), this relationship did not hold for stationary surfaces in a rotating liquid. A model relating the local ω value to dissolution rate from a stationary surface in a rotating fluid (Khoury et al., 1988) only predicted the experimental dissolution rate accurately when the centre of the surface is located on the axis of rotation. It is clear from the CFD-determined local ω values that the difference in dissolution rate for the off-centre compacts cannot be reflected by the local ω value, as the ω value at the central top planar surface is 6.467 and the ω value at the top planar surface in position 1 is 6.785. The difference between these ω values is minimal ($< 5\%$) whereas there is a significant difference between the dissolution rates from the top planar surfaces in these positions. CFD-generated hydrodynamic data was used with some success, however, in predicting dissolution rates using several different methods. Use of tangential velocity data to calculate a local P_e and R_e value resulted in a predicted dissolution rate which was in reasonable agreement with experimental values for the top planar surfaces in the central position and position 1 on application of the equation from Colton and Smith (1972), presented in this work as equation 4.6. Some approximations had to be employed as the original equation applied to a vessel with a flat base, and the vessel used in the current work had a hemispherical base. Although the predictions for the central position and position 1 were in reasonable agreement (within 1 standard deviation) with experimental dissolution rates, the predictions from position 2 were higher than the experimental results, possibly due to the angle of the compact to the horizontal in this position. CFD-generated flow-field solutions were also used to simulate diffusion of a saturated solution of benzoic acid from each surface in each position within the flow field. From this simulation, the thickness of the diffusion boundary layer (h) was calculated at a range of points on each surface. The “edge” of the diffusion boundary layer was determined through comparison with the thickness of the diffusion layer which gave an accurate dissolution rate prediction from the curved side surface in the central position. The predicted dissolution rates using these calculated h values were within 10% of the experimental value for the curved side surfaces in positions 1 and 2, but the predictions from the top planar surfaces were lower than the experimental rates, in particular in the central position. This may be due to the greater density of the saturated solution not being incorporated into the simulation and therefore not being subject to movement through

gravitational effects. Additionally, the low velocity region was simulated as a static rather than a dynamic feature due to the time-averaged nature of the solution. Therefore, the simulation of diffusion of the saturated solution from the compact surface through the solved fluid-flow field resulted in the saturated solution remaining in this low velocity central region rather than being swept away by the bulk flow.

Rather than using the CFD-generated flow-field solutions to simulate convective-diffusion of a saturated solution in this flow field, it would be preferable to actually simulate dissolution from the surface of a dosage form. There are several numerical solutions of dissolution models in various systems (Neervannan et al., 1993; Southard et al., 1992). The thickness of the diffusion boundary layer was considered to be finite, and theoretical equations (Levich, 1962) were used (or functions thereof) to determine a finite thickness (Neervannan et al., 1993; Southard et al., 1992). As the 3-D fluid velocity profile is known around the dissolving surface from the CFD simulation, one finite value for h need not be employed. Use of a convective diffusion numerical simulation could therefore be employed using CFD-generated local velocity values to predict dissolution rates. A solution which not only predicted the dissolution rate from a surface, but would model the loss in mass from the surface as the solution progresses would be a primary objective in diffusion-rate limited dissolution simulation.

In addition to local values for ω , h and tangential velocities being determined from CFD-generated flow-field solutions, and employed in predictive dissolution-rate models, two other variables were used to predict dissolution rates: the maximum velocity at 1 mm from the compact surface (or in the region a compact would be located), and the rate of shear at a compact surface. There was a linear relationship between dissolution rate from the surface investigated and the maximum velocity at a distance of 1 mm from this surface, as depicted in Figure 3.8. This data was plotted along with the dissolution rate from a compact of benzoic acid within the basket of the basket apparatus rotating at 50 rpm, with the CFD-generated maximum velocity value to which the dissolving surface is exposed within the basket. The linear equation (equation 5.1) of the regression line in this graph (Figure 5.24) was used to predict dissolution rates from benzoic acid compacts within the basket apparatus at 50, 100 and 150 rpm, and a modification of the equation used to predict dissolution from salicylic acid compacts at the same agitation rates (Table 5.3). The modification of the equation to predict dissolution of salicylic acid compacts involved division of the constants by the diffusion coefficient and the saturated solubility of benzoic acid and multiplication of the constants by the corresponding values for salicylic acid. A similar modification of equation 5.1 was carried out to predict the dissolution rate of ASA and HFMI from the Levy beaker dissolution apparatus. The maximum velocity value from the 10 mm diameter plane, 2 mm from the centre of the vessel base was taken from the validated simulation of 350 ml at 59 rpm. The values for D for both ASA and HFMI were obtained from Corrigan (1973).

The resulting equations used in these predictions are presented as equation 7.1 (ASA) and equation 7.2 (HFMI). The dissolution rate predictions and the experimental dissolution rates are presented in Table 7.1.

$$\text{Dissolution Rate (mg min}^{-1}\text{ cm}^{-2}\text{)} = (4.92 \times \text{Velocity (ms}^{-1}\text{)}) + 0.271. \quad \text{Equation 7.1}$$

$$\text{Dissolution Rate (mg min}^{-1}\text{ cm}^{-2}\text{)} = (0.399 \times \text{Velocity (ms}^{-1}\text{)}) + 0.022. \quad \text{Equation 7.2}$$

	Predicted dissolution rates (mg min ⁻¹ cm ⁻²)		Experimental dissolution rates (mg min ⁻¹ cm ⁻²)	
	ASA	HFMI	ASA	HFMI
20 rpm	0.274	0.022	0.290	0.031
59 rpm	0.543	0.044	0.519	0.054
100 rpm	0.845	0.069	0.739	0.077
174 rpm	1.240	0.101	1.026	0.103

Table 7.1 Experimental and predicted dissolution rates of ASA (Equation 7.1) and HFMI (Equation 7.2) from the Levy beaker dissolution apparatus.

The predicted dissolution rates in Table 7.1 are in reasonable agreement with the experimental rates at 20 and 59 rpm for ASA, and 100 and 174 rpm for HFMI. The extent of the contribution from natural convection to the dissolution rate may be a contributing factor to the prediction error. The average maximum shear rate value from lines projecting from the compact surface into the bulk, as depicted in Figure 2.16, was employed to predict dissolution rates using the equations presented by Nelson and Shah (1975). Predictions for the top planar surface in each position were in good agreement with experimental results, using an equation which applied to a circular disk surface. Predictions from the curved side surfaces were lower than the experimentally determined rates, using an equation which applied to a rectangular surface. Originally the rectangle length was defined as the compact perimeter length and the width as the compact height, however, although the tangential flow around the side surface of the compact in the central position may be comparable to flow over a rectangle, this was not the case in the off-centre positions. As the flow stream could generally be seen to separate on meeting the curved side surface of the off-centre compacts, and flow around the compact on both sides and onward around the vessel, the dimensions used were altered for the off-centre compacts to define the length of the rectangle as half of the perimeter, and the compact height as half of the rectangle width. When these altered dimensions were used the predicted dissolution rate for the curved side surface of the off-centre compacts were increased, but were still lower than the experimental rates. The effect of the surface curvature is not accounted for in the equation for dissolution from a rectangular surface using shear rates (Shah and Nelson, 1975). When the dissolution under natural convection

conditions from a curved side surface is added to the predicted dissolution rate using shear rate values, the results are in good agreement with experimentally determined rates (Figure 5.29). The results from Figure 5.29 are presented again in Table 7.2.

	Central position	Position 1	Position 2
Predicted dissolution rate (mg hour ⁻¹)	40.28	46.14	53.06
Experimental dissolution rate (mg hour ⁻¹)	40.48 ± 0.84	52.21 ± 3.14	51.50 ± 2.80

Table 7.2. Predicted dissolution rates using equation 4.8 combined with measured dissolution rates under conditions of natural convection and corresponding experimental dissolution rates from the curved side surfaces of benzoic acid compacts in the central position, position 1 and position 2.

Addition of dissolution under natural convection conditions to the predicted rates from the top planar surface, however, results in predicted dissolution rates that are higher than the experimental rates (Figure 5.28). A possible explanation, therefore, is that the effect of natural convection at the curved side surfaces increases the rate of shear, and this is obviously not reflected in the CFD-generated shear rate values, as these values result from forced convection only. If natural convection at the top planar surface does not appreciably affect local shear rates, then addition of the observed dissolution under natural convection from this surface will result in an over-prediction of the dissolution rate. This supports the observation that when a dissolving rectangular surface is inverted, at low flow rates the relationship between dissolution rate and flow rate (representing a theoretical function of the rate of shear) deviates from that predicted due to the contribution from natural convection (Shah and Nelson, 1975).

7.4 Factors affecting dissolution under conditions of natural convection.

When dissolution rates from the surfaces investigated were plotted against the maximum CFD-generated fluid velocity that the dissolving surface was exposed to, the regression equation through these points was presented as equation 5.1, presented again as equation 7.3:

$$\text{Dissolution Rate (mg min}^{-1} \text{ cm}^{-2}) = (4.62 \times \text{Velocity (ms}^{-1})) + 0.254. \quad \text{Equation 7.3}$$

The intercept value in this equation was $0.254 \text{ mg min}^{-1} \text{ cm}^{-2}$. This represented the dissolution of benzoic acid under conditions of natural convection, but did not take the orientation of the dissolving surface into account.

The effect of orientation on the rate of dissolution under conditions of natural convection was, therefore, investigated. It was found that for both benzoic and salicylic acid, the dissolution rate was lowest for the horizontal top planar surface, followed by the curved side surface. There was no significant difference between rates from the lower planar surface and the top planar surface orientated vertically for benzoic acid, but the rate from the lower planar surface was higher than the top planar surface orientated vertically for salicylic acid. This suggested a combined effect between the solubility and resulting density gradients of the dissolving substance, and the viscosity of the saturated solution. There was a higher dissolution rate with the more soluble substance, benzoic acid, from all surfaces than from the salicylic acid surfaces. However, there was a greater increase from salicylic acid compacts compared to benzoic acid compacts in the dissolution rate from the top planar surface orientated vertically and the lower planar surface, compared to the dissolution rate from the horizontal top planar surface. It has been previously considered that the dissolution rate under natural convection conditions, when significantly affected by gravitational forces as is the case with a vertical or downward facing surface, does not increase linearly with increased solubility. Krause and Kildsig (1972) related dissolution in a descending direction to the interfacial energy at the solute-solvent interface. There was an increase in dissolution rate with decreasing interfacial energy, and an inverse relationship with solubility. It was postulated (Nedich and Kildsig, 1972) that the interfacial concentration at the dissolving surface was not that of the saturated solution, but lower. A solvent front was noted to move through the descending column with time, and it has been suggested that movement of this solvent front may be parabolic in nature (Shively and Kildsig, 1972). If this were the case, a solvent front with a lower velocity would allow more radial diffusion of the solute, which may therefore decrease the concentration at the surface and promote further dissolution. It can be concluded, therefore, that the relationship between dissolution rate and solubility in a descending model is complex. The diffusion coefficient is independent of concentration only in dilute solutions. If the solute concentration is sufficiently high, the increased solvent viscosity affects the diffusivity of the solute (Flynn et al., 1974). In the current work, the effect of solubility and resulting viscosity on the dissolution rate at the lower planar surface and top planar surface orientated vertically is evident in the difference in the increase in dissolution rates from these

surfaces with compounds of differing solubility. The curved side surface, however, is also a vertically orientated surface, but the dissolution rate from this surface with both salicylic and benzoic acid was lower than from the top planar surface orientated vertically. Furthermore, dissolution rate predictions using equations derived from the copper cathodic deposition method predicted dissolution rates in good agreement with experimental rates for the lower planar and vertically orientated top planar surface (Tables 5.7 and 5.8). Experimental rates from the curved side surface, however, were much lower than rates predicted from equations derived from cathodic copper deposition (Table 5.7). As the compacts with the curved side surfaces exposed were located at the base of the dissolution vessel, it was postulated that the saturated solution had pooled at the base of the jar at the dissolving surface. In effect, the solute had to diffuse from the surface, with no contribution from convective forces to mass transfer, as natural convection due to gravitational effects was impeded by the geometrical constraints of bottom of the jar. Dissolution from the horizontal top planar surface was also from a compact located at the base of the vessel, although the effects of natural convection at this surface are less predictable as convection through gravitational effects is limited until the saturated solution reaches the edge of the surface. The pooling of a saturated solution at the dissolving surface implies that the dissolution rate should decrease over time, as the thickness of the unstirred layer affects the time taken for a molecule to traverse this layer. A molecule with a diffusivity in the range of 10^{-5} to 10^{-6} $\text{cm}^2 \text{s}^{-1}$ in liquid water (which is the order of the diffusivity of benzoic and salicylic acid in the systems investigated in the current work) would take 1 to 10 years to cross a 1 cm thick unstirred layer (Flynn et al., 1974). The dissolution rates in the current work were not seen to decrease with time from the horizontal top planar or curved side surfaces, as can be seen in Figures 5.26 and 5.27. The sampling method employed, however, involved removal of the compact at each time point, mixing of the dissolution medium and replacing the disk after sampling. To determine whether the dissolution rate changed with time, separate studies were conducted for each time point, from both the lower planar surface and the horizontal top planar surface. The results are presented in Figure 7.6.

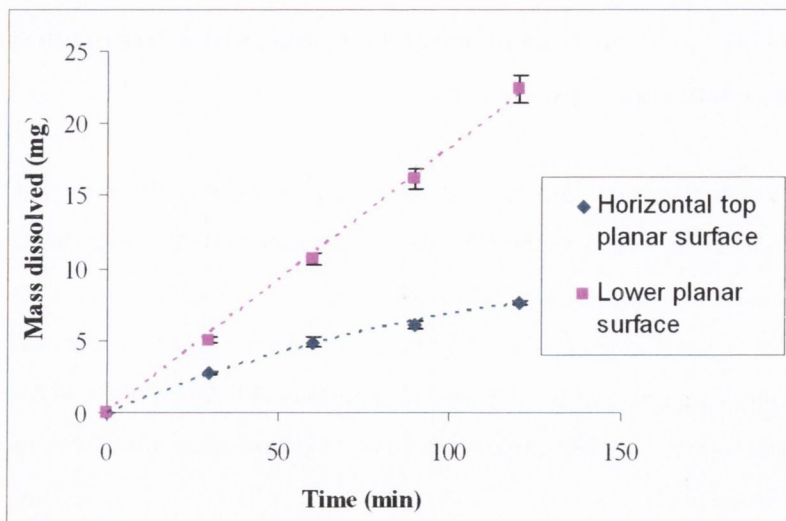


Figure 7.6. Mass benzoic acid dissolved (mg) vs. time (min) from the horizontal top planar surface and the lower planar surface under conditions of natural convection. Each time point represents a separate dissolution study.

It is clear from Figure 7.6 that the dissolution rate does decrease with time from the top planar surface, but not from the lower planar surface. When a line was fitted through the data points from the top planar surface, the rate ($0.051 (\pm 0.001) \text{ mg min}^{-1} \text{ cm}^{-2}$) was significantly less than that determined when the medium was mixed at each sampling time ($0.065 (\pm 0.005) \text{ mg min}^{-1} \text{ cm}^{-2}$). The rate from the lower planar surface, however, was not significantly different when separate studies were conducted for each time point to when the medium was mixed at each time point, implying that sink conditions were effective in the vessel over the course of the dissolution study using this method. This fact is of use when contemplating further studies investigating dissolution under natural convection conditions, for example with different compounds or mixtures of compounds, provided the volume present is adequate to provide sink conditions. Dissolution studies from the lower planar surface can be conducted using the less time consuming method of repeated sampling at consecutive time points rather than separate studies from each time point. Similarly, the fact that the equations empirically derived from the cathodic copper deposition method (equations 5.5-5.7) predicted the dissolution rate from the lower planar surface and the top planar surface orientated vertically with reasonable accuracy implies that these equations can be used in future experimental design and potentially in numerical models of dissolution.

A final point to be noted with regard to studies of dissolution rates under conditions of natural convection is that of the geometry of the system used. As is evident from the dissolution rate being lower than predicted from the curved side surface when placed at the base of the jar, locating the compacts in different positions in a vessel may affect the potential of the solute to pool in a particular region and thus affect the observed dissolution rate.

7.5 Using *in vitro* hydrodynamic and dissolution rate data to interpret *in vivo* dissolution/absorption data.

The relationship between *in vivo* and *in vitro* dissolution rates was characterised in terms of the Apparent Gastro-intestinal Velocity (AGV) value. Calculated AGV values from *in vitro* studies using the paddle and Levy apparatus were variable, but were in general considerably lower than the *in vitro* velocities used in official test conditions (Tables 6.3 and 6.4), for example 50 rpm for the paddle apparatus and 100 rpm for the basket apparatus (FDA, 1997b). The exception to this trend was when the release of the active ingredient from a dosage form was mediated through destructive or erosive effects.

To determine AGV values in the basket apparatus is a more complicated issue, as a dosage form which disintegrates and passes through the basket mesh will be exposed to much lower velocities than a dosage form which remains within the basket. An attempt to establish an *in vitro in vivo* correlation with paracetamol immediate release tablets (Radovanovic et al., 1998) found that there was a correlation with numerical convolution of the data from *in vitro* dissolution time using the basket apparatus at 50 rpm and *in vivo* mean dissolution time. The tablets disintegrated rapidly, but most of the disintegrated mass remained within the basket (personal communication from author), which implies that an AGV value using the velocity the tablet is exposed to within the basket is applicable in this case. From Table 5.2, this results in an AGV value of 0.0263 ms^{-1} , which is of the same magnitude as AGV values calculated for the paddle and Levy apparatuses. An *in vitro in vivo* correlation using the basket apparatus and HPMC-based metoprolol tablets, however, was established at an agitation rate of 150 rpm (Eddington et al., 1998). This is equivalent to the dosage form being exposed to a velocity of 0.0914 ms^{-1} (according to Table 5.2), and the higher velocity was required to simulate *in vivo* erosive processes.

These results suggest that AGV values from the basket apparatus can be determined from studies employing dosage forms which will remain within the basket rather than pass through the mesh. The erosion resulting from the shearing force of the basket side on, for example, a swelling HPMC tablet, will not be simulated by CFD. Additionally, CFD-simulated pressure values within the basket apparatus are considerably lower than those simulated within the paddle and Levy apparatuses, which in turn are lower than contact pressure present *in vivo*. Incorporation of a numerical function to a dissolution simulation model which would simulate the effect of destructive or erosive forces would be imperative if future simulations of *in vitro* dosage form dissolution were to be applied to dosage forms which depended in erosive forces for drug release. A potential problem with the calculation of AGV values is that dissolution may occur at a site proximal to absorption, which will influence the temporal data on *in vivo* absorption. It is preferable, therefore, to use mean *in vivo* dissolution data for comparative purposes when this is available, rather than absorption data.

From Figure 7.4, the AGV values presented in Tables 6.3 and 6.4 are lower than the fluid velocity values present in the paddle apparatus at 25 rpm or the velocities relative to a dosage form rotating in the basket apparatus at 50 rpm. The *IVIVC* for HPMC tablets in the basket apparatus was achieved by Eddington et al. (1998) at 150 rpm. This produces fluid velocities relative to the tablet surface of a magnitude similar to that produced in the paddle apparatus at 100 rpm. The % drug release from hydrogel-based dosage forms was less than the *in vivo* rate at 150 rpm in the paddle apparatus (Aoki et al., 1992), further supporting the influence of erosive effects from the basket side.

Use of canine models in *in vitro in vivo* studies.

The issue of *in vivo* data from canine models was considered in section 6.6.1.2. The AGV values calculated from studies using canine models were significantly greater than those from human studies. This should be considered in the dissolution test design if data from *IVIVCs* using canine models are used in attempts to establish *IVIVCs* in humans. The apparent increase in *in vivo* hydrodynamics present in canine subjects is not only relevant to drug release studies, but to general *in vivo* dosage form behaviour. An *in vitro in vivo* relationship was established between the dissolution rate (in the paddle apparatus, containing 900 ml of bio-relevant media at 50 rpm) of a specific formulation of a poorly soluble lipophilic drug candidate, EMD 50733, and the time to maximum plasma concentration ($t_{\max}$) (Schamp et al., 2006). Beagle dogs were used in the study, and the formulation involved melting (65–80°C) Gélucire (mono-, di- and triglycerides and esterified PEG), adding the drug and 2-vinyl-pyrrolidone, and filling the drug-melt dispersions into hard gelatin capsules. The formulation was intended to provide a self-emulsifying drug delivery system, and the dissolution results support the occurrence of this phenomenon. The influence of canine hydrodynamics on the *in vivo* formation of micelles in addition to the effect on dissolution rate should therefore be considered. Finally, intraluminal solubility in human small intestine contents may be over-estimated in the fed state when using canine models, due to the higher bile salt content in canine bile (Kalantzi et al., 2006 (b)).

Clinical considerations in determining *in vitro in vivo* dissolution/absorption relationships.

It is recognised that there are many variables which influence the pharmacokinetics and pharmacodynamics of a dosage form within any one individual. Although most absorption studies are carried out in healthy patients, disease state and concurrent drug therapy effects can affect absorption. These effects, however, are difficult to quantify. Factors which may be more obvious such as achlorhydria and altered gastro-intestinal motility have been recognised as complicating factors in *in vitro in vivo* correlations (Levy, 1967). Drug degradation *in vivo*, biotransformation in the gastro-intestinal mucosa, volume and nature of food and fluid intake and direct actions of the active ingredient on the mucosa or the rate of gastric emptying are just some examples of factors which can result in poor *in vitro in vivo* correlations of dissolution/absorption

rate. An example of a clinical consideration when determining *in vitro in vivo* correlations involved a study on five different formulations of erythromycin tablets (Stavchansky et al., 1980). This study found that a range of *in vitro* tests conditions (including a disintegration test) had to be combined to produce an accurate *in vivo* predictor equation. However, the effect of erythromycin on gastro-intestinal motility (potentially affecting the *in vivo* dissolution rate) stemming from its prokinetic action as a motilin-receptor agonist (De Ponti and Malagelada, 1998) was not considered. As patients would generally receive erythromycin as a course in the range of 1g orally daily for several days, *in vivo* dissolution of erythromycin may not be adequately described by the pharmacokinetics following a single dose.

Use of bio-relevant media in dissolution testing.

When comparing *in vivo* and *in vitro* dissolution data, it is advisable that comparative dissolution media is employed, in particular for BCS (Biopharmaceutics Classification System, (Amidon et al., 1995)) class II drugs, which have low solubility but high gastro-intestinal permeability i.e. dissolution-rate-limited absorption. A biorelevant dissolution test is one which aims to simulate the environment in the GI tract. The choice of media will depend on whether the drug is ionisable or not, and use of simulated gastric fluid (SIF), fasted state simulated intestinal fluid (FaSSIF) and/or fed state simulated intestinal fluid (FeSSIF) should be considered (Galia et al., 1998). Research is ongoing in the area of characterisation of human gastrointestinal contents in order to simulate accurately the dissolution medium a dosage form will be exposed to *in vivo* (Kalantzi et al. (2006a)). The density and viscosity of the dissolution medium used should, therefore, be applied to materials defined in CFD simulations in order to accurately determine AGV values. A more useful application of CFD at this stage is to identify conditions within a particular apparatus which closely resemble *in vivo* conditions rather than determining AGV values. This approach essentially involves using CFD technology to design the required apparatus geometry and agitation conditions to replicate *in vivo* parameters.

7.6 Use of CFD technology to design informative dissolution testing systems.

As CFD provides more information than was previously available regarding fluid flow in the vicinity of a dissolving surface, this knowledge should be utilised in the design of dissolution testing systems in order to optimise their utility. In section 3.2.3.2, it was demonstrated that controlling the location of a dissolving dosage form reduced the repeatability limit to a level where the compacts which were not in a fixed position did not pass the repeatability test. The difference in the CFD-generated maximum facet velocity at a 1 mm distance from each dissolving surface is presented in Figure 3.8, illustrating the variation in fluid velocities that a compact not fixed to a particular position might be exposed to. Any systematic error which may bias the results from a testing system, or contribute to the variability therein, should if possible be “designed out” of a testing system. As suggested in section 3.2.3.2, if there is a known contribution to variability from the apparatus due to the random location of a dosage form, when it is desirable to identify variation in results from the dosage form only, the location of the dosage form should be controlled when the test is being performed. A more useful manner in employing CFD to improve dissolution testing systems would be to define regions within a testing system which have less hydrodynamic variability. This might involve identifying regions within the paddle or basket apparatus, or the use of an apparatus with simpler flow. The flow-through apparatus (USP dissolution apparatus 4) may provide such a system, and the simulation of hydrodynamics within this apparatus is required to determine its suitability. If a region within an apparatus is identified within which a dosage form should be located to minimise variability, it is important that the CFD-generated data has been produced with parameters such as density and viscosity appropriately defined. As bio-relevant dissolution media are being employed in the development of dissolution tests in bio-waiver applications (FDA, 2000), it is essential that the material properties of the test media employed are input parameters in the CFD simulation. In this manner accurate flow simulations can be generated and regions within an apparatus providing the required hydrodynamic conditions can be identified.

Although minimisation of systematic variability is of importance in routine quality control testing, dissolution testing may also be employed in the anticipation of gaining some insight into the *in vivo* performance of a dosage form. Defining suitable hydrodynamic conditions for this purpose requires a different approach to that of repeatability testing in quality control. As discussed in section 6.6., *in vivo* hydrodynamics are generally of a lower magnitude and less homogenous than the hydrodynamics generated in the compendial dissolution apparatuses. It has been suggested that the unidirectional flow in the flow-through apparatus does not represent the mixing conditions in the small intestine and proximal colon (Dressman et al., 1998). Bearing this in mind, the rotating flow of the basket and paddle apparatuses, combined with the shearing force and sieving effects from the basket sides, may actually be more characteristic of *in vivo* flow patterns than the flow-through apparatus. To replicate *in vivo* hydrodynamics, however, the flow rates in the apparatus should be closer to those encountered *in vivo* than current recommended

agitation rates of e.g. 50 rpm (paddle apparatus) and 100 rpm (basket apparatus) (FDA, 1997b). An appropriate stirrer agitation rate could be determined using CFD, taking account of whether the dosage form would be taken in the fasting or fed state. This would affect the *in vivo* hydrodynamics as well as the *in vitro* media used. Furthermore, ideally the flow should be variable to provide alternating fluid conditions which would be found in the fed stomach. An approach to this could be to use dimensional analysis or similarity theory (Levich, 1962). In an incompressible flow any hydrodynamic variable, U , v or L_c may be expressed as a function of the Reynolds number. Two flows can be considered similar if they are of similar geometry, with equal boundary conditions and equal Re . Different flow rates of different media *in vivo* will provide a different Re . Alternating Re *in vitro* could be used to simulate different *in vivo* media conditions, for example an increase in kinematic viscosity could be simulated by a corresponding decrease in velocity resulting in the same Re in the bulk flow near the dissolving surface. Additionally, dimensional analysis by its nature can be scaled to use, for example, faster flows which will produce the same Re in media with a higher viscosity as slower flows in a media with a lower viscosity. A limitation of this approach is that the diffusion coefficient will be decreased in a more viscous media, which will affect the dissolution rate. This phenomenon would not be replicated using an *in vitro* dimensional analysis approach.

As illustrated in section 6.6.3, the CFD simulations of the compendial dissolution apparatuses do not generate contact pressure data. Moreover, the inflexible nature of the vessel and basket sides are not representative in the gastro-intestinal wall, which is not only flexible in nature but also comprises micro-villi which will contribute to mechanical shearing forces at the surface of a dosage form. A novel *in vitro* dissolution method has recently been used to develop a level A *IVIVC* for immediate release paracetamol tablets (Souliman et al., 2006). The method used an Artificial Digestive System (ADS) known as TNO intestinal model (TIM 1). The ADS does not simulate absorption therefore the BCS class I drug, paracetamol, was chosen (high solubility, high gastro-intestinal permeability). The ADS consists of four consecutive compartments representing the stomach, duodenum, jejunum and ileum, and can maintain the conditions corresponding to the physiological state in terms of enzymes, pH, removal of digestion products, mixing, transit times and peristaltic dynamics (Souliman et al., 2006). A delay in *in vivo* absorption was replicated by a delay in the *in vitro* “absorption” in the fed state. The difference in the *in vitro* model which produced this effect was a predetermined delay in gastric emptying. Dissolution results from the same paracetamol formulation in the paddle apparatus using FaSSIF, FeSSIF and soaking of the dosage form in olive oil to simulate fatty meal conditions did not result in a detectable slower release in the fed state. Use of CFD and other high performance computing tools, such as molecular dynamics, could potentially be employed to simulate the TIM 1 apparatus. As the contents and transit parameters can be modified, and the dimensions are defined, such a model of this section of the gastro-intestinal tract would be more straightforward to simulate *in silico* than actual *in vivo* conditions.

A numerical simulation of gastric flow and mixing in the human stomach (Pal et al., 2004) was referred to in section 6.6. This numerical simulation of fluid motions and fluid forces was further developed to calculate the motions of a finite-sized tablet and determine the shear stress on the tablet surface as it moved through the virtual stomach. A dimensional analysis approach was then taken to design an *in vitro* test simulating *in vivo* conditions (R_e and shear stresses), as defined by the numerical *in vivo* simulation (Abrahamsson et al., 2005), using media with different viscosities and different rotation rates. Erosion data from the *in vitro* test was compared to shear stress data calculated from a CFD simulation of the *in vitro* test to determine the relationship between physiologically relevant shear stresses and hydrophilic matrix tablet erosion. The *in vitro* test consisted of the tablet being held in place on a rigid steel rod, placed in a rotating beaker containing the dissolution medium, in a location adequately distant from the beaker walls to minimise wall effects. A mathematical model relating the *in vitro* mass erosion rate to the shear stress at the surface (calculated from the numerical solution) was developed. This illustrates the potential for application of CFD to the design of testing systems which create the required hydrodynamic conditions for a particular application. Use of CFD to predict *in vivo* dissolution/erosion of a range of dosage forms remains, however, a significant objective of dissolution modelling.

7.7 Solution validation.

The nature of the approximations employed in generating a solution should also be borne in mind when validating the flow field solution, as should the limitations of computational resources imposed on the model in terms of grid refinement and convergence approaches. Attempts to quantitatively validate a solution with specific time-dependent data at precise locations is not appropriate for a time-averaged solution with the approximations described in section 7.2. This was discussed in section 5.3, where UPE maximum velocity data was consistently higher than the CFD-generated data. In this situation, however, there was a correlation between ratios of velocity data at different locations within the flow field solution from both the CFD and UPE data. Furthermore, the CFD-generated velocity values within the basket apparatus were utilised to predict dissolution rates within the apparatus, with reasonable agreement with experimental dissolution rates. For the purposes described in Chapter 5, therefore, the flow field solution to the basket apparatus was “useable”, as it could be used to predict real physical phenomena with reasonable accuracy. In this sense, “validation” is a term which must be defined by the user with regard to the intended purpose of the solution. There are several definitions of validation of a CFD model (Oberkampf and Trucano, 2002), including the following from the Society for Computer Simulation (SCS): “substantiation that a computerised model within its domain of applicability possesses a satisfactory range of accuracy consistent with the intended application of the model”. In this definition the crucial aspect is that of “substantiation”, in other words evidence of the accuracy of the model. Validation processes, however, should be considered as ongoing activities, as the accuracy of a model cannot be demonstrated for all possible conditions. Substantiation implies that a model can be correctly solved, and that this is then verified (the approach taken in the current work). Errors and inaccuracies present in both the computational and experimental data can actually cancel one another and give the appearance of a verified solution. Sources of error in CFD validation studies include experimental error, error from the spatial grid, from the size of a time step, from initial and boundary conditions, from the partial differential equations (PDE)’s used, from the convergence parameters and from the computer itself (Oberkampf and Trucano, 2002). It is recommended that some estimate of the order of magnitude of the error in the computational simulation be determined, in order to assess the accuracy of the agreement of CFD data with experimental data. Variation of input variables, such as changing mesh density, and input of a probabilistic distribution (reflecting physical measurement variability) of input variables rather than a single value enables the calculation of a range of solutions. The consequent variability present in the data generated in these solutions can then be used to gauge the magnitude of error present in the simulated data. It is recognised that budget and computational resources often limit the extent to which the accuracy of a validated solution can be determined (Oberkampf and Trucano, 2002). The similarity of the solutions from the paddle apparatus at 50 rpm containing no compact and the apparatus where the off-centre compact volume is described as fluid, using a multiple reference frame and an unstructured

mesh, suggests that the magnitude of the error in the simulations is low. In this case the region of interest was the region at the base of the vessel where a dosage form was located. The graphs in Appendix 6 can be compared to determine regions where the variability between solutions is greater than at the base of the vessel. The predictive ability of the simulations might not be as high if the region of interest was elsewhere. Prediction is related to validation in the manner shown in Figure 7.7.

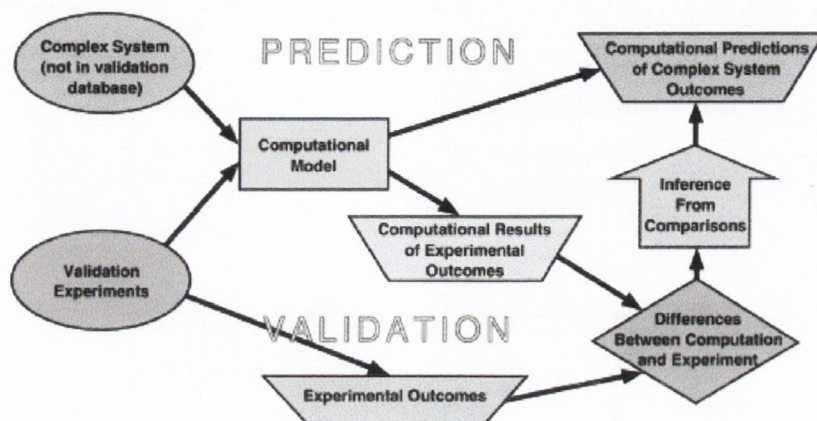


Figure 7.7. Relationship between prediction and validation. Taken from Oberkamp and Trucano, 2002.

The use of the validated solution containing the off-centre compacts defined as fluid in the paddle apparatus to simulate fluid flow around these compacts defined as solid volumes is actually a predicted solution developed from a validated solution rather than a validated solution itself. The accuracy of a predicted solution can be inferred from the accuracy of a validated solution.

In this work, several methods were used to validate the flow field solutions: laser Doppler data for the paddle apparatus at 50 rpm taken from Bocanegra et al. (1990), and UPE data from Diebold and Dressman (2001) for the paddle apparatus at agitation rates of 25-200 rpm and the basket apparatus at 50-150 rpm. The nature of the UPE local velocity maximum data was not as critical in comparisons with CFD-generated data at the higher fluid velocities present in the paddle apparatus than in comparisons with the lower velocities in the basket apparatus. This again illustrates the importance of using physical data relevant to the intended use of the system under investigation. Qualitative validation was also carried out with the basket apparatus and Levy apparatuses, using flow visualisation data. Quantitative validation of the Levy apparatus involved an indirect method, where dissolution rates from the basket and Levy apparatuses were compared to CFD generated fluid velocity values within each apparatus. As the basket apparatus was already quantitatively validated, data from it was used as reference velocity data.

Ideally, validation of a CFD solution should use data which has been generated for this purpose alone. With such an approach, the type of data appropriate to the solution (e.g. average velocity at a particular location, or a general location in an area where the mesh is less dense) can be measured. Furthermore, appropriate locations in which the physical velocity should be measured can be defined, for example comprehensive data in the region a non-disintegrating dosage form is

located. If the dosage form is disintegrating, then data from a broader region where the disintegrated particles are likely to be located should be determined. Initial flow visualisation exercises could be used to highlight areas where the fluid flow may be complex, and to plan locations for validation data to be generated. In this manner, measurement of physical data from a well-planned validation study can contribute to assurance of the accuracy of the flow field solution and its subsequent utilisation. Figure 7.8 illustrates a tiered approach to validation, although where a commercial software package such as FluentTM is used, code verification steps should be carried out by the software supplier.

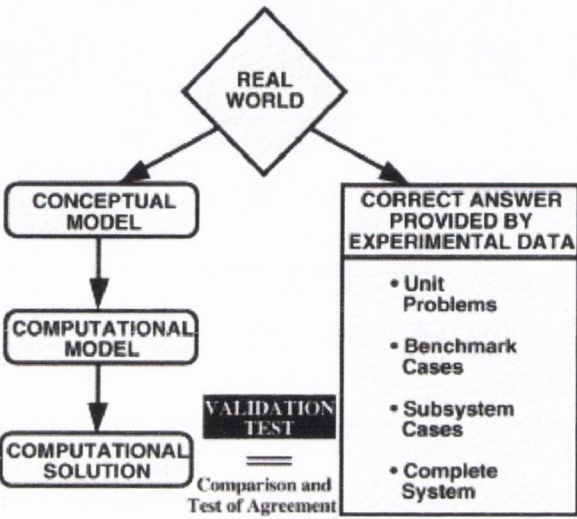


Figure 7.8. Flow diagram of a validation process. Taken from Oberkampf and Trucano, 2002.

In summary, validation of a CFD solution should be considered a comprehensive project in itself. The validation process should be designed and updated to reflect the desired use of the solution, and predictive ability of a solution should be quantified as far as possible through quantification of the error in the initial simulation.

7.8 Conclusions and future work.

7.8.1 Conclusions.

The main findings of the current work are as follows:

- A time-averaged CFD model can be used to simulate primary and secondary hydrodynamic features of the flow field in the paddle apparatus at different agitation rates. Complex secondary flow features are present, which are more evident at higher rates of agitation. A multiple reference frame model can be used to simulate fluid flow around compacts located off-centre in the base of the paddle dissolution apparatus.
- A time-averaged periodic CFD model can be used to simulate the fluid flow in the basket apparatus at different agitation rates. Notable secondary flow features included radial emanations at the basket sides and positive axial flow beneath the basket.
- A time-averaged CFD model can be used to simulate the fluid flow field in the Levy beaker dissolution apparatus, at different agitation rates and with different vessel dimensions containing different fluid volumes. Again, secondary flow features were complex and varied in nature with the agitation rate, vessel dimensions and volume of dissolution medium.
- Maximum fluid velocities at 2 mm from the centre of the base of the Levy beaker apparatus (at agitation rates ≥ 50 rpm) were faster than those at 2 mm from the centre of the base of the paddle apparatus at the same agitation rate, which was faster than the relative velocities in the basket of the basket apparatus. However, velocities around the sides of cylindrical compacts located at the centre and off-centre of the base of the paddle apparatus were faster than those at 2 mm from the centre of the base of the Levy beaker apparatus, at the same agitation rate. Therefore, it is important to determine the location of a dosage form within a dissolution apparatus to ensure it is exposed to the intended hydrodynamic conditions.
- Dissolution rates from both the top and side surfaces of a compact increased in the paddle apparatus when the compact was located adjacent to the central position (position 1) compared to when it was located at the centre of the base of the vessel (central position). This was due to the compact being removed from the low velocity vortex region at the centre of the base of the vessel. Dissolution rates did not increase from this off-centre position when the compact was located directly adjacent to this again (position 2). The hydrodynamic boundary layer thickness was approximately 1 mm, however it varied at different points on each surface, between surfaces on the same compact and between compacts at different locations. The

magnitude of the bulk velocity at the edge of the hydrodynamic boundary layer also varied with surface and location investigated, but not always in the same manner that the hydrodynamic boundary layer thickness varied. Therefore the thickness of the hydrodynamic boundary layer is dependent on both the local bulk velocity and the geometry of the of the flow field.

- The shape of the compacts after dissolution for 1 hour in each position was affected by the local hydrodynamics. Regions of the compact surface in low velocity conditions dissolved slower than regions exposed to higher velocities, resulting in slopes and grooves being visible on these surfaces after a period of exposure to the dissolution conditions. Furthermore, regions of low velocity in the CFD simulations enabled prediction of the development of a “hump” on the surface of a compact after a prolonged exposure to dissolution conditions of 5 hours. CFD simulations also revealed areas of potential flow instability at the off-centre compact side surfaces. CFD can therefore be used to predict variation in dissolution rate with local hydrodynamic conditions, and also the effect of local hydrodynamics on the shape of a non-disintegrating dosage form, if the flow-field around the dosage form in a specific location is simulated.
- There is a decrease in variability when a compact is fixed to particular location in the paddle apparatus compared to when it is unfixed, as is the case in routine dissolution testing. As random location within the vessel has been identified as a source of variability in dissolution test results, the location of a dosage form should be specified to ensure that exposure to hydrodynamic conditions is consistent between dosage forms.
- Local CFD velocity and shear rate data can be used to predict dissolution rates with reasonable accuracy (i.e. within two standard deviations of experimental data) if an appropriate dissolution model is used. The relationship between the maximum CFD-generated fluid velocity values and dissolution rate holds for data from both the paddle and basket apparatuses, from dissolving surfaces in different locations and exposed to different rates of agitation. The addition of dissolution rates under conditions of natural convection to dissolution rate predictions from shear rate data improved the accuracy of predictions for a surface with a vertical orientation but not for a surface with a horizontal orientation. This implied that the contribution from natural convection to dissolution rates is more significant from a vertically orientated surface than an upward-facing horizontal surface.
- The orientation and solubility of a dissolving surface significantly affects its dissolution under conditions of natural convection, but this effect varies with solubility of the dissolving surface and the density and viscosity of the saturated solution formed. Equations derived empirically

from limiting-current cathodic copper deposition experiments, describing mass transfer to a surface, designed to mimic heat transfer, were useful in predicting mass transfer from dissolving surfaces in the systems examined. The accuracy of the prediction decreased when the surface was located near the base of the vessel and the effect of gravitational force on the saturated solution was compromised, resulting in pooling of the saturated solution and a decreasing dissolution rate with time.

- AGV values calculated from simulated velocities in each apparatus were lower than the velocities generated at compendial or common operating speeds, implying that velocities in the human GI tract are lower than those generated in the paddle or Levy beaker apparatuses at 50 rpm. Dosage forms for which destructive or mechanical forces contribute to drug release, however, resulted in higher calculated AGVs, implying that the increased hydrodynamic pressure and erosive forces from physical contact with the apparatus were required to simulate *in vivo* conditions. CFD can be used to simulate the hydrodynamic pressure forces but not force resulting from contact with the vessel or basket sides.
- In order to appropriately judge convergence of the CFD simulations, both residuals and velocity magnitudes on a range of surfaces should be monitored. In some cases, velocity magnitudes had levelled while residuals were still decreasing to very small fractions of their original value, e.g. 10^{-6} to 10^{-7} . In this situation, a saving in computational resources could be made in accepting a specified decrease in residuals as convergence criteria, if the resulting solution was of adequate accuracy.
- Hydrodynamic simulations in this work were validated using a number of methods. Qualitative flow visualisation studies can be used to compare secondary hydrodynamic characteristics with those generated by time-averaged CFD simulations, and quantitative validation can be achieved by comparisons with averaged velocimetry data. Comparisons of time-averaged velocity data from CFD simulations with local maxima velocimetry data yielded a relative correlation only, highlighting the importance of the design of a validation experiment. A time-dependent simulation which captured time-dependent effects would potentially have resulted in a more accurate prediction of local velocity maximum data. When considering convergence criteria and appropriate validation data for a CFD simulation, the proposed application of the simulation data must be considered in determining the “useability” of a simulation.

7.8.2 Future work.

Following the simulation of hydrodynamics within the paddle, basket and Levy vessel dissolution apparatus, velocities within the apparatuses were related to dissolution rates from compacts within the apparatuses. The hydrodynamic simulations were also used to calculate apparent gastrointestinal velocity estimates from published *IVIVC* studies. The following suggestions are recommended as future work to expand on and develop the findings in the current work:

1. As the hydrodynamics of the paddle and basket dissolution apparatuses were simulated in the current work, simulation of the hydrodynamics in the flow-through (USP 4) dissolution apparatus is recommended. Velocities at a range of flow rates in the flow-through apparatus could then be compared to the other common compendial dissolution apparatuses, the basket and paddle apparatus. Additionally, knowledge of velocities generated in conditions used in *IVIVC* studies would contribute to further studies designed to replicate *in vivo* conditions.
2. Should predicted or exact events at specific times within the flow field of any of the apparatuses investigated be required, use of a time-dependent solution employing turbulence modelling should be considered. These options are available in FluentTM.
3. Simulation of a “moving boundary” problem, where the flow field would be subject to forces from a moving boundary. This would be an initial step towards modelling the *in vivo* situation of gastric contractions, emptying and intestinal peristalsis.
4. Modelling of actual dissolution as opposed to predicted dissolution from CFD-generated velocity data. Convective diffusion equations, such as that used by Whelan (2002), can be combined with CFD-generated velocity data to predict dissolution under specific hydrodynamic conditions. In order to accurately model dissolution, the natural convection component for each individual system would need to be determined and incorporated into the model, rather than forced convection alone.
5. Further work on natural convection could include the effect of mixtures of more and less soluble components, in different proportions. Measurements of the density and viscosity of resulting saturated solutions would also contribute to the understanding and therefore future prediction of dissolution rates under natural convection conditions. Additionally, the extent to which forced convection interferes with natural convection in a particular system, and the manner in which this effect changes with the magnitude of the forced convection should be examined. Following this, situations could be identified where the

contribution from natural convection is insignificant, thereby simplifying dissolution rate predictions for such situations.

6. Determination of relevant *in vivo* velocity magnitudes, viscosity values and pressure data would facilitate the design of an *in vitro* dissolution/drug release test which replicates these conditions for use in *in vitro in vivo* correlations. Simulations of hydrodynamics within a proposed test apparatus would facilitate its design in ensuring optimal location of a dosage form in order for it to be exposed to conditions simulating the *in vivo* situation.

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Appendices

Appendix 2

The visualisation of size functions on a face attached to a volume.

Gambit includes a facility which enables viewing of a size function by means of an isosurface reflecting the region of influence of the size function. The isosurface can be created any distance from the source entity so the effect of the size function with distance from the source entity can be seen. Although a size function when viewed appears to have an effect in every direction from the source entity, only the attachment entity is affected.

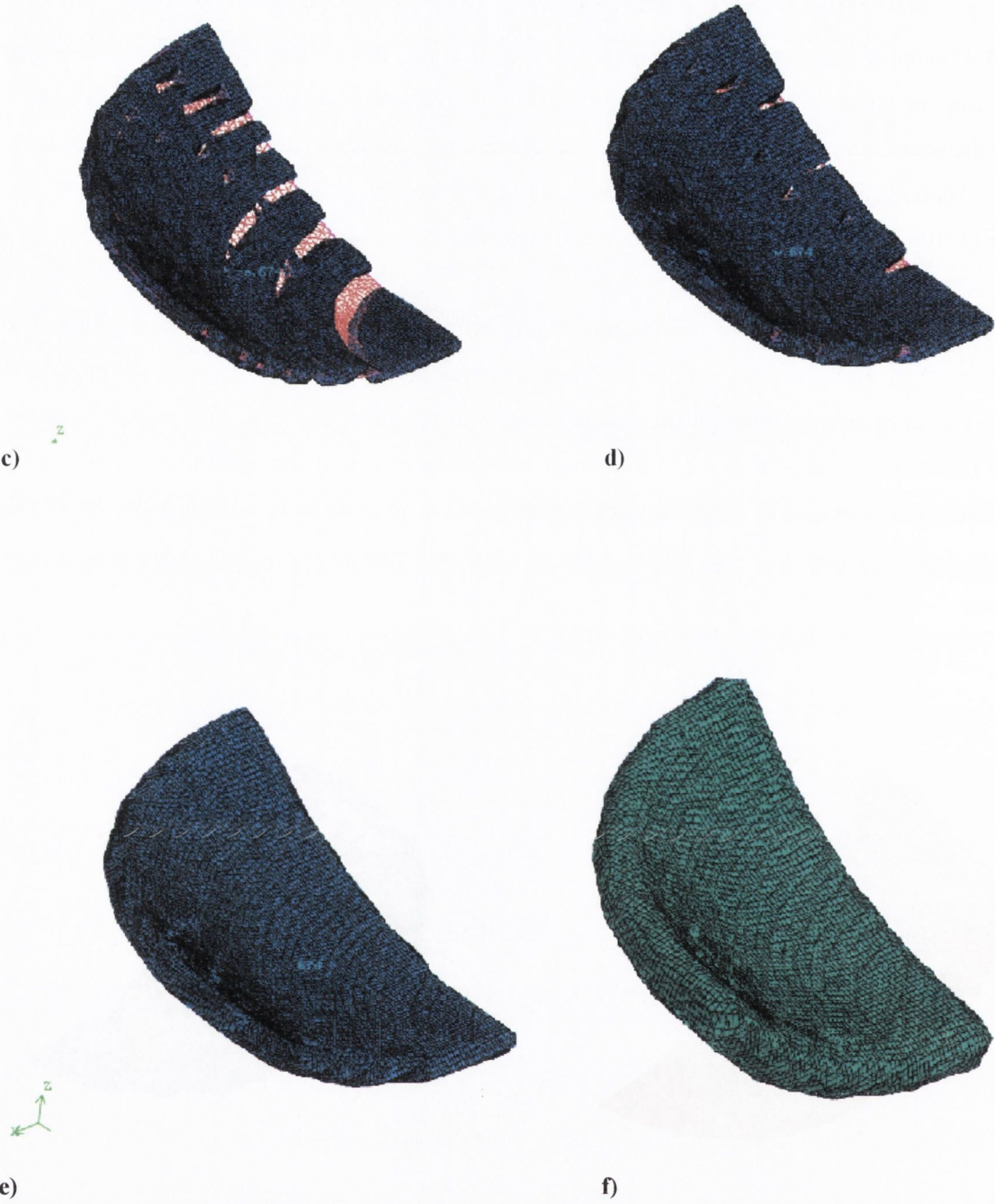
The following series of graphics (in Figure A.2.1) extracted from Gambit illustrate a typical size function effect from the outer wall of the lower quadrant below the plane (dividing the upper and lower reference frames) through the volume of this lower quadrant. The first picture is of the mesh on the source face, then a series of isosurfaces at increasing distances from the source face illustrate the size function. The image in Figure 2.3 is of the source face along with one of the side faces of this volume so the effect of the size function continuously through this volume can be seen.



a)



b)



Figures A.2.1.a-f. A series of isosurfaces illustrating the effect of the size function with increasing distance from the source entity.

Appendix 3

Procedure used to change a case and data file (containing a converged solution of the fluid flow) to a case and data file to be used to simulate mass transfer.

1. Create “tracer” - Materials panel – fluid - water (liquid) – name tracer – formula t1 – change/create – do not overwrite water (liquid).
2. Create Mixture – Materials panel – mixture – edit – add tracer, water (liquid) (bulk component (water (liquid))) must be at the bottom of the list).
3. Mixture properties – Density: volume weighted mixing law.
Viscosity: mass weighted mixing law.
Mass diffusivity: $1.236 \times 10^{-09} \text{ m}^2 \text{ s}^{-1}$.
Change/create.
4. Define models – Species transport: on.
Reactions: switch off volumetric, turn on wall surface.
5. Solve - Controls – solution – turn off flow, turn on tracer.
6. Define models - Solver – unsteady.
Energy – off.
7. Define Boundary conditions -
Tablet top and tablet sides:
Momentum: moving wall, velocity zero, rotational.
Species: change zero diffusive flux to Mass fraction of Tracer, value 1.
8. File – Write – autosave – save every 10 time steps.
9. Initialize - Time step size: 0.2 seconds.
Number of time steps: 60.
10. File - Write: case and data file (using different file name).
11. Initialize - Iterate.

Appendix 4

Samples of profiles from plots of mass fraction of tracer against distance from the compact surface at different compact locations, with exponential equation fitted.

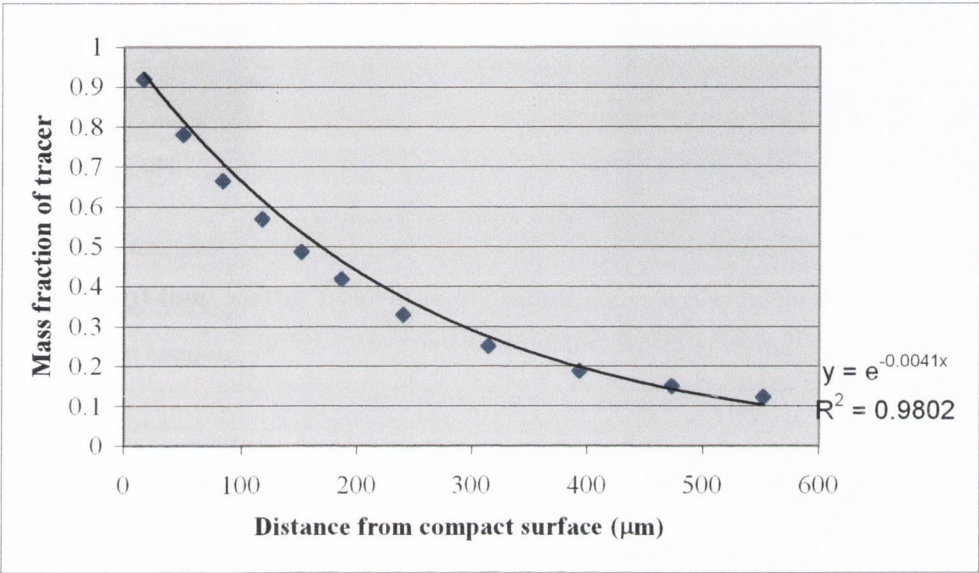


Figure A.4.1. Mass fraction of tracer vs. distance from compact surface (μm) from the top planar surface of the 3 mm compact in the central position, line y=1.

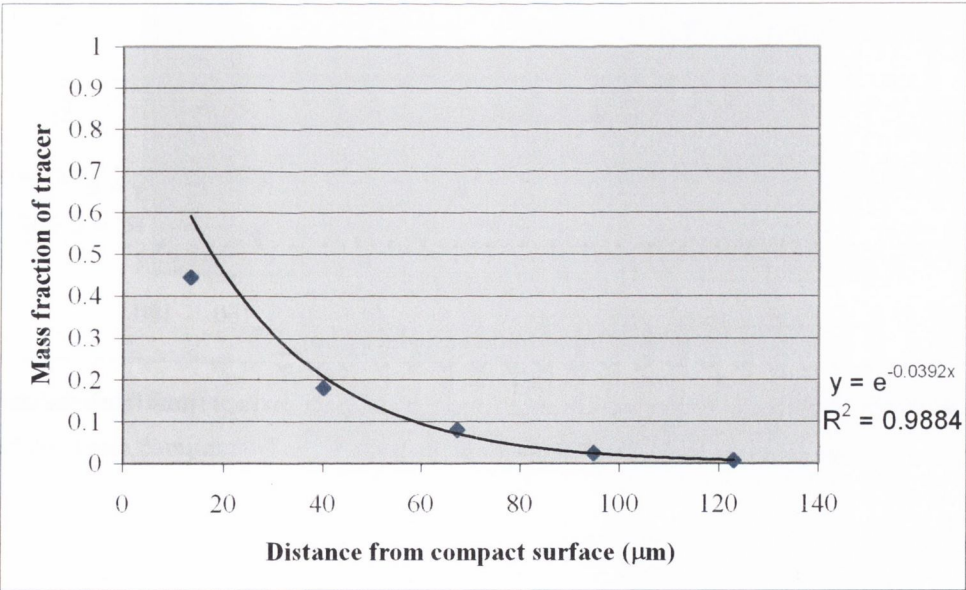


Figure A.4.2. Mass fraction of tracer vs. distance from compact surface (μm) from the curved side surface of the 3 mm compact in the central position, line z5.

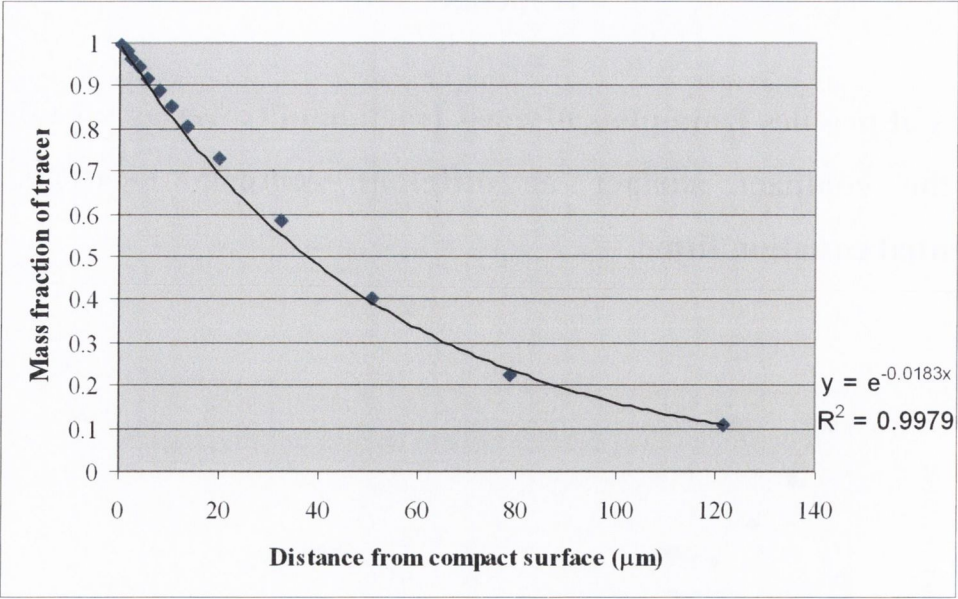


Figure A.4.3. Mass fraction of tracer vs. distance from compact surface (μm) from the top planar surface of the 8.5 mm compact in the central position, line y=6.

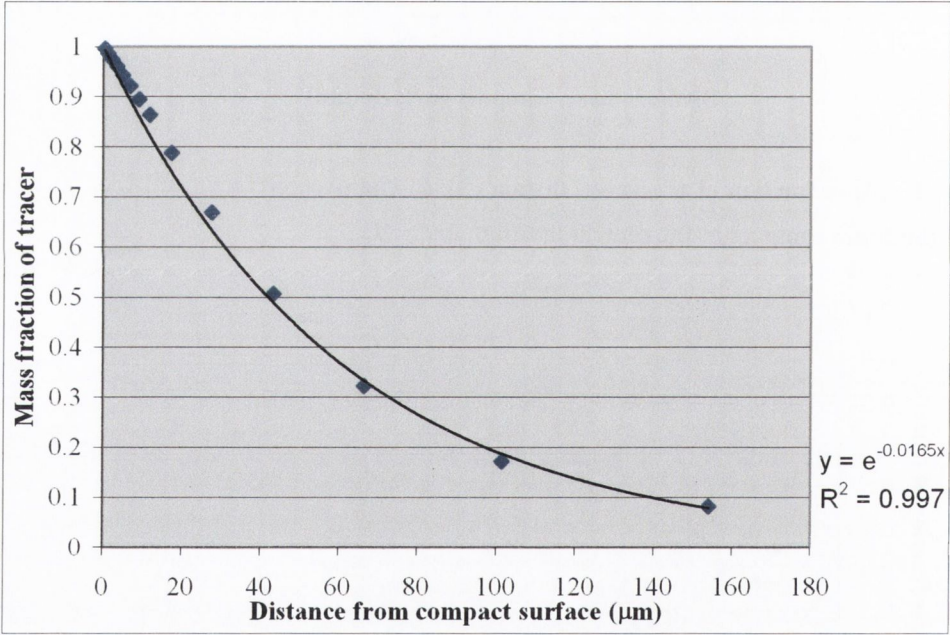


Figure A.4.4. Mass fraction of tracer vs. distance from the compact surface (μm) from the curved side surface of the 8.5 mm compact in the central position, line z8.

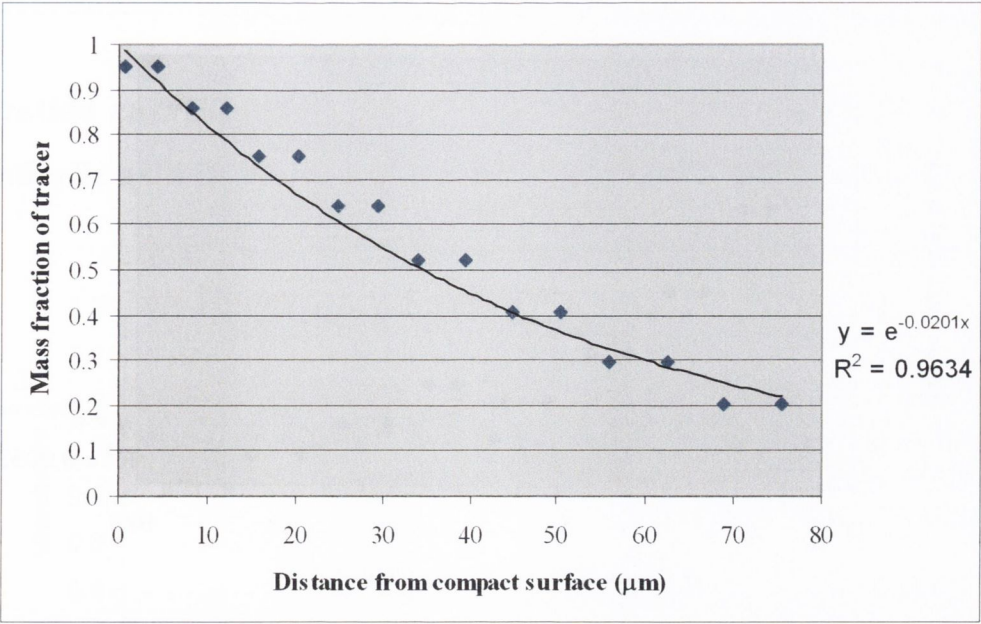


Figure A.4.5. Mass fraction of tracer vs. distance from compact surface (μm) from the top planar surface of the 3 mm compact in position 1, line $y=-2$.

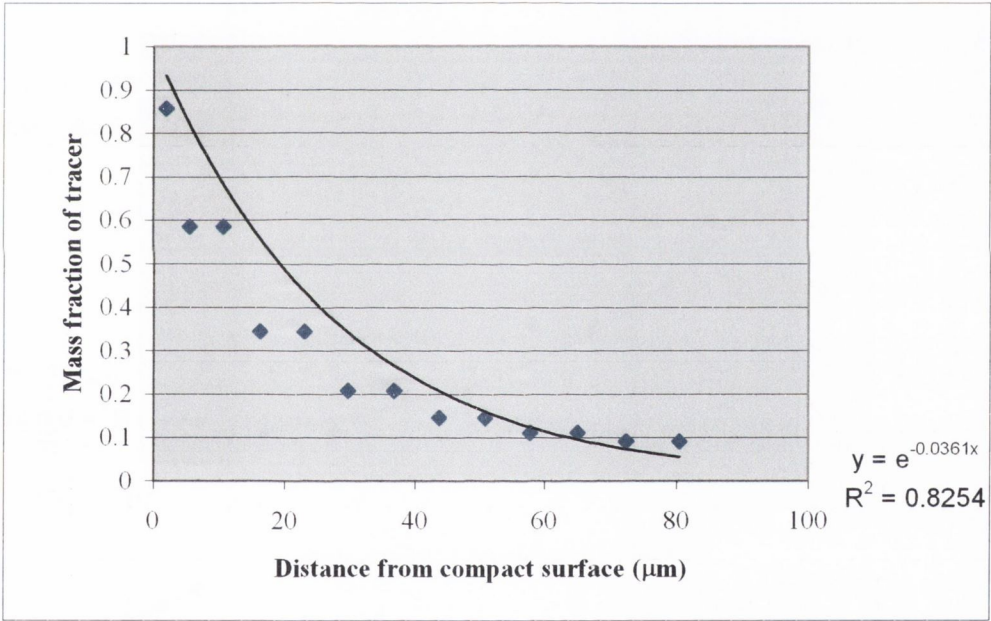


Figure A.4.6. Mass fraction of tracer vs. distance from compact surface (μm) from the curved side surface of the 3 mm compact in position 1, line $z7$, x -negative direction.

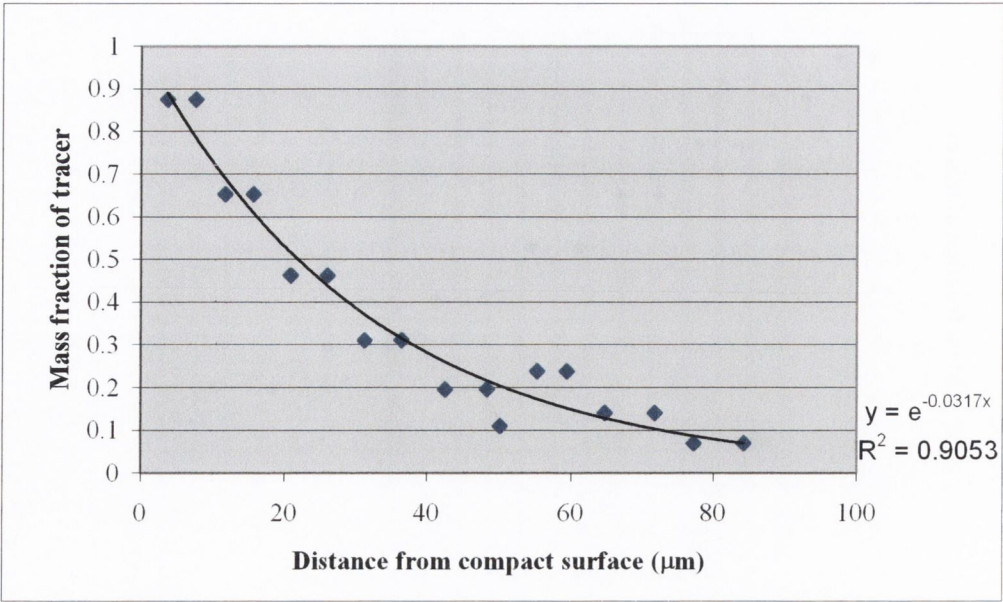


Figure A.4.7. Mass fraction of tracer vs. distance from compact surface (μm) from the top planar surface of the 3 mm compact in position 2, line x=-6.

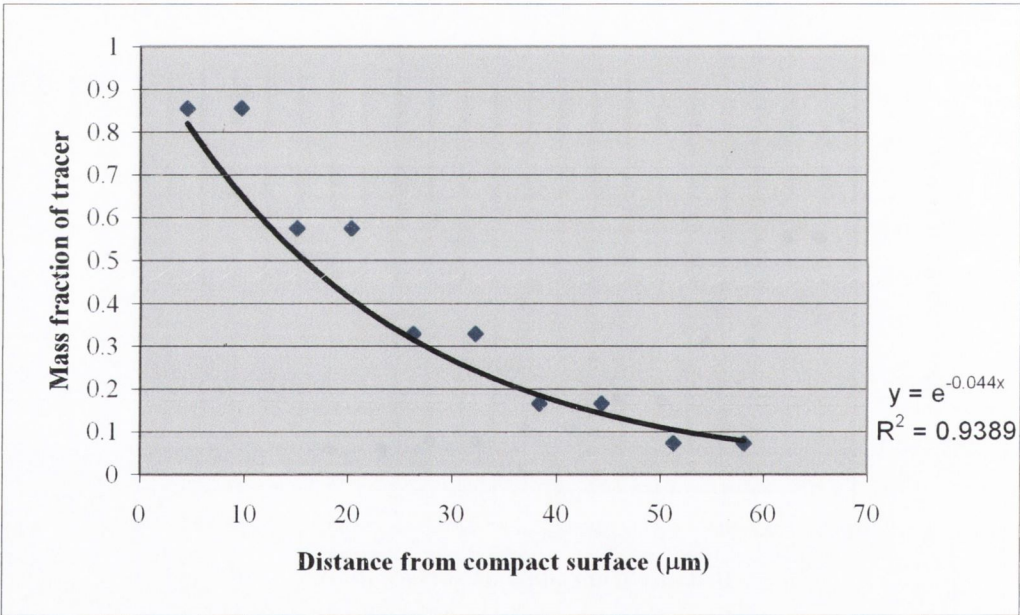


Figure A.4.8. Mass fraction of tracer vs. distance from compact surface (μm) from the curved side surface of the 3 mm compact in position 2, line z7, y-positive direction.

Appendix 5

Calibration curves used to determine the amounts dissolved of benzoic and salicylic acid in a sample.

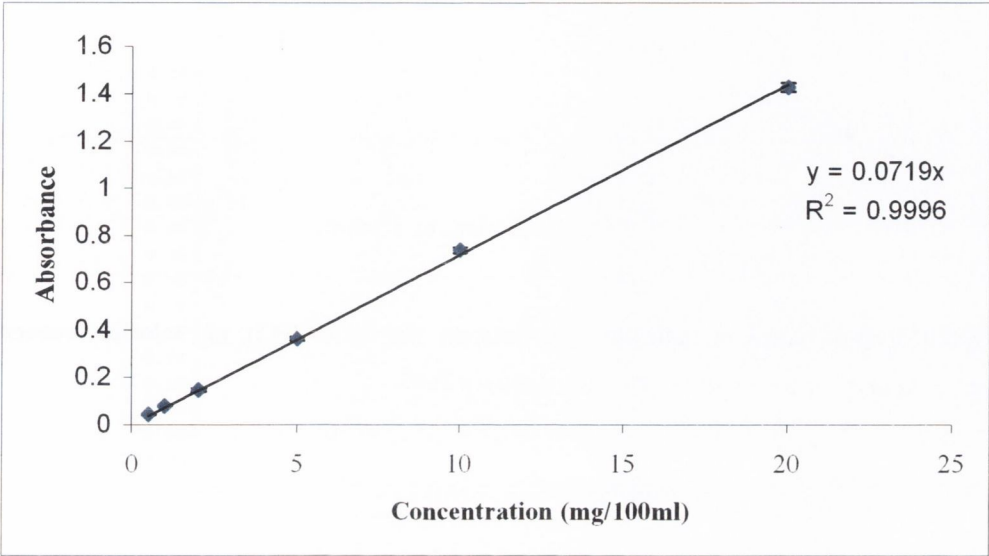


Figure A.5.1. Absorbance of benzoic acid solution (in 0.1M HCl) vs. solution concentration (mg/100ml). Analytical wavelength: 274 nm. February 2004.

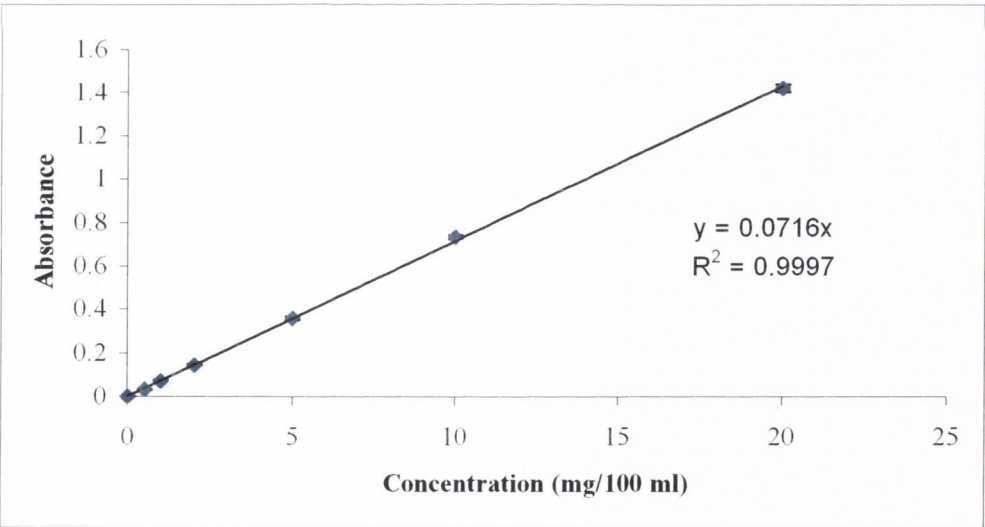


Figure A.5.2. Absorbance of benzoic acid solution (in 0.1M HCl) vs. solution concentration (mg/100ml). Analytical wavelength: 274 nm. July 2004.

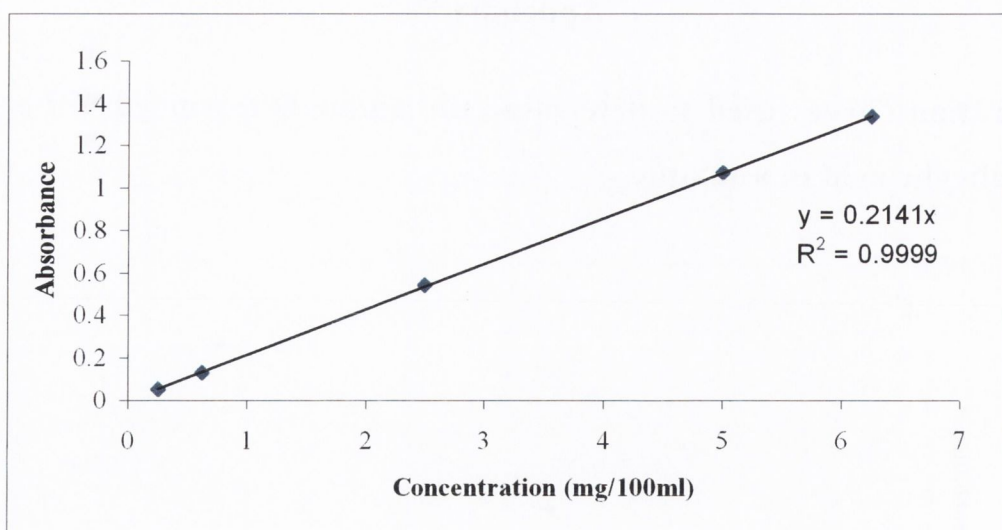


Figure A.5.3. Absorbance of salicylic acid solution (in 0.1M HCl) vs. solution concentration (mg/100ml). Analytical wavelength: 296 nm. January 2005.

Appendix 6

Laser Doppler velocimetry data (Bocanegra et al., 1990) and corresponding graphs from validated CFD models.

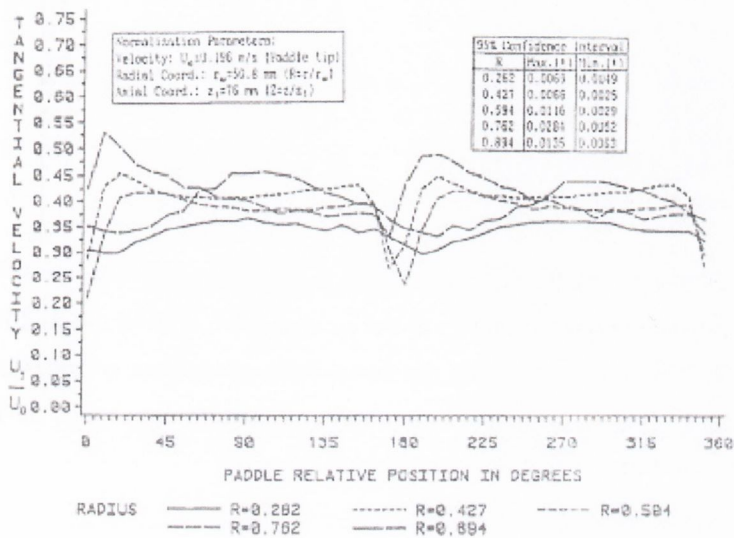


Figure A.6.1.a. Tangential velocity normalised to the velocity of the paddle tip at the axial position of $Z=-0.066$ and radial positions of $R = 0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

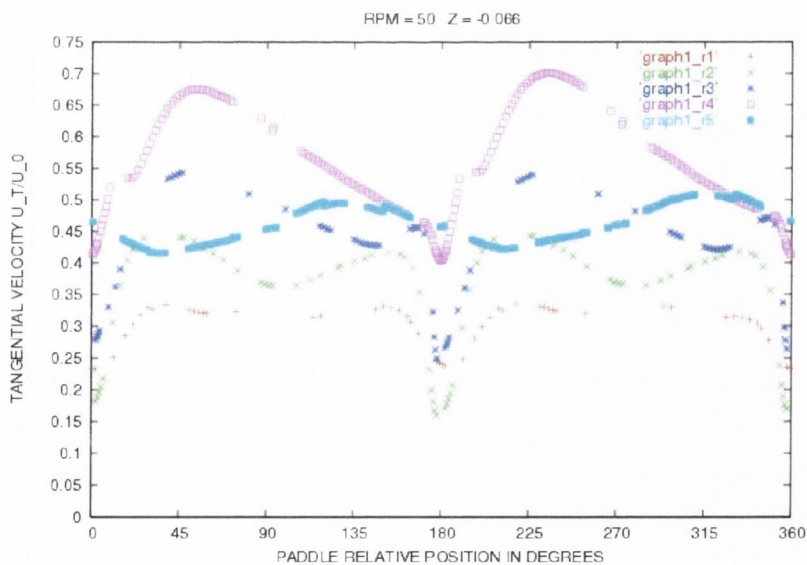


Figure A.6.1.b. Normalised tangential velocity at the axial position of $Z=-0.066$ and radial positions of $R = 0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

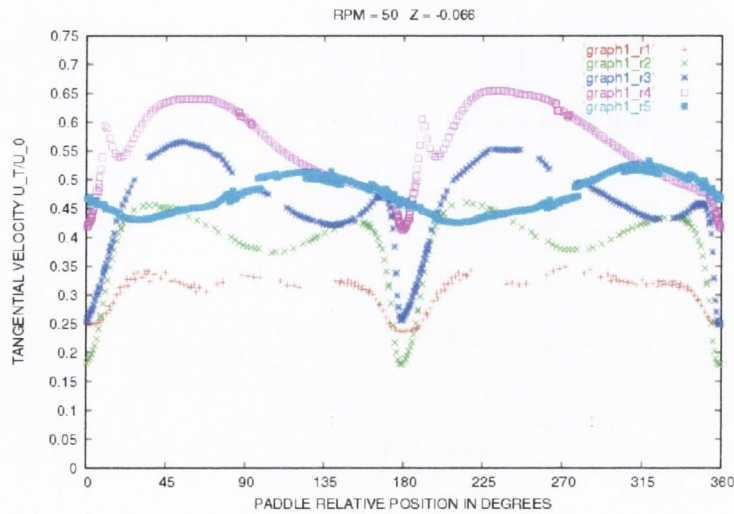


Figure A.6.1.c. Normalised tangential velocity at the axial position of $Z=-0.066$ and radial positions of $R = 0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in central position defined as fluid.

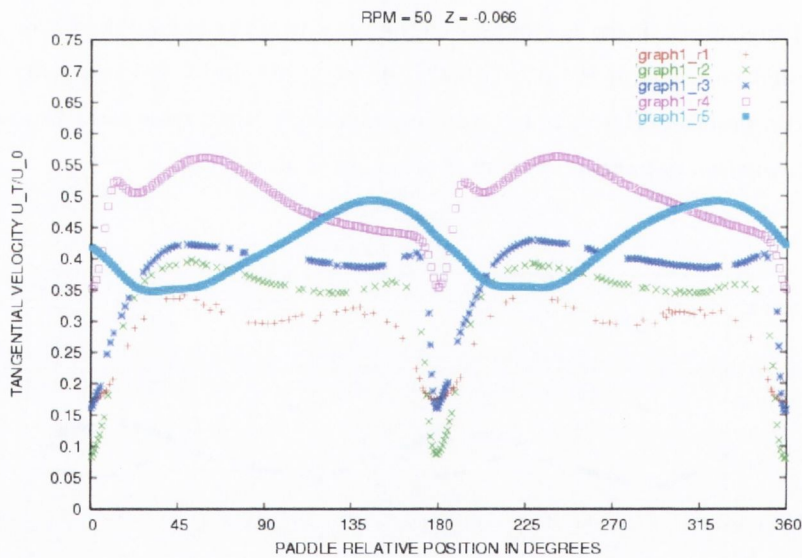


Figure A.6.1.d. Normalised tangential velocity at the axial position of $Z=-0.066$ and radial positions of $R = 0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 1 defined as fluid.

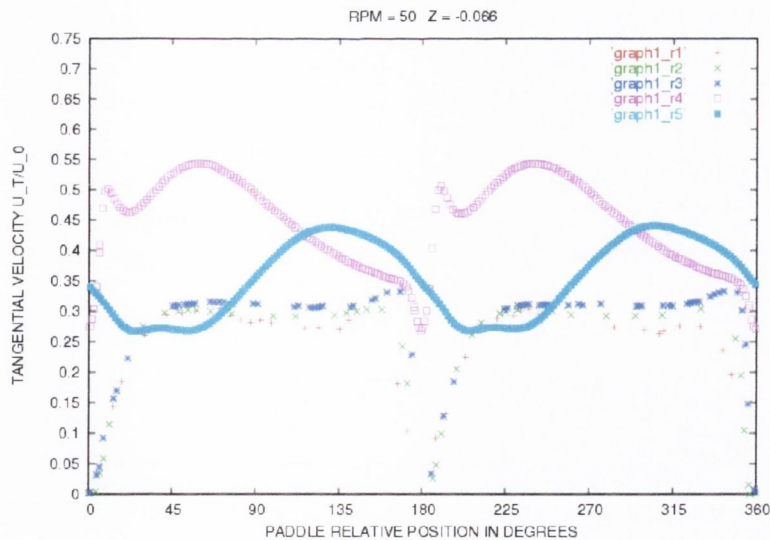


Figure A.6.1.e. Normalised tangential velocity at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 2 defined as fluid.

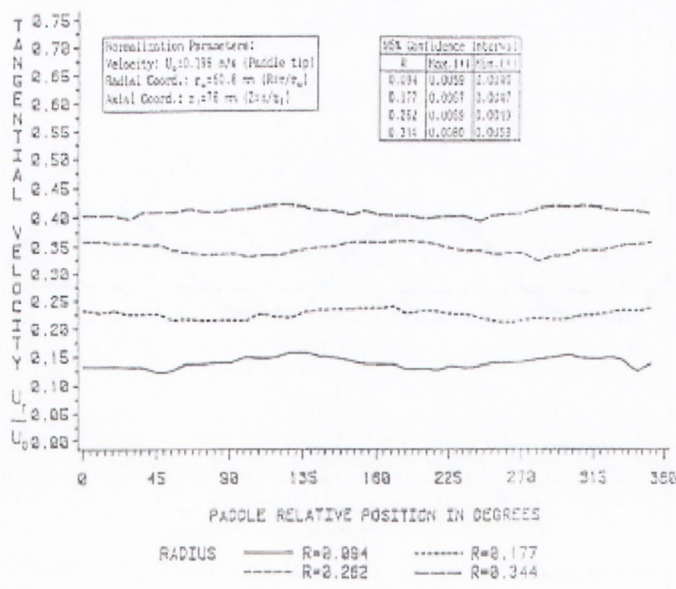


Figure A.6.2.a. Tangential velocity normalised to the velocity of the paddle tip at the axial position of $Z=-0.605$ and radial positions of $R=0.084$, 0.177 , 0.262 , and 0.344 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

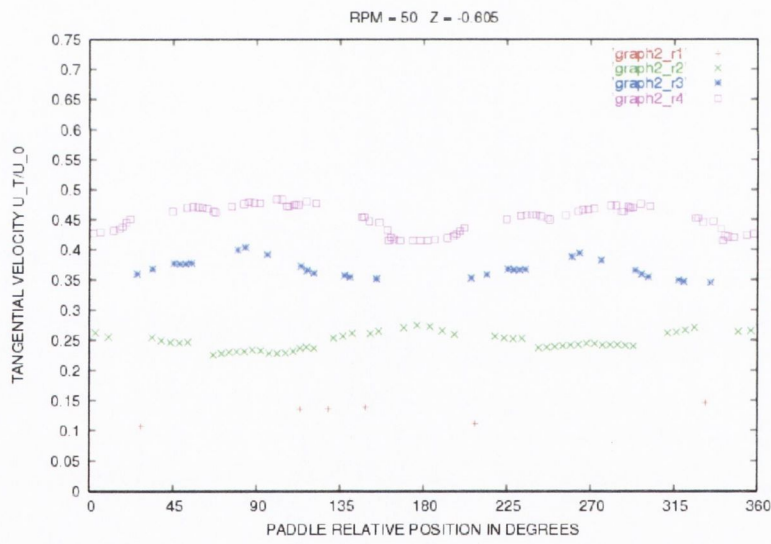


Figure A.6.2.b. Normalised tangential velocity at the axial position of $Z=-0.605$ and radial positions of $R=0.084$, 0.177 , 0.262 and 0.344 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

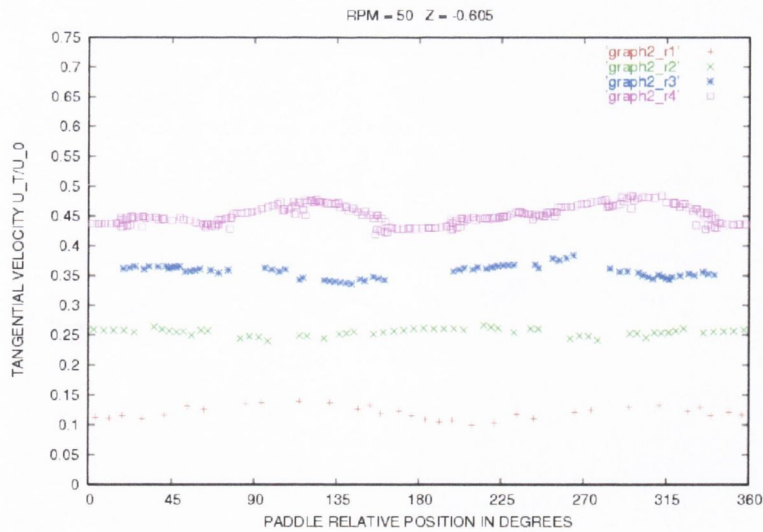


Figure A.6.2.c. Normalised tangential velocity at the axial position of $Z=-0.605$ and radial positions of $R=0.084, 0.177, 0.262$ and 0.344 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in central position defined as fluid.

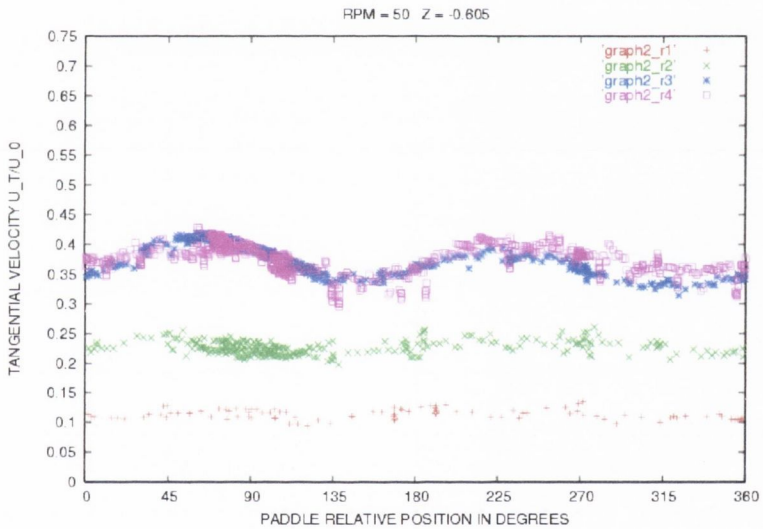


Figure A.6.2.d. Normalised tangential velocity at the axial position of $Z=-0.605$ and radial positions of $R=0.084, 0.177, 0.262$ and 0.344 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 1 defined as fluid.

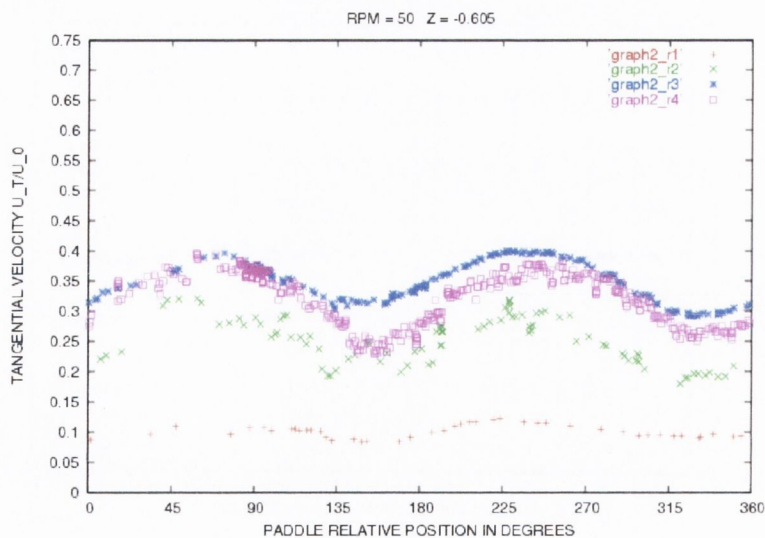


Figure A.6.2.e. Normalised tangential velocity at the axial position of $Z=-0.605$ and radial positions of $R=0.084, 0.177, 0.262$ and 0.344 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 2 defined as fluid.

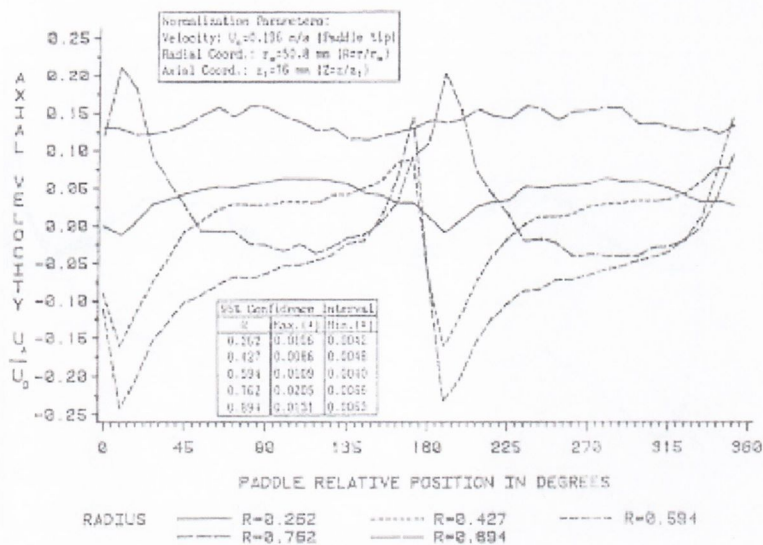


Figure A.6.3.a. Axial velocity normalised to the velocity of the paddle tip at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

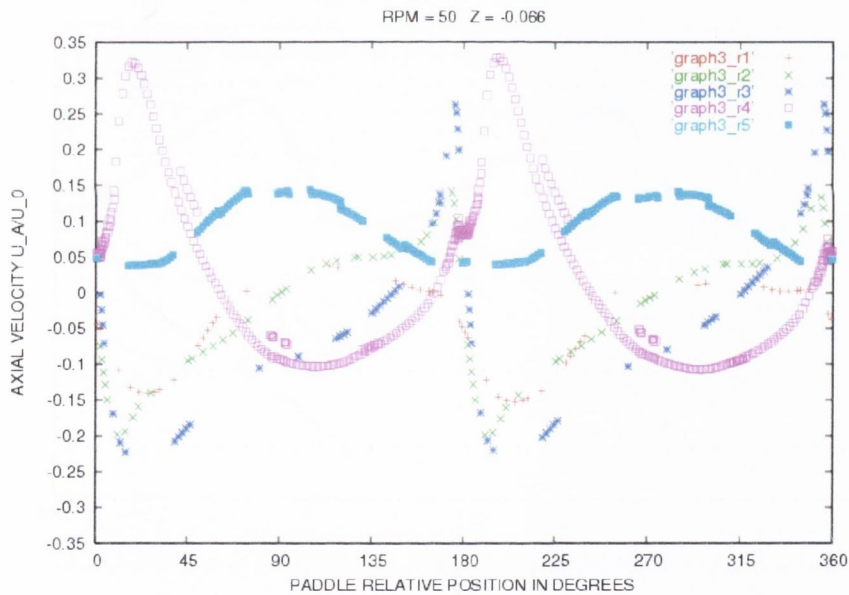


Figure A.6.3.b. Normalised axial velocity at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

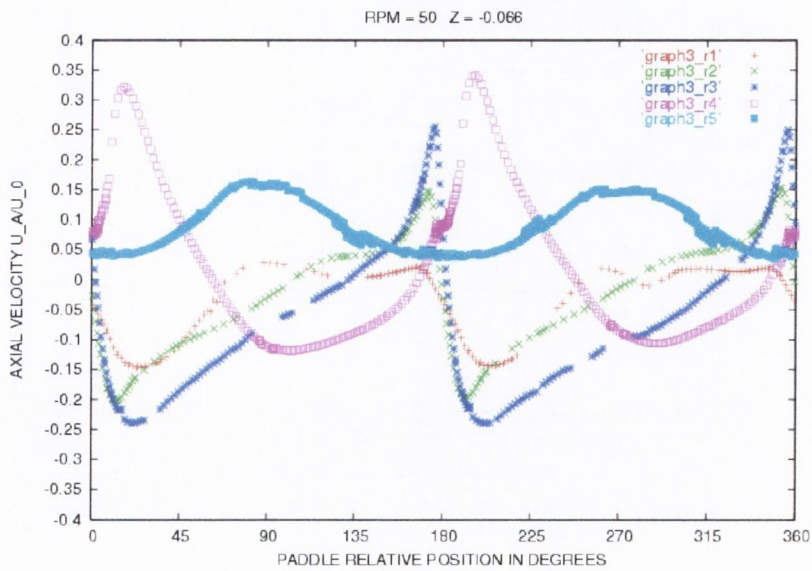


Figure A.6.3.c. Normalised axial velocity at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in central position defined as fluid.

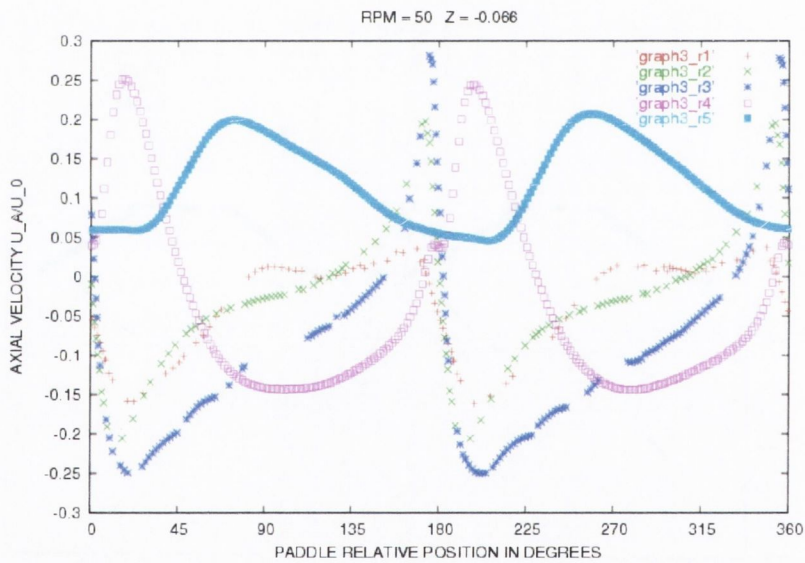


Figure A.6.3.d. Normalised axial velocity at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 1 defined as fluid.

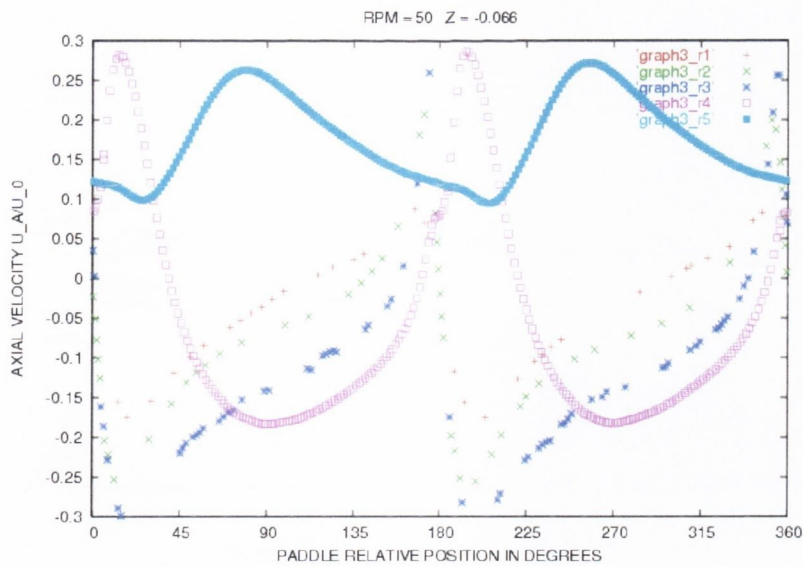


Figure A.6.3.e. Normalised axial velocity at the axial position of $Z=-0.066$ and radial positions of $R=0.262, 0.427, 0.594, 0.762$ and 0.894 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 2 defined as fluid.

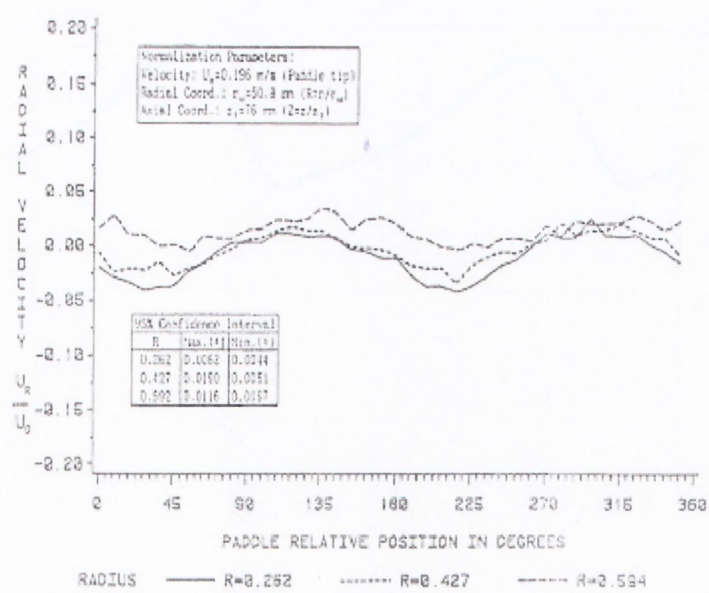


Figure A.6.4.a. Radial velocity normalised to the velocity of the paddle tip at the axial position of $Z=-0.461$ and radial positions of $R = 0.262, 0.427$ and 0.594 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

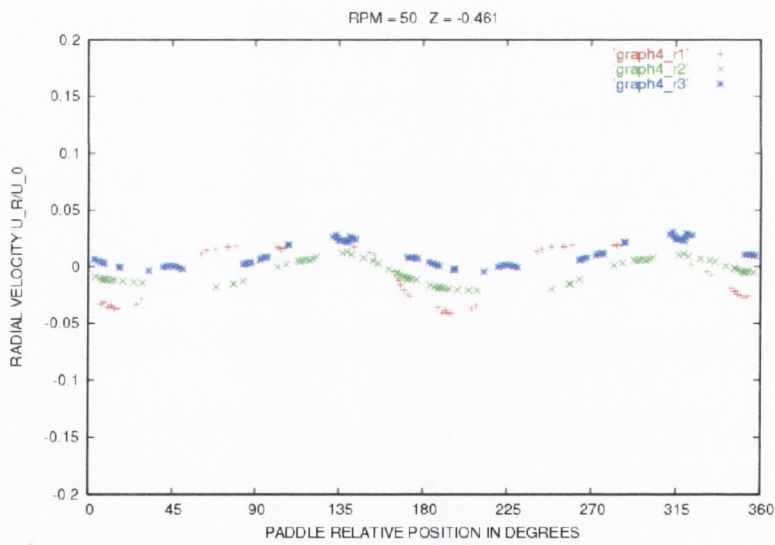


Figure A.6.4.b. Normalised radial velocity at the axial position of $Z=-0.461$ and radial positions of $R = 0.262, 0.427$ and 0.594 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

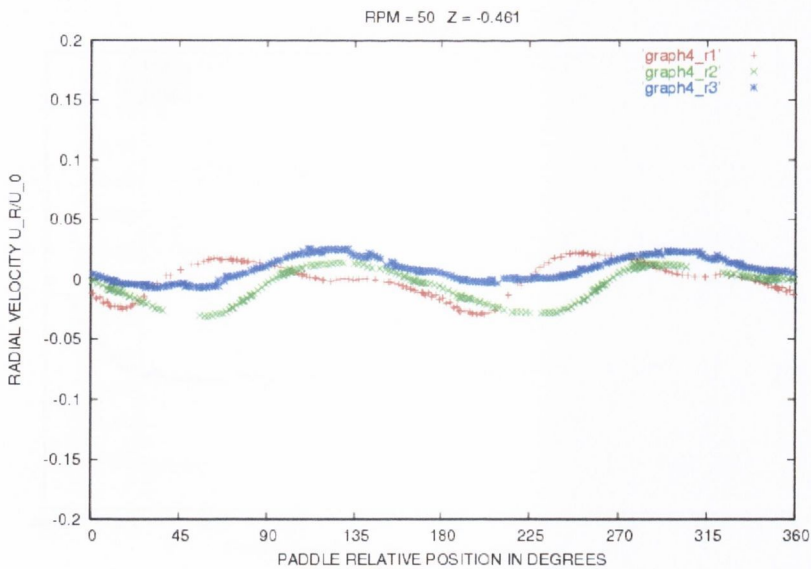


Figure A.6.4.c. Normalised radial velocity at the axial position of $Z=-0.461$ and radial positions of $R=0.262, 0.427$ and 0.594 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in the central position defined as fluid.

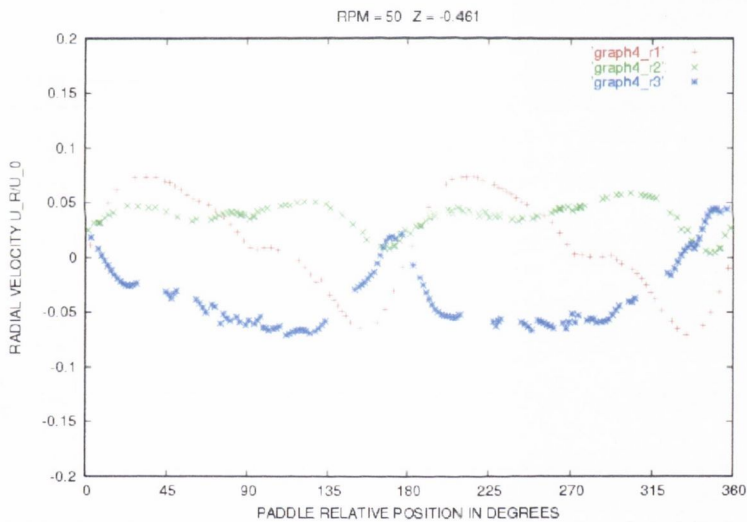


Figure A.6.4.d. Normalised radial velocity at the axial position of $Z=-0.461$ and radial positions of $R=0.262, 0.427$ and 0.594 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in the position 1 defined as fluid.

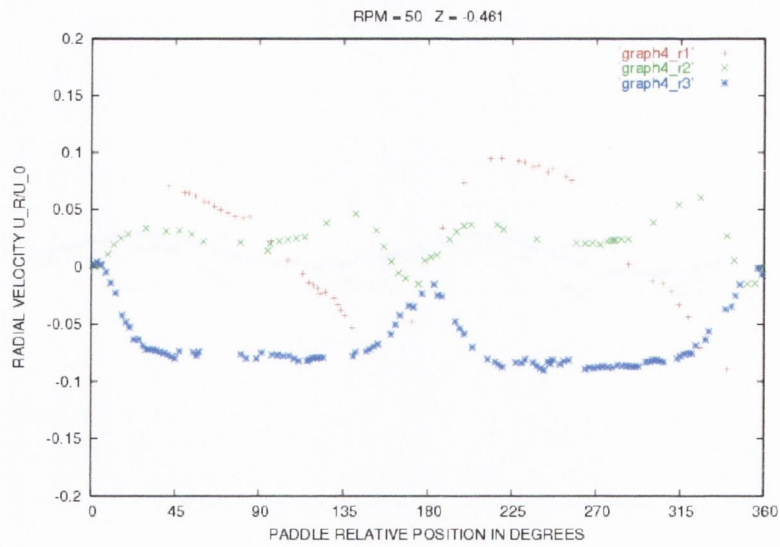


Figure A.6.4.e. Normalised radial velocity at the axial position of $Z=-0.461$ and radial positions of $R=0.262, 0.427$ and 0.594 using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in the position 2 defined as fluid.

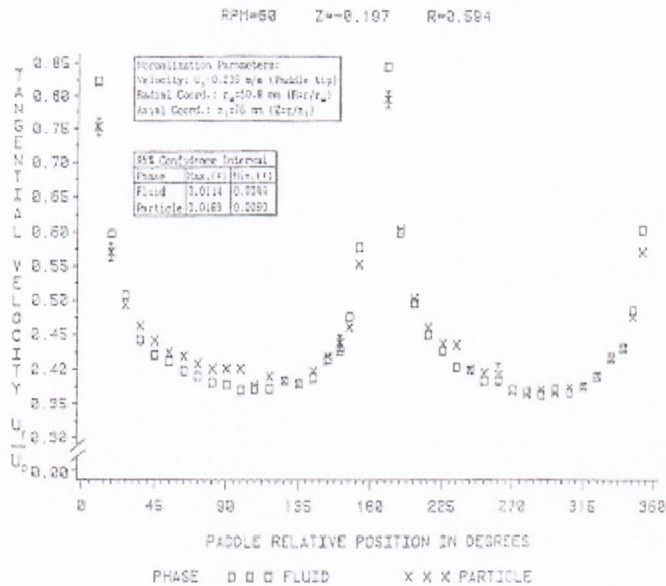


Figure A.6.5.a. Tangential velocity normalised to the velocity of the paddle tip at the axial position of $Z=-0.197$ and radial position of $R = 0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

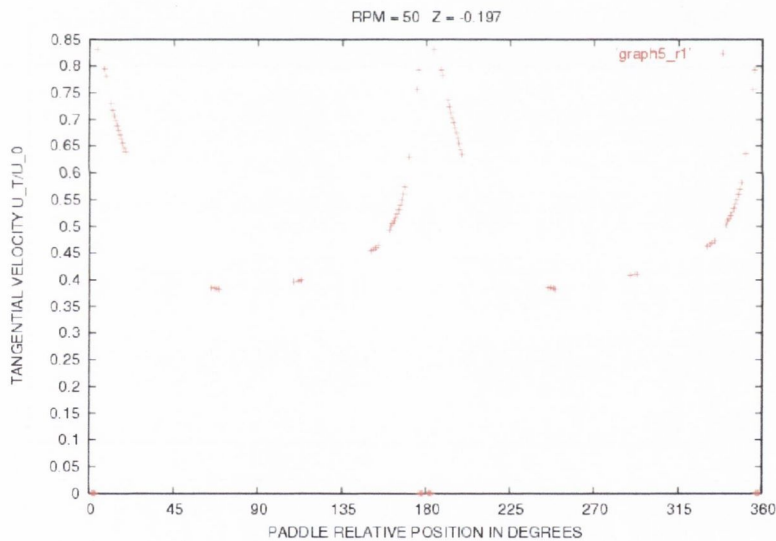


Figure A.6.5.b. Normalised tangential velocity at the axial position of $Z=-0.197$ and radial position of $R = 0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

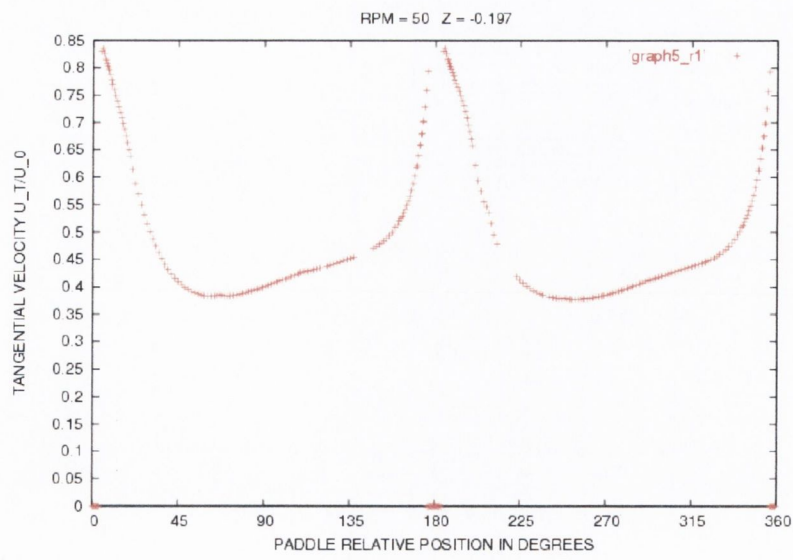


Figure A.6.5.c. Normalised tangential velocity at the axial position of $Z=-0.197$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in the central position defined as fluid.

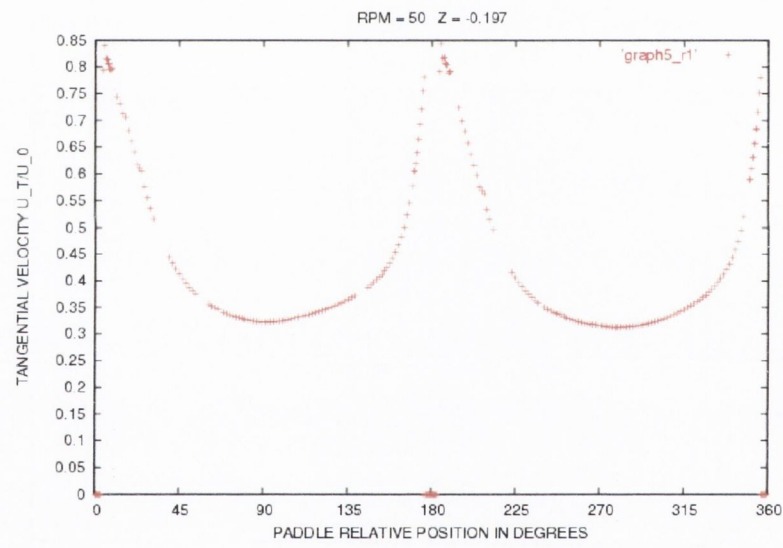


Figure A.6.5.d. Normalised tangential velocity at the axial position of $Z=-0.197$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 1 defined as fluid.

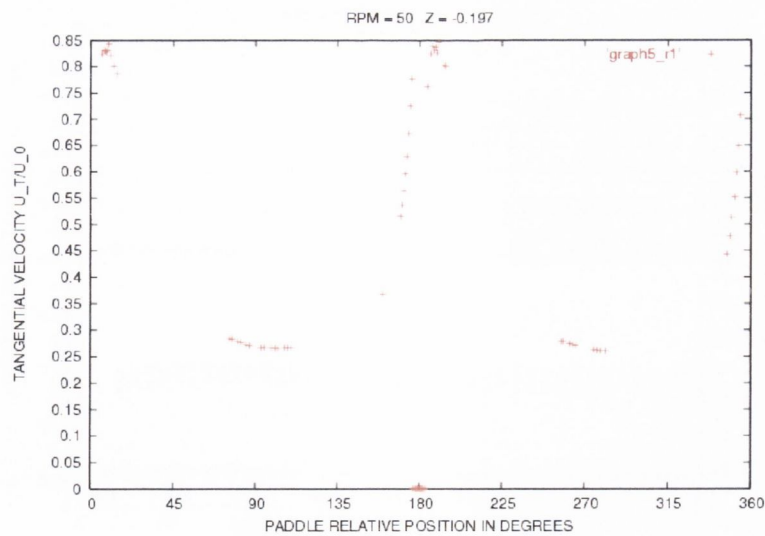


Figure A.6.5.e. Normalised tangential velocity at the axial position of $Z=-0.197$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle (°). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 2 defined as fluid.

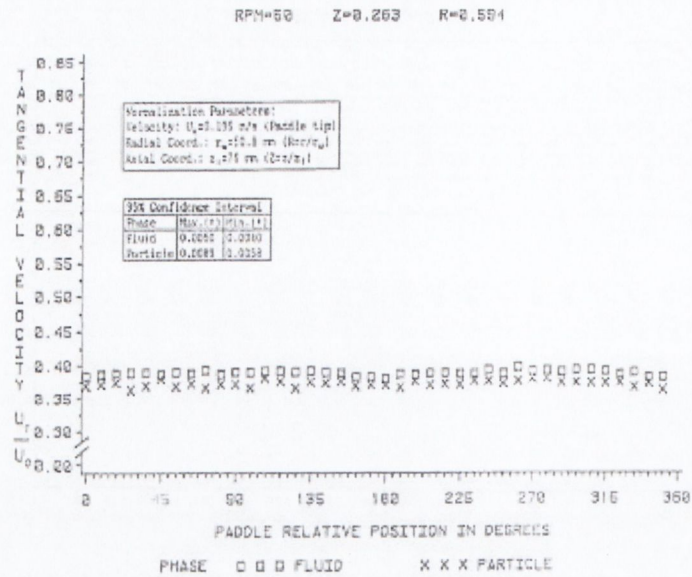


Figure A.6.6.a. Tangential velocity normalised to the velocity of the paddle tip at the axial position of $Z=0.263$ and radial position of $R = 0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from laser Doppler velocimetry studies, paddle dissolution apparatus, 50 rpm (Bocanegra et al., 1990).

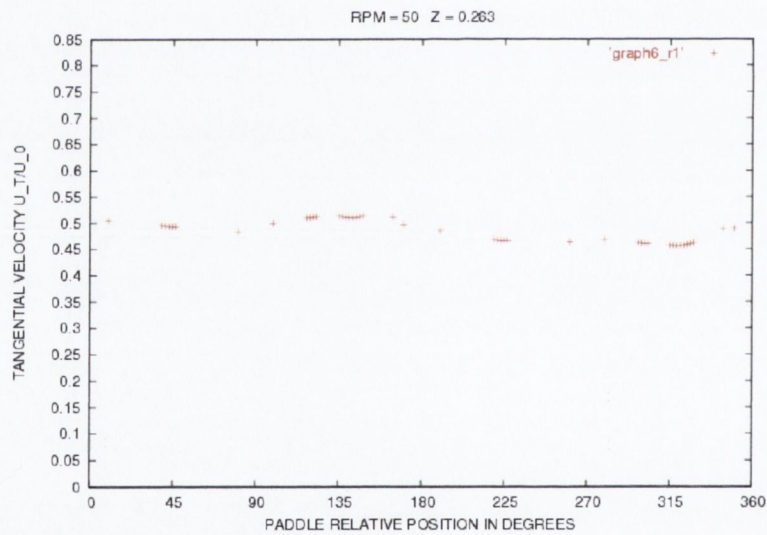


Figure A.6.6.b. Normalised tangential velocity at the axial position of $Z=0.263$ and radial position of $R = 0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, no compact.

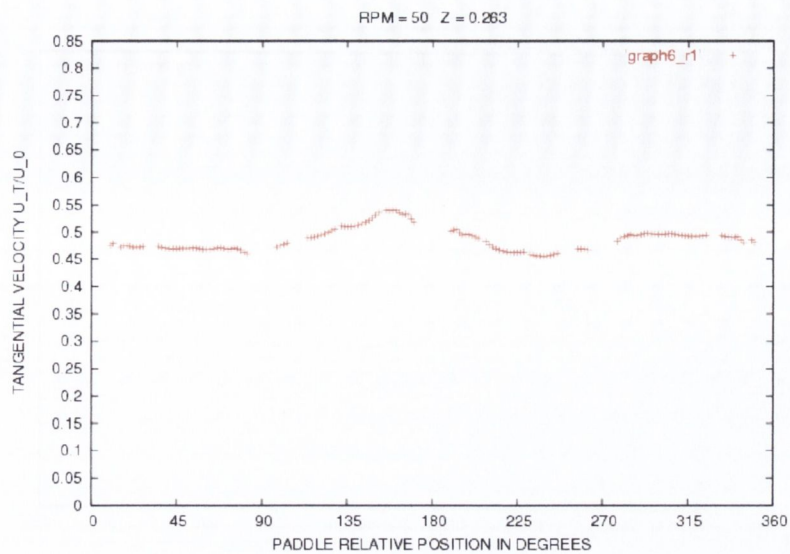


Figure A.6.6.c. Normalised tangential velocity at the axial position of $Z=0.263$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in the central position defined as fluid.

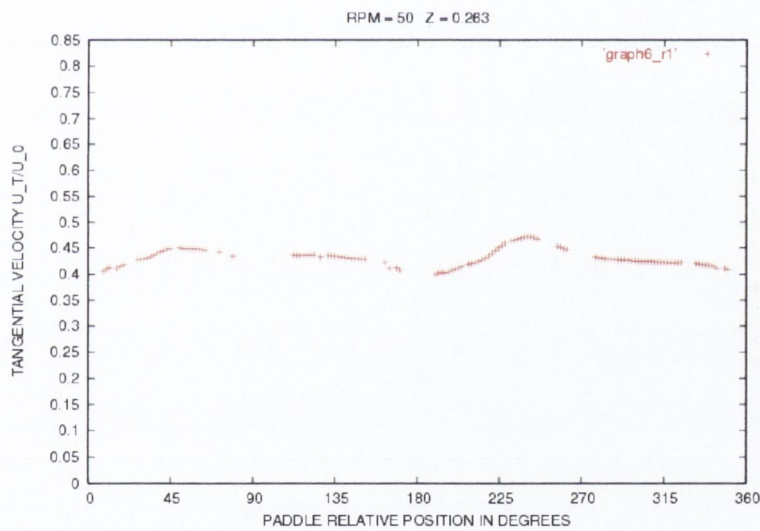


Figure A.6.6.d. Normalised tangential velocity at the axial position of $Z=0.263$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 1 defined as fluid.

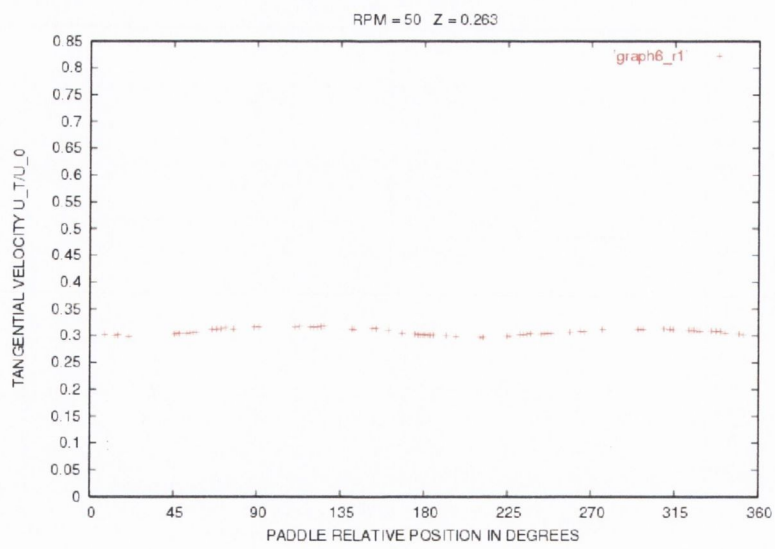


Figure A.6.6.e. Normalised tangential velocity at the axial position of $Z=0.263$ and radial position of $R =0.594$ using the normalised co-ordinate system, vs. position relative to the rotating paddle ($^{\circ}$). Data from CFD simulation of paddle apparatus, 50 rpm, compact in position 2 defined as fluid.