THE ROLE OF SURFACE ENERGETICS IN
THE MIXING OF POWDERS

BY
NATHALIE MARILYN WANG AHFAT
BPharm., MRPharmS
LONDON SCHOOL OF PHARMACY

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To my parents
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ABSTRACT

The mixing of powders is governed by the presence of interparticulate forces, which are dependent on the surface nature of powders. Surface energy, which provides a measure of the hydrophilic and hydrophobic nature of surfaces, was found to play a significant role in the behaviour of powders in mixes. Preliminary work involved the use of surface energetics to predict the spreading behaviour in binary mixes of iron oxide with three excipients: microcrystalline cellulose, magnesium stearate and titanium dioxide. Subsequent work was carried out on binary and tertiary mixes of an active compound, zamifenacin, with starch and/or lactose. The surface nature of the powders was determined using the Wilhelmy plate (DCA) technique, sessile drop technique (DAT), inverse gas chromatography (IGC) and triboelectric charging. These techniques (except for triboelectric charging) involve the use of non-polar and polar liquids to probe the surfaces of powders. Spreading coefficients determined from the DCA data, correctly predicted the spreading behaviour of powders in binary and tertiary systems of iron oxide, as confirmed by visual inspection and scanning electron microscopy of the mixes.

The suitability of each technique in characterising surfaces of pharmaceutical powders was assessed and IGC was found to be superior to the DCA and DAT techniques since IGC relied on the direct interaction between the vapour probes and the powder surface. The interaction parameter (I) derived from IGC and the electrostatic charges developed on charging with stainless steel predicted that the interaction between zamifenacin and starch would be more favourable than between zamifenacin and lactose. These predictions were confirmed by homogeneity studies on binary and tertiary mixes of zamifenacin using high-pressure liquid chromatography and near-infrared spectroscopy (NIRS). NIRS was found to be a good alternative analytical technique for monitoring the mixing of powders, in particular the order of addition of excipients to zamifenacin.
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<tr>
<td>( \theta )</td>
<td>contact angle</td>
</tr>
<tr>
<td>( \phi )</td>
<td>interaction parameter</td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>permittivity of medium</td>
</tr>
<tr>
<td>( \delta )</td>
<td>solubility parameter</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>spreading coefficient</td>
</tr>
<tr>
<td>( \Sigma )</td>
<td>sum of</td>
</tr>
<tr>
<td>( \gamma^e )</td>
<td>electron-acceptor contribution to surface energy (or tension)</td>
</tr>
<tr>
<td>( \gamma^o )</td>
<td>electron-donor contribution to surface energy (or tension)</td>
</tr>
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<td>( \varepsilon_0 )</td>
<td>permittivity of free space</td>
</tr>
<tr>
<td>( \sigma_0 )</td>
<td>standard deviation of an unmixed system</td>
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<td>( \theta_a )</td>
<td>advancing contact angle</td>
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<tr>
<td>( \sigma_a^2 )</td>
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</tr>
<tr>
<td>( \sigma_{AA} )</td>
<td>strengths of cohesion within A</td>
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<td>( \gamma^{AB} )</td>
<td>Lewis acid-Lewis base contribution to surface energy (or tension)</td>
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<tr>
<td>( \sigma_{AB} )</td>
<td>strengths of adhesion between A and B</td>
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<tr>
<td>( \phi_B )</td>
<td>work function of B</td>
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<td>( \sigma_{BB} )</td>
<td>strengths of cohesion within B</td>
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<tr>
<td>( \gamma^d )</td>
<td>dispersion component of surface energy (or tension)</td>
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<tr>
<td>( \delta_d )</td>
<td>dispersive contribution to solubility parameter</td>
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<tr>
<td>( \sigma_d )</td>
<td>standard deviation of drug content</td>
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<tr>
<td>( \pi_e )</td>
<td>equilibrium spreading pressure</td>
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<td>( \Delta G )</td>
<td>Gibbs free energy</td>
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<tr>
<td>( \Delta G_{ads} )</td>
<td>free energy of adsorption</td>
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<tr>
<td>( \Delta G_{ads}^{AB} )</td>
<td>specific free energy of adsorption</td>
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<tr>
<td>( \Delta G_{ads}^D )</td>
<td>dispersive component of free energy of adsorption</td>
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<tr>
<td>( \Delta G_{des} )</td>
<td>free energy of desorption</td>
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<tr>
<td>( \Delta H )</td>
<td>enthalpy change</td>
</tr>
<tr>
<td>( \delta_h )</td>
<td>hydrogen bonding contribution to solubility parameter</td>
</tr>
</tbody>
</table>
\( \gamma_{LV} \) surface tension of liquid in equilibration with vapour
\( \gamma_{LW} \) Lifshitz-van der Waals contribution to surface energy (or tension)
\( \theta_m \) measured contact angle
\( \sigma_m^2 \) variance of the mixing process
\( \gamma^p \) polar component of surface energy (or tension)
\( \delta_p \) polar contribution to solubility parameter
\( \sigma_{POR}^2 \) variance of a partially ordered random mix
\( \theta_r \) receding contact angle
\( \sigma_R \) standard deviation of a completely random system
\( \Delta S \) entropy change
\( \sigma_s^2 \) variance due to sampling
\( \gamma_{SL} \) interfacial tension of liquid with solid
\( \gamma_{SV} \) surface energy of solid with equilibrium with vapour
\( \sigma_i^2 \) variance of a mix
\( \gamma_{TOT} \) surface energy (or tension)
\( \sigma_{TOT}^2 \) variance of a total mix
\( \sigma_c \) standard deviation of zamifenacin content
\( a \) surface area of liquid probe molecules
\( A \) total surface area
\( AN \) acceptor number
\( AN^* \) corrected acceptor number
\( B \) constant
\( b \) number of moles of water sorbed per gram of powder at the saturated vapour pressure of water at 25 °C
\( c \) BET constant
\( C \) concentration of probe in gas phase
\( \text{con} \) condensation
\( \Gamma \) concentration of probe on solid surface
\( C_v \) coefficient of variation
\( d \) drug content per sample
\( D \) flow rate
\( DN \) donor number
\( E \) mean drug content of zamifenacin
\( F \) force recorded by DCA microbalance
f  weight fraction of each component within a given particle size range

F_q  force exerted between two charged bodies

g  gravity

G  percentage of one component in mix

g_1, g_2  constants

H  enthalpy

H_l  homogeneity index of a mix with standard deviation of 1%

H_i  homogeneity index

Hom  homogeneity

I  interaction parameter

i  rows of spectra

J  correction factor

j  wavelengths in a spectrum

K_A  acid parameter

K_{ads}  equilibrium constant

K_b  bulk partition coefficient

K_D  basic parameter

K_s  surface partition coefficient

l  liquid

L  loading

M_i  mixing index

mon  monolayer

N  Avogadro’s number

n  number of particles in sample

n_i  mean of spectrum z_i

p  perimeter

P  pressure

P_0  atmospheric pressure

P_i  pressure at inlet of chromatographic column

P_{s,g}  vapour pressure of probe in gaseous state

P_{s,s}  vapour pressure of probe in equilibrium with the standard state

q  point charge

q'  image charge of q

r  distance
R gas constant
RH relative humidity
s solid
S standard deviation of mix
$S_a$ specific surface area
$s_i$ standard deviation of spectrum $z_i$
T temperature
$T'$ transpose
$t_0$ retention volume of methane
$t_r$ retention volume of probe
U internal energy
V volume
$V_N$ net retention volume
W sample weight
w weight of one particle
$W_1$ sample weight required to give a standard deviation of 1%
$W_{ads}$ work of adhesion
$W_{coh}$ work of cohesion
x proportion of X particles in mix
$x_d$ fractional non-polarity
$x_p$ fractional polarity
y proportion of Y particles in mix
$y_i$ standard normal variate transformed spectrum of $z_i$
Z matrix of spectra
$z_i$ raw near-infrared spectrum
1. INTRODUCTION

Powder mixing is one of the most frequently used operations in the production of dosage forms. It is such a simple task yet, so complex in itself that scientists have spent more than 50 years studying and optimising the factors that influence the mixing process. Problems encountered during the mixing of solids are solved in a trial and error manner and there are no set controls to which mixes or their components are subjected, either prior to or during in-process manufacture, to determine the potential factors that may be responsible for the problems. Considering that mixing is involved in the manufacture of various dosage forms of which solid dosage forms account for 90%, it is essential that the problems faced in the process are resolved in a logical manner.

In a typical pharmaceutical mixing process, an active compound is blended with several excipients for a certain length of time until the different components of the mixture are uniformly distributed. The addition of excipients is essential to improve the performance of the mix. Some of the most commonly used excipients are: lactose, microcrystalline cellulose which are added to increase the bulk of the powder and improve handling qualities; starch used as a disintegrant and magnesium stearate to prevent adhesion of powder to metal surfaces and ensure the smooth production of the final dosage forms. The well-blended mix is then transferred to a hopper and to a tablet press or encapsulator for the production of the final dosage forms. If one of the processes in the production line is inadequate, the quality of the resulting mix would be affected and the finished products rejected. Hence, it is of vital importance to achieve and maintain homogeneous blends in particular if the dosage forms being produced contain small amounts of a very potent drug.

The quality of the resulting mix depends on a number of factors such as the order of mixing of the drug with the excipients, the mixing time, the type of mixer used, the blender loading, the size, shape, density and surface properties of the drug and excipients. These can be subdivided broadly into two categories: (i) manufacturing processes and equipment and (ii) properties of powders and excipients. All these factors
must be concurrently optimal for a homogeneous mix to be produced. The complexity of the mixing process and reasons why the subject is so poorly understood can now be appreciated. A vast amount of work has been published on the development of a mixing theory (Lacey 1943, 1954, Poole et al 1964, Ashton and Valentin 1966, Hersey 1967, Buslik 1973, Hersey 1975, Hersey et al 1979 and Staniforth 1981) and on the optimisation of process conditions and mixers (Yip and Hersey 1977, Yeung and Hersey 1979, Staniforth et al 1981, Staniforth 1982, Staniforth 1984, Staniforth 1985). Although it is acknowledged that surface forces between particles are responsible for the homogeneity of a mix (Staniforth and Rees 1981, Staniforth 1981, Staniforth and Rees 1982a and Staniforth et al 1982), few studies have been done to investigate how surface energetics can be used to predict mixing (Rowe 1989a). Surface energetics is an area whereby powders are characterised in terms of their polar and nonpolar (or apolar) nature and is greatly overlooked. The formation of a mix is governed by the presence or absence of interactive forces between particles of the mix as a result of their non-polar and/or polar nature. Since mixing involves the interaction of particles and that interactions occur at surfaces, it would be expected that the surface properties of powders would influence how well powders would mix. It would be of great interest to establish the extent to which experimentally determined surface energies of powders could be used to understand and predict the mixing behaviour of powders.

1.1. MECHANISMS OF MIXING

The first step involved in mixing following the loading of the components in the mixer is the dilation of the powder bed. Mixing then proceeds by repeatedly splitting and recombining the blend to create disorder and randomly distribute the components in the mixture. The optimum time when mixing is complete would be the equilibrium state where maximum disorder is achieved. Mixing of powders occurs by a combination of mechanisms depending on the type of mixer used. Mechanisms of mixing can be described under three main types (Lacey 1954):

1. Convective mixing involves the movement of a mass of material from one part of the powder bed to another. This is usually done by means of revolving paddles or blades within the mixer so as to shuffle the system in three dimensions.
2. Shear mixing occurs as a result of slip planes that are set up by the rotational movement of the mixer. It can be described as a cascading motion of particles, which fall past their angle of repose onto dissimilar surfaces of powder.

3. Diffusive mixing occurs when there is a random motion of particles relative to one another in a powder bed. It may be as a result of shear mixing where the particles intermingle and roll down the slopes formed; by agitation of the mixer or simply due to vibration which causes particles of smaller sizes to percolate through gaps formed between coarse particles.

1.2. CLASSIFICATION OF MIXES

Extensive studies have been done in the past to develop a mixing theory. Powder mixes were classified into several types according to the forces occurring between particles in the mix. In order to understand the mixing process, an understanding of the forces acting on the particles of a multi-component mix is essential. The two main forces present are: (i) gravitational forces and (ii) interparticulate forces (i.e. adhesion, cohesion, friction and electrostatic). The magnitude of the forces present in a mix depends on the properties of the powder. Gravitational forces operate when particles are of relatively large sizes whereas interparticulate forces become more significant with a decrease in particle sizes. The transition from when gravitational forces become less significant and interparticle forces more dominant occurs when the particle sizes fall below 100 μm (Hersey 1974, Staniforth 1987). This is an arbitrary value and is quoted to merely represent a division in the influence of the two forces in a mix.

The quality of a mix is determined by its homogeneity. Homogeneity is a measure of how well the different components of the mix are distributed in the blend and is assessed by taking samples from different locations of the blend or at set time intervals during the mixing process. Samples are assayed analytically for content of the active. Assay of the content of the excipients is never carried out as it is assumed that if the active compound is well distributed, the excipients too are uniformly distributed. The assessment of homogeneity of a mix is carried out by the statistical analysis of a number of samples withdrawn from the mix to obtain the content and standard deviation of the active compound in the mix.
Consider a binary mixture of X and Y particles. At equilibrium, a state of maximum disorder would be reached where the X and Y particles would rearrange themselves until the mixture composition approaches a binomial distribution. Assuming the mix is completely random where the only forces present are gravitational forces, the laws of probability apply and the quality of the mix can be assessed statistically using parameters such as the variance or standard deviation.

1.2.1. Random mixing

Random mixes are only formed if the particles in the mix are equally sized, equally dense, spherical and have identical surface characteristics. The only forces present in random mixes are the forces of gravity with no surface forces such as adhesion or interparticle interaction acting on them. The probability of obtaining X particles in a sample withdrawn from the mix will be equal to $x$, the proportion of X added to the mix.

Based on the standard deviation of the mix and that of a completely random mix, several mixing indices have been derived. Mixing indices are dimensionless numbers used to characterise the degree of homogeneity achieved during mixing. Some of the indices ($M_i$) proposed are:

$$M_i = \frac{S}{\sigma_R}$$

(1.1)

$$M_i = \frac{\sigma_0^2 - S^2}{\sigma_0^2 - \sigma_R^2}$$

(1.2)

by Lacey (1943, 1954) who was one of the pioneers to develop a mixing index derived from the standard deviation of the mix, $S$, the standard deviation of an unmixed system, $\sigma_0$ and that of a completely random mix, $\sigma_R$. 

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\[ \sigma_0 = (xy)^{1/2} \]  
\[ \sigma_R = \left( \frac{xy}{n} \right)^{1/2} \]

where \( x \) and \( y \) are the proportions of the individual components in the binary mix and \( n \) is the number of particles in the sample. In the derivation of the mixing indices, a few assumptions had to be made; all particles in the mix had to be non-interacting and identical in all respects except for colour and the system has to follow a normal distribution.

The mixing index shown in equation (1.2) would tend to unity as mixing proceeds since the variance of the mix \( S^2 \) decreases and eventually becomes close to \( \sigma_R \), the variance of a completely random mix. Differentiation between mixtures of varying homogeneity would thus be difficult.

To overcome the above problem, a variation of the index was given by Ashton and Valentin (1966) who introduced the log scale to the mixing index in equation (1.2):

\[ M = \left( \frac{\log \sigma^2 - \log S^2}{\log \sigma^2 - \log \sigma_R^2} \right) \]

The above mixing indices suffer from the following drawbacks: all indices would tend to vary with the number of particles \( n \) in the sample i.e. \( \sigma_R \) would vary according to \( n \). Also, the indices are based on the fact that mixes formed were random mixes consisting of particles which are identical in size, shape and density with only forces of gravity acting on the particles. These types of mixes very seldom occur in practice and the indices are not applicable to real systems.

An alternative mixing index was proposed by Hersey (1967) and is based on the ratio of the standard deviation of the mix \( S \) over that of the required (whether by a pharmacopoeia or as an in-house quality control) standard deviation, \( \sigma_A \):

\[ M = \frac{S}{\sigma_A} \]
The advantages of using a required standard deviation $\sigma_A$ as opposed to the standard deviation of a completely random mix $\sigma_R$, is that $\sigma_A$ gives a definite indication as to when an acceptable standard has been attained for the mixture and not a theoretically achievable standard deviation, $\sigma_R$.

A better homogeneity index that takes into account the differences in particle sizes, size distributions of the components of the mix was given by Poole et al (1964):

$$\sigma_R = \frac{\sqrt[5]{x\left(\sum f_v\right) + y\left(\sum f_v\right)}}{W}$$  \hspace{1cm} (1.7)

where $W$ is the sample weight and $f$ is the weight fraction of each component within a given particle size range; $w$ is the mean particle weight of a given size fraction and $\sum f_w$ is the effective mean particle weight of a component. The above expression incorporates sample size, composition and particle size distribution of each component.

All the indices described so far are based on the standard deviation or variance and hence measure the heterogeneity of mixes. It would be more meaningful to measure the homogeneity in order to obtain an indication of the extent of mixing. Buslik (1973) proposed a universal homogeneity index, which is based on the weight of sample ($W_i$), required to give a standard deviation of 1% in sample composition. $W_i$ was used as an inverse measure to homogeneity, Hom:

$$\text{Hom} = \frac{1}{W_i}$$  \hspace{1cm} (1.8)

Since mixes exhibit such a wide range of homogeneity states, use of the log of the homogeneity index, $H_i$, was made:

$$H_i = \log (\text{Hom}) = -\log W_i$$  \hspace{1cm} (1.9)

In a completely random binary mix,

$$\sigma_R^2 = G(100-G)w/W$$  \hspace{1cm} (1.10)
where \( G \) is the percentage of one component, \((100-G)\) is that of the other component and \( w \) is the weight of one particle (assumed to be monosized) and \( W \) is the sample weight.

If the required standard deviation is 1\% (Buslik 1973), then \( \sigma_R = 1\% \), then \( W = W_1 \):

\[
W_1 = G(100-G)w \tag{1.11}
\]

and

\[
H_1 = \log (W_1) = \log [G(100-G)w] \tag{1.12}
\]

1.2.2. Interactive (ordered) mixing

The theory of random mixing does not apply in practice as the conditions for random mixing to occur are seldom satisfied. Mixes that are encountered in practice usually consist of materials made up of different sizes and even within one material there may be a size distribution. Besides, forces of gravity are rarely the only forces present in mixes. The first observations that forces of adhesion occurred between two components of a mix were made by Travers and White (1971) and Shotton and Orr (1971). Hersey (1975) however described this new concept fully and termed it 'ordered mixing'. This theory applied to the mixing of cohesive interacting particles. Contrary to random mixing where no forces (except for gravity) were exerted on the particles, ordered mixing depends on interparticle interaction i.e. adsorption, electrostatic, friction, adhesion and surface energies to hold particles in a state of equilibrium during mixing. As described above, these forces tend to increase with decreasing particle size. It was found that homogeneous mixes were rapidly achieved if coarse large particles were added to the fines (Crooks and Ho 1976, Yeung 1979). The fines would adhere strongly to the coarser particles to form ordered units. The mechanism by which they do so is described as the carrier mechanism. This carrier mechanism is the basis of ordered mixing. Ordered mixing is also used to describe mixing where both constituents are fines (Shotton and Orr 1971). Ordered mixing is more reflective of situations that occur in practice where particles of all sizes are incorporated in one mix.

Controversy emerged when Egermann (1980) and Egermann & Orr (1983) challenged the use of the term 'ordered mixing'. Ordered mixes are obtained if the fines adhere in a regular pattern onto the surface of the large carrier particles. In practice, ordered
mixing randomly distributes the fines onto the carriers. For a mix to be termed ‘ordered’, its standard deviation, $\sigma$ must be lower than the theoretically calculated standard deviation of a random mix, $\sigma_R$ i.e. $\sigma < \sigma_R$. No evidence of ordered mixes i.e. where the fines adhere to the monosized carrier particles in a regular manner and in identical quantities has been found and it is argued that adhesion is a process of interaction and not of order (Egermann et al 1985). To avoid all the ambiguities of the use of the term ‘ordered mixing’, it is more appropriate to employ the term ‘interactive mixing’ when describing systems consisting of particles adhering to other carrier particles.

1.2.3. Partially ordered mixing

It is hard to imagine a system that consists of randomly mixed monosized spherical materials or of an orderly distribution of fine particles adhering onto coarse particles. As neither truly random nor ideal ordered mixing occur in practice, a new concept was developed to describe systems more realistically. The term ‘Partially Ordered Random’ (POR) mixing was used to describe systems which consist of interactive units (fine particles of one component Y adhered to coarse particles of another component X) randomly mixed with agglomerates of the fine particles, Y. This situation arises frequently in practice as although fines tend to adhere to the coarse carriers, the adhesion sites on the carriers become saturated. The excess fines can either adhere as multi-layers on the carriers but very often become aggregated and randomly mix with the interactive units (Hersey et al 1979). In such cases, the theoretical variance used to describe the homogeneity of the mix is adapted to:

$$\sigma_{POR}^2 = \frac{(x + F_y)(y - F_y)}{n}$$

(1.13)

where $F_y$ is the fraction of the fine component Y, which adheres to the coarse component X, $n$ is the total number of particles in the sample and $\sigma_{POR}^2$ denotes the variance of partially ordered random mixes. $F_y$ values may range from 0 to nearly 1 and $0 \leq \sigma_{POR}^2 \leq \sigma_R^2$. 

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1.2.4. Total mixing

A theory of total mixing was introduced by Staniforth (1981) to describe the situation where both mechanisms of ordering and randomisation are in dynamic equilibration. This is an extension to the theory of ‘Partial Ordered Random’ mixing whereby only one set of particles adhered to the other set. In total mixing, fine particles of both components adhere to coarse particles of the other component. This theory is quite justifiable since it cannot be expected that only one component adheres to the other component considering that both components may have a size distribution of particles. In total mixes, the combination of random and interactive mixing gives rise to both surface electrical and gravity forces in the mix. In interactive mixes, surface forces tend to predominate in relation to gravitational forces whereas in random mixes the reverse is true. The extent to which the two types of forces develop depends on the size of the particles in the mix; a decrease in particle size leads to increasing surface forces and an increase in particle size to an increase in gravitational forces. As mentioned earlier, ordering is seen if one of the components of the mix has particles in the size of approximately 100 µm. The theoretical variance of a total mix would depend on both the amount of x particles adhering to y particles and vice versa.

\[
\sigma_{TOTAL}^2 = \frac{(x + Fy - Fx)(y - Fy + Fx)}{n}
\]  \hspace{1cm} (1.14)

where \( Fx \) is the fraction of the coarse component X adhering to the fine component Y; \( n \) is the total number of particles in the sample; \( Fy \) is the fraction of fines adhering to coarse particles X and \( \sigma_{TOTAL}^2 \) is the variance of the total mix.

Of the four mechanisms of mixing outlined above, the mechanism that best describes mixes encountered in practice is that of total mixing. It encompasses all the possible combinations of particle adhesion and distribution in a mix. The numerous mixing indices mentioned above have been developed in view to describe as accurately as possible the degree of homogeneity of mixtures containing different proportions of ingredients of different particle sizes. In practice, the parameter more frequently used in assessing homogeneity of mixes is the coefficient of variation. The coefficient of variation describes the variation in the drug content, \( \sigma_d \), as a percentage of the drug content per sample (\( d \)):
The fundamental issue remains in the fact that the value of the standard deviation or variance will always be a function of sample size, sampling errors and the use of an empirical number of samples to give an accurate representation of the entire batch.

Problems of mixing are inevitably linked to problems of sampling. Sampling is the most important step in the assessment of the homogeneity of mixes. No matter how good the homogeneity index is, the sample ultimately represents the system. Sampling is a subject that deserves considerable attention but will be discussed in minimal detail although this does not reflect a lack of importance in the subject. It is essential to recognise sampling as a potential source of error in the determination of the homogeneity of a mix and that precautions should be taken to ensure that adequate sampling is carried out to accurately represent the mix. Wherever possible, the two golden rules of sampling should be followed: (i) sampling must be done from a moving stream and (ii) the whole of the stream of powder should be taken at frequent time intervals. Sampling can be done mechanically during the discharge of powder from the blender or manually from different locations in a static powder bed. It is advisable if possible, to use of a spinning riffler, which is an entirely automatic process of sampling. It consists of a ring of containers rotating under a powder stream and collects fraction of material from the stream. However, the most common approach to sample a mix of small volume is to use a sample thief, which can be of two main classes: side-sampling or end-sampling. A typical side-sample thief has one or more cavities stamped in a hollow cylinder enclosed by an outer rotating tube. The outer tube has holes that align with the cavities allowing powder to flow into the cavities. An end-sampling thief has a single cavity at the end of the probe. Problems associated with thief sampling are that the mixture would be extensively disturbed when the probe is inserted in the powder bed and powders may flow unevenly into the cavities depending on their properties. Sampling can also be done using a spatula although the above problems associated with thief sampling also apply and in addition the process is operator-dependent and hence more variable.

Sampling whether using a thief or spatula is a laborious process and in real mixes, the number and size of samples and locations being sampled are limited. It is rarely
practical to take more than 30 samples from a mix. The size of the sample to be taken is sometimes referred as the 'scale of scrutiny', which is the smallest amount of material within which the quality of a mix is important. Statistically, the larger the sample size, the less would be the variance. It is usual to use a sample size equivalent to the size of the final dosage form. It would appear that analysis of the samples of the size of the final dosage form would allow the prediction of variation in the final stages of production. However, even if the homogeneity of a final mix has been accurately determined, it is not guaranteed that the blend would conserve its present distribution of particles during transfer or feeding into a tablet press or capsule-filling machine. Thief sampling should thus be only used to give a gross indication of the homogeneity of mixes. Finally, it should be remembered that the experimentally determined variance of a mix ($\sigma_t^2$) would consist of a collective variance of the mixing process ($\sigma_m^2$), the assay method ($\sigma_a^2$) and the sampling method ($\sigma_s^2$):

$$\sigma_t^2 = \sigma_m^2 + \sigma_a^2 + \sigma_s^2$$  \hspace{1cm} (1.16)

### 1.3. FACTORS AFFECTING MIXING

To achieve a reasonable degree of homogeneity in mixes is not the sole aim in mixing. Preventing segregation is as important as segregation occurs during mixing as well as during the subsequent handling of the completed mix. Segregation is discussed here in conjunction with mixing as the factors that promote mixing are very often responsible for segregation in mixes. The homogeneity of a mix is a balance of the mixing and segregating tendencies of the powders. The extent to which mixing and segregation proceed depends on the properties of the particles and the powder mass as well as on the transfer and processing equipment used. The effects of scaling up in formulation are a major consideration during manufacture. It is common that good formulations have to be abandoned due to insoluble problems encountered during scaling up. From the knowledge available on scaling up processes, several areas have been identified as potentially prone to problems (Staniforth 1987). Although it is desirable to keep all conditions identical from pilot studies to manufacturing plant, practically it is inevitable that changes have to be made. Changes in blender material e.g. from metal to polyethylene; transferring techniques from the mixer to the hopper e.g. from scooping to
pouring all bear consequences on the resulting mix. The factors that affect mixing and segregation are broadly classified into two main groups: (i) properties of powder such as size, shape and density and (ii) process conditions e.g. types of mixers.

1.3.1. Properties of powders

1.3.1.1. Particle size and size distribution

From the theories of random mixing, the particle sizes of actives and excipients should be as close as possible for good mixing. However in practice, the drug particles tend to be of much smaller sizes than excipients. Evidence that inhomogeneous mixes were produced when both drug and excipient particles were fine was given by Johnson (1975). In another study carried out by Staniforth (1982), the size of the fine particles was kept constant and two sizes of carrier particles used (250-500 μm to 500-700 μm respectively). An increase in carrier sizes increased both the adhesion force between fines and carriers and the percentage of fines adhering. It is thought that the number of strong adhesion sites on the large carrier particles is greater than on small carriers.

Particle size is the most frequent and significant cause of segregation in mixes. Sifting segregation (or percolation) occurs when small particles fall through the voids formed between larger particles. Percolation of particles occurs vertically and causes the coarse particles to migrate to the surface and the fines to the base of the powder bed. The risks of segregation are higher with a wide size distribution of the active and excipient particles. By decreasing the spaces between the particles or by increasing the size of the fines, segregation can be prevented. Fine powders tend to exhibit cohesiveness and a high angle of repose compared with coarse particles, which have better flow properties and lower angles of repose. When solids are allowed to flow past each other, particles with a high angle of repose tend to cohere into a pile allowing the free-flowing coarser particles to collect on either side of the pile. Various processes during manufacture involve pouring of materials and segregation as a result of percolation and differing angles of repose of powders would occur whenever there is disruption of the packing of particles e.g. transfer of powders to hoppers, chutes from batch mixers.

Vibration is a major cause of segregation and occurs in various equipment. Coarse particles even if located at the bottom of the powder bed would migrate to the surface
when vibrated, regardless of the density of the particles (Williams 1968/69). This may be explained by the fact that under vibration the large particles exert pressure on the particles underneath them and compact the bed causing the fines to percolate down the voids formed by the rising large particles.

The effects of varying frequencies of vibrations on several areas on the equipment and at the different stages of mixing were studied by Staniforth (1982). Several areas were identified as being critical to segregation e.g. the powder feed hopper of several tabletting machines. Powder mass segregation was also influenced by low frequencies (below 100 Hz) and high acceleration (above 2 g) conditions and the two conditions combined were more detrimental to the homogeneity of the system. Although homogenous mixes could be achieved during mixing, it would be required that the subsequent processes leading to the production of the dosage forms do not disrupt the state of equilibrium of the mix. By obtaining vibration signatures of pharmaceutical equipment, it would be possible to optimise the vibration frequencies and accelerations of the equipment and reduce segregation.

1.3.1.2. Shape and roughness

It is well known that particle shape and roughness affect many properties related to powder handling such as the bulk density, flow properties and angle of repose. However, little has been done to study the effects of shape and roughness of particles on mixing. Particles that deviate from a perfectly spherical shape would take longer to mix e.g. needle-like or plate-like particles would tend to bundle during the mixing process and vigorous treatment would be required to break up the assemblages. The area of contact between particles is dependent on the shape and roughness of particles. Irregular and rough particles provide more points of contact for interaction with the other components of the mix and a state of equilibrium would take longer to be achieved. The advantage of acicular i.e. needle-shaped particles is that they give rise to mixes that are more robust to segregation. Once particles are adhered, it is harder to separate them and subsequent handling and manufacturing procedures would result in less segregation. A study had been carried out on the different shapes of lactose and calcium carbonate and confirmed the above theories (Wong & Pilpel 1990). The effects of shape and roughness of particles on mixing would not be studied here although it is known that they affect bulk properties of powders and their mixing behaviour.
1.3.1.3. Density

Compared with particle size, differences in density of particles have little effects on mixing except in the case of a fluidised bed where density is more important than particle size. Rising air bubbles causes segregation to occur, with a layer of the denser material forming at the bottom of the powder bed and the less dense particles to be lifted to the top of the bed. Another mechanism by which segregation occurs is when the dense particles percolate through spaces formed by the rising air bubbles (Chowhan 1995). The most important factor that influences segregation in a fluidised bed is the air velocity. A uniform gas flow through the powder bed is critical in avoiding the disturbance of the powder bed and segregation.

1.3.2. Process conditions

1.3.2.1. Time of mixing

It has been found that most stable mixes are produced after short mixing times, usually within 30 minutes. The time taken for a mix to attain a required coefficient of variation (usually below 2%) depends on the nature of the interaction formed between particles in the mix. Interactive mixes with an optimum number of fines will form stable mixes rapidly due to the presence of interparticle forces. Stephenson and Thiel (1980) found that interactive mixes were obtained between 4 and 10 minutes. Yip and Hersey (1979) used a revolving cube blender to produce interactive mixes after 10 minutes. Interactive mixes that require long blending times to be produced are more prone to segregation (Staniforth et al 1981). This has been attributed to the fact that if long mixing times are required, the adhesion between the fines and carrier particles were not very strong. As mixing is prolonged, the adhered fines are dislodged from the carrier surfaces, leaving an excess of fines to mix with the remaining interactive units (fines adhered to carriers) or to form aggregates.

1.3.2.2. Type of mixers

Mixers are classified in two most common types: tumbling (segregating) blenders and convective (non-segregating) blenders. The two types of mixers operate on very different principles. Tumbling mixers are available in various forms: V-blenders, Y-blenders, double cone blenders, etc. In a tumbling mixer, particles fall past their angle
of repose in a cascading motion as the vessel rotates. In V and Y blenders, the powder mass is alternatively recombined at the bottom of the vessel, then split into two portions when inverted. The slip planes formed in tumbling mixers are the basis of shear mixing. Mixing also proceeds by the diffusive mechanism and causes the random movement and intermingling of particles rolling over sloping surfaces of powder. The efficiency of the tumbling blenders depends very much on the speed of rotation. The distance travelled by the particles is determined by both the speed of rotation of the blender and the size of the particles. It should be remembered that the mechanisms that promote mixing are also responsible for segregation.

Convective type blenders are widely used and are composed of a stationary vessel and a rotating impeller that stirs the powder. Ribbon mixers are of the convective type and consist of a rectangular container with a helical ribbon impeller fixed to a horizontal axle. Adaptations of the ribbon mixer include the Nauta mixer, which is a vertical conical vessel with a rotating screw fitted at the base and fastened by a rotating arm at the upper end. The screw conveys the material to the top of the vessel where it cascades back into the powder bed. This mixer operates by a combination of all three mechanisms of mixing i.e. convective, shear and diffusive. The mixture would become less prone to segregation as mixing occurs by mass movement of particles. It is important to select a mixer to suit the properties of materials so as to produce stable mixes. Free-flowing powders should not be mixed in a tumbling blender as their inherent tendency to segregate due to the lack of interparticulate forces would be worsened by the shearing and diffusive mechanisms of the tumbling mixers; convective mixers are hence more appropriate for mixing free flowing powders. Cohesive powders tend to have a high angle of repose and require the shearing action of tumbling blenders to increase the movement of particles more effectively in the mix.

The use of continuous and batch mixing has been mentioned in the literature. In pharmaceutical industries, batch mixers are normally used and the different types available have been discussed above. Continuous mixing possesses certain advantages over batch mixing. The scale of powders being mixed can be reduced and the entire output fed directly into the tablet press or capsule filling machine. This is associated with a decreased risk of segregation especially if free flowing powders are being mixed. There is no handling and storage problems and delay between mixing and the

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production of dosage forms is greatly minimised. The feasibility of such a process
however depends on the rapid in-process analytical procedures.

1.3.2.3. Order of adding excipients

The order in which excipients are added to form a mix has a significant effect on its
final quality. The nature of interactions between excipient and drug varies depending
on the size and surface forces at the interface between the excipient and the drug
particles. It is known that the addition of a third component causes a decrease in
homogeneity in a binary mix. Lai and Hersey (1979) observed that the addition of
magnesium stearate to a stable binary mix of salicylic acid and sucrose causes the
salicylic acid to be displaced from the sucrose carrier particles. This was attributed to
the 'stripping' effect magnesium stearate has on the salicylic acid-sucrose interactive
units as a result of the competition for adhesion sites on the sucrose particles. Staniforth
et al (1982) showed that when a tertiary component is added to a glass bottle containing
a binary mix of salicylic acid and sucrose, the quality of the resulting mix depended on
the electrostatic charges of the three components. If the third component was
magnesium stearate or starch, the mix was destabilised whereas if talc was added a
stable ternary mix was produced. The adverse effects of the third component were
explained by the fact that both magnesium stearate and starch develop positive
electrostatic charges with glass. Since both salicylic acid and sucrose charged
negatively with glass, both the positively charged magnesium stearate and starch would
compete for adhesion sites on sucrose carriers, causing an increase in the number of
dislodged salicylic acid particles, thus destabilising the mix. Talc had a stabilising
effect on the binary mix as it charges electronegatively with glass. Hence the relevance
of the order of addition of excipients to a mix comes into light. The homogeneity of
mixes can be improved greatly if the electrostatic charges developed by the powders as
well as the order in which excipients are added to form a blend are considered.

1.3.2.4. Lubricants

Although lubricants are known to destabilise homogeneous mixes and decrease the
dissolution rate of tablets, they are an essential excipient in a powder formulation. They
are added at the end of the mixing process for a minimum length of time to reduce the
powder-metal friction. Magnesium stearate is the most commonly used lubricant and exerts its destabilising effects on mixes by competing for sites on surfaces of carrier particles (Lai & Hersey 1979, Staniforth et al 1982). The deleterious effects of magnesium stearate extend to the dissolution of solid dosage forms due to the formation of a hydrophobic layer on drug particles. Studies have shown that the dissolution profiles of solid dosage forms can be improved by first mixing the magnesium stearate with surfactants (Wang & Chowhan 1990, Ong et al 1993). When the magnesium stearate-surfactant mix was added to the drug-excipient premix, a great improvement in dissolution rate was observed. This was thought to be due to the surfactant (sodium lauryl sulphate) particles interacting with the lubricant particles, preventing them from covering the drug particles. The order in which the excipients were added to the drug appears to be important in improving the dissolution profile of the dosage forms.

1.4. ROLE OF SURFACE ENERGETICS IN MIXING

Despite the theories proposed to date and an awareness of the factors discussed above, problems during mixing are still encountered. The reasons why some powders would mix well with some excipients but not with other excipients remain unclear. Scientists still strive to achieve an ideal mix that should take minimum time to achieve homogeneity, does not segregate during the different stages of transfer during manufacturing and most important of all, enables removal of samples, however small, that would still have the same composition as the bulk.

Past studies have mostly centred on the mixing theory and the optimisation of the manufacturing equipment and conditions used during mixing. Little work has been done to study the effects of surface energetics of powders on mixing. Since pharmaceutical powders often have different shapes and particle sizes, their surface properties would, to a great extent determine their behaviour. It would be useful to characterise the surface properties of solids and relate them to the interactions occurring at surfaces on a particulate level. Small levels of impurities in powders if concentrated at the surface would have considerable impact on their behaviour during manufacturing processes. Considering that powders are used as received from suppliers, it is important that the presence of surface contaminants is detected before being used in the
manufacture of dosage forms. This can be achieved if powders are subjected to surface characterisation techniques. During manufacture, powders undergo several processes such as crystallisation and milling. These processes give rise to groups of different nature and proportion on the surface of crystals. Other characteristics such as the degree of amorphous content are potential sources of variability between powders. All these factors may cause variation in surface properties and could give rise to problems during mixing. Hence, a rational approach would be to study and understand the surface properties of powders so as to optimise their performance in further processing stages such as mixing.

1.4.1. Surface energy

Surface energy is best explained if an analogy is made to liquids. Molecules in the bulk of the liquid experience forces of attraction to other neighbouring molecules from all directions whereas molecules found at the surface of the liquid experience a net inward force pulling them into the bulk of the liquid (figure 1.1). To maintain these molecules at the surface, energy known as surface tension is required.

Figure 1.1 shows the forces exerted on molecules at the surface and in the bulk of a liquid.

Although molecules of a solid are unable to move, similar forces are experienced by the molecules found at the surface, pulling them towards the bulk. In solids, the energy required to maintain the molecules at the surface is known as the surface energy. It is a measure of the ease with which a surface can be expanded. The force required to form a
unit surface area of the solid would be termed the surface energy and is usually measured in \( \text{mJm}^{-2} \).

Surface energy is a function of the hydrophilic and hydrophobic groups on the solid surface resulting from processing history e.g. crystallisation of solids from different solvents gives rise to different crystal habits with different orientations of the functional groups on the surface. The effects of physical pre-treatment of powders e.g. different comminution techniques have been shown to result in different surface energies of powders (Buckton et al 1988). Although surface energy is a function of particle size, and surface properties of powders become more significant with a decrease in particle size, there is no direct relation between surface energy and size i.e. a decrease in particle size does not infer a proportional increase in surface energy.

As discussed previously, surfaces of powders are known to be heterogeneous and consist of polar and apolar groups. The surface energy of solids, \( \gamma_s^{\text{tot}} \) is usually described as the additive contribution from a polar \( (\gamma_s^p) \) and apolar component \( (\gamma_s^d) \) (Fowkes 1964):

\[
\gamma_s^{\text{tot}} = \gamma_s^d + \gamma_s^p
\]  

(1.17)

The apolar component arises from dispersive forces that are made up of three parts: London, Keesom and Debye forces. London forces occur between molecules that have no permanent or induced dipoles. They arise as a result of the momentary location of electrons spinning round an atom of a molecule causing a temporary induced dipole moment. An electric field capable of inducing a dipole moment in adjacent molecules leads to attractive forces between the two neighbouring induced-induced dipoles. London dispersion forces are thus present in all materials.

The second component of the dispersive forces is the Keesom forces originating between permanent dipoles in adjacent molecules. Debye forces are the third component and arise between a molecule containing a permanent dipole and an adjacent molecule with induced dipole. The collective dispersion forces are also referred to as the Lifshitz-van der Waals forces and denoted by \( \gamma_{\text{LW}} \). They are the most significant forces in the adhesion of particles in the size range where gravitational forces become less significant.
The polar component of the surface energy arises from polar forces due to polar groups present on the surface of a material. Polar forces include interactions from electrostatic charges and hydrogen bonding and may be repulsive or attractive depending on the nature of the materials. Work by van Oss (1987) showed that the polar term of the surface energy of a solid could be further characterised in terms of its electron-donor and electron-acceptor parts.

\[ \gamma_{AB} = 2 (\gamma^\oplus \cdot \gamma^\ominus)^{1/2} \]  

(1.18)

where \( \gamma_{AB} \) denotes the acid-base component; \( \gamma^\oplus \) is the electron acceptor contribution to \( \gamma_{AB} \) and \( \gamma^\ominus \) the electron-donor contribution to \( \gamma_{AB} \).

In his work, van Oss (1987) considered the surface of a material as consisting of groups that show a tendency to accept electrons and denoted these as Lewis acids and similarly Lewis bases are used to denote electron donor groups. The polar component of the surface energy would thus be a non-additive contribution from the Lewis acids and bases as shown in equation (1.18). The overall surface energy however, is still the sum of the Lifshitz-van der Waals (\( \gamma^{LW} \) or dispersive) and acid-base (\( \gamma_{AB} \) or polar) components:

\[ \gamma_{s}^{tot} = \gamma_{s}^{LW} + \gamma_{s}^{AB} \]  

(1.19)

Hence, with this new approach, solids can be classified in various ways. Solids can be described as being apolar i.e. having no polar entities; monopolar with either positive or negative polarities or bipolar. This increases the possible interactions that can arise within a molecule and gives scope for a better understanding of the interactions between molecules of different solids.

### 1.4.2. Interparticulate forces

Interaction between two particles is based on two main types of forces: gravitational and surface forces. What is of more interest in this project is the occurrence of surface forces as materials encountered have sizes below 150 \( \mu \)m. Surface forces consist of only a few primary forces (Rumpf 1977, Zimon 1982):
1. Liftshitz-van der Waals (LW);
2. Electrical forces;
3. Electrostatic (Coulombic) forces and
4. Capillary forces.

These primary forces do not occur between particles of solids only and may arise between two phases e.g. vapour of a liquid and a solid surface in which case they are known as interfacial forces. These interactions are due to physical bonding and are characterised by low energies (less than 40 kJmol\(^{-1}\)) and operate over long distances (up to 10 μm, Simons 1996).

These forces give rise to a variety of forces e.g. cohesion when Liftshitz-van der Waals forces develop between two particles of the same material or adhesion in the case of particles of two different materials. Polar or acid-base forces would only arise if polar groups are present on the two particles. It should be remembered that interactions may be attractive or repulsive depending on the nature of the materials. Electrostatic forces are the result of different work functions of materials; work function being defined as the energy required to remove an outer electron from a solid. A solid when rubbed against a surface such as stainless steel or glass acquire or donate electrons depending on the relative work functions of the solid and surface. Hence, charges of a positive or negative nature arise. If a charged particle is placed in the vicinity of another charged body, attraction or repulsion occurs depending on the charge carried by the two materials. At low relative humidities, the moisture associated with the particles of a powder is adsorbed water vapour. As the relative humidity rises, water vapour condenses into multilayers over the particles until liquid bridges form between two particles and this is often known as surface tension or surface pressure forces (Coelho and Hamby 1978).

The magnitude of these different types of forces and the range over which they occur vary. Surface pressure forces are the strongest followed by van der Waals forces but in both cases, the particles need to be within close range for hydrogen bonding and dipole-dipole forces to form respectively. Liftshitz-van der Waals forces vary with separating distance according to the inverse 7\(^{th}\) power over distances less than 20 nm and over larger distances, to the inverse 8\(^{th}\) power (Staniforth 1982). Polar and electrostatic
forces are the weakest with electrostatic forces arising only in conditions of low relative humidity. Although the weakest, electrostatic forces operate over a long range, up to 10 μm; once electrostatic forces develop between particles, van der Waals forces take over retaining the particles more strongly together.

1.4.3. Determining surface energy

All the techniques used to determine the surface energy of a solid rely on the interaction of liquids with the solid. Liquids of different properties are used to probe the solid surfaces. Apolar liquids such as hexane would interact by dispersive forces only whereas polar liquids such as water would interact by dispersive as well as polar interactions. Hence, information on the surface energy of solids is obtained by assessing the interaction of well chosen liquids with the solids. There are various techniques by which the surface energy of solids can be determined. It is however not possible to measure the surface energy of solids directly. All techniques involve the measurement of a parameter, which is then used to determine the surface energy of the solid.

1.4.3.1. Contact angle

An indirect method is by the determination of the contact angle a liquid makes with the solid. Contact angle by definition, is the angle that a drop of liquid forms on a solid surface. A low contact angle would indicate that the liquid spreads easily and conversely, a high value implies that the drop shows no tendency to spread over the surface. Contact angles range from 0 to 180°. If a polar liquid (e.g. water) is placed on a hydrophobic surface such as wax, there would be no tendency for the drop to spread on the surface and a high contact angle would be observed (figure 1.2b).
Figures 1.2 a and b show the contact angle formed by a drop of liquid on a solid surface.

This contact angle can be measured by different techniques. It is used to obtain the dispersive and polar components of the surface energy of solids, \( \gamma_s^d \) and \( \gamma_s^p \) respectively (see chapter 3).

1.5. AIMS OF PROJECT

The main aim of my project is therefore to investigate the suitability of surface characterisation techniques to obtain surface energy parameters, which would be used to understand and predict the important factors governing the mixing of solids. The techniques used to determine the surface energy components of powders would be the well-known Wilhelmy plate technique; a novel instrument based on the sessile drop technique and Inverse gas chromatography (IGC). The development of electrostatic charges as a result of friction with surfaces such as stainless steel would also be investigated. To prove the success of the predictions, methods of assessing the homogeneity of mixes are required. Mixes of active drug and excipients would be prepared and samples taken from the blends at set time intervals would be assayed by high-pressure liquid chromatography (HPLC). Another part of my project would be involved in the determination of the suitability of near-infrared spectroscopy (NIRS) as a secondary analytical technique to substitute high-pressure liquid chromatography.

With the need for more in-process controls in the manufacture of dosage forms (Staniforth et al 1989), rapid methods of analysis are required. If near-infrared spectroscopy is found suitable as an analytical technique, it would find great use in the
quality assurance procedures in providing a fast assessment of the homogeneity of powders.

### 1.5.1. Wilhelmy plate technique

This technique is a very popular method used to determine the surface energy parameters of materials. As would be explained in more detail in chapter 3, the Wilhelmy plate technique is an indirect way of determining the surface energy parameters of solids. The popularity of this technique stems from its ease of use and operator independency. Materials of various types can been studied. In the past, the most frequently quoted method of preparing samples were by compressing the powder under conditions of high pressures to form plates that are used for measurement. More recently, another method of preparing samples was investigated. It involves the adhesion of the powder onto a glass slide that had been sprayed with adhesive. This method first described by Shanker (1994) has been little used apart from Dove et al (1996) who compared this novel method of preparing samples with plates of powders conventionally prepared by the compaction method. It was concluded that coating powder onto the adhesive covered glass slides provided the most realistic and consistent surface energy data for powders studied. Hence this little used method of preparing samples would be employed to study materials as it has the advantages of assessing powders 'as received' from suppliers and would provide more accurate data on the properties of powders during subsequent manufacturing processes. It does not involve the compression of powders which is known to give rise to surface deformation. The electronic microbalance to be used is the Dynamic Contact Angle or DCA analyser (C.A.H.N.). Various liquids of differing properties are used to determine the contact angles formed on the solids. The contact angle is then used to determine the dispersive and polar components of the surface energy, $\gamma_s^d$ and $\gamma_s^p$ respectively.

### 1.5.2. Sessile drop technique (Dynamic Angle Tester)

This technique is the most cited in the literature for the determination of contact angles of liquids on solids. Variations based on the same principle have been used in the past (Harder et al 1970, Lerk et al 1976, Fell and Efentakis 1979). The sample used in this technique may be smooth surfaces of crystals (Buckton and Newton 1986) although this...
is seldom the case as crystals of sufficiently large sizes are not easily available for such experiments. The most frequently used method of sample preparation is the compaction of powder under high pressure into discs using a flat-faced punch and die and a hydraulic press. The compacts are supported by a ring and saturated with the test liquid. The liquid used to form a drop on the solid surface is usually a saturated solution of the powder in the test liquid. An accurate amount of liquid is dispensed from the tip of an Agla syringe and the angle (or height of the drop) formed on the solid is measured directly using an eye piece protractor attached to a goniometer. Photographs may also be taken of the drop and the angle determined.

In this project, an instrument based on the sessile drop technique and adapted with a video camera would be used. This novel instrument, known as the Dynamic Angle Tester (DAT) has been used in the paper industry to determine the adhesion of ink drops on various grades of paper covered with different coatings. Its use in the pharmaceutical field was investigated here for the first time with the instrument on loan from Scientific & Medical Products Ltd. for a duration of four weeks. In this technique, a drop of liquid is dispensed onto the surface of the solid of interest and images of the drop on the surface are taken by the video camera as a function of time. The contact angle is determined from calculations made on two-dimensional images captured; the contour of the drop is traced and the curve used to calculate the average contact angle by the computer software. The advantages and limitations of this novel technique would be discussed in chapter 5. As in the Wilhelmy plate technique, the parameters to be determined from the Dynamic Angle Tester would be the dispersive and polar components of the solids, $\gamma_s^d$ and $\gamma_s^p$ respectively.

### 1.5.3. Inverse Gas Chromatography (IGC)

Inverse gas chromatography (IGC) is another surface characterisation technique that will be used to study the surface nature of pharmaceutical solids. Until recently, IGC has been mostly used to study surfaces of polymers, paper and fibres (Dorris and Gray 1981, Schultz et al 1987, Papirer 1988). In the pharmaceutical field, IGC was used to obtain information on the surface characteristics of pharmaceutical solids (Dove et al 1996) and also proved to be of high sensitivity to differentiate between batches of the same material (Ticehurst et al 1994 and 1996).
As in the Wilhelmy plate and sessile drop techniques, IGC uses organic liquids of different properties to probe surfaces of powders. IGC operates on similar principles to conventional gas chromatography. It involves the injection of a solute onto a stationary phase. The difference in IGC is that the solute is a well characterised liquid probe and the stationary phase is the powder of interest packed into a glass column. The liquid probes would react with the solid phase to different extents due to the intrinsic polar or apolar properties of both the liquids and solid. The time it takes a probe to elute from the powder column is the parameter that is measured and used subsequently in thermodynamic equations to derive the surface energy parameters of the solid.

1.5.4. Triboelectric studies

Charging most often encountered in industry involves the friction of materials relative to each other or with surfaces and is commonly termed frictional charging, triboelectric charging or tribocharging. Triboelectric charging is a difficult area of study as the factors causing electrostatics are numerous and poorly controlled. In pharmaceutical industries, electrostatic charges build up easily during handling operations, during pneumatic transport of powder along pipes, grinding, pouring of powder from bags to hoppers and sieving operations. Charge build up in powders is most significant at the surface of powders since these are good insulators and charge does not transfer easily to the bulk of the mass. Greatest electrostatic charge development is associated with fine powders and under conditions of low humidity.

Unwanted build up of charges on surfaces of equipment or powders during processing can significantly affect how powders behave during and after mixing. Staniforth and Rees (1981) showed that if powders were charged prior to mixing, the homogeneity of the resulting mix was reached sooner and segregation of the mix greatly reduced compared with uncharged powders. It was later observed that if powders were mixed in vessels of various nature such as glass or polyethylene, electrostatic charges of differing polarities developed (Staniforth and Rees 1982a). Triboelectric charging certainly has an effect on the mixing of powders and would be studied with the use of a Faraday well connected to an electrometer. A Faraday well was built in-house according to British Standards (BS 7506) so that triboelectric studies can be carried out. Since the surface characterisation techniques mentioned above give information on the surface nature of...
powders, it would be of interest to see whether the data so obtained correlate with those from triboelectric studies.

1.5.5. HPLC and Near-Infrared Spectroscopy (NIRS)

The first aspect of the project would involve predicting the mixing behaviour of powders based on their surface energetics. However, it is also necessary to confirm the theories derived from surface forces. This will be achieved by preparing and assaying binary and tertiary blends using high-pressure liquid chromatography (HPLC) and the less conventional near-infrared spectroscopy (NIRS) to assess the homogeneity of the systems. NIRS is a technique that is gaining interest in the pharmaceutical field as a possible substitute to conventional HPLC. NIRS operates on similar principles to conventional infrared. Energy is directed onto the sample and the absorbance or reflectance of the light is detected and measured. The wavelength of the light used is in the region of 800-2500 nm for near infrared experiments. The use of NIRS to study mixing on-line, in particular the order of addition of excipients to the active compound is hoped to provide a better understanding of the mixing process. Comparison of HPLC data with NIRS data is another area that would be considered. If a correlation exists, this would prove that NIRS can be used confidently as a quantitative analytical technique able to supersede conventional tedious HPLC assays.

1.5.6. Dynamic vapour sorption (DVS)

Various other techniques have been used throughout this project to characterise powders. Dynamic vapour sorption (DVS) is one such technique and is based on the uptake of water by powders when exposed to increasing levels of humidity. This uptake can be the result of adsorption only or in conjunction with absorption and is registered on an electronic microbalance as a change in weight of the sample. The difference between adsorption and absorption is that adsorption describes a process whereby more water molecules are found on the surface of the powder than the bulk and absorption occurs when molecules pass into the bulk of the powder. This change in mass as a function of the % relative humidity of the vapour gives information on the surface nature of the powder. Water molecules act as a probe as they form monolayers or
multilayers on the surface of the powder depending on the % relative humidity of the vapour.

1.5.7. Isothermal microcalorimetry

Microcalorimetry was also used to study surfaces of powder. The samples were exposed to water of varying % relative humidity and the energy evolved following adsorption or absorption of water onto the powders were measured as a function of time. Experiments were carried out under isothermal conditions and adsorption isotherms (i.e. plots of changes in mass as a function of % relative humidity) drawn. As in DVS experiments, the first few layers of water molecules binding to the solid surface are of greatest significance and give information on the surface nature of powders. Subsequent water-water interactions are considered as condensation and as such are of no relevance to the surface properties of powders.

1.5.8. Miscellaneous techniques

Other properties of the powders such as the density, angle of repose, surface area and particle sizes were also measured and detailed in chapter 10.

1.6. Plan of work

The only attempt to predict mixing using the solubility parameters was by Rowe (1989a) who used binary blends of iron oxide or carbon black with white pharmaceutical excipients. The solubility parameter approach involved the theoretical determination of the overall polar and nonpolar forces based on the individual atoms and groups in the molecules of solids. Although this approach has its advantages (as the values of solubility parameters are readily available from the literature), it may not accurately reflect the surface characteristics of powders. It would be more relevant to use well-established surface characterisation techniques to obtain surface energy parameters. The parameters to be obtained from the Wilhelmy plate and sessile drop techniques are the dispersive and polar components and those from IGC would be the
dispersive component and acidic and basic parameters. Triboelectric charging studies using stainless steel would yield charges that would indicate the electron-donating and electron-accepting tendencies of the powders. Since all parameters give an indication of the surface nature of materials, an attempt will be made to compare data obtained from all techniques used. A direct comparison is however not always possible, as the theoretical considerations of each technique are slightly different.

Preliminary studies would hence be done to attempt to reproduce Rowe's work. The Wilhelmy plate technique would be used to experimentally determine the surface energy parameters of powders. The spreading of powders in the binary mixes would be predicted from these surface energy parameters. To confirm the behaviour of the systems, the powders were inspected visually. This approach if suitable would be extended to predict interactions in ternary mixes. However, this model has its limitations as most pharmaceutical powders are white and visual inspection cannot be used to confirm theoretical findings. Instead, homogeneity studies on blends would be carried out on white mixes using HPLC and NIRS as discussed above.

The model pharmaceutical powder to be studied would be an active compound, zamifenacin, developed at Pfizer Central Research. This compound was chosen as problems of mixing were encountered during the development stage. It was impossible to reproducibly obtain good mixes in various batch sizes and range of strengths of the active compound. It was found from homogeneity studies that zamifenacin had a greater adhesive particulate interaction with maize starch than lactose. If lactose was added to a zamifenacin-starch premix, it destabilised the uniform mix and increased the coefficient of variation. However, starch was found to improve the homogeneity of a zamifenacin-lactose blend. The order of adding excipients to the active therefore appeared to be a determining factor to the quality of mixes produced and would be studied in more detail.

If surface forces are found to significantly influence the behaviour of powders during mixing, the characterisation of powders prior to mixing would be useful in predicting whether homogeneous blends can be produced without the need to blend powders and hence reduce extensive formulation studies. The work will be discussed under separate chapters for the different techniques used and the data from each technique discussed and related where appropriate.
2. MATERIALS

2.1. IRON OXIDE MIXES

The surface energies of iron oxide and three commonly used pharmaceutical powders, namely a filler (Avicel PH101 or microcrystalline cellulose), a lubricant (magnesium stearate) and an opacifier (titanium dioxide) were determined. Iron oxide was chosen as the model powder as: (i) experiments were being done as an extension to Rowe’s (1989) work and (ii) iron oxide is deep red in colour and it would be possible to visually assess the mixes once formed with the white excipients. Details of the sources of the materials are shown below:

<table>
<thead>
<tr>
<th>Material</th>
<th>Supplier</th>
<th>Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Oxide</td>
<td>Aldrich</td>
<td>03522TF</td>
</tr>
<tr>
<td>Avicel PH101 (MCC)</td>
<td>Aldrich</td>
<td>C2480R</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>BDH</td>
<td>26125</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>Wellcome</td>
<td>09205PP</td>
</tr>
</tbody>
</table>

Table 2.1 shows the list of powders used for coloured mixes.

2.2. ACTIVE COMPOUNDS AND EXCIPIENTS

Pharmaceutical powders were provided by Pfizer Central Research for mixing and surface characterisation studies. The active compound was zamifenacin, which was chosen as the model drug, as it gave poor mixes during development on site. The excipients included in the formulation of zamifenacin tablets were lactose monohydrate, starch and magnesium stearate. Anhydrous lactose and spray-dried lactose were also provided for surface characterisation studies as a comparison with lactose monohydrate. Two batches of lactose monohydrate, maize starch and magnesium stearate were studied, since the initial batches provided were completely used in preliminary surface
characterisation work. Details of the materials and batches used in specific techniques are included in table 2.2.

The chemical structure of zamifenacin is shown below:
<table>
<thead>
<tr>
<th>Material</th>
<th>DCA (Wilhelmy plate technique)</th>
<th>DAT (Sessile drop technique)</th>
<th>IGC (Inverse gas chromatography)</th>
<th>Triboelectric Studies</th>
<th>Mixing studies (HPLC/NIRS)</th>
<th>Vapour Sorption Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamifenacin fumarate</td>
<td>UK-76654-42</td>
<td>UK-76654-42</td>
<td>UK-76654-42</td>
<td>UK-76654-42</td>
<td>UK-76654-42</td>
<td>UK-76654-42</td>
</tr>
<tr>
<td>Maize starch</td>
<td>4416-029</td>
<td>4416-029</td>
<td>97EXC046</td>
<td>97EXC046</td>
<td>97EXC046</td>
<td>97EXC046</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>3005-197</td>
<td>3005-197</td>
<td>4416-003</td>
<td>4416-003</td>
<td>4416-003</td>
<td>4416-003</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>3005-088</td>
<td>3005-088</td>
<td>3005-088</td>
<td>3005-088</td>
<td>3005-088</td>
<td>-</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>96EXC002</td>
<td>96EXC002</td>
<td>96EXC002</td>
<td>96EXC002</td>
<td>96EXC002</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4416-027</td>
<td>4416-027</td>
<td>97EXC038</td>
<td>97EXC038</td>
<td>97EXC038</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.2 shows the batch numbers of the active compound and excipients provided by Pfizer Central Research as used in the following techniques.
2.3. LIQUIDS USED

In order to study the surface nature of the materials, liquids were used as probes. Liquids of different nature i.e. non-polar and polar were chosen. The non-polar liquids would interact by non-polar forces only and the polar liquids would give rise to interactions due to polar groups in addition to non-polar interactions. Liquids used for each specific technique are shown in tables 2.3 to 2.4.

2.3.1. Dynamic Contact Angle and Dynamic Angle Tester

The liquids used in the Wilhelmy plate technique were also used in the sessile drop technique as comparison of the data obtained from these two techniques would later be made.

<table>
<thead>
<tr>
<th></th>
<th>DCA</th>
<th>DAT</th>
<th>Supplier</th>
<th>Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Bromonaphthalene</td>
<td>1-Bromonaphthalene</td>
<td>Aldrich</td>
<td>KG04115JG</td>
<td></td>
</tr>
<tr>
<td>Diiodomethane</td>
<td>---</td>
<td>Sigma</td>
<td>45H3475</td>
<td></td>
</tr>
<tr>
<td>Formamide</td>
<td>Formamide</td>
<td>Acros</td>
<td>76321/1</td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>---</td>
<td>Aldrich</td>
<td>04551MN</td>
<td></td>
</tr>
<tr>
<td>Double distilled water</td>
<td>Double distilled water</td>
<td>Lab</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3 shows the liquids used in the Wilhelmy plate (DCA) and sessile drop techniques (DAT).

2.3.2. Inverse Gas Chromatography (IGC)

The liquid probes used in IGC were of 99% purity or higher. The probes were of apolar, acidic, basic and amphoteric nature. They were chosen as they were well characterised in terms of their physical properties, which is important in the interpretation of IGC data. Details of the probes used and their suppliers are shown in table 2.4. In IGC experiments, the stationary phase support used to house the powder is a glass column that required silanisation. Silanisation ensured that the inner surface of the glass column was coated with a hydrophobic coating. This was carried out using a Repelcote® solution.
Table 2.4 shows the volatile liquid probes used in Inverse Gas Chromatography.

### 2.3.3. High Pressure Liquid Chromatography (HPLC)

Solvents used in the assays of mixes for zamifenacin content by high performance liquid chromatography (HPLC) are shown in table 2.5.

<table>
<thead>
<tr>
<th>Mobile Phase</th>
<th>Supplier</th>
<th>Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>Fisher</td>
<td>---</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Fisher</td>
<td>---</td>
</tr>
<tr>
<td>Tri Ethyl Amine</td>
<td>Fisher</td>
<td>9629615 077</td>
</tr>
<tr>
<td>Sodium Acetate</td>
<td>Fisher</td>
<td>9627869B027</td>
</tr>
<tr>
<td>Glacial Acetic Acid</td>
<td>BDH</td>
<td>K23614036 702</td>
</tr>
</tbody>
</table>

Table 2.5 shows the details of solvents and materials (used in buffers) for the mobile phases used in HPLC.
3. SURFACE ENERGETICS

3.1. INTRODUCTION

In a study published by Rowe (1989a), surface properties of powders were used to predict and explain the mixing behaviour of binary systems. These consisted of red iron oxide and three commonly used pharmaceutical powders, which are white in colour. When the red iron oxide was mixed with microcrystalline cellulose (MCC), a uniform red coloured mix was obtained. If mixed with magnesium stearate (Mg Stearate), the resulting mix was predominantly white with red specks of iron oxide. The third mix containing iron oxide and titanium dioxide (Ti dioxide) was pink in colour. This was a surprising observation as certain factors were clearly influencing the way iron oxide interacted with the white powders. The explanation to this observation was based on the surface energetics of the powders, their cohesive energy densities and solubility parameters (solubility parameter being a measure of the intermolecular forces that exist within a system).

The possible interactions in a binary system of components A and B are the adhesion of particles of components A with B and the cohesion of particles within each component i.e. A-A and B-B. In the iron oxide mixes, the strength of the adhesive interactions between iron oxide and MCC was found to be higher than the cohesive interactions in iron oxide but lower than the cohesive interactions within MCC. As such, it was more favourable for the iron oxide particles to spread over the MCC particles and a deep red uniform mix was obtained. In the case of the magnesium stearate mix, the strength of the adhesive interactions between the lubricant and iron oxide was higher than the cohesive interactions within magnesium stearate but lower than that within iron oxide. Magnesium stearate would thus spread over the iron oxide particles to give a predominantly white mix. The third mix was similar to the MCC-iron oxide system where the adhesive interactions were higher than the cohesive interactions in iron oxide but lower than that within titanium dioxide. However, the extent of spreading of the red iron oxide particles over the white component was less and a pink mix (as opposed to a deep red mix) was obtained. This could be due to the difference between the adhesive
interactions and the cohesive interactions within the white excipient being greater in the MCC mix compared with the titanium dioxide mixes (strength of interactions in MPa: iron oxide-MCC 207; iron oxide-Ti dioxide 238; MCC-MCC 386 and Ti dioxide-Ti dioxide 296).

- Solubility parameter approach

The study detailed above was an example of the use of solubility parameters to predict interactions in powder systems. The solubility parameter of a compound is determined from its molecular fragments. Values for the solubility parameters of molecules and fragments can be obtained from the literature (Hansen and Beerbower 1971); a molecule nearest to that of the molecule of interest is chosen and the extra functional groups added to compute the final value of the solubility parameter of the unknown compound. The solubility parameter of a solid ($\delta_s$) is expressed in terms of its dispersive ($\delta_d$), polar ($\delta_p$) and hydrogen bonding ($\delta_h$) contributions:

$$\delta_s = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{1/2}$$ (3.1)

Partial solubility parameter values obtained from literature have also been used successfully to predict interactions in various powder systems (Rowe 1988a, 1988b and 1992). This theoretical approach was based on the determination of the interactive forces between components. The solubility parameters of the solids were used to determine the strengths of adhesion ($\sigma_{AB}$) and strengths of cohesion ($\sigma_{AA}$ and $\sigma_{BB}$) as well as an interaction parameter, $\phi$, between the components as shown by Rowe (1988b, 1988c).

The adhesive strengths between components A-B can be determined from:

$$\sigma_{AB} = 0.25\phi \delta_A \delta_B$$ (3.2)

where $\delta$ is the solubility parameter of material A and B. Similarly, the cohesive strengths between components A-A and B-B are determined from:

$$\sigma_{AA} = 0.25\delta_A^2 \quad \sigma_{BB} = 0.25\delta_B^2$$ (3.3)
The interaction parameter \((\phi)\) can be calculated from:

\[
\phi = 2 \left[ \frac{x_d^A \cdot x_d^B}{x_d^A \cdot g_1 + x_d^B \cdot g_2} + \frac{x_p^A \cdot x_p^B}{x_p^A \cdot g_1 + x_p^B \cdot g_2} \right]
\]

where \(x_d\) and \(x_p\) are the fractional non-polarity and polarity respectively of materials A and B:

\[
x_A^d = \left[ \frac{\delta_A^d}{\delta_A} \right]^{\gamma^2} \quad x_A^p = 1 - \left[ \frac{\delta_A^d}{\delta_A} \right]^{\gamma^2}
\]

and \(g_1\) and \(g_2\) are constants for the system:

\[
g_1 = \sqrt[1/3]{\frac{\delta_A^{2.5} V_A^{1/3}}{\delta_B^{2.5} V_B^{1/3}}} \quad g_2 = \frac{1}{g_1}
\]

where \(V\) is the molar volume (i.e. the molecular weight divided by its volume) of the material.

The value of the parameter \((\phi)\) ranges from near zero to unity. The closer the value is to unity, the greater are the adhesive interactions between the two components involved.

The deleterious effects of lubricants on tablet strength were investigated by Rowe using the solubility parameter approach (Rowe 1988a, 1992). Interactions in a binary mix of microcrystalline cellulose (MCC), or anhydrous lactose with three lubricants, magnesium stearate, stearic acid and polytetrafluoroethylene (PTFE) were studied. Predictions based on the strength of the adhesive forces between lubricant-MCC particles in relation to cohesive forces within the lubricant-lubricant and MCC-MCC particles were made. In the case of magnesium stearate, the lubricant-MCC interactions were found to be higher than the lubricant-lubricant interactions whereas the reverse is true for PTFE. Adhesive forces between stearic acid and MCC were slightly lower than the lubricant-lubricant interactions. The practical significance of these predictions is seen when the strengths of the tablets produced from the binary mixes were determined. The higher the ratio of the adhesive to cohesive strengths, the most significant would be the weakening effect of the lubricants on the tablet strength. Similar conclusions were drawn in binary mixes of anhydrous lactose with the three lubricants.
This solubility parameter approach has been applied to a ternary system consisting of microcrystalline cellulose (MCC), magnesium stearate and colloidal silica (Rowe 1988b, 1992). Again, the use of solubility parameter values from literature gave trends that were in agreement with experimental data obtained by Staniforth and Ahmed (1986). Addition of a third component, colloidal silica, altered the tablet strength. The strength of adhesive interactions was highest between colloidal silica and MCC followed by colloidal silica and magnesium stearate and lowest between MCC and magnesium stearate. It can thus be predicted that colloidal silica will preferentially coat both MCC and magnesium stearate. Experimental evidence showed the weakening effect of magnesium stearate to be less in the tablets formed from the ternary mix (with colloidal silica premixed with magnesium stearate prior to mixing with MCC) than when MCC and magnesium stearate only were used.

- **Surface free energy approach**

The application of surface free energy in the prediction of spreading of binders over powders is in principle very similar to the solubility parameter approach. The first study reporting the use of surface energy was by Rowe (1989b). If the surface free energies of both the binder and substrate are known, it is possible to calculate their fractional polarity and non-polarity in a manner analogous to solubility parameters.

\[
x_A^d = \frac{\gamma_A^d}{\gamma_A} \quad x_A^p = \frac{\gamma_A^p}{\gamma_A}
\]  

(3.7)

The constants \(g_1\) and \(g_2\) are thus defined as:

\[
g_1 = \sqrt{\frac{\gamma_A^d}{\gamma_B^d}} \quad g_2 = \sqrt{\frac{\gamma_B^d}{\gamma_A^d}}
\]

(3.8)

In addition, the work of cohesion (\(W_{coh}\)) of both components and the work of adhesion (\(W_{adh}\)) between the two components can be determined. The work of adhesion being the energy required to separate the unit area of two particles of two different phases adhering together and the work of cohesion that required to separate the unit area of two particles within one phase.
If the works of adhesion and cohesion are known, it is possible to calculate the spreading coefficients between components A and B. Spreading coefficients (\( \lambda \)) give an indication of the spreading behaviour of powders in a system. It is the difference between the work of adhesion between two phases (1 and 2) and the work of cohesion of the phase (1) that is to spread:

\[
\lambda_{1/2} = W_{\text{ads}} - W_{\text{coh}}
\]  

(3.11)

It was found that if the spreading coefficients of the binders over the powders were positive (as in the case of all binders with highly polar drugs), strong granules were formed as the binders spread over the powder. For low polarity drugs, the spreading coefficients of all binders over the drug particles were found to be negative but that of the drugs over the binders were positive. Granules so produced were different from the ones where the binder spread over the drug; more porous granules were obtained as the drug adhered to the binder at contact points. Rowe (1989c) pursued this line of research in the determination of the optimum binder to be used in wet granulation. Using literature values of solubility parameters, the reduced spreading coefficient (defined as the ratio of the work of adhesion to the work of cohesion of the binder) was determined to study the suitability of different types of binders on different substrates. It was predicted that granulation of low polarity substances would be more successful if polyvinyl pyrrolidone (PVP) was used and conversely, for highly polar substances, cellulose binders such as hydroxypropyl methylcellulose (HPMC) were more suitable. This spreading coefficient approach was also used in the prediction of properties such as granule friability, tablet strength and capping, from the surface energies of paracetamol and several binders Rowe (1990).

In the above studies, the interactions between powders and binders were successfully predicted but it must be remembered that both the solubility and spreading coefficient approaches were based on theoretical values obtained from the literature. Although solubility parameters give a good indication of surface energies, they remain an
idealised representation of real powders. Powders as mentioned previously are heterogeneous and possess varying proportions of hydrophilic and hydrophobic groups in the different regions of their surface. If the solubility parameters of powders are used, only an approximation of the true nature of their surfaces would be obtained. As such, these approaches are crude and simplified and the results obtained should only be used to predict trends in the system. In cases where values of the solubility parameters are unavailable, it would be advantageous if the surface nature of the powders could be measured. This can be achieved by measuring the surface energies of materials of interest; the methods by which this is done would be discussed below in section 3.2.2. Once measured, the values of the surface energies (instead of solubility parameters) would be used to build a model based on the spreading coefficients of powders instead of solubility parameters to predict the spreading behaviour of powders in the binary systems as an extension to Rowe’s work (Rowe 1989a). If successful, this approach would then be applied to ternary systems.

3.2. THEORY

The use of experimentally measured surface energetics data and spreading coefficients to predict interactions in two component systems has been explored in the past. Zajic and Buckton (1990) used surface energy values to predict the optimum binder (either HPMC or PVP) for the granulation of MCC. The surface energy of MCC was assessed using the Wilhelmy plate technique and the spreading coefficients of the binder-MCC systems calculated. The predicted superiority of HPMC over PVP as a binder for MCC was confirmed in terms of improved flow properties and less friable granules. A further study by Young and Buckton (1990) using the Wilhelmy plate technique to assess the surface energies of powders showed how the spreading coefficient approach was used to predict the aggregation of powders dispersed in water. The ease of dispersion of solids in forming non-aqueous suspensions (Parsons et al 1992) was found to be related to both the work of cohesion and spreading coefficients of the powders.
3.2.1. Surface energy considerations

3.2.1.1. Contact angle

There are different ways of measuring the angle formed by a liquid on a solid surface. If the surface is smooth and consistent in chemical composition, measuring the contact angle is easy and the value obtained would be reproducible. However, very often, surfaces of materials to be studied have a degree of roughness, as in the case of pharmaceutical powders. The determination of contact angles of liquids on solids is valuable in providing information on the surface characteristics of powders but is not simple. There are various aspects of the subject the scientist has to be aware of, such as the limitations of each technique and above all, how to interpret the data collected accordingly.

It is necessary to clarify the different variations of contact angles that can be encountered. The intrinsic contact angle is the angle measured at a distance of a few liquid molecules thick from the solid. However, this is practically impossible to measure and instead, the apparent contact angle (i.e. the angle seen at the macroscopic level) is measured. Furthermore, a range of apparent contact angles can be observed in practice. If the system is at rest, a static contact angle would be measured. A system at rest may however be in stable equilibrium (if the solid surface is ideally smooth and homogeneous) or in metastable equilibrium (when the solid surface is rough) in which case the contact angle measured would be a metastable angle that varies with drop volume and external factors such as vibration. Contact angles can be measured as the advancing angle ($\theta_a$) i.e. during formation, the drop advances across the surface or the receding angle ($\theta_r$) i.e. where a drop retracts over a previously wetted surface. Of all the contact angles mentioned, the most useful angle that workers measure is the advancing apparent angle, which for simplicity, would be referred to as the ‘contact angle’ in this study.

3.2.1.2. Factors affecting contact angle

a) Hysteresis

The occurrence of hysteresis is common in the field of surface energetics. It is defined as the difference between the measured advancing and receding contact angles:
Hysteresis \( = \theta_a - \theta_r \) \hspace{1cm} (3.12)

The two main causes of hysteresis are surface roughness and chemical heterogeneity at the surface of powders. Consider a liquid drop placed on an uneven surface. Depending on whether the drop falls into a cavity on the surface, the resulting measured contact angle would vary (figure 3.1).

Figure 3.1 shows how a drop of liquid on a rough surface can give rise to two different apparent contact angles when in fact both drops had identical true contact angles.

The effect of hysteresis as a result of chemical heterogeneity cannot be visualised as easily as surface roughness. Hysteresis occurs if the surface of the material consists of chemically different groups. On wetting the solid sample with liquid, the hydrophilic or hydrophobic groups would tend to rearrange themselves at the surface to optimise the interaction with the liquid. In the Wilhelmy plate technique, different values of contact angle are obtained when the plate is immersed (angle measured is the advancing angle) and subsequently removed (angle measured is the receding angle) from the liquid. In the sessile drop technique, the advancing angle is the one measured when the drop advances on the surface; as liquid is added, the base of the drop increases. If the drop is withdrawn from the solid surface using a needle and syringe, the drop decreases in height but the base remains the same until the contact angle equals the receding angle, after which the base retracts and decreases in size (figures 3.2a and b).
Figures 3.2 a and b show the effect of hysteresis arising due to the chemical heterogeneity of the surface.

b) Method of measurement

There is no ideal way of measuring the contact angles of liquids on solids (with the exception of polymer films, which have smooth homogeneous surfaces). All techniques used to measure contact angles of liquids on powders are flawed to some extent and the values of the measured angles are approximations of the true values. The limitations of the Wilhelmy plate and sessile drop techniques would be outlined here but a more detailed review of the limitations of other contact angle measurement techniques can be found in Buckton (1995a). In the past, samples were prepared by compacting the powder into wafers or discs for the Wilhelmy plate and sessile drop techniques respectively. This compaction process has been reported to cause plastic deformation at the surface of the compact (Buckton and Newton 1986, Kiesvaara and Yliruusi 1991 and Sheridan et al 1994), resulting in an alteration of the measured contact angles.

Both techniques are also subject to limitations due to surface roughness of the sample. For instance, in the Wilhelmy plate technique, one of the parameters required in the determination of the contact angle is the perimeter of the sample plate. This is measured using a micrometer and it was suspected that due to the roughness of the powder sample, the measured perimeter of the plate was lower than the true perimeter. Buckton et al (1995) and Pepin et al (1997) showed that the measured perimeter was in fact underestimated by approximately 1.78 times its true value. The implications are that the values of the contact angles measured need to be corrected accordingly,
otherwise the resulting measured angles would be greatly underestimated. The sessile drop technique is also subject to limitations due to the surface roughness of powders. This point was illustrated previously and shown in figure 3.1.

It was usual in the sessile drop technique to saturate the sample of interest with the liquid, which was to be used to form a drop on the compact. This may cause the sample to swell and the angle measured would not be the true contact angle. Another drawback associated with this procedure is that the liquid drop may rest partly on the surface of the powder and partly on the liquid used to saturate the sample. The measured contact angle ($\theta_m$) would hence be a weighted average of the fraction of the drop resting on both surfaces:

$$\cos \theta_m = f_s \cos \theta_s + f_l \cos \theta_l \quad (3.13)$$

where $f$ represents the fraction of the area of material (solid or liquid) with which the drop is in contact; $s$ denotes the solid and $l$, the liquid.

If the drop rests on both the liquid and solid surfaces, the measured angle would be an underestimate of the true contact angle. This is because the contact angle of a liquid drop on the surface of the same liquid would most certainly be zero and the $\cos$ of this angle would equal to 1. This causes the value of the $\cos$ of the measured angle to be higher than if the drop was placed entirely on a solid surface and hence, the value of $\theta_m$ would be lower than expected.

### 3.3. Calculation of Surface Energy

If the contact angle of only one liquid on a solid is measured, the data obtained is specific to only these two interacting systems. In order to obtain more information on the surface energy of the powder, more than one liquid should be used to probe the surface of the powder. A minimum of two liquids is required, of which preferably one should be apolar and the other polar in nature. The dispersive and polar components of the surface energy can thus be determined. If the polar component is to be described more specifically i.e. in terms of its electron donor and electron acceptor contributions, an additional polar liquid is required.
As outlined in section 1.4.1, the surface energy of a solid is the sum of its apolar (Lifshitz-van der Waals) component ($\gamma_{s}^{LW}$) and polar or acid-base ($\gamma_{s}^{AB}$) component:

$$\gamma_{s}^{tot} = \gamma_{s}^{LW} + \gamma_{s}^{AB}$$ (3.14)

The apolar and acid-base components are also referred as the dispersive ($\gamma_{s}^{d}$) and polar ($\gamma_{s}^{p}$) components respectively. Knowledge of these parameters would indicate the nature of the polarity and non-polarity of the surfaces of materials.

When a drop of liquid is placed on the surface of a solid, it forms a three-phase interface from which the contact angle of the liquid on the solid can be determined. The three forces acting on the drop (figure 3.3) are:

(i) $\gamma_{lv}$, which is the surface tension of the liquid in equilibrium with its vapour;
(ii) $\gamma_{sl}$, the interfacial tension of the liquid with the solid preventing the drop from spreading and
(iii) $\gamma_{sv}$, the surface energy of the solid in equilibrium with the vapour, acting to promote spreading of the liquid on the solid.

![Figure 3.3](image)

Figure 3.3 shows the forces acting at the interfaces when a drop of liquid is placed on a solid surface.

Assuming the solid surface is smooth and homogeneous, the contact angle, $\theta$, can be determined from the Young’s equation:

$$\gamma_{lv} \cos \theta + \pi c = \gamma_{sv} - \gamma_{sl}$$ (3.15)
where \( \pi_e \) is the change in surface energy of a solid, \( \gamma_s \), as a result of adsorption of vapour onto a solid:

\[
\pi_e = \gamma_s - \gamma_{sv} \tag{3.16}
\]

and \( \gamma_{sv} \) is the surface energy of the solid following adsorption of vapour. The existence of \( \pi_e \) has been ignored by past workers as it was assumed that for systems where wetting is poor, \( \pi_e \) is zero. Hence, equation (3.15) is reduced to:

\[
\gamma_l \cos \theta = \gamma_s - \gamma_{sl} \tag{3.17}
\]

where \( \gamma_s \) is the surface energy of the solid and \( \gamma_{sl} \) is the interfacial tension between the liquid and the solid.

The surface energy of the solid can be obtained from equation (3.17), as all the parameters can be measured except for the interfacial tension of the liquid with the solid, which remains unknown. It is thus necessary to consider the interfacial tension between the solid and liquid phases, \( \gamma_{sl} \).

### 3.3.1. Fowkes geometric mean approach

Fowkes (1964) proposed that for an apolar liquid, the relationship between the interfacial tension, the surface energy of the solid, \( \gamma_s \) and surface tension of the liquid, \( \gamma_l \) in terms of the geometric mean of the dispersive and polar components is:

\[
\gamma_{sl} = \gamma_s + \gamma_l - 2 (\gamma^d_s \cdot \gamma^d_l)^{1/2} \tag{3.18}
\]

where \( \gamma^d \) is the dispersive component of the solid (s) and liquid (l) respectively.

Combining equations (3.17) and (3.18),

\[
\gamma_l \cos \theta = \gamma_s - [\gamma_s + \gamma_l - 2 (\gamma^d_s \cdot \gamma^d_l)^{1/2}] \tag{3.19}
\]

i.e.

\[
\gamma_l (1 + \cos \theta) = 2 (\gamma^d_s \cdot \gamma^d_l)^{1/2} \tag{3.20}
\]
a) **Dispersive component**

If the contact angle of an apolar liquid on the solid is measured, the dispersive component of the solid ($\gamma_s^d$) can be determined from equation (3.20). The dispersive component of the liquid (equal to its surface tension) can either be measured or obtained from the literature. The only unknown in the above equation is $\gamma_s^d$.

b) **Polar component**

For a polar liquid, the interfacial tension between the solid and liquid takes into account the interaction due to the polar groups in both phases:

$$\gamma_s(1 + \cos \theta) = 2 \left( \gamma_s^d \gamma_l^d \right)^{1/2} + 2 \left( \gamma_s^p \gamma_l^p \right)^{1/2} \tag{3.21}$$

where $\gamma^p$ is the polar component of the solid (s) and liquid (l) respectively.

If the contact angle of a polar liquid on the solid is measured and substituted in equation (3.21) as well as the dispersive components of the liquid and solid and the surface tension of the liquid, the polar component of the solid can be determined.

### 3.3.2. Wu’s harmonic mean approach

Wu (1971) suggested a similar approach, which uses the harmonic mean of the surface energy components instead of the geometric mean as proposed by Fowkes (1964). The approach described below is recommended for more polar systems.

a) **Dispersive component**

For an apolar liquid, the interfacial tension between the liquid and the solid, $\gamma_{SL}$, becomes:

$$\gamma_{SL} = \gamma_s + \gamma_l - 4 \left( \frac{\gamma_s^d \gamma_l^d}{\gamma_s^d + \gamma_l^d} \right) \tag{3.22}$$

Combining equations (3.17) and (3.22),

$$\gamma_l(1 + \cos \theta) = 4 \left( \frac{\gamma_s^d \gamma_l^d}{\gamma_s^d + \gamma_l^d} \right) \tag{3.23}$$
As in the previous approach using Fowkes equation, the known values of the components of surface tension and contact angle are substituted in equation (3.23) to give the value of the dispersive component of the solid.

b) Polar component

For a polar liquid, the contributions from the polar group modifies equation 3.23 to:

\[
\gamma_i(1 + \cos \theta) = 4 \left[ \frac{\gamma_s^d \gamma_l^d}{\gamma_s^d + \gamma_l^d} + \frac{\gamma_s^p \gamma_l^p}{\gamma_s^p + \gamma_l^p} \right]
\]  

(3.24)

The polar components of the solid can thus be calculated if the contact angles of two liquids (one apolar and the other polar in nature) on the solid are measured. By substituting all known or measured parameters in equation (3.24), the value of the polar component can be obtained.

The values of the surface energy of a solid should not be significantly different if either the Fowkes or Wu’s equations were used. However, the choice of liquids may give varying values for the polar component of the surface energy of the solid depending on the polar liquid being used. This becomes important in cases where the polar component of the solid is higher than that of the polar liquid. The polar component of the solid would be influenced and tend towards the polar component of the liquid, to give an artificially low value (Buckton 1995a). Hence, it is advisable to use polar liquids of high surface tension and polarity for surface energy determination.

3.3.3. Van Oss approach

In this approach, the surface energy of a solid is considered in terms of its Lifshitz-van der Waals (LW) component and the electron donor and electron acceptor contributions to the acid-base component.

a) Dispersive component

The Young’s equation can be adapted using the Good-Girifalco (Good and Girifalco 1960) combining rule:
\[ \gamma_l (1 + \cos \theta) = 2 (\gamma_{LW}^l \cdot \gamma_{LW}^l)^{1/2} \]  

(3.25)

By first substituting the literature values of the surface tension and the LW component of the liquid in the above equation, the LW component of the surface energy of the solid can be determined, providing the contact angle of an apolar liquid on the solid is measured.

**b) Electron-donor and electron-acceptor components**

The acid-base parameter of the surface energy component (\(\gamma^{AB}\)) is a non-additive combination of the electron-acceptor (\(\gamma^\circ\)) and electron-donor (\(\gamma^\oplus\)) contributions:

\[ \gamma^{AB} = 2 (\gamma^\circ \cdot \gamma^\oplus)^{1/2} \]  

(3.26)

The interaction component between a polar liquid and a solid can be described as:

\[ \gamma_{sl} = 2 \left[ (\gamma^\circ_s \cdot \gamma^\circ_s)^{1/2} + (\gamma^\oplus_s \cdot \gamma^\circ_s)^{1/2} - (\gamma^\circ_s \cdot \gamma^\oplus_s)^{1/2} - (\gamma^\circ_s \cdot \gamma^\circ_s)^{1/2} \right] \]  

(3.27)

The Young’s equation can be expressed in terms of Lifshitz and acid-base interactions:

\[ \gamma_l (1 + \cos \theta) = 2 \left[ (\gamma_{LW}^l \cdot \gamma_{LW}^l)^{1/2} + (\gamma^\circ_s \cdot \gamma^\circ_s)^{1/2} + (\gamma^\circ_s \cdot \gamma^\circ_s)^{1/2} \right] \]  

(3.28)

This equation appears complicated but is based on the same principles as the Fowkes’s and Wu’s equations. However, in order to obtain all three components (\(\gamma_{LW}^l\), \(\gamma^\circ_s\) and \(\gamma^\oplus_s\)) of the surface energy of a solid, the contact angles of three liquids (one apolar and two polar) on the solid are required. If the LW component of the solid is known, the only two unknowns in equation (3.28) are the electron donor (\(\gamma^\oplus_s\)) and electron acceptor (\(\gamma^\circ_s\)). By substituting the contact angles, surface tension, electron acceptor and electron donor contributions of the liquids, two equations are obtained which when solved simultaneously, yield the electron-acceptor and electron-donor components of the solid.

It is worth noting that the absolute values of the electron donor and electron acceptor contributions of the surface tension of liquids are unknown and the values quoted in the literature are all relative to that of water. In surface energetics, the assumption
(although possibly incorrect) that the electron-acceptor component of water is equal to the electron-donor component is made:

$$\gamma^0_{\text{water}} = \gamma^0_{\text{water}}$$  \hspace{1cm} (3.29)

3.3.4. Calculation of spreading coefficients

As explained previously, spreading coefficients ($\lambda$) are useful in giving information on the spreading tendencies in binary systems. The calculation of $\lambda_{1/2}$, the spreading coefficient of phase 1 over 2 is achieved by taking the difference between the work of adhesion between components 1 and 2 and the work of cohesion of component 1:

$$\lambda_{1/2} = 4 \left[ \frac{\gamma_1^d \cdot \gamma_2^d + \gamma_1^p \cdot \gamma_2^p}{2} - \frac{\gamma_2^p}{2} - \frac{\gamma_1^p}{2} \right]$$ \hspace{1cm} (3.30)

If $\lambda_{1/2}$ has a value $\geq 0$, it implies that spreading of phase 1 over 2 will occur since the work of adhesion between the two phases is greater than the work of cohesion between phase 1. Conversely, a negative value of $\lambda_{1/2}$ shows that there is no tendency for phase 1 to spread over phase 2.

Similarly, the spreading coefficient, $\lambda_{2/1}$, of phase 2 over 1 can be determined and would give an indication of the tendency of phase 2 to spread over phase 1:

$$\lambda_{2/1} = 4 \left[ \frac{\gamma_1^d \cdot \gamma_2^d + \gamma_1^p \cdot \gamma_2^p}{2} - \frac{\gamma_1^p}{2} - \frac{\gamma_2^p}{2} \right]$$ \hspace{1cm} (3.31)

Surface energetics has proved to be useful in understanding and predicting the interactions in powder-liquid and powder-powder systems. The determination of contact angles, surface energies and hence the use of the spreading coefficient approach in the prediction of mixing behaviour would be the basis of the work in the following chapter.
3.4. SURFACE ENERGY USING IGC

Surface energetics of powders can also be determined using inverse gas chromatography (IGC). This technique would be discussed in more detail in chapter 6 but a brief mention is made here as the parameters determined by IGC are slightly different from the parameters outlined so far. IGC yields the dispersive component of the surface energy ($\gamma^d_s$) but the polar component is expressed in terms of the acid parameter ($K_A$) i.e. electron acceptor or basic parameter ($K_B$) i.e. electron donor parameters. There is as yet no known method of relating the polar component of the surface energy ($\gamma^p_s$) to the acid and basic parameters.


4. WILHELMY PLATE TECHNIQUE

SECTION A. IRON OXIDE MIXES

4.1. INTRODUCTION

The Wilhelmy plate technique can be used to determine the surface tension of liquids as well as the surface energetic properties of pharmaceutical solids. The reasons why this technique was chosen to obtain surface energy parameters of solids were its relative ease and speed of operation from which information on the surface nature of powders could be obtained. As an extension to Rowe’s work (Rowe 1989a, 1992), the surface energies of iron oxide, microcrystalline cellulose (MCC), magnesium stearate (Mg stearate) and titanium dioxide (Ti dioxide) were determined using the Wilhelmy plate technique. The limitations of this technique were discussed in the previous chapter. It is an indirect way of measuring the contact angles of liquids on solids as it measures the force exerted on the sample plate, which is then related to the contact angle. In order to determine the surface energy of a powder, it is necessary to measure the contact angles of various liquids of different nature on the solid. The contact angles will be used subsequently to calculate the surface energy of the solids. The spreading coefficient approach would be applied to understand and predict the mixing behaviour of powders in binary systems. Binary mixes of 50 %w/w iron oxide with a white excipient were prepared and in order to study the mixing of the particles, the mixes would be assessed by visual inspection as well as scanning electron microscopy. An attempt will be made to extend this approach to a three component mix, using glass as the third component.

4.2. METHOD

4.2.1. CLEANING SURFACES

Surface cleanliness is of utmost importance in surface science. Surfaces of glassware and samples used should be free from surface contaminants. Surfaces should never come in contact with bare hands as the surface grease from the skin could greatly affect
the surface tension or contact angle measurements. The established procedures for cleaning beakers were as follows: firstly, the beakers were cleaned using distilled water containing small amounts of detergent and placed in an ultrasound bath for 10 minutes; the beakers were then rinsed, filled with double distilled water and placed in the ultrasound bath for a further 10 minutes to remove excess detergent. To ensure the beaker was suitably cleaned, the beaker was filled with pure double distilled water and its surface tension measured at 20 °C. A value of 72.8 ± 0.5 mNm⁻¹ was deemed acceptable. The beakers can be drip-dried or wiped dry with a tissue. Once the cleaning technique was established, the beakers were filled with probe liquids and the surface tensions of the pure liquids were checked using flamed (to remove any impurities on the glass surface) glass slides or microscope cover slips prior to any contact angle measurement.

### 4.2.2. CHOICE OF LIQUID PROBES

The liquids were chosen if they satisfied a series of criteria. The solids should not dissolve nor swell on contact with the liquids. The liquids used should have relatively high surface tensions, as it should be remembered that liquids of low surface tension (e.g. decane) would tend to spontaneously spread over solids. The liquids used in this study and their surface tensions are shown in table 4.1.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Surface energy components (mJm⁻²)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>γTOT</td>
<td>γLW</td>
<td>γAB</td>
<td>γ∅</td>
<td>γΩ</td>
</tr>
<tr>
<td>Bromonaphthalene</td>
<td>44.4</td>
<td>44.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diiodomethane</td>
<td>50.8</td>
<td>50.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Formamide</td>
<td>58.0</td>
<td>39.0</td>
<td>19.0</td>
<td>2.3</td>
<td>39.6</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>48.0</td>
<td>29.0</td>
<td>19.0</td>
<td>1.9</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Table 4.1 shows the surface tension of liquids expressed in terms of the Lifshitz-van der Waals and their acid-base contributions.
The polar liquids used in this study were formamide and double distilled water. There are very few apolar liquids of sufficiently high surface tensions that can be used in this technique. Only two apolar liquids are suitable: diiodomethane and α-bromonaphthalene. However, it was found that these liquids very often did not yield the required surface tensions, and this was attributed to the presence of impurities from the supplying source. This problem was overcome by ordering liquids from various suppliers until liquids of acceptable surface tension were obtained. Details of the suppliers are given in chapter 2. In all cases, liquids should be of high purity (99% or higher) and give surface tensions within ± 0.5 mN/m of literature values.

4.2.3. PREPARATION OF BINARY MIXES

The mixes were prepared by blending 25 g of iron oxide with 25 g of white excipient in 100 ml clear glass jars with screw top lids in a Turbula mixer (T 2C) for 20 minutes:

Mix A consisted of iron oxide and MCC;
Mix B consisted of iron oxide and Mg stearate and
Mix C consisted of iron oxide and Ti dioxide.

4.2.4. SAMPLE PREPARATION

One of the well-known limitations of this technique lies in the sample preparation. It was found that samples prepared by compacting the powder under high pressures yielded samples that had been subjected to surface deformation (Buckton and Newton 1986, Sheridan et al 1994). Hence, another method of sample preparation was required. Following the encouraging results obtained by Dove et al (1996) in the use of glass slides coated with powder, their method of sample preparation was adopted. Initially, the glass slide (22 x 26 mm) was sprayed with adhesive (3M Spraymount) and was left to dry for 1 minute. The glass slide was then shaken in a glass jar containing powder until it was well covered; excess powder was removed by blowing with nitrogen gas. This method did not produce an evenly covered powder surface on the glass slides with titanium dioxide and iron oxide. An alternative method of coating the adhesive-covered glass slides was used. Instead of shaking the adhesive-covered slides, powder was gently brushed onto the glass slides and excess powder brushed away. It is important to
spray the adhesive as evenly as possible on the plate to ensure a uniform surface for contact angle measurement. The length of time the adhesive was left to dry before being covered with powder had to be judged accordingly. If left to dry for too long, the powder would not adhere adequately to the adhesive but if not sufficiently dry, brushing the powder would remove the adhesive from the glass slide. The samples were used for contact angles measurement 24 hours after sample preparation. The sample plates for the binary blends were prepared by brushing the mix (instead of the individual powder) over glass plates sprayed with adhesive, in the same manner as for individual powders. The importance of good laboratory practices in the measurement of surface properties of materials cannot be overstated and care should be taken not to contaminate the sample while preparing and loading the sample on the microbalance.

4.2.5. CALIBRATION OF THE ELECTRONIC MICROBALANCE

The balance was calibrated on a daily basis using a 500 mg weight. The metal weight was handled with tweezers to ensure the accurate calibration of the balance. The balance was first tared and the weight suspended on the hang-down wire. When consistent readings, corresponding to the weight used were recorded, the balance was deemed ready for use.

4.2.6. MEASUREMENT OF CONTACT ANGLE

The sample plate was suspended onto the hang-down wire of the electronic microbalance using crocodile clips, ensuring that the plate hung vertically above the liquid. The beaker of probe liquid was placed in a water jacket through which water of a set temperature circulated (figure 4.1). It was important that the temperature inside the chamber was kept at 20 °C throughout the experiment as the surface tension of a liquid is altered by changes of temperature. The DCA microbalance is interfaced with a computer, which initiates the movement of the platform as well as records the force required to suspend the plate vertically.
Figure 4.1 shows the starting position for a contact angle or surface tension experiment by the CAHN DCA (Dynamic Contact Angle analyser).

Certain parameters were required to be entered in the software so that calculations of contact angles or surface tensions can be made. One such parameter was the perimeter of the sample plate, which was measured using a micrometer. For contact angle measurements, the surface tension of the liquid should also be entered. The balance was tared as soon as the plate was still and no longer oscillating. The platform was raised by a distance of 1 cm from the starting position, at a speed of 151.7 μmsec⁻¹. Following immersion of the plate into the liquid, the platform was lowered back to its original position. Both the distance moved by the platform and the forces exerted on the plate were recorded to give an output shown in figure 4.2. In surface tension measurements, the sample plate is a glass plate suspended to the electronic microbalance.

All the stages of measurement as shown in figure 4.2 are now discussed. Line AB corresponds to the stage when the platform was being raised but the liquid had not yet contacted the plate. At the point of contact of the sample plate with the liquid, the plate experiences a downward pull into the liquid. In order to suspend the plate vertically, a force is required. This force was registered by the microbalance and corresponds to line BC. As the platform continued rising, the plate was immersed and the output is shown by line CD. The platform was then raised as illustrated by the dashed line XY.
Figure 4.2 shows a typical output trace of a Wilhelmy plate measurement.

Calculation of contact angles from these force measurements requires the determination of the force exerted on the plate on first contact with the liquid. A vertical line is drawn at point B, which corresponds to the point of contact of the liquid with the sample plate. The intersection of the vertical line with the extrapolated line CD gives the value of the force experienced by the plate on contact with the liquid. This force is used to calculate the advancing contact angle ($\theta$):

$$\cos \theta = \frac{F}{p \gamma_L}$$  \hspace{1cm} (4.1)

where $F$ is the force recorded at the point of contact, $p$ is the perimeter of the sample plate, $\gamma_L$ is the surface tension of the liquid.

Similarly, the receding contact angle is obtained by measuring the force at which the line XY intersects the vertical line drawn at point B. The advancing angles were recorded in this study as they reflect more accurately the nature of the sample surface. The receding angles may be subject to hysteresis due to reorientation of the polar and non-polar groups at the surface of the powder following wetting of the plate.
4.2.7. **Assessment of mixing behaviour**

The spreading behaviour of the powders in the binary mixes was determined by visually examining the colour and appearance of the mixes. Scanning electron micrographs of the individual powders and binary mixes were taken using a scanning electron microscope (Philips XL 20) to study the powders at a particulate level. The spreading tendency of the binary mixes on glass was assessed in terms of the amount of the blend adhering to the wall of the glass jar.

4.3. **RESULTS AND DISCUSSION**

The three mixes were very distinct in appearance (figure 4.3). Mix A (iron oxide and MCC) was uniform and deep red in colour; mix B was predominantly white with red specks of iron oxide interspersed in the mix and mix C was pink in colour and contained spheroids which when crushed showed a white core of titanium dioxide particles.

Figure 4.3 shows mixes A (iron oxide and MCC), B (iron oxide and magnesium stearate) and C (iron oxide and titanium dioxide).
It should be noted that the mixes showed different tendencies to adhere to the glass walls of the containers. Mix A showed no tendency to adhere leaving a clear glass wall; mix B adhered strongly to the glass wall and mix C to a lesser extent.

**4.3.1. PREDICTIONS BASED ON SPREADING COEFFICIENTS**

**4.3.1.1. Binary mixes**

- **Contact angles, dispersive and polar components of individual powders**

The results of the contact angles of the liquids on the solids are a mean of five measurements. The contact angles of the liquids on the solids were corrected by a factor of 1.78 to account for the underestimated perimeter of the plate due to surface roughness (as discussed in section 3.2.1.2b). Both the measured and corrected contact angles are shown in table 4.2.

<table>
<thead>
<tr>
<th>Material</th>
<th>Measured contact angle (°)</th>
<th>Corrected contact angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formamide</td>
<td>Diiodomethane</td>
</tr>
<tr>
<td>Iron oxide</td>
<td>60.2 (3.4)</td>
<td>57.4 (3.7)</td>
</tr>
<tr>
<td>MCC</td>
<td>16.6 (2.0)</td>
<td>31.9 (3.9)</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>89.6 (0.6)</td>
<td>90.3 (2.5)</td>
</tr>
<tr>
<td>Ti dioxide</td>
<td>63.8 (2.7)</td>
<td>48.6 (3.1)</td>
</tr>
</tbody>
</table>

Table 4.2 shows the contact angle data of formamide and diiodomethane on the powders with the values in ( ) showing the standard deviation.

The dispersive and polar components of the surface energy of the individual powders were determined using Wu’s equation as outlined in section 3.2.2. Table 4.3 shows the dispersive and polar values prior to and after correction of the contact angles by a factor of 1.78.
Table 4.3 shows the dispersive and polar components of the surface energy of the individual powders.

- **Spreading coefficients of binary systems**

The spreading coefficient approach has until now, always been applied to systems in which one phase was a powder and the other a liquid (except by Rowe 1989a). In the present study, all the phases studied were solid phases, either powders or glass. In principle, the spreading coefficient approach should apply to solid-solid systems. The spreading coefficients of the two components in a binary mix were calculated as shown in section 3.3.4. The spreading coefficients of phase 1 over 2 and of phase 2 over 1 for the binary mixes were calculated (using both experimentally measured and corrected values) and the data shown in table 4.4.

Table 4.4 shows the spreading coefficients of the binary powders.

The values of the spreading coefficients calculated from the corrected values were slightly different from those using experimentally measured contact angles but the overall trend was the same. In mix A (iron oxide and MCC), the spreading coefficient of iron oxide over MCC was positive and that of MCC over iron oxide negative. This
implies that iron oxide was spreading over the MCC particles to give a uniform red
coloured mix as seen from figure 4.3. This was further confirmed by scanning electron
micrographs of the powders taken before and after mixing, as shown in figure 4.4 (a, b
and c). Figure 4.4c shows the iron oxide particles adhering to the surface of MCC
particles. It should be noted that the scanning electron micrograph of iron oxide was
taken at a higher resolution (magnitude 15,000x and scale 1 μm) compared with those
of MCC and the mix (magnitude 400x and scale 50 μm).

Figure 4.4a shows the scanning electron micrograph of iron oxide particles.
Figure 4.4b shows the scanning electron micrograph of MCC particles.

Figure 4.4c shows the scanning electron micrograph of mix A (iron oxide and MCC).
Mix B, of iron oxide and magnesium stearate gave a negative value for the spreading coefficient of iron oxide over magnesium stearate but a positive value for that of magnesium stearate over iron oxide. The prediction in this case, is that the magnesium stearate would enrobe the iron oxide particles and this is clearly seen as the mix was predominantly white (figure 4.3). The scanning electron micrographs further support these findings (figure 4.5 a and b) and it can be seen from figure 4.5b that the iron oxide particles tend to cohere together, which is seen macroscopically as red specks interspersed within the white mix.

Figure 4.5a shows the scanning electron micrograph of magnesium stearate particles.
Figure 4.5b shows the scanning electron micrograph of mix B (iron oxide and magnesium stearate).

The third mix containing iron oxide and titanium dioxide was pink in colour and both spreading coefficients of mix C were found to be negative, implying that neither iron oxide nor titanium dioxide had any tendency to spread over the other component in the mix. This mix was slightly different from mixes A and B in that the components balled up to form spheroids. On crushing the spheroids with a spatula, a white core of titanium dioxide was seen suggesting the formation of aggregates in mix C (figure 4.6). This observation is in keeping with the predictions from the spreading coefficients of either component over the other being negative. The overall pink colour of the mix can be considered as an equal contribution from each component: iron oxide and titanium dioxide. The scanning electron micrographs show titanium dioxide particles cohering together before mixing (figure 4.7a) as well as after mixing (figure 4.7b).
Figure 4.6 shows spheroids formed in mix C. A white core was revealed on crushing the spheroids with a spatula.

Figure 4.7a shows the scanning electron micrograph of titanium dioxide.
Figure 4.7b shows the scanning electron micrograph of mix C (iron oxide and titanium dioxide).

- **Comparison with Rowe’s data**

The data for the adhesive and cohesive strengths of the above mixes were taken from Rowe’s paper (Rowe 1989a, 1992) and shown in table 4.5.

<table>
<thead>
<tr>
<th>Material</th>
<th>Adhesive strength (MPa)</th>
<th>Material</th>
<th>Cohesive strength (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Oxide/MCC</td>
<td>207.3</td>
<td>Iron Oxide</td>
<td>196.0</td>
</tr>
<tr>
<td>Iron Oxide/ Mg Stearate</td>
<td>121.8</td>
<td>MCC</td>
<td>386.1</td>
</tr>
<tr>
<td>Iron Oxide/ Ti Dioxide</td>
<td>237.5</td>
<td>Mg Stearate</td>
<td>82.3</td>
</tr>
<tr>
<td>Ti Dioxide</td>
<td>-</td>
<td>Ti Dioxide</td>
<td>295.8</td>
</tr>
</tbody>
</table>

Table 4.5 shows the strengths of interaction in the iron oxide mixes determined from solubility parameters.

The conclusions drawn using the experimentally measured surface energies of powders are in keeping with the findings by Rowe. The spreading coefficient approach using experimentally measured surface energies predicted similar results in mixes A (iron
oxide and MCC) and B (iron oxide and magnesium stearate). However, in the third mix, Rowe proposed that iron oxide should spread over titanium dioxide due to the higher adhesive strength between the two components relative to the cohesive strength within iron oxide. The findings of the present study, based on experimentally determined surface energy of the powders, suggest that neither of the two components spread over the other. This was confirmed by scanning electron micrographs of the mix: both iron oxide and titanium dioxide particles showed no adhesion tendency. The pink appearance of the mix further confirmed that the iron oxide could not be spreading over titanium dioxide otherwise the mix would have been deep red as in the MCC mix. Hence, the measurement of surface energies of powders is more accurate in predicting the mixing of powders compared with the use of theoretically determined solubility parameters.

- **Particle size analysis**

An attempt to study the importance of particle sizes on the spreading behaviour in the binary mixes was made. The particle sizes of the materials were determined using scanning electron microscopy and laser diffraction (Malvern 2600C) and are shown in table 4.6.

<table>
<thead>
<tr>
<th>Material</th>
<th>Median particle size ($\mu$m) (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEM with manual count</td>
</tr>
<tr>
<td>Iron Oxide</td>
<td>0.6 (0.4)</td>
</tr>
<tr>
<td>MCC</td>
<td>70.1 (47.7)</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>5.9 (6.0)</td>
</tr>
<tr>
<td>Ti Dioxide</td>
<td>0.2 (0.1)</td>
</tr>
</tbody>
</table>

Table 4.6 shows the median particle size of the materials used in the binary mixes.

In mix A, the smaller particles of iron oxide adhered to larger MCC particles. This observation has been thoroughly discussed in the literature and is referred to as the carrier mechanism. However, it was surprising to observe the spreading of the larger particles of magnesium stearate over the smaller iron oxide particles. In the third mix (iron oxide and titanium dioxide), even though both components had similar particle sizes, neither titanium dioxide nor iron oxide particles showed any tendency to adhere to each other. Hence, although particle size is an important factor in mixing, the studies
carried out here showed that the spreading of powders in binary mixes is not governed entirely by the particle sizes of the components.

4.3.1.2. Tertiary systems

Following the successful use of the spreading coefficient approach to predict mixing in binary mixes, an attempt was made to extend this approach to a three component system. These systems consisted of the two components of the binary mixes with glass being the third component. For all intents and purposes i.e. in the preparation of sample plates as well as in the visual assessment and analysis of the data, the mixes were treated as if they were composed of only one entity. The contact angles of liquids on the mixes and glass are shown in table 4.7.

<table>
<thead>
<tr>
<th>Material</th>
<th>Measured contact angle (°)</th>
<th>Corrected contact angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formamide</td>
<td>Diiodomethane</td>
</tr>
<tr>
<td>Iron oxide/ MCC mix</td>
<td>24.6 (4.6)</td>
<td>14.9 (0.7)</td>
</tr>
<tr>
<td>Iron oxide/ Mg stearate mix</td>
<td>89.6 (0.2)</td>
<td>88.9 (2.4)</td>
</tr>
<tr>
<td>Iron oxide/ Ti dioxide mix</td>
<td>38.6 (1.9)</td>
<td>53.6 (2.6)</td>
</tr>
<tr>
<td>Glass</td>
<td>17.8 (1.7)</td>
<td>56.9 (0.8)</td>
</tr>
</tbody>
</table>

Table 4.7 shows the contact angles of formamide and diiodomethane on the mixes and glass with the values in () showing the standard deviation.

- **Dispersive and polar components of binary mixes**

The dispersive and polar components of the surface energy of the mixes were calculated for the mixes. The resulting surface energies of the systems using both experimentally measured and corrected values of contact angles are shown in table 4.8.
### Table 4.8

<table>
<thead>
<tr>
<th>Material</th>
<th>Surface energy (mJm$^2$)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to correction</td>
<td>After correction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dispersive</td>
<td>Polar</td>
<td>Dispersive</td>
</tr>
<tr>
<td>Iron oxide/MCC mix</td>
<td>49.1</td>
<td>8.7</td>
<td>31.9</td>
</tr>
<tr>
<td>Iron oxide/Mg stearate mix</td>
<td>17.3</td>
<td>3.0</td>
<td>17.2</td>
</tr>
<tr>
<td>Iron oxide/Ti dioxide mix</td>
<td>33.6</td>
<td>13.1</td>
<td>25.4</td>
</tr>
<tr>
<td>Glass</td>
<td>32.0</td>
<td>24.6</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Table 4.8 shows the dispersive and polar components of the surface energy of the mixes and glass.

**Spreading coefficients of tertiary systems (binary mixes and glass)**

As mentioned earlier, the three mixes tend to adhere to different extents to the glass walls of the jars. The spreading coefficients of the binary mixes over glass were used to predict their adhesion tendencies to glass. The values are shown in table 4.9 as well as the spreading coefficients of the individual powders over glass.

<table>
<thead>
<tr>
<th>Material 1</th>
<th>Material 2</th>
<th>Spreading coefficients (mJm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Using experimental values</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 over 2</td>
</tr>
<tr>
<td>Iron oxide/MCC mix</td>
<td>Glass</td>
<td>-12.4</td>
</tr>
<tr>
<td>Iron oxide/Mg stearate mix</td>
<td>Glass</td>
<td>15.0</td>
</tr>
<tr>
<td>Iron oxide/Ti dioxide mix</td>
<td>Glass</td>
<td>6.3</td>
</tr>
<tr>
<td>Iron oxide</td>
<td>Glass</td>
<td>7.2</td>
</tr>
<tr>
<td>MCC</td>
<td>Glass</td>
<td>-5.5</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>Glass</td>
<td>15.6</td>
</tr>
<tr>
<td>Ti dioxide</td>
<td>Glass</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

Table 4.9 shows the spreading coefficients of the binary mixes and individual powders with glass.
As expected, the spreading coefficients calculated using experimentally measured and corrected values of contact angles were different. However, if the data were studied within each class i.e. using either the measured or corrected values, the trend was found to be the same. In mix A (iron oxide and MCC), both the spreading coefficients of the iron oxide/MCC over glass and of glass over the mix were negative. This implies that both phases had no tendency to spread over the other, resulting in the glass wall of the bottle being clear with no particles adhering to the walls (figure 4.3). In the second mix, B (iron oxide and Mg stearate), the spreading coefficient of the mix over glass was positive and that of glass over the mix was negative. This indicates that mix B would have a tendency to coat the glass wall of the bottle as seen from figure 4.3. In the iron oxide/titanium dioxide mix, the spreading coefficient of the mix over glass was again positive whereas that of glass over the mix was negative and the mix coated the glass wall. It is interesting to note that the relative magnitudes of the spreading coefficient values for mixes B and C over glass reflected the extents to which the powders coated the glass. A higher value of the spreading coefficient of mix B compared to C over glass suggested that the iron oxide/magnesium stearate mix would adhere to a greater extent to the glass wall than the iron oxide/titanium dioxide mix.

When using the spreading coefficients to predict mixing in a binary mix, it is easy to visualise the spreading of one component over the other (or in some cases, the complete separation of both). However, in the three component systems, the spreading behaviour of the mixes was slightly harder to explain. One hypothesis is that the powder, which predominantly covers the other powder in a binary mix, would govern how the mix would behave on contact with glass. This is certainly true in the case of mix B, where magnesium stearate enrobed the iron oxide particles. The resulting mix adhered strongly to glass, as would be predicted from the positive value of the spreading coefficient of magnesium stearate over glass (10.0 in table 4.9). However, this theory does not hold in the case of mix A, where although iron oxide adhered to the surface of MCC particles, the resulting mix showed no tendency to adhere to glass. A value of 4.0 was calculated for the spreading coefficient of iron oxide over glass which indicates that if this hypothesis holds true, mix A should have adhered to glass. In the case of mix C, both iron oxide and titanium dioxide were present as aggregates. Contrary to what would be expected from the positive spreading coefficients of the two individual components over glass, the mix showed limited adhesion to glass. It is concluded that the adhesion tendency of mixes cannot be predicted from the surface energies of the
individual powders. There seems to be some interaction between the two components of the mix resulting in an overall surface energy of the mix being different from that of either component. A more accurate prediction is obtained if the surface energies of the mixes are used.

4.4. CONCLUSIONS

The spreading coefficient approach based on experimentally determined surface energy values successfully predicted the mixing behaviour in binary mixes of iron oxide and a white excipient (MCC, magnesium stearate and titanium dioxide). The predictions were confirmed by the visual assessment of the colour and appearance of the mixes as well as by scanning electron microscopy on the powders before and after mixing. The data are in agreement with and improve upon the findings made by Rowe (1989a, 1992) on the predictions of the mixing of powders in binary systems.

The application of the spreading coefficient approach was extended to predict the spreading behaviour of tertiary systems. The mix was considered to form one phase with the other phase being glass. The overall surface energy of the mix was found to be different from that of its constituents. One useful observation was that it was not possible to predict how the mixes would coat the glass wall by consideration of the surface energies of the individual powders. Instead, the extent of adhesion of the mixes over the glass walls of the bottles was accurately predicted using the surface energy data of the mixes.

In this study, only the influence of surface energetics has been considered. Other factors such as electrostatics and particle shape and humidity of the environment would be expected to play an important role in determining how powders mix. The presence of all these factors has been ignored but it does not imply that they are not relevant. Surface energetics of powders appear to play a significant role in the behaviour of powders during mixing. This is very promising as the characterisation of powders is a relatively easy and non time-consuming task. The Wilhelmy plate technique has the advantage of being automated and hence not operator dependent. It does not require extensive training and can be operated with minimum skills. Only a small amount of
powder is required for sample preparation (approximately 2 g), which is an advantage in cases where active compounds are available in limited quantities.
4.5. INTRODUCTION

Following the positive outcome of the spreading coefficient approach in predicting mixing, the surface energies of the pharmaceutical powders provided by Pfizer Central Research: zamifenacin and the excipients used in its formulation were determined.

4.6. METHOD

Initially the surface energies of only three powders: zamifenacin, maize starch and lactose monohydrate were studied. The purpose was to check the suitability of the spreading coefficient approach to predict mixing of pharmaceutical powders. The sample plates were prepared and contact angles of several liquids measured on the solids in the same way as described in section 4.2.4 and 4.2.6. The liquids used were bromonaphthalene as the apolar probe, since the surface tension of diiodomethane was significantly lower than expected. The polar probe used was ethylene glycol.

4.7. RESULTS AND DISCUSSION

4.7.1. CONTACT ANGLES

The measurement of the contact angles, \( \theta \), of liquids on lactose powder proved to be problematic. The contact angles measured for bromonaphthalene on lactose monohydrate were found to be highly variable. It was also not possible to measure the contact angle of ethylene glycol on lactose monohydrate. It should be recalled that the computer software interfacing the DCA microbalance uses the force exerted on the sample plate to calculate the value of \( \cos \theta \), from which \( \theta \), the desired contact angle is derived. Hence, whenever the value of the \( \cos \) of the contact angles were higher than 1, mathematically, the contact angles would be less than zero. In such cases, the values of the \( \cos \) of the angles were recorded. These were then corrected by a factor of 1.78 to
account for the underestimation of the perimeter of the sample plate due to surface roughness and the corrected values are shown in table 4.10.

<table>
<thead>
<tr>
<th>Material</th>
<th>Measured contact angles (°)</th>
<th>Corrected contact angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromonaphthalene</td>
<td>Ethylene Glycol</td>
</tr>
<tr>
<td>Zamifenacin</td>
<td>36.0 (0.9)</td>
<td>77.8 (1.9)</td>
</tr>
<tr>
<td>Starch</td>
<td>35.9 (1.9)</td>
<td>60.2 (2.8)</td>
</tr>
<tr>
<td>Lactose</td>
<td>21.3 (9.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.10 shows the contact angle values of bromonaphthalene and ethylene glycol on solids.

The following suggestions as to why contact angles of lactose samples could not be obtained are:

a) Lactose was dissolving in ethylene glycol. A saturated solution of lactose in ethylene glycol was made up and the excess lactose filtered. Undefined angles (θ < 0) were obtained.

b) The surface tension of the liquid is being altered as a result of the dissolution of lactose from the glass plate. The surface tension of the saturated liquid was measured before and after lowering the lactose glass plates. No significant change in surface tension of the liquid was noted (less than 0.5 mN/m).

c) The liquid is migrating up the lactose plate at a faster rate compared with the speed at which the plate is being lowered; the contact angle measured would be that of liquid over liquid (hence instant spreading) and a contact angle around zero would result. To counteract this, the speed at which the platform rose was altered. The speed was increased from 151.7 to 200 μmsec⁻¹ (which is the maximum speed available). Still undefined angles were obtained. If the speed was reduced to 20.1 μmsec⁻¹ (lowest speed available), undefined angles were obtained.

d) The water content of lactose samples could affect the measurement of contact angle. The water content of Lactose monohydrate was found to be 0.04% after drying for 1 hour at 50 °C. Glass plates were coated using lactose held at 97% RH for 3 days. Undefined angles were obtained and the water content could not be the cause.
e) Lactose could be dissolving in the adhesive used to coat the glass plates with powder. In order to investigate the effects of adhesive on lactose, Differential Scanning Calorimetry (DSC) thermographs of lactose and adhesive samples were obtained. The samples were prepared by spraying adhesive on the lid of a DSC pan. The adhesive was allowed to dry to constant weight and approximately 2 mg of lactose was placed on the adhesive. The lid and pan were crimped with the adhesive and lactose enclosed inside the pan. By varying the amount of adhesive sprayed on the lid and keeping the amount of lactose constant, the effects of adhesive over lactose can be studied. The samples were heated from 25 to 225 °C at a rate of 10°C/min\(^{-1}\). The enthalpies of evaporation of water and of fusion were plotted as a function of increasing % adhesive and are shown in figures 4.8 and 4.9 respectively.

![Graph showing enthalpy of evaporation of water from lactose monohydrate as a function of % adhesive used.](image)

Figure 4.8 shows the enthalpy of evaporation of water from lactose monohydrate as a function of % adhesive used.

The DSC thermographs of adhesive only did not show any enthalpy change over the temperature range used for scanning. It was deduced that there was no interaction between the adhesive and lactose. The enthalpy values decreased as the % adhesive increased. For instance, in figure 4.8, the enthalpies of evaporation at 20% adhesive (i.e. 80% lactose) and 80% adhesive (i.e. 20% lactose) are approximately 80 and 20 J/g.
respectively. The fourth-fold decrease in the % lactose gave a fourth-fold decrease in the enthalpy of evaporation. Similar observations were made when the enthalpies of fusion of lactose-adhesive samples were considered (figure 4.9).

![Figure 4.9](image_url)

Figure 4.9 shows the enthalpy of fusion of lactose monohydrate as a function of % adhesive used.

### 4.7.2. DISPERSSIVE AND POLAR COMPONENTS

The dispersive and polar components of the three powders were determined using the corrected contact angles in Wu’s and Fowkes’s equations. The data is shown in table 4.11.

<table>
<thead>
<tr>
<th>Material</th>
<th>Wu’s equation</th>
<th>Fowkes’s equation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surface energies (mJm⁻²)</td>
<td>Surface energies (mJm⁻²)</td>
</tr>
<tr>
<td></td>
<td>Dispersive</td>
<td>Polar</td>
</tr>
<tr>
<td>Zamifenacin</td>
<td>25.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>Starch</td>
<td>25.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>27.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Table 4.11 shows the dispersive and polar components of the surface energy of the above powders determined using Wu’s and Fowkes’s equation.
The first point to note is that the polar component of the surface energy of zamifenacin determined using Wu’s equation was found to be negative. This could be approximated to zero, hence assuming that zamifenacin has a negligible polar component, and is entirely a non polar compound. This fact would be confirmed later using subsequent characterisation techniques. The second point to note is that the dispersive components of all three powders calculated from both Wu’s and Fowkes’s equations were found to be similar, being identical in the case of zamifenacin and starch. The polar components were almost the same for starch and lactose monohydrate when determined using Wu’s equation. The fact that the surface energies of all three powders were so similar indicates that these values were not reflecting the actual surface properties of the powders.

4.8. CONCLUSIONS

The measurement of contact angles and surface energies of the three pharmaceutical powders studied: zamifenacin, starch and lactose monohydrate proved to be complicated. In some cases, undefined contact angles (i.e. \( \theta < 0 \) or \( \cos \theta > 1 \)) of liquids on solids were obtained by the Wilhelmy plate technique. This could be due to experimental artefacts such as the surface roughness of the sample plate. Correction of the measured contact angles by a factor of 1.78 yielded more realistic values for the angles. However, when the surface energies of the powders were calculated using the corrected angles, the dispersive and polar components were found to be unexpectedly similar. The presence of adhesive in the sample preparation was studied using lactose as the model powder. DSC thermographs were taken of lactose-adhesive samples and no interaction between lactose and adhesive could be detected.

It was concluded that the use of powder-coated glass slides and the Wilhelmy plate technique were not suitable for studying surfaces of the above pharmaceutical powders. No further analysis of the data was undertaken as there was little confidence that the measured surface energies were true reflections of the surface nature of the powders. Another instrument, the Dynamic Angle Tester (DAT) based on the sessile drop technique would be used to determine the contact angle of powders.
5. DYNAMIC ANGLE TESTER (DAT)

5.1. INTRODUCTION

A novel instrument known as the Dynamic Angle Tester, DAT (DAT 1100 from Fibro Systems AB, Sweden) was used for the first time to measure contact angles of liquids on pharmaceutical powders. It operates on the basis of the sessile drop technique and measures directly the contact angles of liquids on powders. The advantage of the DAT is that it is entirely automated. A syringe and pump system dispenses the drop of liquid, and a video camera captures images of the drop. Parameters such as the contact angle and the volume of the drop are generated by the software, as a function of time. Since the Wilhelmy plate technique using powder-coated glass slides as samples were found to give unrealistic surface energy values for zamifenacin and other excipients, it would be advantageous if this novel instrument yielded more realistic data. It is well documented that the limitations of the sessile drop technique lie primarily in the preparation of the sample and the measurement of the angle (Buckton 1995a). In the past, if the sample of interest was a powder, compaction of the powder was required to form a disc onto which a drop of liquid was placed. Although reproducible values were obtained, the angles measured were not a true reflection of the surface of the powder as used (Buckton and Newton 1986). It was also usual to saturate the sample with the test liquid and as explained in section 3.2.1.2, this led to an underestimation of the contact angle measured. However, sample preparation in the DAT does not involve compaction of the powder or the saturation of the sample with liquid.

Other limitations associated with the measurement of contact angle by the sessile drop technique were due to operator dependency. The measurement of the angle was either done directly as the drop was deposited on the sample or following reconstruction of the drop on a photograph taken as soon as the drop contacted the surface. If the angle was measured directly, problems such as reflex time (as the drop gradually sinks into the powder bed) and parallax errors would lead to variations in data obtained from different operators. An indirect way of obtaining the contact angle was by the measurement of the maximum height of a drop of the liquid formed. This method is known as the h-ε...
method (Heertjes and Kossen 1967) and from this height measurement, the contact angle (θ) can be derived. Because of the porous nature of the compact, the true angle at the point of initial contact would be difficult to measure. Reconstruction of the drop would give a more accurate measurement of the angle. A circle was first drawn to complete the outline of the drop. From the centre of the circle, a line was drawn to intersect the circle at the point where the drop met the surface. A tangent drawn to the surface of the drop at that point and perpendicular to the line drawn from the centre was used to give the angle the drop made with the horizontal. The sessile drop technique, as used in the past, yielded results that were highly dependent on the skill of the operator. The design of the DAT is such that it precludes the sources of error originating from the operator in the measurement of the contact angle. Hence, none of the above problems should be encountered.

5.2. METHOD

5.2.1. Instrumentation

The DAT consists of a sample stage, a liquid delivery system, a light source (halogen lamp) and a video camera. These are interfaced with a computer, which initiates the delivery of the drop of liquid, the capture of the images of the drop and the measurement of the contact angles, and hence substitute entirely the manual input from the operator. The liquid delivery system consists of a PTFE tube, connected on one end to a 1 ml micro-syringe, with the other end suspending freely over the sample surface after being threaded through an applicator. The micro-syringe is driven by a pump, which when activated moves the plunger forward to deliver a droplet of the required size. As the DAT is triggered, a drop is formed on the tip of the tube and the stroke pulse (which is a sharp downward motion of the applicator) is applied to the applicator. This causes the drop to detach from the tip and fall on the surface of the sample located underneath it (figure 5.1). Immediately, images of the drop on contact with the surface are taken and viewed on the computer screen.
Figure 5.1 shows a schematic representation of the DAT with the insert showing a magnified picture of the applicator with a drop being deposited onto the sample. The two sample holders used are also shown.

5.2.2. Sample preparation

The powders studied were zamifenacin and a series of 5 excipients: starch, lactose monohydrate (Lactose Mono), anhydrous lactose (Anh. Lactose), spray-dried lactose (Spray. Lactose) and magnesium stearate (Mg stearate). Binary mixes of the active compound with all 5 excipients were blended in a Turbula mixes (T 2C) for a period of 20 minutes. Contact angles of liquids on the individual powders and binary mixes were measured.

Two types of sample holder were available. The first type was a block with a smooth flat surface onto which adhesive (3M SprayMount) was sprayed. The adhesive was allowed to dry and powder was brushed onto the adhesive in a manner analogous to the
preparation of powder coated slides. The second holder contained circular cavities (1cm diameter x 0.5cm deep) into which powder was packed using a metal block of the appropriate diameter. An equal amount of pressure was applied for each sample. The excess powder was scraped off using a blade, to leave a levelled surface. Each sample holder had a total of 10 spots available for contact angle measurement. The surface of the sample was as expected, rough and if the roughness exceeded a certain level as marked on the screen, the camera rejected the measurement spot and moved on to the next spot.

5.2.3. Liquids used

The apolar liquid used was bromonaphthalene and the polar liquids were double distilled water and formamide. Details of the suppliers from which these liquids were obtained can be found in chapter 2. The syringe was filled with the liquids to be used. The surface tensions of the liquids used were tested before and after passage through the liquid delivery system. There was no alteration in the surface tension of the liquids and it could be concluded that no contamination of the liquid occurred through the delivery system. A PTFE tube of 1.3 mm diameter was used for the liquids chosen in this study but if more viscous liquids are to be used, tubes of 2.3 mm diameter are available.

5.2.4. Calibration of instrument

Calibration is required only if the instrument has been moved. Calibration of the instrument involves adjusting:

• the light entering the system;

Since the DAT system works on the basis of image capture, it is important that an adequate amount of light enters the system. The DAT has a built-in function that enables the instrument to differentiate between black and white at 108 pixels. To adjust the amount of light, the applicator is held down and measurements of the applicator are taken. A threshold value of 109 should be achieved.

• the scale factor;

The scale factor is also set by pressing the applicator down. The image of the applicator is then set to 2.49mm.
The accuracy of the instrument in measuring contact angles is carried out using an artificial drop. This consisted of a steel ball pressed into a flat metal body. When put into the instrument, it appeared as a drop and images of the ball were captured. The contact angle and other parameters should correspond to the following settings:

<table>
<thead>
<tr>
<th>Parameter of steel ball</th>
<th>Contact angle (°)</th>
<th>Volume (mm$^3$)</th>
<th>Height (mm)</th>
<th>Area of Base (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83.60 (1.00)</td>
<td>1.74 (0.05)</td>
<td>0.89 (0.02)</td>
<td>1.99 (0.05)</td>
</tr>
</tbody>
</table>

Table 5.1 shows the parameters of the steel ball used to verify the accuracy of the DAT with the values shown in () referring to the limits.

If the angle recorded is outside the limits, the vertical tilt of the camera has to be adjusted. The value of the volume recorded is used as a guide e.g. if the volume is less than expected, the drop is being viewed at an angle by the camera. The front of the camera has to be tilted upwards so that the camera is aligned horizontally with the drop and not underestimating it.

5.2.5. Contact angle measurement

5.2.5.1. Procedure used

There are two test methods available for the operation of the DAT. Both methods are similar and vary slightly according to the angle formed by the droplet on the surface. Procedure A is chosen if contact angles less than 100° are formed whereas procedure B is recommended for contact angles greater than 100°. To identify which procedure was appropriate for the pair of liquid and sample used, the following test is performed. A droplet of liquid is formed at the tip of the PFTE tube; the drop is slowly lowered manually towards the specimen surface until the drop is in contact with the sample surface. If the drop releases immediately from the tip on contact with the sample, procedure A is to be used. In procedure A, a drop of standard size (4.0 µl) is pumped out at the tip of the tube. The drop is moved to a distance of 0.5 ± 0.1 mm towards the sample surface. With the drop suspending freely over the surface, the stroke pulse is...
gradually increased until the drop releases from the tube but the tip does not reach the sample surface when the applicator is triggered.

Procedure B is adopted in cases where the drop remains attached to the tip of the tube. In procedure B, a drop is formed on the tip of the tube. The tube is lowered manually until the drop touches the surface but remains attached to the tube. The tube is gradually raised until the drop releases from the tube. This determines the minimum travel distance of the drop. Another drop is formed over a fresh sample spot and the stroke pulse is adjusted until the drop releases on contact with the solid. It is important to determine the right procedure so that the droplet is applied as gently as possible and the highest possible contact angle is measured. If appropriate, procedure A should be employed as the first option, as the drop is applied with a very short stroke pulse.

**5.2.5.2. Drop size, stroke pulse and capture delay**

Drop sizes ranging from 0.2 to 20 μl can be used but the standard drop size of 4.0 μl is recommended. The drop size varied for each liquid used. The size was determined by trial and error and the appropriate size should be such that the drop would suspend freely from the tip of the tube and required minimum stroke pulse to detach from the tip. The drop sizes used were 4.0 μl for bromonaphthalene and 6.0 μl for water and formamide. For each pair of liquid and sample used, the stroke pulse required would vary, as it is dependent on the interaction between the liquid and sample. The minimum stroke pulse was determined by trial and error and a value of 5.1 was used for bromonaphthalene, 6.5 for water and 5.6 for formamide. Capture delay is another feature of the instrument that enables images of the drop to be captured as soon as it contacts the sample surface. The value of the capture delay can be adjusted from 1 to 19 (milliseconds) and is useful if the drop spreads quickly over the surface. The capture delay varied for each pair of liquid/solid used.

Once all the parameters were set, the sample holder was loaded onto the DAT and the drop was automatically deposited on the surface. The video camera captured images of the drop every 20 milliseconds for a period of 1 second. Replay images showed the detachment of the drop from the tube tip followed by its deposition onto the surface and a gradual sorption into the solid surface. The contact angles of the drop on the solid were recorded as a function of time. The contact angle was taken at the time point at which the drop first makes contact with the surface. Care was taken that the surface of
the solid to be tested was reasonably smooth and that the drop had properly formed on
the surface before measurements were recorded.

5.2.5.3. Calculation of contact angle

The contact angles were generated automatically by the computer software. All
calculations were made on two-dimensional images taken from the video camera and it
is assumed that the drop is symmetrical around its vertical axis. When the sample
surface is rough, the outline of the drop cannot be traced all the way down to the
surface. A distance of 0.1 mm from the sample surface is excluded from the analysis
and the contour of the drop is traced from the remaining outline of the drop.

5.3. RESULTS AND DISCUSSION

The contact angle data are a mean of 20 measurements of each liquid on each powder
studied. A large number of samples were taken since the DAT was being used for the
first time to measure contact angles on pharmaceutical powders, which are rough in
nature.

5.3.1. Loosely pressed powder sample

5.3.1.1. Contact angle

In order to investigate the method of sample preparation, the contact angles of
bromonaphthalene and water were measured on 2 powders: lactose monohydrate and
spray-dried lactose. The values of the contact angles are shown in table 5.2.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Contact angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromonaphthalene</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>124.4 (6.4)</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>139.7 (4.1)</td>
</tr>
</tbody>
</table>

Table 5.2 shows the contact angles of bromonaphthalene and water measured on
lactose monohydrate and spray-dried lactose with the values in ( ) showing the standard
deviation.
The contact angle of water on lactose was found to be surprisingly high (106°) compared with a literature value of 30° (Lerk et al 1976). An explanation based on electrostatic effects is being suggested. When a droplet of water was deposited on lactose, particles of powder were seen to adhere instantaneously to the surface of the droplet. The lactose-coated drop may have decreased affinity for the powder surface and hence give an artificially high contact angle. An antistatic gun (Zerostat 3 discharger) was used to minimise the charges but the contact angles measured were again high. Similar observations were made by Buckton and Newton (1986) and the high contact angle values were attributed to a true reflection of the hydrophobic nature of the surface studied.

5.3.1.2 Surface energy of powders

The dispersive and polar components of the powders as determined using Wu’s equation are shown in table 5.3. The values of the dispersive component of both lactose powders were unexpectedly low when compared with the values obtained by different workers (1 and 2). It was concluded that this method of sample preparation may not be appropriate and another method, using the smooth sample block was investigated.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Surface energy (mJm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dispersion</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>5.4</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>2.8</td>
</tr>
<tr>
<td>Lactose monohydrate¹</td>
<td>19</td>
</tr>
<tr>
<td>Lactose monohydrate²</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 5.3 shows the surface energy of lactose monohydrate and spray-dried lactose where ¹ refers to Kiesvaara and Yliruusi (1993) and ² to Ticehurst et al (1996).
5.3.2. Powder coated onto adhesive

5.3.2.1. Contact angle

The alternative method of sample preparation involved spraying the smooth sample holder with adhesive followed by brushing the adhesive with powder, in a similar manner to the preparation of sample plates for the Wilhelmy plate technique. Only the advancing contact angles of liquids on the individual powders and the binary mixes are shown in tables 5.4a and 5.4b respectively.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Contact angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromonaphthalene</td>
</tr>
<tr>
<td>Zamifenacin</td>
<td>49.1 (1.7)</td>
</tr>
<tr>
<td>Starch</td>
<td>55.6 (1.6)</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>60.8 (1.2)</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>53.6 (2.0)</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>50.9 (2.2)</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>97.9 (4.8)</td>
</tr>
<tr>
<td>Adhesive</td>
<td>56.1 (0.4)</td>
</tr>
</tbody>
</table>

Table 5.4a shows the contact angles of bromonaphthalene and formamide on the individual powders and adhesive with the values in ( ) showing the standard deviation.

The highest contact angles were obtained in the case of magnesium stearate. This is to be expected, as magnesium stearate is hydrophobic in nature. It should be recalled that the powders studied in the Wilhelmy plate technique were zamifenacin, starch and lactose monohydrate and the liquids used were bromonaphthalene and ethylene glycol. Comparison of the angles measured by the two techniques could only be done in the case of bromonaphthalene with the three powders mentioned. The angles obtained from the DAT were generally lower than the corrected values obtained from the Wilhelmy plate technique. This could be due to the fact that the instrument was designed to measure contact angles of liquid on paper sheets, which are less rough than the powders used in this study. The drop of liquid may be falling on cavities on the sample surface, making contact with areas of powder as well as adhesive. This could give rise to experimental artefacts such as hysteresis, as explained in section 3.2.1.2 and the angles recorded may be low.
The contact angles of liquids on binary mixes of zamifenacin and excipients are shown in table 5.4b. With the exception of the zamifenacin/magnesium stearate mix, the contact angles measured for the two liquids on all zamifenacin/excipient mixes were very similar in value. This suggests that either the zamifenacin/excipient mixes exhibited similar surface properties or that the DAT is not sufficiently sensitive for differentiating between the different mixes. The first explanation seems more probable as contact angles measured with the individual powders showed a range of values with the different powders.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Contact angles (°)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromonaphthalene</td>
<td>Formamide</td>
<td></td>
</tr>
<tr>
<td>Zamifenacin/Starch</td>
<td>49.7 (1.4)</td>
<td>135.3 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Zamifenacin/Mg stearate</td>
<td>104.5 (3.1)</td>
<td>126.3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Zamifenacin/Lactose mono.</td>
<td>47.0 (2.0)</td>
<td>130.5 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Zamifenacin/Anh. Lactose</td>
<td>50.9 (1.5)</td>
<td>131.8 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Zamifenacin/Spray. Lactose</td>
<td>51.2 (2.2)</td>
<td>129.7 (4.2)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4b shows the contact angles of bromonaphthalene and formamide on the binary mixes with the values in ( ) showing the standard deviation.

**5.3.2.2. Surface energy of powders and mixes**

The surface energies of the individual powders and binary mixes were determined using both Wu's and Fowkes's equations and are shown in table 5.5. As can be seen from table 5.5, the polar components of the surface energies of most powders and mixes when determined using Wu's equation were either negative or equal to zero. This indicates that either the DAT was not suitable to measure the surface energetics of the powders or that Wu's equation was not appropriate for the analysis of the data. Hence, Fowkes’s equation was used to derive the surface energetics of the powders using the same contact angle values.
Table 5.5 shows the surface energy of the powders. The first two columns refer to values obtained when Wu’s equation was used and the last two columns show the surface energy of the powders when Fowkes’s equation was used.

More realistic values were obtained for both the polar and dispersive components of the surface energy of the powders when Fowkes’s equation was used. Literature values for the surface energy of starch are 21.7 and 34.4 mJm\(^{-2}\) for the dispersive and polar components respectively (Odidi et al 1991). It thus appears that Fowkes’s equation was superior to Wu’s equation for the determination of the surface energetics of powders. It may be that most of the pharmaceutical powders studied here have a low polarity, which indicates the application of Fowkes’s equation.

### 5.3.2.3. Spreading coefficient approach

Following the successful use of the spreading coefficient approach in predicting mixing in iron oxide mixes, the spreading coefficients of the powders were calculated using the surface energy values obtained from Fowkes’s equation. The spreading coefficients of only two systems: zamifenacin with starch (or lactose monohydrate) are shown in table 5.6.
Table 5.6 shows the spreading coefficients of zamifenacin over starch and of zamifenacin over lactose monohydrate.

The spreading coefficient data predict that zamifenacin should spread over starch. Scanning electron micrographs of the active drug and starch taken before and after mixing however do not support the above findings (figures 5.2a, b and c).

Figure 5.2a shows the scanning electron micrograph of zamifenacin.
Figure 5.2b shows the scanning electron micrograph of starch.

Figure 5.2c shows the scanning electron micrograph of zamifenacin/starch mix.
In the case of the zamifenacin and lactose monohydrate mix, the spreading coefficient values suggest that lactose monohydrate should spread over the zamifenacin. The scanning electron micrographs again did not give any evidence of this prediction (figures 5.3a and b).

Figure 5.3a shows the scanning electron micrograph of lactose monohydrate.

Figure 5.3b shows the scanning electron micrograph of zamifenacin/lactose monohydrate.
5.4. CONCLUSIONS

The DAT enabled the contact angles of liquids to be measured on all the powders. It is a fully automated instrument with minimal input required from the operator. The most important feature of the instrument was the automatic capture of images of the drop and generation of the contact angle value. The preferred method of sample preparation used was the brushing of powder over the sample holder sprayed with adhesive. Neither compaction nor saturation of the sample was used. Another advantage of this novel technique was that the powder surface was studied as received.

Negative values of the polar component of the surface energy were obtained when Wu’s equation was used to calculate the parameters. When Fowkes’s equation was used, more realistic values of the surface energy components were obtained.

In an attempt to predict the mixing of pharmaceutical powders, the spreading coefficients of two binary systems: zamifenacin-starch and zamifenacin-lactose monohydrate were determined. The predictions made from the spreading coefficient values were not supported by scanning electron micrographs of the binary mixes. These data should not be interpreted as a failure of the spreading coefficient approach to predict mixing. Visual assessment could not be used to support any surface energy findings since the mixes were made up of white powders. Further confirmation would be provided by HPLC and NIRS studies on zamifenacin blends as would be discussed in chapter 8. It should be remembered that the DAT has never been used on rough surfaces as it was designed to measure contact angles of liquids on paper. In the limited time spent studying the DAT as a surface characterisation technique, useful information on the surface energy data of the powders as well as on the operation of the instrument were gained.
6. INVERSE GAS CHROMATOGRAPHY

6.1. INTRODUCTION

The techniques discussed in the previous chapters were found to have certain limitations in the surface characterisation of pharmaceutical powders. Hence, another method, Inverse gas chromatography (IGC), was used to study surfaces of powders further. Unlike the Wilhelmy plate or sessile drop techniques, which are indirect methods of obtaining surface energy parameters of powders, IGC relies on the direct interaction between the vapour of liquid probes and the powder, allowing surfaces of the powder to be characterised. IGC had been used extensively in the past to study the surface characteristics of polymers and fibres (Fowkes 1990, Panzer and Schreiber 1992). IGC is a sensitive and reliable technique; it is versatile and can be used to measure adsorption properties and for estimating dispersive and polar forces acting at surfaces and interfaces.

The first pioneers to use IGC as a method to characterise pharmaceutical powders were Ticehurst et al (1994, 1996). They showed that IGC was capable of showing batch-to-batch variation of salbutamol and lactose samples otherwise undetected by thermal techniques. Studies on caffeine and theophylline by Dove et al (1996) recently showed that IGC yielded data that was comparable with other well established technique such as the Wilhelmy plate technique.

The use of IGC to further study the surfaces of pharmaceutical powders would be investigated in this project and the dispersive components of the powders compared with those obtained from the sessile drop technique (DAT). However, no direct comparison of the polar (acid-base) parameters can be made between the IGC and DAT data due to different data manipulation involved.
6.2. THEORY

Chromatography is a process that involves the distribution of a solute component between two phases: a mobile and a stationary phase. In conventional gas-solid chromatography, the solute is an unknown vapour that is adsorbed, separated and identified using a well-known solid stationary phase. In inverse gas chromatography, the solute is a well-characterised volatile liquid, also referred to as a probe and is vaporised and injected onto the stationary phase which is the unknown solid of interest. The powder is packed into a narrow column, usually made of stainless steel or glass of varying lengths. The volatile probe is carried by the mobile phase, an inert carrier gas that can be hydrogen, nitrogen or helium. When the vapour of the probe liquid is injected, it is carried through the column by the carrier gas and its emergence at the other end of the column is detected. The time the liquid probe takes to travel through the column would depend on the partition coefficient of the liquid between the mobile and stationary phases. If several probes of different nature were injected in the column, they would interact with differing capacity with the solid. The liquids would be detected at differing times out of the column, this time being known as the retention time of the liquid and is the basis on which IGC operates.

Measurements in IGC can be done at finite concentration or infinite dilution of the probe liquid. If the same material is studied under both conditions, the interpretation of data from each condition yields complementary information on the nature of the solid. At infinite dilution, the amount of probe liquid injected is very small and probe molecules would only interact with part of the surface of the solid, forming a monolayer of vapour on the solid. At infinite dilution, the polar and apolar nature of the surface can be determined. When finite concentrations of probe liquid are injected onto the solid, the vapour molecules form multilayers on the surface. The information which can be obtained using finite concentrations of probe liquid are the spreading pressure, enthalpy and entropy of adsorption (Papirer et al 1988) as well as the surface heterogeneity of the solid (Fafard et al 1994). Under both chromatographic conditions, the surface nature of the solid can be studied. However, experiments done at finite concentrations of probe liquid are more time consuming and the use of infinite dilution is preferred and would be investigated here.
The fate of a vapour molecule of a volatile probe following injection onto the column is that it could either:

(i) bind to the surface of the solid stationary phase;
(ii) bind to the bulk of the solid;
(iii) bind to other vapour molecules or
(iv) pass unbound through the column.

Of the four possibilities outlined, only the vapour-solid surface interaction is desirable so that the surface of the powder can be studied. To achieve this, liquid probes are injected at infinite dilution or zero coverage so that physical or reversible adsorption between the probe molecules and sites on the powder may take place. Infinite dilution is the most important region in studying phase interactions as there is no interaction between the liquid-liquid molecules.

The probes are volatile liquids having various properties and capacities to bind to the solid. Non-polar liquids such as hexane, heptane and octane will only exhibit dispersive or van der Waals interactions with the solid; polar liquids can be of acidic, basic or amphoteric nature resulting in basic, acidic or acid-base (AB) interactions respectively. The interaction of probe molecules with the stationary phase varies between different liquids. These would elute at differing speeds from the column and the retention times ($t_r$) are measured for each probe injected (figure 6.1). The volume of carrier gas required to elute a non-interacting gas through the column needs to be taken into account and was determined by injecting air or methane. By subtracting the retention time ($t_0$) of air or methane from the retention time of the probe, the net volume ($V_N$) of carrier gas required to elute the injected probe molecules is determined from:

$$V_N = J \cdot D \cdot (t_r - t_0) \quad (6.1)$$

where $V_N$ is the net retention volume; $t_r$ is the retention time of the given probe; $t_0$, the retention time of the reference gas, methane; $D$ is the flow rate of the eluting carrier gas and $J$ is the correction factor that takes into account the compressibility of the gas as the pressure drops across the column.

$$J = \frac{3 \left[ \left( \frac{P_i}{P_e} \right)^2 - 1 \right]}{2 \left[ \left( \frac{P_i}{P_e} \right)^{3/2} - 1 \right]} \quad (6.2)$$

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where $P_i$ is the pressure at the inlet of the column and $P_0$ is the atmospheric pressure.

Figure 6.1 shows the chromatogram obtained by elution chromatography.

The net retention volume, $V_N$, would thus be a reflection of the interaction between the liquid probe and the solid. Since the probe would partition between the surface and the bulk of the solid, $V_N$ can be expressed as:

$$V_N = K_s A + K_b V$$  \hspace{1cm} (6.3)

where $K_s$ and $K_b$ are the surface and bulk partition coefficients respectively; $A$ and $V$ are the total surface area and total volume of the powder respectively.

At infinite dilution, bulk sorption of the vapour is considered to be negligible and the amount of probe adsorbed is proportional to the total surface area of the solid:

$$V_N = K_s A = K_s W S_a$$  \hspace{1cm} (6.4)

where $W$ is the weight of dried powder and $S_a$ is the specific surface area of the powder.
6.2.1. Free energy of adsorption (\(\Delta G^o_{\text{ads}}\))

The free energy of adsorption (\(\Delta G^o_{\text{ads}}\)) of a molecule from the standard gaseous state to the standard adsorption state under isothermal conditions is given by:

\[
\Delta G^o_{\text{ads}} = -\Delta G_{\text{des}} = -RT \ln\left(\frac{P_{s.g}}{P_{s.s}}\right) \tag{6.5}
\]

where \(\Delta G_{\text{des}}\) is the free energy of desorption; \(P_{s.g}\) is the vapour pressure of the probe in the gaseous state; \(P_{s.s}\) is the vapour pressure in equilibrium with the standard adsorption state; \(R\) is the gas constant and \(T\) is the temperature in K.

The net retention volume \((V_N)\) and free energy of adsorption \(\Delta G^o_{\text{ads}}\) can be related by first defining \(K_s\):

\[
K_s = \frac{\Gamma}{C} \tag{6.6}
\]

where \(\Gamma\) and \(C\) are the concentrations of the probe on the surface and in the gas phase respectively.

Under ideal conditions,

\[
C = \frac{P}{RT} \tag{6.7}
\]

where \(P\) is the partial pressure of the probe.

Substituting equation (6.7) into equation (6.6),

\[
K_s = \frac{\Gamma RT}{P} \tag{6.8}
\]

The surface concentration, \(\Gamma\) is related to the surface pressure, \(\pi_s\), by the Gibbs equation:

\[
\Gamma = \left(\frac{P}{RT}\right) \left(\frac{d\pi_s}{dP}\right) \tag{6.9}
\]
At infinite dilution of probe liquid,

\[ \frac{d\pi_e}{dP} \rightarrow \frac{\pi_e}{P} \]  

(6.10)

Substituting equation (6.10) into equations (6.8) and (6.9),

\[ \frac{\Gamma RT}{P} = \frac{\pi_e}{P} = K_s \]  

(6.11)

In the standard adsorption state,

\[ P_{s.s.} = \frac{\pi_e}{K_s} \]  

(6.12)

Substituting equation (6.12) first into equation (6.4) and then, equation (6.4) into (6.5),

\[ \Delta G^0_{ads} = -RT \ln \left( \frac{V_N \cdot P_{s.s.}}{\pi_e \cdot W \cdot S_a} \right) \]  

(6.13)

where \( P_{s.g.} = 1.013 \times 10^5 \) Pa; \( \pi_e = 3.38 \times 10^4 \) Nm\(^{-1}\) (DeBoer 1953); \( W \) is the weight and \( S_a \) is the specific surface area of the powder. Equation (6.13) thus enables the total free energy of adsorption of probes on the solid to be determined.

It can be seen that equation (6.13) contains many constants which when substituted reduces the equation to:

\[ \Delta G^0_{ads} = -RT \ln (V_N) + B \]  

(6.14)

where \( B \) is a constant which takes into account the weight, surface area and vapour pressure of probes in the gaseous state.

Depending on the nature of the probes injected, the free energy of adsorption will be the result of polar and apolar forces. Apolar probes would interact by dispersion forces only:

\[ \Delta G^0_{ads} = \Delta G^0_{ads} \]  

(6.15)
For a polar probe, additional acid-base interactions with the solid would give a higher free energy of adsorption due to the contribution of the specific free energy of adsorption, $\Delta G_{ads}^{AB}$ to give:

$$\Delta G_{ads}^{o} = \Delta G_{ads}^{D} + \Delta G_{ads}^{AB}$$ (6.16)

### 6.2.2. Dispersion component ($\gamma^d_s$)

Since apolar liquids interact by dispersive interactions only, the dispersion component of the surface energy of the solid can be found from the free energy of adsorption of apolar probes such as hexane, heptane and octane on the solid. The free energy of adhesion, $\Delta G_{ads}^{o}$ is first related to the work of adhesion:

$$\Delta G_{ads}^{o} = N.a.W_{ads}$$ (6.17)

where $W_{ads}$ is the work of adhesion; $N$ is the Avogadro's number and $a$ is the surface area of the liquid probe molecules.

According to Fowkes (1964), the work of adhesion $W_{ads}$ of an apolar liquid (l) onto a solid (s) can be expressed as the geometric mean of the dispersion components of the solid and liquid, $\gamma^d_s$ and $\gamma^d_l$ respectively:

$$W_{ads} = 2 (\gamma^d_s \cdot \gamma^d_l)^{1/2}$$ (6.18)

Combining equations (6.14), (6.17) and (6.18) leads to:

$$RT \ln V_N = 2 N. (\gamma^d_s)^{1/2} \cdot a. (\gamma^d_l)^{1/2} + B$$ (6.19)

If a plot of the free energy of adsorption of liquid probes onto solids ‘$RT \ln V_N$’ was drawn as a function of the dispersion component of the alkanes, a straight line is obtained (figure 6.2). The dispersion component of the solid, $\gamma^d_s$ can thus be obtained from the slope of the line:

$$\gamma^d_s = \left( \frac{\text{gradient}}{2N} \right)^2$$ (6.20)
To be able to draw the above plot, the values of a, the area occupied by the adsorbed liquid molecules and the dispersion components, $\gamma ^d$ (i.e. the surface tensions) of n-alkanes are required. The values of a and $\gamma ^d$ were obtained from the literature (Schultz et al 1987, Nardin and Papirer 1990) and are shown in table 6.1.

Figure 6.2 shows the free energies of adsorption of alkanes as a function of $a . (\gamma ^d)^{1/2}$.

### 6.2.3. Acid and basic behaviour

Polar liquid probes such as chloroform (acidic nature) or ether (basic nature) have the ability to interact by polar forces in addition to dispersive forces with the solid. These polar interactions are termed specific or acid-base (AB) interactions. The interactions of polar probes with the solid would be expected to give higher energies of adsorption than with non-polar alkanes. If the total free energies of adsorption of polar probes were plotted in the same manner as for apolar alkanes, the polar probes would be located above the alkane line (figure 6.3).
6.2.3.1. Acceptor-Donor concept

Since the specific free energy of adsorption of polar probes on a solid are available, it would be an advantage to be able to describe the solid surface in more quantitative terms i.e. its acidic and basic nature. This can be achieved by further manipulating the thermodynamic data and using semi-empirical scales such as that devised by Gutmann (1978).

According to the Gutmann acid-base concept, liquids are characterised as either a Lewis base (or an electron donor), characterised by a donor number (DN) or a Lewis acid (an electron acceptor), characterised by an acceptor number (AN). The interactions in organic liquids were studied and a scale devised to characterise the strengths of acidic and basic groups in liquids. The reasons why the scale of Gutmann was used were that a vast amount of information was available for organic volatile probes but more
importantly that the Gutmann approach took into account the amphoteric nature of liquids such as acetone.

The scale was devised by reacting bases with a strong acid, antimony pentachloride (SbCl₅) in a neutral solvent, 1,2-dichloroethane. The bases were then assigned donor numbers (DN) which is the negative of the enthalpy of formation of the product with antimony pentachloride and are expressed in kcal mol⁻¹. To complement bases, acids were given acceptor numbers (AN) which were determined by reacting the acids with triethylphosphine oxide (Et₃PO), the basic reference probe. AN was the magnitude of the chemical shift in ³¹P in NMR spectra of triethylphosphine oxide when dissolved in the acid being studied. A value of 0 is assigned to the NMR shift in n-hexane and a value of 100 to the shift of Et₃PO when reacted with antimony pentachloride in 1,2-dichloroethane. AN by contrast is a dimensionless number and has no units. Riddle and Fowkes (1990) corrected AN to AN* values as it was found that strong bases such as pyridine had large acceptor numbers due to the contributions from van der Waals forces to the chemical shift. In so doing, AN* had the same units as DN i.e. kcal mol⁻¹.

6.2.3.2. Polar interactions between liquids and solid

The liquid probes used had been well characterised in the literature in terms of their acid-base nature. Assuming entropic contributions are neglected (Papirer et al. 1988), the acid-base interaction of these probes with solids can thus be described as the specific free energy of adsorption, ΔG⁰_{ads} in terms of the acid and basic parameters and corresponding donor (DN) and corrected acceptor (AN*) numbers:

\[
\Delta G_{\text{ads}}^{AB} = K_A \cdot \text{DN} + K_D \cdot \text{AN}^*
\]

(6.21)

where \( K_A \) and \( K_D \) are the acid and basic parameters of the solid respectively.

Rearranging equation (6.21) gives a linear plot of ‘\( \Delta G_{\text{ads}}^{AB}/\text{AN}^* \) versus DN/AN*’ from which the acid and basic parameters can be obtained as the slope and intercept respectively.

\[
\Delta G_{\text{ads}}^{AB}/\text{AN}^* = (\text{DN}/\text{AN}^*), K_A + K_D
\]

(6.22)
All polar solids can thus be characterised in terms of their electron-accepting ($K_A$) and electron-donating ($K_D$) capacity giving a semi-quantitative indication of their acid-base nature. Values of DN used in this study were obtained from the literature (Schultz et al 1987) and AN* were obtained from Panzer and Schreiber (1992) and Mukhopadhyay and Schreiber (1995) and shown in table 6.1.
Table 6.1 shows the values of parameters used in the determination of IGC surface energy data.

- $a$ (Å$^2$) is the surface area of probe molecules determined by injecting probes on neutral reference solids e.g. PTFE (Schultz et al 1987, Nardin and Papirer 1990).
- $\gamma^d$ (mJm$^{-2}$) is the dispersive component of the surface energy of probe liquids measured by contact angle methods on reference solids (Schultz et al 1987, Nardin and Papirer 1990).
- DN (kcalmol$^{-1}$) is the donor number of probe liquids obtained from the literature (Schultz et al 1987).
- AN* (kcalmol$^{-1}$) is the corrected acceptor number of probe liquids obtained from the literature (Panzer and Schreiber (1992) and Mukhopadhyay and Schreiber (1995)).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pentane</th>
<th>Hexane</th>
<th>Heptane</th>
<th>Octane</th>
<th>THF</th>
<th>Diethyl Ether</th>
<th>Acetone</th>
<th>Ethyl Acetate</th>
<th>Benzene</th>
<th>Carbon Tetrachloride</th>
<th>Chloroform</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>45.0</td>
<td>31.5</td>
<td>57.0</td>
<td>62.8</td>
<td>45</td>
<td>47</td>
<td>42.5</td>
<td>48</td>
<td>46</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>$\gamma^d$</td>
<td>15.5</td>
<td>18.4</td>
<td>20.3</td>
<td>21.3</td>
<td>22.5</td>
<td>15</td>
<td>16.5</td>
<td>19.6</td>
<td>26.7</td>
<td>26.8</td>
<td>25.9</td>
</tr>
<tr>
<td>DN</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.0</td>
<td>19.2</td>
<td>17.0</td>
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<td>0</td>
</tr>
<tr>
<td>AN*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>1.4</td>
<td>2.5</td>
<td>1.5</td>
<td>0.17</td>
<td>0.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>
6.2.4. Interaction parameter (I)

Having established that polar solids have electron-donating and electron-accepting sites, it follows that if two such powders are mixed, interaction would occur between the electron-acceptor and donor sites of two solids. The interaction between two solids 1 and 2 can be represented as a parameter (I) in terms of acid and basic parameters, $K_A$ and $K_D$ respectively. This parameter represents the magnitude of interaction between solids 1 and 2:

$$I = K_A^1 \cdot K_D^2 + K_A^2 \cdot K_D^1$$  \hspace{1cm} (6.23)

The specific interaction parameter has been used successfully in the past to describe the interaction in composite materials made from carbon fibres and epoxy matrix (Schultz et al 1987). There was a strong correlation between the strength of the interface and the specific interaction parameter, demonstrating the importance of acid-base interactions in the fibre-matrix adhesion. The application of this specific parameter approach to pharmaceutical powders has never been investigated and it would be interesting to find out whether it is of any relevance in the prediction of mixing.

6.3. METHOD

6.3.1. Silanisation of column

The columns used in IGC were silanised so that injected probes would only interact with the solid stationary phase under study and the retention time recorded for probes can be related to the interaction between liquid probes and sites on the powder only. Before silanisation, the glass columns were thoroughly cleaned so that they were free from grease. A solution of Repelcote® (which is a 2% solution of dimethyl dichlorosilane in octamethyl cyclotetrasiloxane) was applied to the dried glass column ensuring that the entire surface was wetted. The solution was left in contact with the glass for five minutes as treatment occurred almost immediately. The column was then washed thoroughly with alcohol followed by water to remove excess Repelcote® solution.
6.3.2. Sample preparation

The powders studied were zamifenacin, starch, lactose monohydrate, anhydrous lactose, spray dried lactose and magnesium stearate. Each powder was packed into a single loop silanised glass column (~50 cm in length and 3 mm internal diameter except for magnesium stearate where a shorter column of ~ 20 cm was used) using a rotational vibrator. Weights of powder used ranged from 0.2 to 2.5 grams depending on the density of the powders. Once the columns were packed and visually inspected to ensure uniform packing with no air pockets, the ends of the column were plugged with silanised glass wool. Use of silanised wool ensured that the probe liquids injected would only interact with the powder under study. Differential scanning calorimetry thermographs of the samples were taken to determine the temperature at which the powders can be exposed without irreversible changes occurring. Purging nitrogen (35 kNm\(^2\)) and a temperature of 50 °C were used to remove surface moisture from the powder. The powders were allowed to equilibrate for 24 hours by passing nitrogen (28 kNm\(^2\)) under the operating conditions of 35 °C.

6.3.3. Operating conditions

Conditions used were very similar to those used by Dove et al (1996) apart from a few modifications. The temperature of the oven housing the column was set at 35 °C; a maximum/ minimum thermometer was used to monitor the temperature of the oven throughout the experiment. If the temperature of the oven exceeded the set temperature by more than ± 2 °C, the data collected would have to be disregarded, as small changes in temperature would affect the rate the probes pass through the column and hence the retention time. The pressure of the carrier gas used was 28 kNm\(^2\) for all solids apart from magnesium stearate. In the case of magnesium stearate, a shorter column was used and the inlet pressure increased to 200 kNm\(^2\) due to the small sizes and high surface area of particles. Under the operating conditions of 28 kNm\(^2\) for the inlet pressure, the retention times of probes for magnesium stearate were approximately 1 hour for hexane and hence, excessively long. The injection port temperature was held at 100 °C.
6.3.4. Choice of liquids

Liquids used as probes in the IGC were chosen on the basis that they were well characterised. The apolar liquids were the three n-alkanes: Hexane, Heptane and Octane. These were used to determine the dispersive component of the solids. In the case of magnesium stearate, n-Pentane instead of Octane was used due to long retention times. A range of polar probes was used to study the acid and basic behaviour of powders. The polar liquids of basic nature were Tetrahydrofuran (THF) and Ether; the acid probes were Benzene, Carbon tetrachloride (CCl₄) and Chloroform (CHCl₃) and the amphoteric probes used were Acetone and Ethyl acetate.

6.3.5. Injection of probe liquids

The experiment was carried out using a Perkin Elmer F33 gas chromatograph. A schematic representation of the instrument used is shown in figure 6.4. Methane gas was used as a reference probe and injected at regular intervals to ensure the operating conditions remained constant.

Figure 6.4 shows a schematic representation of the inverse gas chromatograph.
The liquid probes were injected manually using a 10 μl Hamilton syringe. The syringe was first rinsed with liquid. It was then flushed out several times with air to achieve infinite dilution. Infinite dilution was achieved by trial and error: the amplifier was first set to the lowest sensitivity; the number of times the syringe was flushed with air was increased and the eluted peaks studied following the injection of vapour. Infinite dilution was known to be reached when eluted peaks of equal retention times but differing heights were obtained. It can be easily detected if liquid was injected instead of vapour of infinite dilution; an artificially low retention time would be measured as the liquid molecules pass unbound through the column. 1 μl of air containing the liquid vapour was injected into the column and simultaneously the chart recorder started. The eluted vapour was detected by flame ionisation using a mixture of air (20 kNm⁻²) and hydrogen (16 kNm⁻²). The retention times (t₀ or t₁) were taken as from the point of injection to the point of maximum peak height (figure 6.1). An average of five injections was recorded for each liquid probe. The flow rate of carrier gas through the column was measured using a soap bubble flowmeter and the weight of the powder after drying was recorded. Three sets of runs were performed for each powder so that for each liquid probe, fifteen injections were made.

6.3.6. Experimental considerations

Although IGC is popular as a result of its relatively ease and speed of operation, the limitations of the technique must not be overlooked. From the thermodynamic interpretation of the data discussed above (equations 6.1 and 6.2), it has become clear that a number of experimental factors may become cumulative sources of error that may lead to inaccuracies in the final data (Bolvari et al 1989). The column is the most important feature of the experiment as it is responsible for the accurate partitioning of the probe between the mobile and stationary phase. Packing the column is thus crucial as it may constitute a source of variation in measured retention times. The other parameters measured in an IGC experiment are the flow rate of the carrier gas, pressures and the weights. The flow rate is measured from the column end using a soap bubble flowmeter. The entire length of the walls of the flowmeter should be thoroughly dampened by passing 20 bubbles before taking any measurements otherwise the flow rate may appear lower as liquid passes over the dry walls of the flowmeter. An average of five readings for the flow rate and atmospheric pressure was taken.
6.4. RESULTS AND DISCUSSION

6.4.1. Free energies of adsorption

As discussed in sections 6.2.1. and 6.2.3., the specific free energies of adsorption of the polar probes with the solids can be determined by the difference between the polar probes and the alkane line. The free specific energies of adsorption as shown in table 6.2 are the result of polar interactions of the polar probes with the solids. It is hard to determine from the magnitudes of the values of the specific free energies with each individual probe whether the powders are acidic or basic in nature. The determination of the acid and basic parameters would be treated in section 6.4.2.2.

The total free energies of adsorption of the probes with each powder were determined according to equation (6.13) shown in section 6.2.1. The values of the overall free energies of adsorption are shown in table 6.3. The free energies of adsorption resulting from the apolar interactions of the polar probes with each solid can be obtained by subtracting its specific free energy from its total free energy of adsorption.
Table 6.2 shows the specific free energy of adsorption, $-\Delta G^\text{AB,ads}$ (kJ mol$^{-1}$) of polar probes on the powders with the standard deviation values in ().
Table 6.3 shows the total free energy of adsorption, $-\Delta G^\circ_{ads}$ (kJmol$^{-1}$) of probes on the powders with the standard deviation values in ( ).
6.4.2. Surface energy parameters

6.4.2.1. Dispersion component of solids

To determine the dispersion component of the solid, plots of ‘RT ln $V_n$’ of the alkanes were drawn as a function of ‘a $(\gamma^d)^{1/2}$’ for each solid and shown in figures 6.5 to 6.10. From the slope of the line, the dispersion components of powders, $\gamma^d$, can be calculated as described in section 6.2.2. The data points for the polar probes were also plotted on the same graphs to give an indication of the specific free energy of adsorption with the solids.

Figure 6.5 shows the plot of ‘RT ln $V_n$’ as a function of the square root of the dispersion components of liquids on zanifencin.

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Figure 6.6 shows the plot 'RT lnVn' as a function of the square root of the dispersion components of liquids on starch.

Figure 6.7 shows the plot of 'RT lnVn' as a function of the square root of the dispersion components of liquids on magnesium stearate.
Figure 6.8 shows the plot of ‘RT ln V_n’ as a function of the square root of the dispersion component of liquids on lactose monohydrate.

Figure 6.9 shows the plot of ‘RT ln V_n’ as a function of the square root of the dispersion component of liquids on anhydrous lactose.
Figure 6.10 shows the plot of ‘RT lnVₙ’ as a function of the square root of the dispersion component of liquids on spray dried lactose.

It can be seen that in most cases, benzene and carbon tetrachloride gave total free energies of adsorption that were located below the alkane line i.e. the specific free energy of adsorption, ΔG⁰_ads was positive. This occurrence has been observed in the past by other workers. It could be due to repulsion forces, suggesting that the interactions between the acid probes and the solids were not favourable (van Oss 1991). Or it could be that the use of n-alkanes as references for subtracting the dispersion forces from the total interactions, was not reliable. The n-alkanes could be diffusing and retained in the solid, causing the alkane reference line to be raised. Hence, positive ΔG⁰_ads values for acid probes would be obtained (Balard and Papirer 1993).

6.4.2.2 Acid and basic parameters

The acid and basic parameters of the powders were determined from the plots of ‘ΔG⁰_ads/AN*’ as a function of ‘DN/AN*’ and shown in figures 6.11 to 6.16. A combination of basic and amphoteric probes (Acetone, Ethyl Acetate, Ether and THF) was used in determining the acid-base nature of the solids due to the uncertainty concerning the interaction of acidic probes with the solids. It should be noted that the
acceptor number (AN*) values were quoted in kcal mol\(^{-1}\) in the literature and table 6.1. A simple conversion to kJ mol\(^{-1}\) before the figures were plotted was thus required. The slopes and intercepts of the plots gave the acid (\(K_A\)) and basic (\(K_D\)) parameters of the solids respectively. \(K_A\) and \(K_D\) are dimensionless numbers with no units.

Figure 6.11 show the plot of \(\Delta G_{\text{ads}}^{AB}/\text{AN}^{*}\) as a function of \(\text{DN}/\text{AN}^{*}\) for zamifenacin.
Figure 6.12 shows the plot of $\Delta G^{\text{ Bald}}_{\text{ads}}/\text{AN}^*$ as a function of $\text{DN/AN}^*$ for starch.

Figure 6.13 shows the plot of $\Delta G^{\text{ Bald}}_{\text{ads}}/\text{AN}^*$ as a function of $\text{DN/AN}^*$ for magnesium stearate.
Figure 6.14 shows the plot of $\Delta G^{AB}_{ads}/AN^*$ as a function of $DN/AN^*$ for lactose monohydrate.

Figure 6.15 shows the plot of $\Delta G^{AB}_{ads}/AN^*$ as a function of $DN/AN^*$ for anhydrous lactose.
Figure 6.16 shows the plot of $\Delta G_{\text{wet}}^{AB}/\text{AN}^*$ as a function of 'DN/AN*' for spray-dried lactose.

The surface energy parameters of compounds studied by IGC are shown in table 6.4 and were ranked in descending order of magnitude of $K_d/K_a$, which is defined as the ratio of the electron-donating to electron-accepting capacity of the solids.

Table 6.4 shows the dispersion components and acid/basic parameters of powders determined by IGC with the standard deviation values shown in ( ).
The ratio of \( K_D/K_A \) was chosen instead of either \( K_A \) or \( K_D \) to describe surfaces of the solids as both parameters were found to be independent of each other. If a solid exhibited a high \( K_A \) value, it did not imply that it would have a low value of \( K_D \). The ratio of \( K_D/K_A \) would thus more accurately define the overall acidic-basic nature of solids.

The high \( K_D/K_A \) value obtained for zamifenacin shows that the drug is highly basic and has the highest tendency to donate electrons. All three lactoses had intermediate values of \( K_D/K_A \) and had a higher number of basic than acidic sites. Starch was found to be amphoteric with a ratio of 1.5 for \( K_D/K_A \) showing an equal number of acidic and basic sites. Results for magnesium stearate should be interpreted with caution as the experimental conditions differed slightly (shorter column and increased inlet pressure used). A negative \( K_D/K_A \) value obtained suggests magnesium stearate has a strong acidic nature, or a high electron-accepting capacity.

An attempt was made to study the effects of the length of the column. The short column was packed with anhydrous lactose but it was found that retention times of most probes were very similar. It was concluded that in this case, the column was not sufficiently long to adequately separate the probes in terms of their different capacity to interact with the solid. Due to time restrictions, no more work was undertaken to study the effect of column length.

### 6.4.3. IGC data compared with DAT data

Comparison of the values of the dispersion components of the surface energy of powders obtained by IGC and sessile drop technique (DAT) showed that the powders were ranked in the same order of magnitude. The values obtained by IGC were however found to be higher than with the DAT. This has been explained in the literature as being due to the binding of probe molecules to high energy sites on the powders (as the probes were used at infinite dilution) hence reflecting the higher values obtained with the IGC (Ticehurst 1996). It is however not possible to compare the polar parameters of the surface energy of the powders using the two surface characterisation techniques as different parameters were obtained.
6.4.4. IGC/Mixing behaviour

It is worth reiterating that the parameters determined by IGC only give a semi-quantitative indication of the nature of the materials since they were determined relative to reference compounds. The liquid probes were assigned donor and acceptor numbers depending on their reaction with the reference base, triethylphosphine oxide or the reference acid, antimony pentachloride. These semi-empirical acceptor and donor numbers were used in the determination of the acid ($K_A$) and basic ($K_D$) parameters of the solids. The interaction parameters (I) in table 6.5 can be used to compare materials relative to each other but the values cannot be taken as absolute.

The higher interaction parameter obtained between zamifenacin and starch suggested that zamifenacin would interact more favourably with starch than lactose. This is not surprising since zamifenacin has a larger number of basic sites available to interact with starch, which has a larger number of acidic sites relative to basic sites than lactose monohydrate. This finding would be confirmed by homogeneity studies of binary blends of zamifenacin/excipient in chapter 8.

<table>
<thead>
<tr>
<th>Sample</th>
<th>I ($10^{-2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamifenacin/starch</td>
<td>1.4 (0.1)</td>
</tr>
<tr>
<td>Zamifenacin/lactose monohydrate</td>
<td>0.6 (0.1)</td>
</tr>
</tbody>
</table>

Table 6.5 shows the interaction parameter (I) of two-component systems determined by IGC.

6.5. CONCLUSIONS

Inverse gas chromatography has proved to be a sensitive and reliable technique to characterise surfaces of powders. An IGC experiment can be carried out within a short space of time with elution of probe liquids taking only minutes. The use of low temperatures does not affect the morphology of powders. The amount of stationary phase required is relatively large compared with the Wilhelmy plate or DAT techniques (up to 5g) but the volume of volatile probes needed to rinse the syringe to achieve
infinite dilution is very minimal. With the development of automated IGC equipment and use of computer software to analyse the data, IGC has become a superior technique for the surface characterisation of materials.

Compared with the Wilhelmy plate (DCA) and sessile drop techniques (DAT), it is a fundamentally sound technique and presents several advantages. It is based on direct vapour-solid interaction and works on the assumptions that the probes are physically adsorbed onto the surface of the powders and there is no diffusion into the bulk of the powder. The sample preparation does not involve altering the surface of the powder of interest and would reflect the nature of the powder as received and used. IGC does not have drawbacks of the DCA and DAT techniques where adhesive was used in the sample preparation and hence the occurrence of experimental artefacts is fewer. Above all, IGC enabled the surface of the powders to be characterised where other techniques failed to do so.

The surface energy of pharmaceutical powders was described in two parts: apolar dispersion component ($\gamma^d_s$) and polar acid and basic parameters ($K_A$ and $K_D$). As a result, the polar forces exerted between particles in a two component system can be described and the interaction between the acid and basic sites of powders can be predicted using a specific interaction parameter (I). In this study, it was found that the specific interaction parameter for zamifenacin-starch was higher than zamifenacin-lactose indicating that zamifenacin would interact more favourably with starch than lactose.

The electron-accepting ($K_A$) and donating tendencies ($K_D$) of the powders derived from the IGC would be compared with data obtained by triboelectric charging in the following chapter. This aspect of surface energetics has never been studied before and it would be interesting to find out whether findings from these two techniques are in agreement.
7. TRIBOELECTRIC CHARGING

7.1. INTRODUCTION

Electrostatic charging is a common occurrence in everyday life. It ranges from unpleasant electrostatic sparks on touching a metal surface to spark discharges that may potentially ignite a flammable atmosphere. In the pharmaceutical industry, electrostatic charging is significant under conditions of low humidity and during operations such as grinding, sieving and powder transfer from bags to hoppers. Its impact on manufacturing processes is great and usually unwanted. The best way to control electrostatic charging is to first understand how charges occur and recognise their source. It is then possible to minimise charge generation but if this is unavoidable, charge neutralisation can be undertaken thereafter.

When two solids come into contact, charging may occur as a result of contact charging (if there is no sliding between contacting surfaces) or frictional charging (when there is relative movement of the contacting surfaces). The movement of materials relative to other surfaces is however inevitable and electrostatic charging usually encountered in pharmaceutical industries is frictional charging. Other terms employed to describe this type of charging are triboelectric charging or tribocharging. Static electricity is not always undesirable. The application of triboelectric charging in powder mixing was first reported by Staniforth and Rees (1981). By charging the powders in an air cyclone prior to blending, stable binary mixes were obtained which were more resistant than uncharged powders, to segregation induced by vibration. When other surfaces such as glass and polyethylene were used to charge pharmaceutical powders, it was found that charges of different polarities were being measured (Staniforth and Rees 1982a). Most powders when charged with glass, developed a negative charge whereas powders charged with polyethylene charged positively.

The effect of the addition of a third component to a binary mix was studied using an ultracentrifuge technique (Staniforth et al 1982). Binary mixes of salicylic acid and sucrose to which a third component was added showed that the electrostatic charge of
the active, sucrose and the third component all had a significant effect on the amount of active adhering to sucrose. Both salicylic acid and sucrose charge negatively on contact with glass (which was the material of the container used to prepare the binary mixes). The amount of salicylic acid dislodged from sucrose particles increased when increasing amounts of magnesium stearate were added. Magnesium stearate charges positively with glass and would thus compete for adhesion sites on the sucrose particles. This was described as the 'stripping effect' of salicylic acid from sucrose particles, leading to an unstable mix. Starch also charges positively with glass and similar observations were made. Talc however, charged negatively with glass and did not destabilise the mix.

Electrostatic charging indeed plays a significant role in the behaviour of powders during mixing. This aspect of triboelectric charging provides scope for the control of interparticulate forces between particles, which as has been discussed before, are responsible for the production of interactive mixes. The role of triboelectric charging in the mixing behaviour of zamifenacin with starch and lactose had been investigated in this study. The charging behaviour of powders is primarily a surface effect since charges are generated by friction of powders with other surfaces and once acquired, charges do not dissipate rapidly as most powders are poor conductors. Another aim of this study was to see whether the data from triboelectric charging of powders could be related to their surface energy as determined by inverse gas chromatography, since both techniques measure surface properties of powders.

### 7.2. GENERATION OF CHARGES

All matter consists of atoms and each atom has a nucleus around which electrons revolve. An atom has an overall neutral charge since the charge of every proton (positive charge of $1.6 \times 10^{-19}$ C) is counteracted by the negative charge of an electron ($-1.6 \times 10^{-19}$ C). Electrons are easily removed from the atom e.g. on contact with another atom, resulting in an imbalance in the charge of both atoms. Charge is defined as the quantity of electricity which when placed unit distance from an equal quantity of charge, repels it with unit force. The atoms may become positively charged if electrons are removed or negatively charged if electrons are accepted by the atom. Two bodies of
opposite charges would attract and similarly, bodies of similar charges repel (figure 7.1).

\[ F = \frac{qq'}{4\pi\varepsilon_0 r^2} \]  

(7.1)

where \( q \) is a positive point charge, \( q' \) is the image charge of \( q \), \( r \) is the distance between \( q \) and \( q' \), \( \varepsilon \) is the permittivity of the medium and is usually expressed as a multiple of \( \varepsilon_0 \), the permittivity of free space (\( \varepsilon_0 = 8.85 \times 10^{-12} \text{ Fm}^{-1} \)). Permittivity is the ratio of the conductance (measure of the ability to store charge) of two conductors separated by an insulating material and that of the same conductors in vacuum.

The phenomenon of electrostatics is experienced whenever two surfaces of different work functions come into contact. The work function of a material is defined as the energy required to remove an outer electron from the atoms of the particles of the material. Consider two materials A and B, where A has a lower work function than B. When brought in contact, transfer of charges from A to B occurs until the two surfaces are at thermodynamic equilibrium (figure 7.2). If the two materials are good conductors, charges flow back to the last point of contact when the two surfaces are separated. However, if one or both of the materials are poor conductors, charge dissipation is relatively slow and static charges accumulate on the surfaces. On separation, material B acquires a permanent negative charge and A becomes positively charged. Charge transfer usually occurs from a solid of low work function to one of higher work function.
Figure 7.2 shows the transfer of charges from material A to B as a result of differing work functions.

There are three ways by which electrostatic charges can be acquired:

(i) Induction charging, where the charge is induced by a charged body nearby. The charged body would exert an electric field, which is the region of space in which electrical forces act. If a neighbouring object is placed in the electric field, an equal and opposite charge will be distributed on the side of the object nearest to the charged body (figure 7.3).

Figure 7.3 shows the effect of induction of a charged body on a neighbouring body.

(ii) Triboelectric charging

Triboelectric charging is the term applied when the generation of charges occurs as a result of friction of a material relative to another. As explained above, each material has a different work function. A triboelectric series has been compounded by several workers and shows the relative work functions of materials. The triboelectric series by Unger (1981) ranks the materials in order of increasing work functions i.e. materials found at the top of the series have the lowest work functions. Materials found at the top of the series would tend to charge positively when contacted with materials below it.
For instance, when glass is rubbed against silk (found below glass in the series), electrons transfer from glass to silk. As a result, glass acquires a positive charge and silk becomes negatively charged. The spacing between the two materials give an indication of the magnitude of the charges that would develop. The farther the two materials are from each other, the greater would be the charge developed.

<table>
<thead>
<tr>
<th>Charge</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Glass</td>
</tr>
<tr>
<td></td>
<td>Wool</td>
</tr>
<tr>
<td></td>
<td>Silk</td>
</tr>
<tr>
<td></td>
<td>Steel</td>
</tr>
<tr>
<td></td>
<td>Polyethylene</td>
</tr>
<tr>
<td>-</td>
<td>Teflon</td>
</tr>
</tbody>
</table>

Table 7.1 shows the materials in the triboelectric series by Unger (1981).

The list is by no means comprehensive and shows only some of the commonly used materials. In order to produce stable mixes, components of the mix should be charged with a widest difference in magnitude and sign. Triboelectric charging is carried out using an air cyclone or simply by subjecting the vessel containing powder to a mixing operation.

(iii) Corona charging (also referred to as ionisation) involves the application of a high voltage to a sharp point, which can be a fine-tipped steel needle. The area surrounding the needle is highly charged and eventually exceeds the breakdown stress of air (3 MVm\(^{-1}\) under normal atmospheric conditions). The air molecules in the region of the electric field around the needle become ionised resulting in the production of positive or negative ions depending on the voltage applied. Ions of single polarity, corresponding to that of the voltage applied are produced. When a negative voltage is applied, negative ions in air split to form an electron and a neutral atom. The electron is repelled away from the negatively charged needle and as it is accelerated away from the needle, collides with other atoms in its path, detaching another electron from it to leave a positive ion. This avalanche of electrons is propagated until the electrons are too far away from the electric field to remove electrons from atoms. The positive ions move towards the negatively charged point.
charged needle, colliding with it to form secondary electrons. Outside the electric field, electrons in air which have insufficient energy to cause ionisation, attach to a neutral atom to form a negative ion. If a positive voltage is applied to the sharp point, electrons are attracted to it and in so doing, collide with other atoms to remove electrons from them and producing positive ions. These and naturally occurring positive ions drift away from the positive point but do not cause ionisation. Ionisation or corona charging is known to produce charges of higher magnitudes than triboelectric charging (Staniforth and Rees 1982b). Corona charging is also the basis for charge neutralisation. With the production of ions of the correct sign, elimination of most of the unwanted charges on surfaces of objects can be achieved (Pavey 1998).

7.3. FACTORS INFLUENCING CHARGE BUILD UP

7.3.1. Humidity

Humidity is the most important factor influencing the charge generation in powders. The effects of humidity on charge are poorly understood but there is a general agreement that with increasing % relative humidity (%RH) of the environment or samples, there is a decrease in charges. Studies on the effects of increasing humidity on the charging tendencies of several excipients by Mackin et al (1993) and Nguyen and Nieh (1989) reported a decrease in charges with increasing % RH for most materials. An insight of the mechanism by which the environment humidity affects charge was given by Grosvenor and Staniforth (1996). The surface resistivity (which is the resistance measured between two electrodes separated by a width equal to their lengths) of five materials: dibasic calcium phosphate (DCP), sorbitol, lactose, microcrystalline cellulose (MCC) and magnesium stearate was measured. The powders were stored over silica gel prior to charge measurement. The resistivity decreased for all powders with increasing % RH with the largest reduction seen in MCC and sorbitol. Charge dissipation from the powders was proposed to be:

a) by surface mechanism as in the case of DCP, which did not sorb a large amount of water. The adsorbed layers of water provided a conducting path for charge leakage.
b) by bulk conductivity, since at high %RH, surfaces of MCC and sorbitol were saturated and water was being absorbed. A decrease in resistivity of these powders at high %RH was thus attributed to the conduction of charges through the particles.

c) facilitated by the presence of hydrophilic groups on lactose. Lactose showed a decrease in resistivity equivalent to magnesium stearate although the amount of water sorbed by lactose was one tenth that sorbed by magnesium stearate.

7.3.2. Properties of powders

The triboelectric charge in powders is a surface property and particle size and surface area are expected to affect the magnitude of the charge measured. Carter et al (1992) and Eilbeck et al (1993) showed that decreasing size fractions of lactose yielded negative charges of increasing magnitudes on contact with stainless steel. Smaller particles have a higher surface area to mass ratio compared with larger particles, resulting in an increased contact area with the charging surface. The finer the powders, the more complex is the charging mechanism as fine powders tend to adhere to the walls of the charging vessel. The contact surface becomes lined with a layer of powder and instead of charging the particles with the surface of the vessel, powder-powder charging occurs.

The size of particles also affects the polarity of charges acquired. A theoretical model equation derived by Gallo and Lama (1976) was used to demonstrate that the energy required to remove an electron from a sphere decreased with an increase in radius of the sphere. Large particles would thus have lower work functions than smaller particles of the same material and electrons would transfer from large to smaller particles. This results in positive and negative charges being acquired by particles within the same powder and this phenomenon is described as bipolar charging. Evidence of bipolar charging of micronised salbutamol with stainless steel can be obtained from Carter et al (1992) where the mean charge measured was $-24 \text{nC g}^{-1} (\pm 42)$.

The triboelectric charging of a material depends on the contact of its particles with other surfaces. The extent of contact is dependent on the shape and roughness between the particle and the contacting surface. Rough particles would yield a lower surface area for contact than smooth surfaces. Furthermore, once charges are acquired, they will not be readily dissipated. The effect of surface roughness of the charging surface was also
shown to be important in the charging of powders (Eilbeck et al 1993). As the surface roughness of the charging surface increased, the contact area for charge transfer and the magnitude of the charges on lactose decreased. Although the effects of surface roughness and shape are important in the charging of powders, they were not studied in this project.

7.3.3. Nature of contacting surfaces

The surfaces most often used by workers in charging powders are glass, stainless steel, brass and polyethylene (Staniforth and Rees 1982a, Staniforth et al 1982 and Carter et al 1992). The ability of surfaces to accept or donate electrons depends on the work functions of materials (as shown in table 7.1). Polyethylene (found at the bottom of the series) tends to act as an electron acceptor and charges most materials positively. Stainless steel and brass are found midway in the series and may act as an electron acceptor as well as an electron donor.

During manufacturing processes, it is necessary to transfer powders from one vessel to another e.g. following mixing in a blender, the mix is transferred to a hopper. The nature of the surfaces of each vessel with which the powder has been in contact would have an effect on the homogeneity of the mix. Staniforth (1995) studied the effects on the homogeneity of a salbutamol and lactose mix when subjected to two stages of charging. Firstly, the mix is charged with one surface (glass, metal or polyethylene) and the charged mix subjected to charging with a second surface (glass, metal or polyethylene). A total of nine combinations of surfaces were studied and it was found that homogeneity was best when both the first and second contact surfaces were the same. The influence of the nature of contact surfaces on the charging tendencies of powders is significant. It is thus advisable to use identical surfaces for blending from one manufacturing process to another, or from pilot studies to manufacturing plant as the homogeneity of mixes may be affected.

7.3.4. Rate of charging powders

When particles are charged triboelectrically, whether by using a mixer or an air cyclone, the velocity of the particles would determine the magnitude of the charge acquired by
the particles. Staniforth and Rees (1982b) observed an increase in charge on Dipac when the powder feed rate was increased. An increase in the charge values of lactose particles was reported when the feeder gas pressure of the air cyclone was increased (Carter et al 1992). The increase in charges was attributed to an increase in frequency and area of contact between particle-particle and particle-surface collisions.

7.4. METHOD

7.4.1. Faraday well and electrometer set-up

A schematic representation of the Faraday well connected to an electrometer (Keithley 6517A, Keithley Instruments) is shown in figure 7.4. The Faraday well was constructed according to British Standards (BS 7506, Part 2, 1996) using brass tubing of 3 mm thickness. The inner and outer cups were respectively 10 and 25.5 cm high; 7 and 11 cm in diameter respectively. The depth to diameter ratio of the inner cup was 1.5, so as to limit leakage of the charge from materials to a value less than 1%. The cups were fitted with push top lids made of brass with inner and outer openings of 2.5 and 1.5 cm respectively. The inner cup was electrically insulated from the external electric fields by being fixed onto a PTFE block and separated from the outer cup by 1.4 cm of air. A triaxial connector was mounted on the outer cup. The centre conductor was soldered to the inner cup and the inner and outer shields were connected to the outer cup. The other end of the lead was connected to an electrometer. Any charge on the Faraday well originating from the atmosphere was discharged through the outer shield via the electrometer. In low charge measurements, care has to be taken not to introduce effects from external electric fields. A low-noise triaxial cable was used to reduce triboelectric charges that can be generated by friction between the centre conductor and the insulating shield. The cables were also taped to the bench to prevent movement and friction. The electrometer reading was zeroed prior to any charge measurement. The polarity was checked by inserting a polythene rod rubbed against wool in the inner cup. As the rod would have a negative charge, a negative reading should be recorded on the electrometer. The range of charge measurement by the electrometer is 2 nC to 2 μC. Calibration of the electrometer is carried out once a year as specified by the manufacturer.
Figure 7.4 shows a schematic diagram of the Faraday well used in charge measurement.

The Faraday well works on the principle of charge induction. If a particle of charge \(+q\) is introduced in the inner cup, an opposite and equal charge \(-q\) will be induced on the inner surface of the cup. In order to maintain electrical neutrality, a positive charge develops on the outer surface of the inner cup. This positive charge is then measured by the centre conductor of the triax cable and recorded on the electrometer. The polarity of the measured signal will thus be of the same polarity as the charge generated on the powder.

### 7.4.2. Materials used

The powders studied were zamifenacin, maize starch, lactose monohydrate, anhydrous lactose, spray-dried lactose and magnesium stearate. The charging surface was stainless steel as homogeneity studies were carried out on mixes prepared by mixing in a stainless steel Y-cone blender. Methanol of HPLC grade was used to clean surfaces.
7.4.3. Surface cleaning

Surface contamination is known to introduce variation in the measurement of triboelectric charging of powders. Vessels used to charge powders were filled with distilled water and detergent and placed in an ultrasound bath for 10 minutes. The vessels were then rinsed, filled with double distilled water and placed in the ultrasound bath for a further 10 minutes to remove excess detergent. Methanol (HPLC grade) was used to remove traces of water from the vessel and the vessel allowed to drip-dry. The surfaces should not be wiped dry as wiping may introduce electrostatic charges on the walls of the vessel. The Faraday well was cleaned between each sample measurement: powder was first poured out of the inner cup and the remaining traces of powder wiped off using a tissue dampened with methanol. The inner cup and connectors were cleaned and allowed to dry. The charge generated by wiping was discharged using the auto-discharge feature of the electrometer. This process of cleaning and discharging was repeated until a stable zero reading was recorded on the display window. As in surface energy measurements, it is important to avoid contacting surfaces of powder or equipment used in measurement of charges with bare hands.

7.4.4. Powder charging

Prior to charging, the powders were stored for 24 hours in the temperature-controlled room i.e. under the same conditions as for charge measurement. Other workers (Carter et al 1992 and Mackin et al 1993) have used air jet sieving to remove fines from the powders. However, in this study, the sample was used as received so that the charges measured would reflect the properties and behaviour of the powder under subsequent manufacturing processes such as during mixing. Powder was placed in a stainless steel container of 1 litre capacity and the container tumbled on a roller mixer for 20 minutes at 80 r.p.m.

7.4.5. Measurement of charge

Electrostatic charge measurement is one of the most difficult aspects in the study of electrostatic phenomena. Although the numerous factors mentioned above have been identified as potential variables to be encountered in charge measurement studies, rigorous attention to control the experimental conditions may not always yield
reproducible results. In low charge measurements, it is important to eliminate the introduction of electric fields in the vicinity of the Faraday well. The operator should wear cotton laboratory coats to minimise electrostatic charge generation. It is advisable to keep a distance of 60 cm between the operator and the Faraday well (Reis et al 1984). The effects of surrounding external fields and of the operator on approaching the Faraday well were monitored: if a stable value of zero was recorded, the inner cup was being appropriately shielded from external electric fields. The temperature was controlled by carrying out the measurement of charges in a temperature-controlled room. The humidity was monitored using a probe (Ro-tronic Hygroskop DT). A temperature probe connected to the electrometer recorded the conditions under which charge measurement was being made.

The electrometer should be allowed a warming up period of 1 hour to ensure accurate measurements. The electrometer is connected to the Faraday well and after thorough cleaning, the equipment is ready for use. The powders were charged as detailed in section 7.4.4. Immediately after charging, 5 g of the powder was weighed into a stainless steel beaker and poured down a metal funnel into the inner cup of the Faraday well at the rate of 20 g per minute. Powder adhering to the beaker and funnel was gently tapped and the charge on the powders measured and stored in the electrometer. A sample weight of 5g was chosen so as not to occupy more than the lower 30% of the inner cup of the Faraday well (BS 7506, Part 2, 1996). Five measurements were made on each powder and fresh powder samples were used for each measurement. If the charge on an unknown powder was being measured, the ‘autorange’ feature of the electrometer should be switched on. This enables the electrometer to record charges of any value within its measurement range.

7.5. RESULTS AND DISCUSSION

Since the surface area of the powders was expected to have an effect on the magnitude of the charges acquired by the powders, the measured charges were corrected to account for the effects of surface area. The values and determination of specific surface areas of the powders are detailed in chapter 10 in table 10.1.
The charges generated by friction with stainless steel per gram of powder are expressed as a function of unit area \((nCg^{-1}m^{-2})\) under the conditions of humidity and temperature and shown in table 7.2. The values are a mean of five measurements.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Charge ((nCg^{-1}m^{-2}))</th>
<th>% RH</th>
<th>Temperature (^\circ C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamifenacin</td>
<td>2.2 (0.4)</td>
<td>34.1 (0.3)</td>
<td>20.0 (0.2)</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>-0.1 (0.0)</td>
<td>35.8 (1.3)</td>
<td>20.2 (0.3)</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>-8.9 (0.8)</td>
<td>34.0 (0.8)</td>
<td>20.6 (0.1)</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>-9.0 (0.8)</td>
<td>44.7 (4.2)</td>
<td>20.4 (0.3)</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>-10.6 (0.7)</td>
<td>36.1 (0.8)</td>
<td>20.5 (0.2)</td>
</tr>
<tr>
<td>Starch</td>
<td>-13.4 (0.7)</td>
<td>34.2 (0.7)</td>
<td>20.0 (0.1)</td>
</tr>
</tbody>
</table>

Table 7.2 shows the charges per gram and unit area of the powders with the standard deviation values in \((\ ))\), on contact with stainless steel under the above conditions of temperature and relative humidity.

Stainless steel is located midway in the triboelectric series (Unger 1981). Most powders charged negatively with stainless steel, having acquired electrons from the metal surface. Only zamifenacin developed a positive charge with stainless steel.

### 7.5.1. Effect of charge on mixing

It is interesting to note that the negative charge on starch on contact with stainless steel is higher in magnitude than the negative charge on lactose monohydrate. Since zamifenacin charges positively with stainless steel and that opposite charges attract, it would be expected that the interaction between zamifenacin-starch would be more favourable than between zamifenacin-lactose particles. Homogeneity studies on these binary systems were carried out and the data shown in chapter 8. Binary mixes of zamifenacin-starch yielded lower coefficients of variation \((% C.V. 1 \text{ and } 2)\) indicating that they were more stable than zamifenacin-lactose mixes \((%C.V. 5 \text{ and } 29)\). This confirms the influence of triboelectric charging on the mixing of powders. It is thought that the improved stability of mixes was due to the presence of attractive Coulombic forces between oppositely charged particles (Staniforth and Rees 1982b). As the
particles get closer to each other, the distance between them decreases. If the particles are separated by less than 20 nm, van der Waals forces become predominant, resulting in strong interparticulate adhesion and hence, stable mixes.

7.5.2. Electron donating-accepting behaviour

The ability of powders to donate or accept electrons is an inherent property of the powder. It can be measured using a surface characterisation technique such as inverse gas chromatography (IGC) or by triboelectric charging. Charging powders by friction is a surface phenomenon, and is dependent on the work functions of materials and their tendency to donate or accept electrons relative to other surfaces. An attempt was made to relate the electron accepting-donating properties of the powders studied by these two techniques. All powders studied charged negatively with stainless except for zamifenacin. The charges on the powders were corrected for surface area effects and the values plotted as a function of $\frac{K_D}{K_A}$, the ratio of the electron donating to electron accepting tendencies of the materials.

Most data points were located in the negative quadrant (figure 7.5). As expected, all three lactose powders i.e. lactose monohydrate, anhydrous lactose and spray-dried lactose showed similar electron accepting-donating properties and were located closely together. The data point for magnesium stearate was not plotted as the conditions for measurement by IGC differed from that of the other powders. Only the data point for zamifenacin was located in the positive quadrant. It is hence difficult to determine from these results whether a correlation exists between the data obtained from IGC and on charging the powders with stainless steel. More data points are required in the positive quadrant i.e. powders with tendencies to charge positively with stainless steel are required in order to be able to confidently explain this correlation.
Figure 7.5 shows the electron-donor to the electron-acceptor parameter ratios of the powders, $[K_D/K_A]$ as a function of their electrostatic charges with stainless steel.

7.6. CONCLUSIONS

The effects of charging powders with stainless steel produced negative charges for all excipients studied: starch, lactose monohydrate, anhydrous lactose, spray-dried lactose and magnesium stearate except for zamifenacin, which charged positively. The negative charge acquired by starch is higher in magnitude than that acquired by lactose monohydrate, indicating that the interaction between zamifenacin and starch would be stronger than between zamifenacin and lactose monohydrate particles. These findings were indeed supported by homogeneity studies on binary blends assessed by HPLC. Zamifenacin-starch mixes were found to be more homogeneous than zamifenacin-lactose mixes. The triboelectric charging data are also in broad agreement with the predictions made by IGC data, based on the magnitude of the interaction parameter ($I$).
Pharmaceutical powders are poor charge conductors and lead to accumulation of static charges. Although this gives rise to unwanted static electricity in many manufacturing processes, some positive aspect of electrostatic charging has been found in the production of stable mixes. If the surface properties of materials in a mix are manipulated accordingly e.g. by positively charging the particles of the active drug and negatively charging those of the excipient, the adhesion forces between the components can be improved greatly.

The electron donating and accepting tendencies of powders studied by IGC and triboelectric charging showed encouraging results. Preliminary work in this area using a series of 5 powders showed that a correlation may exist between data obtained from these two techniques. However, more work needs to be done using powders that exhibit charges over a wider range of values in order to establish the true relationship between IGC and triboelectric charging. The practical significance of this relationship if confirmed, is that IGC could then be used to support triboelectric charging data as it is acknowledged that charge measurement is problematic and highly variable.
Near-Infrared Spectroscopy (NIRS) has been used in the food industry for the determination of moisture, protein and fat contents for many years but its potential in the pharmaceutical industry was discovered only recently. The applications and use of chemometrics in NIRS are innovative. Chemometrics is a technique that links analytical information to physical and chemical properties of species. The advances in the spectroscopy instrumentation and computer chemometric software have extended the uses of the NIR spectroscopy to the identification, quality control, in-process monitoring and analysis of active ingredients in the pharmaceutical industry. NIRS has become a popular method to complement conventional analytical techniques such as HPLC (high-pressure liquid chromatography) but the aim is to eventually replace those time-consuming assays. NIRS possesses several advantages over conventional methods of analysis. It provides a non-destructive rapid analytical technique with routine analyses taking less than 5 minutes per sample, requires no sample preparation or use of solvents as in chromatographic techniques.

NIRS is very versatile. It can be used at-line (where the spectrophotometer is close to the process stream), on-line (the spectrophotometer is connected to the process line, continuously or intermittently sampling the process) or in-line (where there is direct contact between the spectrophotometer and the interaction in the process stream). In the identification of raw materials, a library of spectra of pharmaceutical excipients within specification limits is built with which the spectra of unknown compounds are mapped. Monitoring of reaction processes such as polymorph conversion gives scope for stability of products to be studied. NIRS when used in monitoring the homogeneity of blends involves the acquisition of spectra throughout the entire mixing process and the determination of an ideal mix from all the spectra collected and comparison of spectra to that of the ideal mix. In the quantitative analysis of intermediate and end-products, NIRS appears very promising compared with other methods of analyses as no sampling, which is known to potentially introduce errors is required. NIRS can also be used in quality control of an entire batch of solid dosage forms since it is rapid and non-destructive. Although NIRS presents all the above advantages, it remains a secondary...
analytical technique as a result of the lack of standardisation of NIR instrumentation. Inter laboratory transfer of NIR data is not feasible due to the non-reproducibility of the spectrophotometers. In the pharmaceutical industry, minute amounts of potent drugs are frequently used and it is of utmost importance that a high level of sensitivity, specificity, accuracy and reproducibility is attained in analytical techniques. Another drawback of NIRS lies in the complexity of the acquired spectra.

8.1. THEORY

The near-IR region was discovered by Herschel in the early 1800s. NIR involves the absorption of electromagnetic radiation in the range of 800-2500 nm (figure 8.1). The range 1100-2500 nm, known as the Herschel region is most often used in the pharmaceutical industry.

![Figure 8.1: Region of the Electromagnetic Spectrum](800-2500 nm)

Figure 8.1 shows the region of electromagnetic spectrum where NIR radiation occurs.

Materials subjected to infrared radiation absorb part of the radiation as a result of vibrations and rotational motions of atoms within the molecule. These are specific for each type of covalent bond and atom present. NIR spectra consist of a mixture of overtones and combinations arising from the hydrogen vibrations of the OH, CH and NH groups in the 800-2500 nm range. These absorbances are much less intense and can

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be as small as a 1000-fold of those in the mid-IR region. The weak absorbances make NIR reflectance advantageous for analysing major components and no sample dilution is required. A depth of penetration of up to 5 mm of the sample can be achieved. However, this particularity makes NIR less sensitive when minor components are to be analysed. NIR gives flexible options for handling all types of materials from solids to liquids. It can be used in transmittance mode as in the case of liquids or transparent substances, reflectance mode for solids and transreflectance (where the radiation is first transmitted through the medium and subsequently reflected onto detectors).

8.1.1. Instrumentation

NIR instruments consist of a light source directed at the sample and the reflected light focused onto a detector. The energy source is from a tungsten-halogen lamp, with the required wavelengths of radiation produced by a scanning grating monochromator. The detectors used depend on the range of wavelengths used: silicon photovoltaic sensors (360-1000 nm range) and lead sulphide (900-2500 nm range). The spectral intensities are expressed as log (1/R') where R' is the reflectance of the sample relative to that reflected by a non-absorbing standard, usually a white ceramic disc. NIR instruments have been adapted to transfer the technology from static laboratory environments to the dynamic processes in manufacturing sites. Spectrophotometers can either be fitted with a remote fibre optic probe to analyse samples several hundreds of feet away from the instrument or have a measurement window to which samples are presented for analysis. The main advantage of NIRS is that glass or quartz do not absorb in the NIR region; this enables fibre optic glass probes, end containers of glass to be used without the need to prepare or destroy samples.

8.1.2. Blending studies using NIRS

So far, NIRS remains a secondary analytical technique and other conventional assay techniques such as HPLC or UV spectrophotometry are required on the final mix to confirm the homogeneity of the mix and content of the active compound. The advantages of using NIRS over HPLC are that spectra of the blend are acquired throughout the entire mixing process as opposed to the end point of the blending process.
for HPLC analysis. As such, the change in homogeneity of the blend can be monitored with time.

Following the loading of the excipient(s) with the active compound in the blending vessel, on-line monitoring of the mixing process by NIRS was started. Blending was initiated and at set intervals, spectra of the blend were acquired throughout the mixing process. Spectra of the pure components of the mix were also acquired, as they would be useful when interpreting the spectra of the blends. NIR spectra so obtained would be a combination of physical and chemical properties of the blend. Physical aspects are due to differences in particle sizes or degree of compaction of the mix. This would give rise to an increase in scatter and as a result, spectra became curved at higher wavelengths following an increase in the log (1/R') or absorbance values. This phenomenon is known as the offset of the spectra and can be overcome by treating the spectra acquired prior to application of statistical equations. Removal of this trend would reduce the variation resulting from non-chemical parameters and clarify the chemical differences between samples. The treated spectra can then be interpreted in several ways to monitor mixing.

8.1.2.1. Pre-treatment of spectra

Several methods can be used to transform spectra, the choice of which depends on the use of the transformed spectra in further chemometric applications:

1) Second derivative as used by Ciurczak (1991) enables removal of the offset but the treated spectra became more complex and difficult to analyse.

2) Standard Normal Variate transformation (SNV)
This removes all possible trends due to difference in sizes, wavelengths and other physical sources but does not give a flat baseline in the spectra. Each spectrum, $z_{ij}$, is standardised to give an SNV spectrum, $y_{ij}$:

$$y_{ij} = \frac{z_{ij} - n_i}{s_i}$$

(8.1)
for $i = 1, \ldots, m; j=1,\ldots,v$ and where $n_i$ and $s_i$ are the mean and standard deviation of the elements of $z_i$ respectively.

3) De-trending results in a flat baseline in the spectra but does not remove all variations arising from physical sources in the blend. Each spectrum is fitted with a second-degree polynomial. The de-trended spectrum is obtained by subtracting this fit from the original spectrum.

8.1.2.2. Interpretation of spectra

The different ways in which NIR spectra in mixing studies can be interpreted will be discussed below.

a) Visual inspection

Visual inspection of overlaid transformed spectra obtained at different time points is one of the approaches used in monitoring powder blending. Initially, the spectra would consist of distinct patterns arising from the individual constituents in the mix. As mixing proceeds, the spectra gradually lose the identities of the constituents and become a composite trace of the blend. However, one drawback of this method is that the homogeneity of penultimate and final mixes of powders cannot be sufficiently defined (Ciurczak 1991). Further interpretation of the spectra would be required.

b) Spectral matching

In spectral matching, an index is generated which gives a measure of the correlation of the unknown mix with a final mix. The spectrum of the unknown mix is treated as a vector and compared with that of the final mix spectrum using a dot-product calculation. The match index will have a value ranging from $+1.000$ to $-1.000$. If the match index is zero, the two vectors are considered to be orthogonal or totally independent of each other. A match index equal to $+1.000$ implies that the endpoint of mixing has been attained.

c) Moving block standard deviation approach

The purpose of using NIRS in monitoring blending is to reduce extensive analytical assays. Since time is the essence during manufacturing operations, it is important to generate results as quickly as possible. Hence, no libraries of spectra are available as
reference when a compound of interest is first mixed. Qualitative information can still be obtained on the mix using spectra acquired throughout the blending period. Since several spectra are acquired at each time point at the same location in the blend, the mean and standard deviation at each wavelength and at each time point can be determined. However, it would be highly likely that the spectra at each time point would be superimposed, as the composition of the blend would not have changed much. To be able to monitor the homogeneity with time, a moving block approach has to be used. The mean of spectra at each time point is first determined and a moving block of spectra at three consecutive time points is used. For each block of 3 spectra, the standard deviation at each wavelength was determined and a pooled standard deviation value obtained by averaging the standard deviation values at all wavelengths. This method was used by Hailey et al (1996), Sonja Sekulic (1996) to study the homogeneity of the blend over time. The time point at which the value of the standard deviation is lowest can be taken as the ideal mixing time and the 'mixture' spectrum would be the average of these spectra.

**d) Simplisma**

Simplisma is based on the choice of a pure variable e.g. the wavelength at which only one component in the mix absorbs. If the Beer law holds, at a certain wavelength, the absorbance of the sample would be proportional to the concentration of the component in the sample. A profile of concentration or absorbance at the selected wavelength against the location or time of sampling would give qualitative information on the blend. The concentration should approach a constant value and can be used to monitor homogeneity throughout the mixing vessel with time.

**e) Quantitative determination using Principal Component Analysis (PCA)**

PCA is a mathematical procedure used to transform complex data into a new set of variables known as principal components (or eigenvectors). This procedure excludes factors e.g. noise from the spectra and makes more apparent the important factors such as the chemical composition of the samples. In PCA, the original spectra are considered as a matrix $Z$ ($i \times j$) consisting of $i$ rows of spectra collected at $j$ wavelengths. Principal component analysis decomposes the matrices into:

$$Z = \text{scores} \times L^T$$

(8.2)
where the scores are the new co-ordinates of points on the new axes, \( L \) is the loading (the angle between the axes for the original data and principle component axes) and \( T' \) means transpose.

A simple example of the use of PCA is in the quantitative determination of the content of the active component in a mixture. First, spectra of a set of calibration and test samples covering a concentration range of the active and excipients in the mix are acquired. The principle components or scores of the calibration samples are plotted against the theoretical amounts used and the calibration equation generated by principal component analysis. The accuracy of the fit of the calibration samples to the theoretical amounts is determined statistically by parameters such as the correlation coefficient. A correlation coefficient value of 1.0 would indicate 100% correlation. The equation is further validated using test samples of known compositions. To ensure the calibration equation is reliable, at least 10 to 15 samples covering a range of \( \pm 5\% \) of drug content are required (Corti et al 1989). A combination of laboratory and production samples should be used to give a more robust calibration equation. If production samples only were used, the samples would encompass a narrow range of concentrations as encountered in production samples. However, if a set of laboratory samples only covering a wider range of concentrations were used, the calibration equation would not be reflective of the variation encountered during production. Hence, the use of equal amounts of laboratory and production samples is recommended in the determination of regression equations.

### 8.2. HOMOGENEITY STUDIES OF ZAMIFENACIN MIXES

Mixing studies were carried out with four main objectives:

1. Firstly, data from the inverse gas chromatography and triboelectric series indicated that zamifenacin would interact more favourably with starch than lactose. In order to investigate whether these findings were in fact true, binary mixes of zamifenacin with lactose or starch were prepared and assayed for homogeneity by HPLC and NIRS.
2. The second purpose of the studies was to use NIRS to monitor the mixing process on-line and throughout the entire mixing process to assess the homogeneity of the blend with mixing time.

3. The third aim was to study the effects of the order of addition of excipients to the active compound using NIRS.

4. The last objective was to compare the data obtained by conventional assay techniques such as HPLC with NIRS data. With the increasing interest and advantages in the use of NIRS in the pharmaceutical field, it would be interesting to find out whether NIRS can be used as an alternative technique to HPLC.

8.3. MATERIALS AND METHODS USED

8.3.1. Experimental design of mixing studies

The composition of the mixes studied reflected the formulations used by Pfizer Central Research in formulation studies. The concentrations of zamifenacin in blends ranged from 6 to 32 %w/w and ratios of lactose to starch in tertiary blends were 1.5 to 4.5 to cover the nominal ratio of 3.0 in zamifenacin formulations. A total of 18 blends, of which 4 were binary and the remaining 14 tertiary blends were studied. The four binary blends consisted of two zamifenacin-starch and two zamifenacin-lactose blends. To study the order of addition of excipients, lactose was added first to zamifenacin followed by starch in seven blends and in the remaining seven, starch was added first to zamifenacin followed by lactose. To introduce variation in the design, the order in which the blends were mixed was allocated randomly as shown in table 8.1.
Table 8.1 shows details of the formulations studied by HPLC and NIRS.

Binary and tertiary blends of zamifenacin with lactose monohydrate and/or starch were mixed according to the experimental design shown in figure 8.2. The difference between the mixing procedures between the binary and tertiary blends is indicated by the boxes.
Figure 8.2 shows the experimental design for the mixing studies, where TMB refers to the Top, Middle and Bottom locations of the vessel from which samples were taken.

8.3.2. Mixing/milling equipment

Mixing was carried out in a Y-cone stainless steel blender of 240 ml capacity, specially modified to hold a near-infrared fibre optic probe stationary while the blender rotated at 20 rpm. The blender was interfaced with a computer via the LabVIEW software (version 4.1, National Instruments, TX, USA) which was used to turn the blender on and off, as well as to initiate spectra acquisition at set time intervals. Since the densities of the active compound, zamifenacin, differed significantly from the excipients, each blend was made up to achieve 67% volume fill of the blender (160 ml). After 20 minutes mixing, the blends were hammer milled using a Glen Creston (Type 14-680) mill of 600μm and subsequently screened using a sieve of 500μm aperture size.

8.3.3. NIR Parameters

The spectrophotometer used was of a Luminar 2000 NIR AOTF (Brimrose) type and set in the reflectance mode. The standard reference used was Spectralon and is 99% reflective. Samples were scanned in the 1200-2000 nm range at 2 nm increments. One spectrum consisted of an average of 100 acquisitions. Spectra were acquired as raw
data with no pre-processing treatment done at that stage. Spectra were acquired as follows for a 20 minutes blending period: 5 spectra every 30 sec for first 2 minutes, then 5 spectra every minute for 8 minutes and 5 spectra every 2 minutes for 10 minutes.

8.3.4. HPLC assay

Samples (400 mg) were collected manually at the top, middle and bottom (TMB) sections of the blender before and after the screening/milling process. Samples of the same blend analysed before and after milling/screening would indicate the effect the milling and screening process has on the homogeneity of the blends. Each 400 mg sample was subdivided into three 100 mg sub-samples, giving a total of nine samples per blend. The sub-samples were first dissolved in the mobile phase and made up to volume in a volumetric flask. The solutions were then filtered through 0.8/0.2 μm filters (Acrodisc PP Gelman Sciences) and the first 5 ml of the filtered solutions discarded. The solutions were assayed at 25 °C using HPLC (Hewlett Packard HP1090) by injecting 20 μl of sample solution onto a Novopak® column (5 μm pore size, 3.9 mm x 150mm Waters USA) at a flow rate of 1 mlmin⁻¹. The active compound, zamifenacin was detected using a UV detector set at 287 nm. The homogeneity of a blend was expressed as the coefficient of variation (C.V. %) of the zamifenacin content in the nine samples.

\[
C.V.\% = \frac{100\sigma_x}{E} \quad (8.3)
\]

where σₓ is the standard deviation and E, the mean of zamifenacin content in the nine samples.

8.3.4.1. Experimental considerations

a) Mobile phase

The mobile phase consisted of buffer, methanol and acetonitrile in a 40:20:40 ratio. Buffer was made up of 0.02 M sodium acetate, 0.5% v/v triethylamine and adjusted to pH 5.2 with glacial acetic acid. Fresh buffer was prepared every two days.
b) **Calibration curves**

Calibration curves were prepared daily using solutions of known concentrations of zamifenacin in the mobile phase.

c) **Validation of HPLC assay, to determine whether:**

- the drug was adsorbed onto the acrylic filters,

Solutions of known concentration of drug only were analysed prior to and following filtration (drug is freely soluble in mobile phase). The % difference between the experimentally determined and theoretical drug content was minimal and was attributed to experimental errors (table 8.2). There was no adsorption of drug onto the filter.

- the injector and elution systems were accurate

From table 8.2, it can be seen that the % differences between the experimentally determined and theoretical concentrations of drug were well within experimental limits (below 2%). The low % difference values showed that the injector system was accurately delivering 20.0 µl of solution and the column was eluting all the drug injected.

<table>
<thead>
<tr>
<th>Theoretical drug Conc. (%w/v)</th>
<th>Procedure</th>
<th>Experimentally determined Conc. (% w/v)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.50</td>
<td>Unfiltered</td>
<td>9.52</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Filtered</td>
<td>9.52</td>
<td>0.23</td>
</tr>
<tr>
<td>11.46</td>
<td>Unfiltered</td>
<td>11.43</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>Filtered</td>
<td>11.42</td>
<td>-0.34</td>
</tr>
<tr>
<td>19.22</td>
<td>Unfiltered</td>
<td>19.25</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Filtered</td>
<td>19.3</td>
<td>0.32</td>
</tr>
<tr>
<td>21.56</td>
<td>Unfiltered</td>
<td>21.52</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>Filtered</td>
<td>21.50</td>
<td>-0.23</td>
</tr>
<tr>
<td>24.08</td>
<td>Unfiltered</td>
<td>24.09</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Filtered</td>
<td>24.10</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 8.2 shows the % difference in calculated and theoretical amounts of drug injected.
• Drug is retained on column between runs,
Solutions of methanol only were injected between each sample run. No peaks were obtained when methanol was injected through the system indicating that no drug was retained on the column between runs.

• The injector and column elution system was reproducible,
Ten samples of the same stock solution containing zamifenacin only in a concentration of 10.7 % w/v were injected. The mean calculated drug content was 10.70 ± 0.05 % w/v with a C.V. of 0.98%, hence within experimental error limits (below 2 %).

• Addition of starch or lactose resulted in interaction with the drug,
Solutions of zamifenacin with lactose and starch in the ratio of 3:1 were made up in two ways. The samples were either allowed to dissolve over 5 minutes or placed in an ultrasound bath for 20 minutes, allowed to cool and made up to volume. The solutions were filtered and 20 µl injected. The concentrations of drug eluted were determined and the % difference from the theoretical concentrations calculated (table 8.3). It was concluded that (i) starch and lactose did not interact with zamifenacin and (ii) the method of preparation of solutions did not have any significant effect on the drug content. Hence, solutions were prepared by allowing the drug to dissolve over 5 minutes as it was more time efficient.

<table>
<thead>
<tr>
<th>Theoretical drug Conc. (%w/v)</th>
<th>Procedure</th>
<th>Experimentally determined Conc. (%w/v)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.46</td>
<td>Dissolved</td>
<td>8.51</td>
<td>-0.62</td>
</tr>
<tr>
<td></td>
<td>Sonicated</td>
<td>8.41</td>
<td>0.55</td>
</tr>
<tr>
<td>12.41</td>
<td>Dissolved</td>
<td>12.45</td>
<td>-0.28</td>
</tr>
<tr>
<td></td>
<td>Sonicated</td>
<td>21.43</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

Table 8.3 shows the effect of excipients and method of preparing solutions.

Chapter 8 Near-Infrared Spectroscopy 173
8.4. RESULTS AND DISCUSSION

8.4.1. Homogeneity of mixes using HPLC

8.4.1.1. Effect of milling and screening

The milling/screening step was included in the experimental design as it was suspected that zamifenacin formed agglomerates with excipients. Samples taken from three blends before and after milling/screening were analysed. The samples collected after milling/screening gave significantly lower values for the coefficients of variation compared with samples taken from the same blend but prior to the milling/screening step (table 8.4). It was concluded that the milling followed by screening step improved the homogeneity of mixes. Hence, only samples collected after milling/screening were analysed by HPLC for the remaining blends.

<table>
<thead>
<tr>
<th>Blends</th>
<th>Zamifenacin Conc (%w/w)</th>
<th>% C.V. before milling/screening</th>
<th>% C.V. after milling/screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>13</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8.4 shows the coefficients of variation of blends before and after milling/screening.

8.4.1.2. Binary zamifenacin blends

Findings from inverse gas chromatography (IGC) predicted that the interaction between zamifenacin and starch (interaction parameter, I=1.4x10^{-2}) would be more favourable than between zamifenacin and lactose (I=0.6x10^{-2}). Triboelectric charging studies using stainless steel indicated that zamifenacin charged positively and the magnitude of the negative charges developed by starch was higher than by lactose. All data indicate that zamifenacin would form more stable mixes with starch than lactose. Samples analysed by HPLC confirmed that the zamifenacin-starch mixes (blends 13 and 14) yielded lower coefficients of variation compared with zamifenacin-lactose mixes (blends 11 and 12) as shown in table 8.5.
Table 8.5 shows the C.V of binary zamifenacin blends.

### 8.4.1.3. Tertiary zamifenacin blends

The coefficients of variation for each tertiary blend (table 8.6) reflect the homogeneity of the mixes at the end of the blending process as samples collected at the end point of the mixing process were analysed by HPLC. As such, it would be hard to draw any conclusions on the effect that the order of addition of excipients to the active compound has on the homogeneity of the mixes.

<table>
<thead>
<tr>
<th>Blends</th>
<th>Concentration (% w/w)</th>
<th>Order of adding excipients to active</th>
<th>% C.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zamifenacin</td>
<td>Lactose</td>
<td>Starch</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>56</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
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<td>3</td>
<td>19</td>
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<td>4</td>
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<td>30</td>
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<td>5</td>
<td>32</td>
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<td>6</td>
<td>77</td>
<td>17</td>
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<tr>
<td>7</td>
<td>13</td>
<td>72</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>66</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
<td>10</td>
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<td>20</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>18</td>
<td>29</td>
<td>57</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 8.6 shows the coefficients of variation of the blends.

*Chapter 8 Near-Infrared Spectroscopy 175*
8.4.2. Homogeneity of mixes using NIRS

As mentioned earlier, data obtained from HPLC assays cannot be used to determine the effect of the order of addition of excipients to the active compound. Instead, NIRS would be used to monitor the mixing process from beginning to end, using spectra continuously acquired during blending. Any change in the homogeneity of the blend would be easily identified, in particular, when the second excipient was added to the active-excipient premix. The use of NIRS in homogeneity studies of mixes involved a series of manipulations of the raw spectra acquired on-line during the blending process. The spectra firstly required pre-processing to remove physical effects.

Data pre-treatment used

A typical NIR raw spectrum is shown in figure 8.3a. At higher wavelengths, the baseline of the spectrum is seen to increase and this is referred to as the offset of the spectrum.

![Graph of log(Absorbance) vs Wavelength (nm)](image)

Figure 8.3a shows a typical untreated raw NIR spectrum.

The first step in the pre-treatment of spectra involved the transformation of the spectrum using the standard normal variate (SNV) treatment. The SNV treated spectrum is shown in figure 8.3b. The baseline offset is still present but the effects of physical sources have been removed. Detrending was then applied to the SNV treated spectrum. This was done by fitting the SNV spectrum with a second-degree polynomial; by subtracting this fit from the SNV treated spectrum, an SNVDT spectrum was obtained.
The resulting SNVDT spectrum with no drift or physical effects was obtained (figure 8.3c).

Figure 8.3b shows the above spectrum undergoing SNV treatment.

Figure 8.3c shows an SNVDT spectrum.
Moving block standard deviation approach

The homogeneity of the mixes was then determined by studying the standard deviation of the treated spectra in both the wavelength and time domains using Microsoft Excel software. During the acquisition of spectra of the blends, slight problems were encountered. At times, the fibre-optic probe was not adequately covered with powder resulting in spectra of air being acquired (as indicated by high baselines, log absorbance value > 0.4 and a distinct peak at around 1300 nm). Five spectra were acquired at each time point but with the problems outlined above, only three out of the five spectra were used. The average of 3 spectra was determined at each of the following time points: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 minutes. Hence, a total of 11 spectra were obtained over the 20 minute blending process.

To observe the homogeneity of a blend as a function of time, moving blocks of three spectra were used. The moving blocks used were for time points: 0, 2 and 4 minutes; 2, 4 and 6 minutes; 4, 6 and 8 minutes; 6, 8 and 10 minutes; 8, 10 and 12 minutes; 10, 12 and 14 minutes; 12, 14 and 16 minutes; 14, 16 and 18 minutes and 16, 18 and 20 minutes. For each block of 3 spectra, the standard deviation at each wavelength (1200, 1202, 1204, ..., 2000 nm) was determined and the average of all standard deviation values calculated to give a single, pooled standard deviation value. If a moving block of 3 spectra was taken from the initial 11 spectra, a total of 9 pooled standard deviation values would be obtained. If these pooled values were plotted against time, the homogeneity of the blend over the entire mixing period can be assessed.

8.4.2.1. Effect of milling/screening

The moving block standard deviation approach was used to study blends before and after milling. Each blend consists of two plots denoted by suffixes a and b which correspond to the process before and after milling respectively. What is relevant from these plots is that the values of the standard deviation at the endpoint of the mixing processes indicate the homogeneity reached by the mix after 20 minutes blending. If the standard deviation values were compared for plots a and b at time 20 minutes for each blend, it can be seen that the values in plots b are either close to or significantly less than the corresponding values in plots a. This infers that the milling process followed by screening either did not alter or significantly improved the homogeneity of the blend. One example is shown below in figures 8.4 a and b.
Figure 8.4a shows the standard deviation/time plot of blend 17 (drug, starch and lactose) before milling/screening.

Figure 8.4b shows the standard deviation/time plot of blend 17 (drug, starch and lactose) after milling/screening.
8.4.2.2. Binary zamifenacin blends

Four binary blends, two of which consisted of zamifenacin and starch and the remaining two being zamifenacin and lactose were studied. However, blend 14, which consisted of drug and starch could not be analysed by NIRS as too many spectra of air were acquired. Hence, only three of the four binary blends were studied. Standard deviation/time plots were drawn and the scale adjusted to a maximum standard deviation value of 1.5 in all plots to enable comparisons to be made. If the standard deviation values of zamifenacin-lactose plots are compared with that of the zamifenacin-starch plot, no conclusive comments can be made. Lactose gave rise to a stable mix (blend 11, figure 8.5) as well as a less stable mix (blend 12, figure 8.6) which gradually improved in homogeneity after approximately 12 minutes after blending had started. The only blend of drug and starch studied gave a standard deviation profile (blend 13, figure 8.7) that indicated the formation of a stable mix. With the limited data available, the effect of the type of excipient on the homogeneity of the binary blends of zamifenacin cannot be confidently determined by NIRS.

![Figure 8.5](image)

Figure 8.5 shows the standard deviation/time plot of blend 11 (drug and lactose) before milling/screening.
Figure 8.6 shows the standard deviation/time plot of blend 12 (drug and lactose) before milling/screening.

Figure 8.7 shows the standard deviation/time plot of blend 13 (drug and starch) before milling/screening.
8.4.2.3. Tertiary zamifenacin blends

The tertiary blends were prepared by adding the first excipient (starch or lactose) to zamifenacin followed by 10 minutes blending. The second excipient (starch or lactose) was then added and blended for a further 10 minutes. The NIR spectra acquired before milling/screening only were processed to obtain standard deviation/time plots to show the effect of adding a second excipient. On addition of the second excipient, the standard deviation would be expected to rise due to some degree of disorder being introduced in the system. The rate at which the homogeneity is restored (or the standard deviation is decreased) would indicate the effect the second excipient has on the binary zamifenacin premix. The order of addition of excipients to zamifenacin is studied by first considering the effect of the addition of starch to a zamifenacin-lactose mix.

• Starch added to zamifenacin-lactose premixes

Blends in which lactose was added as the first excipient are shown in figures 8.8 to 8.14. Addition of starch after 10 minutes caused an immediate increase in the standard deviation of most blends studied but the homogeneity was eventually restored. The time taken for the standard deviation to start decreasing was in the worst case, 6 minutes following the addition of starch to the premix of zamifenacin and lactose.

Figure 8.8 shows the standard deviation/time plot of blend 1 (drug-lactose premix to which starch is added).
Figure 8.9 shows the standard deviation/time plot of blend 3 (drug-lactose premix to which starch is added).

Figure 8.10 shows the standard deviation/time plot of blend 5 (drug-lactose premix to which starch is added).
Figure 8.11 shows the standard deviation/time plot of blend 7 (drug-lactose premix to which starch is added).

Figure 8.12 shows the standard deviation/time plot of blend 9 (drug-lactose premix to which starch is added).
Figure 8.13 shows the standard deviation/time plot of blend 15 (drug-lactose premix to which starch is added).

Figure 8.14 shows the standard deviation/time plot of blend 18 (drug-lactose premix to which starch is added).
• Lactose added to zamifenacin-starch premixes

Of the 7 blends in which starch was added as the first excipient, only 5 blends were studied since some problems in the spectra acquisition were encountered for blends 6 and 10. The standard deviation/time profiles of these mixes showed standard deviation values that increased following the addition of lactose to the zamifenacin-starch premix (figures 8.15 to 8.19). On addition of lactose, the homogeneity of the mix would be expected to decrease but order should eventually be restored as was seen in the case of zamifenacin-lactose premixes to which starch was added. However, this occurred in only one blend (figure 8.15) and the time taken for the standard deviation to decrease following the addition of lactose was longer (8 minutes compared with 6 minutes when starch was added to zamifenacin-lactose premixes). As for the remaining four blends in which starch was added to zamifenacin first, the standard deviation was not restored within the 20 minutes blending process.

Figure 8.15 shows the standard deviation/time plot of blend 2 (drug-starch premix to which lactose is added).

Figure 8.15 shows the standard deviation/time plot of blend 2 (drug-starch premix to which lactose is added).
Figure 8.16 shows the standard deviation/time plot of blend 4 (drug-starch premix to which lactose is added).

Figure 8.17 shows the standard deviation/time plot of blend 8 (drug-starch premix to which lactose is added).
Figure 8.18 shows the standard deviation/time plot of blend 16 (drug-starch premix to which lactose is added).

Figure 8.19 shows the standard deviation/time plot of blend 17 (drug-starch premix to which lactose is added).
The surface energy data determined by the DAT for zamifenacin, starch and lactose was used to provide an insight into the mechanisms of interaction in the binary and tertiary zamifenacin systems, as observed by NIRS. As a reminder, the work of adhesion (\(W_{ads}\)) is the energy required to separate unit area of two different phases whereas the work of cohesion (\(W_{coh}\)) is that required to separate unit area of the same phase. Consider a mix in which lactose is added to zamifenacin first, followed by starch. A schematic representation can be drawn to illustrate the possible interactions in the system (figure 8.20).

![Figure 8.20](image)

\[
\begin{align*}
W_{ads}^{96} & \quad \text{Zami} + \text{Lactose} & \quad W_{ads}^{123} & \quad \text{[Zami-lactose]} + \text{Starch} \\
& \quad + & \quad + & \quad [\text{Zami-lactose}] - \text{starch} \\
W_{coh} & \quad \text{Zami-Zami} & \quad 103 \\
& \quad \text{Starch-starch} & \quad 119 \\
& \quad \text{Lactose-lactose} & \quad 90 \\
& \quad (\text{zami/lac})-(\text{zami/lac}) & \quad 128
\end{align*}
\]

Figure 8.20 shows the possible interactions in a tertiary system where lactose (lac) was added first to zamifenacin (zami) with the strengths of the interactions expressed in units of mJm\(^{-2}\).

When lactose was first added and blended with zamifenacin for 10 minutes, zamifenacin-lactose interactive units would be obtained since the work of cohesion of lactose is lower than the work of adhesion between zamifenacin and lactose. On addition of starch to the premix, four possible interactions may occur and result in: [zamifenacin-lactose]-starch units, zamifenacin-starch (if excess zamifenacin present) units, starch-lactose (if excess lactose present) units or starch-starch interactions. Since the works of adhesion of zamifenacin-starch and lactose-starch interactions are much lower than the work of adhesion between [zamifenacin-lactose]-starch, the most thermodynamically favourable option would be to form [zamifenacin-lactose]-starch units. Since the stability of the tertiary mix would depend on the direction in which equilibrium 2 (in figure 8.20) shifts, a shift to the right would indicate that the mix is stable.
If a mix in which starch was added to zamifenacin first was considered, the relative strengths of the works of adhesion and cohesion indicate that zamifenacin would interact with starch to form zamifenacin-starch interactive units (figure 8.21). On addition of lactose, which has a low cohesive energy, the following interactive units may form: \([\text{zamifenacin-starch}]-\text{lactose}\), \(\text{zamifenacin-lactose}\) (if excess zamifenacin present) and \(\text{starch-lactose}\) (if excess starch present) since their works of adhesion are similar in value.

Figure 8.21 shows the possible interactions in a tertiary system where starch was added first to zamifenacin (zami) with the strengths of the interactions expressed in units of mJm\(^{-2}\).

Hence, equilibrium 2 in figure 8.21 can shift in either direction implying that this tertiary system would not be as stable as the previous system in which lactose was added to zamifenacin first, followed by starch.

From the NIRS and DAT data, it can be proposed that starch had a stabilising effect on the homogeneity of zamifenacin-lactose mixes. Lactose however caused disruption in homogeneous zamifenacin-starch premixes. The homogeneities of mixes in which lactose was added to zamifenacin-starch premixes were not restored within the 20 minutes blending period (except for one blend). DAT in conjunction with IGC and triboelectric data can thus be used to indicate the choice and order of adding excipients to zamifenacin to produce homogeneous mixes.
8.4.3. Correlation between HPLC and NIR data

An attempt was made to find out whether data obtained from HPLC correlated with that from NIRS. The vast amount of information acquired on-line by NIRS had to be filtered and reduced to show the relevant information on the chemical composition of the blends using the Matlab software (Math Works Inc.). Principle component analysis (PCA) was chosen to treat the data. PCA reduces variation due to noise and expresses the variances in the spectra in terms of principal components.

- The first step involves the selection of the last 10 spectra from each blend i.e. at the end point of the mixing process. This would give information on the chemical composition of the blend corresponding to the drug content determined by HPLC.
- The spectra were pre-treated to remove the physical effects as mentioned previously. The second derivatives of the spectra were determined using the Savitzki-Golay approach and a second degree polynomial.
- The spectra were reduced to the spectral region from 1618 to 1718 nm where the active compound, zamifenacin absorbed strongly.
- The data matrix was column-centred around the mean.
- The matrix was then decomposed to give the scores for the first principal component.

If the scores of the first principal component (PC1) were plotted as a function of zamifenacin concentration, a linear relationship was observed. The correlation coefficient of the fit was found to be 0.94. Hence, there was a correlation between the data obtained from HPLC and NIRS (figure 8.22).
Figure 8.22 shows the correlation found between HPLC and NIRS data.

This approach although not pursued here, can be used to find a calibration equation from which the concentration of the active compound in an unknown mix can be determined. The spectra of the unknown mix would require pre-treatment and processing as discussed above to obtain a score value which can be fitted into the calibration equation to give the expected concentration of the active. The use of NIRS as an analytical technique to quantitatively determine drug content is promising.

8.5. CONCLUSIONS

The mixing studies were designed with several objectives. One aim was to confirm the findings from the surface characterisation techniques that zamifenacin interacted more favourably with starch than lactose. Samples from binary blends were assayed by HPLC and the low values of the coefficients of variation (< 2%) of drug content showed that zamifenacin formed more homogeneous mixes with starch but unstable mixes with
lactose (C.V. > 2%). HPLC data from tertiary blends were not used to indicate the effect of the order of addition of excipients to the active after 10 minutes mixing since samples were collected only at the end point of the mixing process i.e. at 20 minutes.

Monitoring the mixing process by near-infrared spectroscopy (NIRS) proved useful as the homogeneity of the blend could be studied throughout the entire blending period. Homogeneity of the blends was based on standard deviation values derived in both the wavelength and time domains. Due to the limited NIRS data available on binary zamifenacin blends (only 3 blends studied), no conclusive remarks could be drawn on the effect of the type of excipient used in binary zamifenacin mixes.

The order of addition of excipients to zamifenacin in tertiary blends was also studied by NIRS. The changes in the standard deviation on addition of the second excipient indicated the effect of the added excipient on the homogeneity of the mix. Although it is expected that disorder would be introduced when another component is added to a mix, the homogeneity should eventually be restored as mixing proceeds. In mixes where lactose was added to zamifenacin-starch premixes, the standard deviation increased and was not restored within the 20 minutes blending period (except for one blend). However, if starch was added to zamifenacin-lactose premixes, the homogeneity initially deteriorated but improved as mixing proceeded. A mechanism into the stabilising effect of starch on zamifenacin-lactose premixes (and destabilising effects of lactose on zamifenacin-starch premixes) was provided based on DAT data.

Another aim of this project was to establish the value of using near-infrared spectroscopy as a secondary analytical technique to substitute the conventional analytical HPLC technique. The homogeneity of 18 blends was assessed by both techniques and it was interesting to find that data from the two techniques were in agreement. A strong correlation was found to exist between data obtained from the two techniques with a value of 0.94 obtained for the correlation coefficient of the line of best fit. This confirmed the relevance of using NIRS as an alternative analytical technique.

The advantages of using NIRS over HPLC are the vast amount of information that can be collected in a considerably reduced period of time. NIRS can be used successfully as both a qualitative and quantitative method of studying homogeneity of blends. NIRS is very versatile and can be used to assess homogeneity and composition of actives as well.
as excipients of mixes at all times during the blending process (Cuesta Sanchez 1995). Determination of optimum blending conditions and quantitative analysis of blends can be achieved in a short space of time. In the age of environmental concern, a reduction in the use of organic solvents has its unstated advantages. All these justify the importance and use of NIRS as a technique to be exploited in the dynamic environment of the development and production plants in pharmaceutical companies.

To date, the regulatory authorities state that the use of NIRS as an analytical technique requires additional confirmation from a conventional assay technique such as HPLC or UV spectroscopy on the penultimate and final mixes. This would prevail until it can be proven that NIRS provides reproducible data independent of the instrument used or the lab in which data were acquired. A positive move has been made to include a general monograph on the use of NIRS in the next European Pharmacopoeia. With its superior ease and time of analysis, NIRS is already proving useful in routine analysis in the early stages of manufacture compared with conventional methods. With further development in the standardisation of instrument and calibration procedures, NIRS would supersede the present analytical methods with respect to a massive reduction in time of manufacture, analysis and quality control.
One of the aims of this project was to determine the suitability of various surface characterisation techniques in the assessment of the surface energetics of pharmaceutical powders. The use of the Wilhelmy plate and sessile drop techniques was discussed in chapters 4 and 5 respectively. Inverse gas chromatography (IGC) has also been used successfully to obtain information on the surface nature of powders. All three techniques mentioned rely on the interaction of either liquid or vapour probes with the sample surface. Hence, the use of other vapour sorption techniques, namely the dynamic vapour sorption (DVS) and isothermal microcalorimetry was also investigated.

Both techniques work on the principle that when a powder sample is exposed to vapour (water being the most commonly used probe), a monolayer of molecules would form on the powder surface (represented by curve AB in figure 9.1).

Figure 9.1 shows a type II isotherm for the adsorption of vapour onto powder, where AB and BC correspond to monolayer and multilayer formation respectively of water molecules on the powder.
When the % relative humidity (%RH) of the vapour is increased, multilayers of water molecules form (represented by curve BC) on the powder surface. The first layer of water molecules formed on the sample gives the most meaningful data on the nature of the sample surface. Subsequent water sorption would lead to the condensation of water molecules, which is not relevant to the surface nature of the powder. The above adsorption profile is an example of a Type II isotherm, exhibited by most pharmaceutical powders when exposed to vapour.

- **Thermodynamic parameters**

The energy of a system consisting of water molecules being sorbed onto the surface of a powder can be explained according to laws of thermodynamics (thermodynamics being an area of physical chemistry involving the interconversion of energy). A system may be described in terms of the temperature, pressure, volume and composition of its constituents. According to the first law of thermodynamics which is the law of conservation of energy, energy cannot be destroyed nor created; instead, it is converted from one form to another. The internal energy of the system can be described as:

\[ U = H - PV \]  

where \( U \) is the internal energy, \( H \) is the enthalpy, \( P \) is the pressure and \( V \) is the volume of the system.

Under conditions of constant pressure, the heat exchanged in a system is called the 'enthalpy' of reaction (\( H \)) and expressed in Joules. The sign convention applied in the field of thermodynamics is such that a positive sign is used to denote an endothermic reaction (i.e. heat is absorbed) and a negative sign used for exothermic reactions (i.e. heat is released). Another thermodynamic term which is used to describe a reaction is the 'entropy', which gives a measure of the degree of disorder in the system. The second law of thermodynamics states that a system will always tend towards a state of maximum disorder and hence, of increased entropy e.g. a gas released in a closed defined space would diffuse spontaneously to fill the space available to it.

The enthalpy and entropy of a reaction can be related to give the Gibbs free energy:

\[ \Delta G = \Delta H - T\Delta S \]  

\( \Delta G \) is the change in Gibbs free energy, \( \Delta H \) is the change in enthalpy, \( T \) is the temperature in Kelvin and \( \Delta S \) is the change in entropy.
where $\Delta G$ represents the Gibbs free energy, $\Delta H$ is the enthalpy change, $\Delta S$ is the entropy change and $T$ is the temperature of the reaction.

The magnitude and sign of all three thermodynamic parameters give an indication of the extent of favourability of the reaction i.e. the more negative the value, the more favourable is the reaction. For a process to occur spontaneously, the balance between the entropy and enthalpy in the system must be such that the value of $\Delta G$ is negative. If these principles are applied to the adsorption of water vapour onto a powder surface, it can be seen why the enthalpy of the process is always negative. The adsorption process causes a rearrangement of the molecules at the surface of the powder and creates order in the system. This results in a decrease in the entropy and if the process is to be thermodynamically favourable, heat must be released so that the overall value of $\Delta G$ is negative.

**Surface energetics**

Contrary to the previous chapters where the surface property of a powder was expressed in terms of their dispersive and polar (electron acceptor-donor) components, the surface nature of powders studied by vapour sorption techniques is described in terms of thermodynamic parameters. The principles of thermodynamics were outlined above and rely on the extent of the interaction of water with the solid to give an indication of the polarity of the surface. An example of the use of vapour sorption techniques to derive thermodynamic parameters of powders was described by Buckton et al (1986). A vacuum microbalance was used to study the wettability of a series of barbiturate powders exposed to water vapour. The uptake of water by each powder under a range of temperature was recorded. In order to derive the thermodynamic parameters of the adsorption of water on the powder, it is first necessary to define a standard state. The standard state chosen was the number of moles of water sorbed per gram of powder ($b$) at the saturated vapour pressure ($P_0$) of water at 25 °C. The equilibrium constant ($K_{ads}$) at that temperature and pressure can be written as:

$$K_{ads} = \frac{b}{P_0} \quad (9.3)$$

The equilibrium constant is related to the Gibbs free energy of adsorption ($\Delta G_{ads}$) by:
\[ \Delta G_{\text{ads}} = -RT \ln K_{\text{ads}} \] (9.4)

where \( R \) is the gas constant and \( T \) is the temperature in K.

The enthalpy of adsorption of water vapour with the powder (\( -\Delta H_{\text{ads}} \)) can be determined using the van't Hoff equation (equation 9.5, in which \( B \) is a constant), provided the water uptake by the powder is recorded for a range of temperatures.

\[ \ln K_{\text{ads}} = \frac{-\Delta H_{\text{ads}}}{R} \cdot \frac{1}{T} + B \] (9.5)

By plotting the graph of \( \ln K_{\text{ads}} \) against \( 1/T \), \( \Delta H_{\text{ads}} \) can be obtained from the gradient of the line since \( R \) is a constant. The entropy of adsorption can be subsequently determined using equation (9.2). It should be remembered that the values of the thermodynamic parameters are not absolute but are relative to the standard state chosen. As such, it is still possible to compare the surface energetics of powders as they are all relative to the same standard state.

The approach described above for determining the surface energetics of powders is time consuming and an alternative method using the isothermal microcalorimetry has been described by Buckton and Beezer (1988). The method combines the enthalpy data obtained from a microcalorimeter as the powder is exposed to water vapour with the water uptake by a vacuum microbalance. Equations (9.3) and (9.4) are used to derive the Gibbs free energy of adsorption for the powder of interest but instead of using the van't Hoff equation, the enthalpy data from the microcalorimeter is substituted in equation (9.2) to obtain the entropy of adsorption. The main advantage of this method compared with the previous approach is that it gives a direct measure of the heat of sorption. Experiments on one powder need only be run at one temperature using both the microbalance and the microcalorimeter. This approach was successfully used by Buckton et al (1988) in determining the surface energetics of powders subjected to a range of milling processes.

An attempt was thus made to determine the surface energetics and thermodynamic parameters of the powders (studied by other techniques) using a combination of the two techniques. A dynamic vapour sorption (DVS) instrument would be used to measure the uptake of water by the sample as it is exposed to increasing % relative humidity or
% RH (in terms of the number of moles of water sorbed per gram of sample). An
isothermal microcalorimeter would measure the heat changes in the sample as vapour is
sorbed at different % RH at a given temperature. By combining the DVS data with the
microcalorimetric data, the enthalpy of adsorption per mole of water by one gram of
powder (Jmol⁻¹) can be calculated. The purpose of expressing the enthalpies per mole
of water sorbed is to compensate for the effects of the surface area of the sample. A
solid with a high surface area may require a larger number of water molecules to form a
monolayer compared with a solid of lower surface area. The larger value of the heat
evolved and detected by the microcalorimeter for the solid with high surface area would
indicate (although possibly incorrectly) a more favourable interaction of water. Hence,
it is necessary to standardise the enthalpies of adsorption per mole of water for each
solid. The free energy and entropy of adsorption of water on the powders can then be
determined as explained above.

If the vapour sorption experiments are carried out at distinct %RH, the entire sorption
process can be evaluated for each powder in terms of the enthalpic and entropic aspects
of the interaction. Since the sorption of water occurs by an initial monolayer formation
followed by condensation, the enthalpy ($\Delta H_{ads}$) and entropy of adsorption ($\Delta S_{ads}$) of the
entire process can be expressed as:

$$\Delta H_{ads} = \Delta H_{mon} + \Delta H_{con}$$  \hspace{1cm} (9.6)

$$\Delta S_{ads} = \Delta S_{mon} + \Delta S_{con}$$  \hspace{1cm} (9.7)

where the subscripts mon and con refer to monolayer and condensation respectively.

Since values of $\Delta H_{con}$ and $\Delta S_{con}$ for water can be found from the literature, the enthalpy
and entropy of monolayer formation of water on the solid can be determined (Buckton
et al 1986). As stated previously, the enthalpy of the monolayer would be the most
significant in providing information on the surface energetics of powders.
SECTION A. DVS MICROBALANCE

9.1. INTRODUCTION

The principles of operation of the dynamic vapour sorption microbalance (DVS-1 Surface Measurement Systems, UK) are similar to that of a weighing balance. It consists of two pans, one reference (empty) and one sample pan in which known amounts of powder are placed. The pans are suspended to a microbalance (Cahn DVS-200 microbalance) interfaced with a computer via the DVS Win Version 1.06 program. The pans and microbalance are enclosed in an incubator in which the humidity and temperature were controlled. If water (although organic solvents may also be used) is used as the probe liquid, the sorption profile of vapour onto a sample over a range of humidities can be studied. Any change in the weight of the sample pan is recorded as a function of time and humidity and represents the changes due to the sample only as the reference pan counteracts any effects on the sample pan.

9.2. INSTRUMENTATION

A schematic representation of the DVS-1 instrument is shown in figure 9.2. The sample pan is located opposite the reference pan with both pans hooked to the hang-down wires on the microbalance. Each pan is enclosed in a glass tube and can be accessed for cleaning and sample loading by lowering the lower portion of the tube. The lower and upper parts of the glass tube are held in place by a metal clip. The purpose of the reference pan is to compensate for any environmental or instrumental interference on the sample pan. The sample pans are made of glass and can load up to a maximum of 1.5 g of sample. However, typical sample masses range from 20 to 100 mg, with factors such as the density of the sample and its affinity for the probe liquid to be taken into consideration.
Figure 9.2 shows a schematic representation of the DVS-1 microbalance.

The rate of the total gas flow is set to a default value of 200 SCCM (standard cubic centimetres). The flow of nitrogen gas from a nitrogen cylinder to the incubator is controlled by two mass flow controllers; one mass controller pumping dry nitrogen (0% RH, if the dry line is set at 200 SCCM) and the other controller delivering nitrogen through a stainless steel tube immersed into the reservoir containing the liquid probe (water). The two mass controllers are regulated to produce the required % RH. The temperature of the incubator can be set from 25 to 80 °C and the % RH from 0 to 98 % RH. The microbalance unit is insulated from the atmosphere with firstly a glass door, and a main door to ensure that the temperature of the incubator is kept constant. The instrument was placed in a temperature controlled room and only minor temperature
fluctuations (± 0.1 °C of the set temperature) were experienced. The humidity and temperature probes record the actual humidity and temperature of the vapour inside the DVS incubator as it rises up the glass tubes to interact with the sample.

Two types of experiments can be carried out: a ramp experiment, in which the % RH is continuously increased from 0 to 98% RH or a step experiment, in which the % RH is increased in increments (of 10 or 15 % RH usually). The ramp experiment is used to obtain a characteristic sorption profile of a material or for determining the % RH for moisture events such as hydration or deliquescence. A step experiment is required if adsorption isotherms (plots of the volume or mass of water sorbed as a function of increasing % RH) are to be drawn. The DVS instrument provides the operator with a variety of experimental design e.g. the sample can be exposed to water vapour for the duration of one full cycle, which consists of an adsorption (half) cycle (where the % RH is increased from 0 to 98 % RH) and a desorption (second half) cycle (whereby the % RH is subsequently decreased from 98 to 0 % RH). A total of 10 full cycles can be used but it is usual to expose the sample to a maximum of three full cycles. Exposure to vapour after the second full cycle is not expected to produce any further change in the sample.

9.2.1. Cleaning of pan and loading of sample

The aspect of the DVS instrument the operator has to be particularly careful of, is the cleaning of the sample pan. Tweezers were used to handle the pan at all times. The established procedure was to rinse the sample pan using firstly double distilled water, then ethanol. Excess solvent was removed by gently shaking the pan. The pan was then carefully suspended onto the hang-down wire, ensuring that the wire or pan is not adhering to the glass tube. The % RH of the incubator is set to 90% RH for 10 minutes to remove any electrostatic charges that may have developed during the cleaning process. The response observed if there were any electrostatic effects would be a sharp increase in the plot of mass uptake as a function of time. The pan is then dried by setting the % RH to 0 and left at that humidity until no change in mass is recorded. The criteria used for determining when the sample pan was sufficiently dry was when the % dm/dt value is less than 0.0001. The % dm/dt represents the rate of change of the sample mass expressed as the % of the initial mass of sample per 20 seconds interval. This drying stage may take a minimum of 20 minutes. Once the %dm/dt reading is
stable, the microbalance is tared and ready to be used. It is good practice to switch off the incubator before opening the outer door of the instrument. The fan is automatically switched off and prevents air turbulence during the loading of the sample. The sample is placed on the sample pan and if electrostatic effects are obvious (as seen by an unstable % dm/dt value), an antistatic gun (Zerostat 3) is aimed at the sample pan and the hang-down wire to try and eliminate any charges. Once the sample is loaded and the reading stabilised, the balance is again tared. Any uptake or loss in mass would be relative to the zero reading.

9.2.2. Calibration

The calibration of the microbalance is required whenever the instrument is moved or repositioned to a new location or there is a power failure and the D-200 microbalance is turned off or if the temperature of the incubator is changed. Before calibrating the microbalance, the temperature is set to the required value and the relative humidity to 0 % RH. When the % dm/dt reading is stable, the microbalance is tared. A 100 mg weight is placed in the sample pan and once the value of the mass is 100 ± 0.002 mg, the calibration weight is recorded and the calibration process is complete.

9.2.3. Materials and method used

The active compound, zamifenacin was studied and 25 mg of sample loaded onto the sample pan. The probe liquid used was water. The temperature of the incubator was set to 25 °C. A step experiment was set up at 10% RH increments from 0 to 98% RH for a duration of two full cycles i.e. adsorption-desorption-adsorption and desorption. The % dm/dt value was set to 0.0005% for a minimum of 30 minutes. If the changes in mass of the sample are less than the specified % dm/dt value i.e. 0.0005 mg per 100mg of sample in 20 seconds for a minimum of 30 minutes, the % RH of the incubator is switched to the next % RH.
9.3. RESULTS AND DISCUSSION

As the % RH is increased, the water molecules bind to the sample surface and an increase in weight is expected to be recorded by the microbalance. A typical adsorption experiment will show an initial increase in mass uptake as the % RH is increased. The mass curve eventually reaches a plateau and remains at that level for the specified length of time before the % RH is changed. Similarly, for a desorption cycle, the mass decreases until the change in mass is so minimal that the % RH switches down to the next step. The output of the DVS microbalance recorded for zamifenacin is shown in figure 9.3 as a plot of the 'mass uptake (mg) as a function of % RH and time. It should be noted that figure 9.3 is not representative of a typical output of a DVS experiment.

Figure 9.3 shows the DVS mass plot of zamifenacin as a function of time and %RH.

In figure 9.3, the blue line represents the % RH steps for the adsorption cycle (10-20.....80-90) and the desorption cycle (90-80...20-10) as the sample is exposed to two full cycles and the red line shows the corresponding changes in mass of the sample as
the % RH is changed. From the DVS ‘mass versus time’ plot of zamifenacin, three observations can be made. As the powder is exposed to 0% RH, a loss in weight is expected as the sample undergoes drying. However, an increase in weight is observed in both the first and second cycles. Secondly, the spiked response is clearly indicative of the presence of electrostatic interference on the sample pan. By exposing the sample or pan to 90% RH, electrostatic charges should disappear. This was not the case for zamifenacin. An antistatic gun was used to discharge any electrostatic effects on subsequent experiments of the same powder but similar observations were made. Although the presence of electrostatic charges preclude the use of the DVS microbalance in sorption experiments, this observation is in line with triboelectric charging data, whereby zamifenacin showed a high tendency to charge on contact with stainless steel. The third observation to be noted is the low affinity of the powder for water. The maximum water uptake by 25 mg of sample at 90% RH was approximately 0.015 mg. This value is too close to the detection sensitivity of the DVS instrument (0.1 μmg) to confidently assess the sorption of water on zamifenacin, in particular at lower % RH. Two suggestions can be made at this stage: a larger weight of powder could be used or another liquid probe, for which zamifenacin has a higher affinity may be used. Unfortunately, the bulk density of zamifenacin is low (0.1 gcm\(^{-3}\)) and the maximum sample weight that could be loaded into the largest sample pan available was 25 mg. The liquid probe may be changed but the fundamental problem remains in the fact that the sample is too electrostatic for measurement.

9.4. CONCLUSIONS

The DVS instrument is automatically operated and requires very small amounts of sample (as low as 5 mg) and minimal skills for operation. It has a high level of sensitivity which has been used to detect amorphous content as low as 0.05% in powders (Buckton and Darcy 1995). The parameter being measured is the change in mass of the sample as a function of time and % RH and the interpretation of the output data is simple.

The high sensitivity of the DVS microbalance however leads to the main drawback of the instrument. Minor disruption to the sample pan would be recorded by the balance,
such as the occurrence of electrostatic charges on the sample pan and the stainless steel hang-down wire. When highly electrostatic materials were studied e.g. zamifenacin, great difficulty was encountered. The low water uptake by zamifenacin coupled with the limited amount of sample that could be loaded on the pan meant that any data obtained would be close to the detection level of the instrument. As a result, the use of the DVS microbalance in this project was thus not fruitful.
SECTION B. ISOTHERMAL MICROCALORIMETRY

9.5. INTRODUCTION

During the past decade, isothermal microcalorimetry has been used in wide ranging applications, from the field of physical pharmacy to microbiology (Buckton 1995b and Buckton and Beezer 1991). The popularity of this technique stems from its versatility and high degree of sensitivity of operation. Some of its uses in physical pharmacy include the detection of low levels of amorphous content in powders (Briggner et al 1994 and Buckton et al 1995b) and the investigation into the mechanism of recrystallisation of powders when exposed to different % RH (Buckton and Darcy 1995b, and Buckton et al 1995c). These are important applications of the technique and would not be discussed here due to the limited scope of this thesis. Instead, the use of the isothermal microcalorimeter in relation to the determination of the surface energetics of materials would be detailed.

The principles of operation of the isothermal microcalorimeter are simple and rely on the absorption or release of heat from physical, chemical or biological processes under isothermal conditions i.e. under a set temperature. Samples used in an isothermal microcalorimetric experiment can be studied 'as received' from the manufacturer. The superiority of the isothermal microcalorimetry in detecting batch variability in lactose powders compared with contact angle measurement was demonstrated by Sheridan et al (1995).

Since the DVS instrument was found to be unsuitable in studying the uptake of water by the active compound, zamifenacin, the interpretation of the data to be gathered by the microcalorimeter would be somehow limited. The adsorption of water by the powders cannot be quantified by the microcalorimetric data alone and it would hence not be possible to determine the surface energetics and thermodynamic parameters of the solids as previously hoped. Instead, the microcalorimeter would only be used to give a measure of the degree of interaction of several pharmaceutical powders with water.
9.6. INSTRUMENTATION

The isothermal microcalorimeter (Thermometric AB, Sweden) consists of a Thermal Activity Monitor (2277 TAM) connected to a 2280 TAM Accessory Interface and a Digitam 3.0 software. A microcalorimeter consists of four different channels and each channel is used independently of the other three, hence giving the possibility of four different experiments to be simultaneously carried out. The channels are enclosed in a large sink containing 25 litres of water at a temperature which can be set from 5 to 80 °C and maintained at ± 2 x 10^-4 °C from the pre-set temperature. Each channel is designed to house a pair of sample and reference cells. Each cell is surrounded by thermopiles, which are sensitive heat conductors capable of detecting temperature changes of the order of 10^-6 °C. Depending on the processes occurring in the sample, heat is absorbed from or released to the heat sink. The heat changes are converted into voltage signals. The voltage difference between the sample and the reference cells is detected and represents the difference in heat between the two cells. The voltage is amplified, recorded in Joules per second (or Watts) and displayed on the digital voltmeter (DVM) of the Thermal Activity Monitor. The microcalorimeter can be used for batch or flow experiments. Batch experiments are carried out using glass ampoules into which the sample and a glass tube containing saturated salt solutions (to provide a certain % RH) are placed. However, the experiments carried out in this project were flow experiments involving the use of a flow or perfusion cell, which is detailed below.

9.6.1. Flow (perfusion) cell

Flow experiments differ from batch experiments in that the powder under study is exposed to a range of % RH in constantly increasing % RH (ramp experiment) or in steps (step experiment) of increasing % RH. A schematic diagram of the flow cell, also referred to as the perfusion cell is shown in figure 9.4. The flow cell consists of a flow divider and five chambers interconnected by stainless steel tubes. The bottom chamber is the stainless steel sample cell of 5 ml capacity in which the sample is placed. The two humidity chambers are emptied and filled with 0.5 ml of double distilled water at weekly intervals. The perfusion cell has one main inlet tube through which nitrogen gas is pumped at a rate of 3 ml/min. The flow of gas from the nitrogen cylinder is regulated by a flowmeter (Cole Parmer, Niles). The nitrogen flow is split into two lines: one tube delivering dry nitrogen directly to the sample cell and the other tube passes
through a series of humidity chambers to produce water vapour of the required % RH over the sample (the arrows in figure 9.4 show the direction of vapour flow in the connecting chambers). A third exhaust tube (dashed line) enables vapour to be removed from the sample cell.

Figure 9.4 shows a flow (perfusion) cell used in isothermal microcalorimetric experiments.
9.6.2. Cleaning and loading of the sample cell

In order to prevent grease from hand surfaces from causing inaccurate readings, latex gloves were worn at all times while handling the perfusion cell. The stainless steel sample cell is released from the perfusion unit using a pair of specially designed tweezers. The cleaning procedure is similar to that of the sample pan of the DVS instrument. The sample cell is firstly rinsed with water, followed by ethanol and wiped dry using tissues. The powder under study is weighed into the sample cell using an analytical balance to an accuracy of at least 4 decimal places. The sample cell is fitted to the perfusion unit and loaded half-way down the sample side of the channel. The flow cell is left in this equilibrating position for 15 minutes after which it is lowered completely down the channel to the measuring position.

9.6.3. Calibration of instrument

The channels are calibrated independently of each other. Calibration is required whenever there has been a power failure (i.e. the TAM is switched off); the sensitivity of the amplifier or temperature of the water in the heat sink are changed. An empty cell made of stainless steel was used as a reference at all times during any microcalorimetric experiment to eliminate instrumental changes such as minor temperature fluctuations of the heat sink. The calibration unit is designed such that a current signal sent to the calibration heaters simulates as closely as possible the power dissipated during a reaction. While performing a calibration, it is advisable to record the instrument response. The procedure for a static calibration is as follows: first, the perfusion and reference cells are lowered to the measuring positions and left to equilibrate until no changes in the value of the output reading on the DVM is noted. If the display value is not zero, a screw driver is used to adjust the ‘zero setting’ to a value of zero. The amplifier is set to the required amplitude and an electrical signal is sent to the calibration heaters e.g. if an amplitude of 3000 µW has been selected, an electrical signal of 2997.4 µW would be used for calibration. The response can be monitored by the power-time curve on the digitam software and once a plateau is reached and maintained for a period of at least 20 minutes, the ‘Fine’ setting is adjusted if necessary, until a reading of 2997.4 is displayed on the DVM. The electrical signal is switched off and the response on the power-time curve gradually drops to a value of zero. Once the value is stable, the ‘zero setting’ may have to be slightly adjusted.

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9.6.4. Materials and method

The materials studied were zamifenacin, starch and lactose. The masses used for the powders were chosen on the basis of the affinity of the powder for water and the density of the powder. The mass used for the lactose monohydrate sample was approximately 50 mg and for zamifenacin and starch, 20 mg samples were used. The reasons for using lower masses are that (i) zamifenacin has a low bulk density and (ii) starch is an amorphous powder and highly hygroscopic in nature and would sorb high amounts of water. For this last reason, an amplifier setting of 3000 μW was selected to enable the full response of the interaction of water with starch to be detected. The temperature of the heat sink was set to 25 °C.

Once the powder is weighed into the sample cell, the perfusion unit is assembled, ensuring that the stainless steel tube delivering nitrogen gas is not connected to the flow divider at that stage. The cell is first lowered to the equilibration position, left to stabilise for 15 minutes and subsequently lowered to the measuring position. Another equilibration period should be allowed until the reading on the DVM stabilises completely (although it may not equal to zero). The reason for equilibrating the flow cell was to allow the sample and flow cell to come to thermal equilibration with the water bath. The reading may be adjusted using the ‘zero setting’ to give a reading of zero.

The Digitam software enables a variety of methods to be set up. The design used in this project is such that each adsorption cycle consisted of 3 stages:

1. A BASELINE stage. A baseline with a reading of 0000 μW is collected to show that the system is in equilibration with the heat sink at this stage. The maximum time period for this stage was set for 20 minutes. After approximately 10-15 minutes, the nitrogen gas tube is connected to the perfusion cell. This brings the experiment to the next stage.
2. The next stage is the MAIN stage in which water vapour of varying % RH is introduced above the sample. The value of the first % RH introduced is zero and corresponds to the drying of the sample. A large endothermic response would be expected as heat is being absorbed from the heat sink and the power output drops to a negative value on the power-time curve. This stage may take hours to complete.
depending on the initial moisture content of the powder. A maximum of 10 hours was set for this stage for zamifenancin and lactose but in the case of starch, this stage was set to a maximum of 40 hours as the sample was highly hygroscopic. Although it may be argued that the powder would not be sufficiently dry after 40 hours, the experimental conditions were kept constant for all replicates of the starch samples. A step experiment was used and the % RH above the powder was increased at increments of 15 %RH (i.e. 0-15, 15-30, 30-45, 45-60, 60-75 and 75-90). The limits of the microcalorimetric signal (which indicate when the % RH should be switched) were set from −2.000 to +2.000 µW. Once the sample is dry, the heat changes would be minimum and the voltage signal should approximate zero. The % RH is switched from 0 to 10% RH. As water vapour is introduced above the sample, an exothermic reaction occurs and the power output recorded is positive. When the sorption at 10% RH is complete, the heat change in the sample cell eventually decreases. If the value of the power output remains between the set limits of −2.000 to +2.000 µW for at least 30 minutes (180 minutes for starch), the experiment moves to the next stage.

3. The next stage corresponds to the collection of another BASELINE for a period of 30 minutes. The % RH then switches automatically to the next step by the TAM accessory interface.

The steps 2 to 3 are repeated until the % RH above the sample reaches 90% RH. In order to ensure that the powder is not undergoing any change when exposed to humidities from 0 to 90 %RH, the adsorption cycle was repeated three times for only one sample of each powder. If no significant changes in the response between the first and the two subsequent cycles are observed, only one cycle would be used for further replicates of the sample.

9.6.5. Analysis of the microcalorimetric output

The output from the isothermal microcalorimeter is commonly referred to as the power-time curve. The heat flow detected by the thermopiles is converted into Joules per second and recorded as the rate of change of heat (dq/dt) as a function of time. A typical output for a step experiment of 15% RH steps from the microcalorimeter is shown in figure 9.5. The areas under each separate response corresponds to the
enthalpy of reaction of water at a certain %RH with the powder. If the area under the curve for each % RH range is integrated using the Digitam 3.0 software, the enthalpy of the sorption of water is obtained. For standardisation purposes, the enthalpies of reaction may be expressed in terms of Joules per gram of sample used. A further correction for the surface area of the powders was made by dividing the enthalpy values per gram of sample by the specific surface areas of each powder. The cumulative values of the enthalpies of adsorption were then calculated and plotted as a function of % RH to obtain adsorption isotherms of water with the powders.

9.7. RESULTS AND DISCUSSION

9.7.1. Power-time curves

The power-time curves as obtained from the microcalorimeter are shown in figures 9.5 to 9.7. The large endothermic peak at the start of the experiment corresponds to the drying of the powder and each subsequent exothermic response to the increase in the % RH of water vapour above the sample.

![Power-time curve](image)

Figure 9.5 show the power-time curve when zamifenacin is exposed to 0-90% RH in step increments of 15% RH.
Figure 9.6 shows the power-time curve when lactose monohydrate is exposed to 0-90% RH in step increments of 15% RH.

Figure 9.7 shows the power-time curve when starch is exposed to 0-90% RH in step increments of 15% RH.
The cumulative enthalpies were calculated for each %RH range and expressed in Jg\(^{-1}\)m\(^{-2}\) after correction by the specific surface area of each powder (table 9.1).

<table>
<thead>
<tr>
<th>% RH range</th>
<th>Cumulative enthalpies (Jg(^{-1})m(^{-2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zamifenacin</td>
</tr>
<tr>
<td>0-15</td>
<td>0.2 (0.0)</td>
</tr>
<tr>
<td>15-30</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>30-45</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td>45-60</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td>60-75</td>
<td>1.5 (0.1)</td>
</tr>
<tr>
<td>75-90</td>
<td>3.0 (0.2)</td>
</tr>
</tbody>
</table>

Table 9.1 shows the cumulative enthalpies of adsorption on the powders when exposed to increasing % RH of water vapour.

9.7.2. Adsorption isotherms

The adsorption isotherms for each powder representing the cumulative enthalpies of adsorption as a function of increasing % RH are shown in figure 9.8. The scale is enlarged for the isotherms of lactose and zamifenacin and shown in figure 9.9.
Figure 9.8 shows the adsorption isotherms of zamifenacin, lactose and starch superimposed on the same set of axes.

Figure 9.9 shows the adsorption isotherms of lactose and zamifenacin from 0-90% RH.
All three powders exhibit a Type II isotherm on exposure to water vapour. The interaction between water and starch is clearly more exothermic (approximately 40 fold at 90% RH) compared with that of zamifenacin and lactose. This is not surprising as starch is an amorphous material and the sorption of water on such materials is known to release large amounts of heat (Van den Berg 1981 and Blair et al 1990). The proposed mechanism of sorption of water with starch was described as consisting of three stages:

(i) Up to approximately 10% RH, sorption of water occurs rapidly and water binds tightly to starch. Each water molecule forms two hydrogen bonds and links two anhydroglucose units together.

(ii) From 10 to about 19% RH, some previously formed hydrogen bonds are broken, leaving one water molecule linked to one anhydroglucose unit. As the % RH introduced above the sample is increased, further hydrogen bonding occurs between water molecules and the vacant anhydroglucose units. This process is relatively slow as it involves the formation as well as the breaking of bonds.

(iii) When the % RH exceeds approximately 80% RH, condensation of loosely bound water molecules occurs and this process is again rapid.

Lactose monohydrate and zamifenacin are crystalline materials and the sorption of water vapour onto such powders would not release a large amount of heat. In section 9.3, zamifenacin has been shown not to sorb much water when studied by the DVS instrument. Of the three powders studied, zamifenacin exhibited the lowest enthalpies of adsorption when exposed under the entire % RH range followed by lactose monohydrate and the highest enthalpies noted for starch.

9.8. CONCLUSIONS

Isothermal microcalorimetry is a highly sensitive technique capable of detecting infinitesimal heat changes (10^{-6} °C) in the sample cell. Only small amounts of sample are required and samples can be studied 'as received'. The operation of the instrument is not subject to the development of electrostatic charges from the sample. The data gathered from the microcalorimeter ranks the three powders studied in decreasing order of the degree of interaction with water vapour: starch, lactose and zamifenacin. With
the unavailability of data relating to the mass uptake of water for each powder, the magnitude of the microcalorimetric response cannot be fully quantified.

The surface energetics of the powders cannot be described in enthalpy terms only as incorrect conclusions may be drawn (Buckton and Beezer 1988). It was shown that although the enthalpy of the wetting of hydrophobic powders with water may be negative (possibly indicating a favourable process), the entropic aspect of the process may be highly unfavourable. This was explained by the fact that the wetting of a hydrophobic powder is limited by the number of adsorption sites available, thus preventing monolayer formation accounting for the entropically unfavoured process. The enthalpy change recorded was however negative due to the subsequent condensation of water molecules. Without supporting data from the DVS microbalance, a complete description of the sorption process and the surface energetics of the powders cannot be obtained.
10. MISCELLANEOUS TECHNIQUES

10.1. SURFACE AREA DETERMINATION

Surface area of powders was determined using a multipoint B.E.T. (Brunauer, Emmett and Teller) isotherm. The BET isotherm represents a monolayer formation of adsorbed molecules at low pressures of vapour, followed by multilayer coverage with increase in pressure of the vapour. The rate of adsorption/desorption of molecules of the first layer is different from that of the second layer. Subsequent layers have identical rates of adsorption and desorption. This situation is similar to a condensation process and the volume of vapour adsorbed tends to infinity (see chapter 9, figure 9.1).

The sample was degassed using nitrogen for 24 hours at 20 °C to remove adsorbed gases and surface moisture (Quantachrome, Quantasorb Corporation). The glass tube containing the powder was then connected to a source of mixed gases. The proportions of nitrogen in a mixture of nitrogen and helium gases were: 10, 20 and 30%. The volume of nitrogen gas adsorbed is measured for all three mixtures of gas.

The B.E.T. equation (10.1) was used to determine the surface area of powders since adsorption of gases onto pharmaceutical solids usually gives rise to Type II isotherms:

\[
\frac{1}{V} \left( \frac{P}{P_0 - P} \right) = \frac{1}{c \cdot V_{\text{mon}}} + \left( \frac{c - 1}{c \cdot V_{\text{mon}}} \right) \left( \frac{P}{P_0} \right)
\]

(10.1)

where \( V \) is the volume of gas adsorbed; \( P \) is the equilibrium pressure and \( P_0 \) is the saturated vapour pressure of gas; \( c \) is the BET constant and \( V_{\text{mon}} \) is the volume of gas adsorbed to form a monolayer of molecules on the solid.

If a plot of \([P/V(P_0 - P)]\) is drawn as a function of \([P/P_0]\), the slope of the line \([(c - 1)/c \cdot V_{\text{mon}}]\) and the intercept \([1/c \cdot V_{\text{mon}}]\) can be used to calculate the volume of adsorbed gas which forms a monolayer, \( V_{\text{mon}} \) on the solid. Since the total volume of gas adsorbed by the sample is measured and the monolayer volume determined as explained above,
the total number of gas molecules adsorbed by the solid can be calculated. The area occupied by each nitrogen gas molecule is 0.16 nm$^2$. The total surface area of the solid can thus be obtained. If the weight of the dried powder was recorded, its specific surface area i.e. m$^2$g$^{-1}$ can be determined using the Quant2pc (version 1.0) software. The specific surface area values shown in table 10.1 were determined from the mean of two different samples.

<table>
<thead>
<tr>
<th>Powder</th>
<th>Specific surface area (m$^2$g$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamifenacin</td>
<td>3.08 (0.23)</td>
</tr>
<tr>
<td>Starch</td>
<td>0.74 (0.02)</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>0.55 (0.17)</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>0.62 (0.04)</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>0.50 (0.02)</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>13.85 (1.55)</td>
</tr>
</tbody>
</table>

Table 10.1 shows the specific surface areas of the powders used with the standard deviation values in ( ).

### 10.2. PARTICLE SIZE DETERMINATION

The particle sizes of the powders studied were determined using the Malvern Autosizer X and shown in table 10.2. The mean particle size for each powder determined by scanning electron microscopy, is shown in table 10.3.

<table>
<thead>
<tr>
<th>Powder</th>
<th>Particle size under ($\mu$m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Zamifenacin</td>
<td>4.6</td>
</tr>
<tr>
<td>Starch</td>
<td>4.0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>18.7</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>11.8</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>18.3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 10.2 shows the size distribution of powders as determined using the Malvern Mastersizer X.
Table 10.3 shows the mean particle size of powders as determined using the scanning electron microscopy.

10.3. BULK DENSITY MEASUREMENTS

The bulk density of the powders was determined as it was necessary to calculate the mass of powder to be used in formulations of zamifenacin mixes for study by HPLC and NIRS. The bulk density was measured by weighing the amount of powder required to fill a measuring cylinder to the 100ml mark. The mean bulk density for three samples was taken for each powder and shown in table 10.4:

<table>
<thead>
<tr>
<th>Powder</th>
<th>Bulk density (g cm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamifenacin</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>Starch</td>
<td>0.56 (0.00)</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>0.79 (0.00)</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>0.66 (0.00)</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>0.56 (0.00)</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.21 (0.00)</td>
</tr>
</tbody>
</table>

Table 10.4 shows the bulk density of powders used with the standard deviation values in ().
11. CONCLUSIONS

Although numerous factors are known to affect mixing, this investigation was centred on the role of surface energetics in understanding and predicting the interactions between powders. Surface energetics is an area of study in which surfaces of powders are characterised in terms of their polar and non-polar entities. Several techniques are available for such studies and those used in this project were the Wilhelmy plate technique (DCA), the Dynamic angle tester (DAT) based on the sessile drop technique, Inverse gas chromatography (IGC), Dynamic vapour sorption (DVS) and isothermal microcalorimetry (TAM). The electrostatic (triboelectric) charges developed on the powders on contact with stainless steel were also measured using a Faraday well connected to an electrometer.

The only previous study involving the application of surface energetics to mixing was by Rowe (1989a, 1992) whereby theoretically determined solubility parameter values were used. Rowe reported that when iron oxide was mixed with three white excipients: microcrystalline cellulose (MCC), magnesium stearate (Mg stearate) and titanium dioxide (Ti dioxide), three differently coloured mixes were obtained. Thus, the initial stage of this project was to extend Rowe’s work using experimentally determined values of the surface energies of the above powders. Surface energies of the powders were determined using the Wilhelmy plate technique with powder coated glass slides as samples. The magnitude and sign of the calculated spreading coefficients of iron oxide over each white excipient (and vice versa) accurately predicted the mixing behaviour of the powders in the binary mixes. The predictions were confirmed by visually assessing the appearance of the mixes and by scanning electron microscopy of the powders before and after mixing. The use of experimentally measured surface energies in predicting the interaction of powders was found to be in agreement with and superior to the theoretically determined solubility parameters used by Rowe. The measured surface energies reflected accurately the heterogeneity and true nature of powder surfaces as opposed to the idealised, theoretical representation of the polar/non-polar nature of powders from solubility parameters (Rowe 1989a).
It was also observed that the mixes adhered to the glass walls of the jars to different extents. An attempt was made to predict the adhesion tendency of the mixes over glass using the spreading coefficient approach. For the spreading coefficient approach to be extended to three-component systems, the binary blends were treated as one phase with the third component being glass. The surface energies and spreading coefficients of the mixes over glass (and vice versa) were determined and again yielded values that were in agreement with the visual assessment of the mixes. The value of the spreading coefficient of the magnesium stearate mix over glass was most positive followed by that of the titanium dioxide mix over glass and negative for the MCC mix over glass. The predictions were supported by the fact that the magnesium stearate mix adhered the most to glass, followed by the titanium dioxide mix whereas the MCC mix showed no tendency to adhere to glass.

Following the positive outcome of the spreading coefficient approach in predicting mixing, the surface energies of an active compound (zamifenacin), starch and lactose monohydrate were measured using the Wilhelmy plate technique. However, this proved to be problematic e.g. undefined contact angles (less than 0) were obtained for ethylene glycol on lactose. On further determination of the surface energy parameters, all samples gave similar values. It was concluded that the use of the Wilhelmy plate technique and powder coated glass slides was not sensitive enough for the measurement of surface energies of these powders.

The use of a novel instrument, the Dynamic angle tester (DAT) based on the sessile drop technique enabled the contact angles of all liquids on any solid to be measured. The surface energy values determined using Fowkes's equation were used to calculate the spreading coefficients of zamifenacin with starch and zamifenacin with lactose. Since these binary systems consisted of white pharmaceutical powders only, the visual assessment of the mixes could not be used to confirm the predictions. Scanning electron micrographs however did not support the predictions made from spreading coefficients. The surface energy data of the powders determined from the DAT (works of adhesion and cohesion) were used to provide an insight into the mixing behaviour of powders in the tertiary zamifenacin blends, as confirmed by near-infrared spectroscopy (NIRS).
The application of IGC in the pharmaceutical field has only been explored recently. IGC has proved to be a very sensitive and sound technique since it relies on the direct interaction between vapour probes and samples. Sample preparation in IGC experiments does not involve the use of adhesive (as in the DCA and DAT) and the occurrence of experimental artefacts is thus fewer. The surface energy of powders studied by IGC is expressed in terms of the dispersive component, electron-donor and electron-acceptor parameters. The dispersive components obtained from the IGC and DAT ranked the powders in the same order but the values obtained by IGC were slightly higher than those obtained from the DAT. This is due to the high-energy spots on the powders interacting preferentially with the injected liquid vapour. It was however not possible to relate the polar component of the surface energies of the powders determined from IGC with those of the DAT since both techniques involved different manipulation of the data and hence yielded different parameters. An interaction parameter (I) calculated from the IGC data was used to give an indication into the nature of the interaction between two components. The interaction parameter was higher between zamifenacin and starch than between zamifenacin and lactose, suggesting that the interaction of zamifenacin with starch would be more favourable than with lactose. These predictions were confirmed by homogeneity studies on binary mixes of zamifenacin with starch and zamifenacin with lactose. Assay of samples by high-pressure liquid chromatography (HPLC) yielded values of coefficients of variation that were considerably lower for zamifenacin-starch mixes than for zamifenacin-lactose mixes.

The study of triboelectric (electrostatic) charging of zamifenacin and excipients revealed an influence on the behaviour of the powders. All powders except for zamifenacin, charged negatively on contact with stainless steel. The magnitude of the negative charge was higher in starch than lactose monohydrate. Since zamifenacin charged positively, it follows that the interaction of zamifenacin with starch would be more favourable than with lactose. These conclusions were in agreement with the interaction parameters derived from the IGC data and confirmed by HPLC assays of binary zamifenacin mixes. Since both IGC and triboelectric studies characterise materials in terms of their electron donating-accepting tendencies, an attempt was made to relate the data from the two techniques. With the limited data available (only 5 powders), encouraging results were obtained. However, more data is required to establish the relationship between IGC and triboelectric charging. If confirmed,
triboelectric charging studies, which are known to be difficult and variable, could be supported by reliable IGC data.

Near-infrared spectroscopy (NIRS) studies were done with two main aims: to follow the mixing process from beginning to end and to investigate its suitability as a possible substitute to HPLC. NIRS was used qualitatively to study the effect of the order of addition of excipients to zamifenacin and quantitatively to determine the zamifenacin content. This data was then correlated to HPLC data. NIRS observations were in agreement with DAT data and an insight was obtained into the mechanism of the interactions in tertiary systems of zamifenacin, starch and lactose. It was found that if starch was added to a zamifenacin-lactose premix, a stable mix would be produced whereas when lactose was added to a zamifenacin-starch premix, destabilising of the premix may occur. If the contents of zamifenacin in binary and tertiary mixes analysed by HPLC were compared with those determined from NIRS, a linear relationship with a regression coefficient of 0.94 was obtained. The use of NIRS as an alternative analytical technique for HPLC is thus promising.

Water vapour sorption studies on the powders using the dynamic vapour sorption microbalance (DVS) and isothermal microcalorimeter (TAM) yielded limited data. The development of electrostatic charges on zamifenacin samples precluded the use of the DVS. Isothermal microcalorimetric studies showed that the enthalpy of sorption of water on starch was highest followed by lactose and least for zamifenacin. Since, data from both the DVS and TAM are required to yield surface energetics of powders, no more conclusive data could be obtained.

The importance of the role of surface energetics during mixing has been clearly illustrated in this project. It is proposed that the surfaces of powders are first characterised and their behaviour in subsequent manufacturing processes predicted from their surface characteristics. With the availability of several surface characterisation techniques, the technique to be used must be chosen on the basis of the property of the material, the quantity and time available and the skill of the operator. IGC would be the technique of choice as it is subject to less experimental artefacts. However, compared with the Wilhelmy plate technique, relatively large amounts of sample (5g) and more elaborate operator training are required. The fastest technique requiring the least amount of sample (2g) and operator skill would be the Wilhelmy plate technique but as
discussed in chapter 4, this technique has a few limitations. It is advisable to characterise powders with at least two techniques to ensure reliable predictions are made. The use of the above techniques can greatly facilitate the work of the formulator. The choice of the excipients, the order in which they are added to the active, and the materials of the containers in which they are mixed, can be made prior to mixing the powders on a large scale. Mixing problems can thus be minimised as well as extensive, time-consuming HPLC assays of samples considerably reduced if NIRS is used to monitor mixing qualitatively or quantitatively on-line.
12. FUTURE WORK

12.1. INVERSE GAS CHROMATOGRAPHY

IGC has been used successfully to predict the interaction in binary mixes. It was predicted that zamifenacin would interact more favourably with starch than lactose monohydrate. There is scope to extend this theory to tertiary mixes. In such studies, the glass column would be packed with a binary mix of zamifenacin and starch and vapours of organic solvents injected at infinite dilution. The data would be analysed as for individual powders. The determination of the acid and basic parameters of the binary mix would thus enable the calculation of the interaction parameter in a three-component system.

12.2. DYNAMIC VAPOUR SORPTION

The Wilhelmy plate and sessile drop techniques have been shown to have certain limitations in the determination of the surface energy parameters of some pharmaceutical powders. Hence, there is still a search for a better technique to obtain a measure of the surface nature of powders. The best approach would be to use a technique in which there is direct vapour-solid interaction such as the dynamic vapour sorption (DVS) microbalance. The DVS is routinely used to study the sorption of water on powders. However, if water is substituted by organic vapours, the changes in mass can be recorded as a function of increasing partial pressure of the vapour. If a non-polar solvent is used, the changes in mass would only be due to non-polar interactions between the solid and vapour. Similarly, polar liquids would yield interactions due to polar and non-polar forces between vapour and solid.

The mass changes would be related to the equilibrium spreading pressure ($\pi_e$), which is the decrease in surface energy of a solid following adsorption of vapour.
\[ \pi_e = \int_0^{P_0} \Gamma d(\ln P) \]  

(12.1)

where \( P_0 \) is the saturated vapour pressure, \( P \) is the vapour pressure and \( \Gamma \) the number of moles of vapour adsorbed on unit area of solid.

The equilibrium spreading pressure can be related to the work of adhesion \( (W_{\text{ads}}) \),

\[ W_{\text{ads}} = \gamma_{LV} (1 + \cos \theta) + \pi_e \]  

(12.2)

where \( \gamma_{LV} \) is the surface tension of the liquid and \( \theta \) is the contact angle of the liquid with the solid.

12.3. TRIBOELECTRIC CHARGING

Charging of more pharmaceutical powders with stainless steel and other surfaces such as glass or polyethylene can be done to confirm the relationship between the triboelectric charging and IGC techniques. Charging of a mixture of two powders can also give some insight into the complex charging mechanisms that occur during mixing of a binary system.

12.4. MOLECULAR MODELLING

There is growing interest in the use of molecular modelling in the field of pharmaceutics. The first step is to construct a model of a crystal, so as to reflect the appropriate crystal faces. If the most significant faces are identified, an indication of the proportion of polar and nonpolar groups on the crystal faces can be obtained. The simulation of water or other solvent molecules attaching onto crystal surfaces can also be studied and the energy with which solvent molecules attach to the crystal face determined. It would be very interesting to see how the energies derived theoretically compare with the surface energy parameters measured experimentally by more conventional methods such as the Wilhelmy plate technique or inverse gas chromatography.
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