

Surface Characterization: Understanding Sources of Variability in the Production and Use of Pharmaceuticals*

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The Powder Surface Will Affect the Product

All materials act, react and interact at surfaces; hence surface characterization can be vital in understanding the behaviour of any type of material. Pharmaceutical products are almost always made from powdered ingredients (drugs and excipients), and it is necessary to understand something of the surface nature of powders, if aspects of product performance are to be understood.

Powders can behave in different manners in products if they have differences in purity, size, crystal habit, polymorphic form, hydrate or solvate form, or degree of crystallinity. The premise of these studies is that the surface of powders is vital in controlling interactions with other phases, and hence the ease of production, the stability and the usefulness of drug products. Consequently it is worth considering briefly how the factors listed above can alter the surface of a powder.

A small amount of an impurity can greatly alter surface properties, not least because many materials which occur as impurities are surface active and can be present at the surface in larger quantities than are present in the bulk. Crystal size will not be considered here, but can obviously affect the rate of solution of a powder, as well as flow properties. Crystal habit and form can be important if, as is often the case, the faces of the crystal express various functional groups in different proportions. However, it may prove to be true that the most important cause of variability in powder properties is the change in the extent of crystallinity at the powder surface. There is much published evidence to show that processing is often sufficiently energetic to cause disruption to crystal structure (see examples below). This disruption will not be distributed uniformly throughout the powder mass, but rather will be predominantly at the surfaces which have interfaced with the processing stress (e.g. Elamin et al 1994). Variability amongst powders from different suppliers or even amongst batches from the same supplier are common.

The prevalence of variability will probably relate to the severity of processing. For example, materials which have been micronized are often more susceptible to variability than those which exist as larger particles; this may be because the surface to bulk ratio is larger for small particles, and also because the highly energetic processing can cause greater disruption to that surface. Thus it can be

postulated that the energetics of processing, and the ability of materials to recover from processing-induced stresses, will affect batch to batch uniformity. For materials which do not readily recover from stresses induced during processing, the exact nature of the processing can affect the behaviour of the material in the product. This explains why apparently identical materials from different suppliers can behave in different ways in products.

In the discussion above a hypothesis is presented which has not been tested to any significant degree within the pharmaceutical field. A major problem has been the fact that physical characterization of powders often indicates that the materials are identical, but the behaviour in the product is different. The problem has been that the product is more sensitive to material (surface) variation than are our analytical techniques. For example, X-ray diffraction has been shown to be able to detect only 10% or more, of amorphous material in powders (Saleki-Gerhardt et al 1994). Stresses induced during processing may result in considerably less than 10% of the material becoming amorphous. This low percentage of amorphous material is consequently hard to measure by techniques such as X-ray diffraction, but as it may cover much of the powder surface, it is very significant with respect to interactions within the product. It is important not to trust an X-ray diffraction experiment as being proof that a material is 100% crystalline, as its resolution is not adequate to justify such a bold assertion. The necessary alternative is to probe the surface nature of the material. This can be done by way of contact angles which lead to surface energy terms, or by use of vapour sorption experiments. Vapour sorption may be gravimetric, microcalorimetric or chromatographic. It has been shown that contact angles may be a more surface-specific probe of certain materials (especially powders) than surface analysis techniques such as X-ray photoelectron spectroscopy (e.g. Buckton et al 1991a). In essence, for powdered materials, the surface analysis techniques measure molecular surface content, whilst contact angles appear to be sensitive to molecular orientations. This observation for powdered systems is not extrapolated to smooth surfaces, where the surface specificity of other techniques may be rather better than on the rough powder samples that are offered for analysis.

Contact Angle Techniques for Powders

All contact angle approaches for powdered samples are flawed for some reason and to some extent (Buckton 1993); the powder does not present a smooth flat surface

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on which to place a drop of liquid, and the powder samples are very susceptible to transformation if manipulated during testing. The approaches that exist for contact angle determination on powders can be divided into those which use penetration of liquid into a powder bed, and those which use compacted samples.

Liquid penetration

Liquid penetration experiments are based upon the Washburn equation:

$$l^2 = \frac{r \gamma_{LV} \cos \theta t}{2\eta} \quad (1)$$

where l is the distance of penetration by the liquid into the powder bed at time t , r is the hypothetical capillary radius of the pores in the powder bed (based on a model of a bundle of parallel capillaries), γ_{LV} is the liquid surface tension, θ is the contact angle, and η is the liquid viscosity. By comparison of the measured penetration rates of two known liquids, one of finite and the other of zero contact angle on the solid, the capillary radius term can be removed from the equation to allow the unknown contact angle to be determined.

There are certain practical difficulties with liquid penetration techniques (Buckton 1993), but the main problem is the fundamental deficiency in the application of the Washburn equation to a system which is clearly not a bundle of parallel capillaries (Yang et al 1988; Buckton 1993). In practice the varying diameters of the pores in the powder bed cause pressure differences to exist which affect the results. The results are generally an overestimate of the true contact angle when determined by this technique (Yang et al 1988; Parsons et al 1993), especially for materials with high contact angles. Whilst contact angles can be obtained from liquid penetration experiments, the fact remains that a more appropriate theory is needed to account for the pore shapes and sizes encountered in the packing of columns of real powders. The extent of errors associated with contact angle values obtained from liquid penetration experiments has been reported elsewhere (Parsons et al 1992a); these centre on the measurement of liquid penetration rates and the difficulties associated with the nomination of the perfectly wetting liquid.

Powder compacts

Sessile-drop techniques. By far the most cited method of obtaining a contact angle for a powdered system is to prepare a powder compact, saturate it with a saturated solution of the test liquid, and then place a drop on the surface. The angle is then measured directly, using photography, image analysis or an eye-piece protractor. The advantage of this approach is simplicity, but there are several disadvantages. The compaction may change the surface (so making the measured result of little relevance) (Buckton & Newton 1986; Kiesvaara & Yliruusi 1991; Sheridan et al 1994). The measurement of an angle on a surface which is part solid and part liquid (that has been used to saturate the bed) will mean that the contact angle will be a weighted average of the fraction in contact with each phase. As the angle of the liquid on itself will usually be zero, the measured angle will be weighted below the true value i.e. underestimating the true angle (Yang et al 1988).

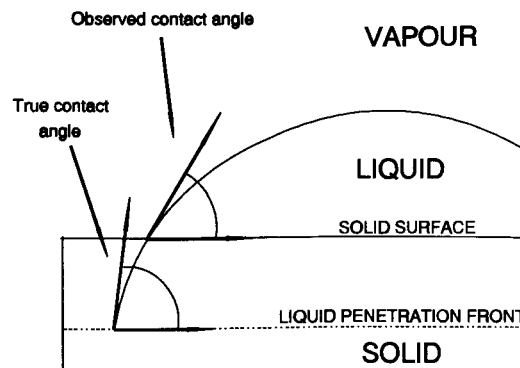


FIG. 1. Schematic representation of a drop which has penetrated below the surface of a powder compact. The measured angle at the powder surface will be an underestimate of the true angle which will exist within the powder mass.

There is a great difference between accuracy and precision, and even though most operators can obtain a value for the contact angle which is reproducible, it is not necessarily the correct angle (Good 1993). This is due to incorrect tangents being drawn to the drop and the inevitable surface heterogeneity. If the liquid saturation front is not exactly at the surface of the bed, the drop will sink into the bed slightly. This minor penetration may not be easily visualized, but will result in an error in measurement, as can be seen from Fig. 1.

It follows that the use of sessile drops on powder compacts will inevitably give a contact angle which differs from the true value. The significance of this deviation may, however, not be too critical, as it often remains possible to use such data to make comparisons between materials. It has even been possible to differentiate between chemically identical materials that have been processed in different manners, by use of this approach. Consequently, the experimental limitations do not require that the approach should be abandoned, but equally workers must be aware that on occasions the results may be misleading.

The Wilhelmy plate technique. Wilhelmy plate approaches to contact angle determination have been used for many years. However, the application to powdered systems is comparatively recent. When using this method it is usual to make a rectangular compact of the powder and suspend this from a balance. The liquid is then raised to contact the plate by use of a motorized platform. From an extrapolated buoyancy slope, to yield a force at zero depth of immersion, it is possible to obtain a contact angle:

$$\cos \theta = f/p\gamma_{LV} \quad (2)$$

where θ is the contact angle, f is the force measured on the balance, p is the measured plate perimeter and γ_{LV} is the surface tension of the test liquid.

One limitation of this approach is that the powder has to be compacted, thus the surface may change, as described above for the sessile-drop technique. A further problem is that of defining the true perimeter of the plate. Recently we have investigated the problems associated with measuring the perimeter of a plate of compacted powder (Sheridan et al 1994; Buckton et al 1995a). By using powder compacts which have been compacted to give different degrees of

surface roughness, and then coated with gold to attempt to ensure identical surface energy for each plate, the error in the perimeter has been shown to be substantial (in the order of twice the estimated external perimeter) (Buckton et al 1995a). This results in a significant underestimate in the value obtained for the contact angle.

On the positive side, however, the Wilhelmy plate technique does not suffer from the need to pre-saturate the powder bed, nor from the error due to operators lining up incorrect tangents to a drop. The simplicity of the Wilhelmy plate approach, together with the fact that all contact angle methods for powders are flawed, means that it is an attractive alternative.

The interesting aspect about contact angle measurements on powdered systems is that, despite the fact that they are all flawed and thus all give a value which deviates from the true contact angle, the data can be used to make predictions about interfacial interactions, although usually this will be best achieved if only one experimental technique has been used for all systems which are to be compared.

Other techniques

Gravimetric. It has been reported that the adsorption of water onto crystalline solids will result in at most 3–5 layers of water on the surface. This water will not have the properties of bulk water and will generally not cause dissolution of the surface of the material (e.g. Kontny et al 1987), although there is a critical relative humidity at which certain solids become deliquescent in atmospheric water vapour. Given that the water will not dissolve the solid surface in most circumstances, there is interest in understanding its interaction as a means of characterizing the nature of the solid. Furthermore, adsorption experiments do not need to be limited to water as a probe; any well-characterized vapour or gas can be used to provide information on the nature of the surface. Care must be taken with respect to differences between adsorption to the surface and absorption into amorphous regions.

It is comparatively simple to utilize adsorption isotherm data (obtained at different temperatures) to calculate isosteric thermodynamic parameters. The thermodynamic parameters provide a useful description of the powder surface (e.g. Buckton et al 1986). It is now generally accepted that calorimetric data are more suitable, as they are readily obtained and the experimental accuracy is generally superior.

Calorimetric. Modern isothermal microcalorimeters offer a sensitive way of probing powder surfaces. Two basic approaches are available, one of which is the immersion of the powder into a liquid (e.g. Hollenbeck et al 1978) and the other is the adsorption of vapour onto the powder surface. There is a reasonable argument that vapour sorption is the preferred method, as it is the first layer of adsorbed molecules which most accurately reflects the interaction between the powder and the surface probe. Experimental techniques have improved significantly over recent years, such that it is possible to pass air of differing humidity over a powder to construct the calorimetric adsorption isotherm data which can demonstrate the surface properties of the material. These flow experiments (e.g.

Sheridan et al 1993a) are much easier to perform, and are more reproducible than the earlier work which utilized a vacuum desorption stage (e.g. Buckton & Beezer 1988; Blair et al 1990). It is now possible to utilize the calorimetric approach to follow adsorption experiments with different vapours (wetting and surface energy characterization), and also to assess the degree of crystallinity of the powder (see below).

Chromatographic. All chromatographic techniques rely on interfacial phenomena and adsorption interactions between the stationary and mobile phases. It is usual to have a known stationary phase and an unknown mobile phase. However, it is equally possible to pack an unknown into a column and then to pass gas with injected known vapours over the surface. The retention of the vapours on the solid allow the surface properties of the solid to be assessed. Conder & Young (1979) describe the applications of gas chromatography for studies of adsorption processes, surface area and pore size distribution of the solid material. Application of inverse phase gas chromatography to pharmaceutical systems has been limited, but includes a study on water adsorption by cyclosporin (Djordjevic et al 1992) and of organic vapours onto different microcrystalline celluloses (Ticehurst et al 1993).

Some Physicochemical Considerations

There is often considerable confusion over issues of how wettability relates to both the chemical nature of the material and to the other physicochemical properties of the powder (such as solubility). There are many errors of simplification that occur with views equating hydrophilicity with high aqueous solubility (and vice versa). This is far from true as many metals are well wetted by water, but are insoluble, as indeed are microcrystalline celluloses and other similar pharmaceutical excipients.

It is logical that molecules which are polar should yield crystals which are polar. However, the situation may not be that simple as most drug molecules will contain regions which are hydrophobic and regions which are hydrophilic. Given this situation, the outer face of a crystal will be influenced by the liquid from which it was crystallized (internalizing functional groups which are less attracted to the liquid). Thus crystal habit and form can alter the surface properties of a crystal. If, however, the crystal is not perfectly crystalline, but is amorphous on the surface, then the surface has some molecular mobility, such that the molecules will reorientate to minimize the free energy of contact between the solid and any other phase with which it is brought into contact. It is often stated that changes in crystal form (e.g. polymorphism), or processing (e.g. milling (see Florence et al 1974; Florence & Salole 1976; Chiou & Kyle 1979; Suryanarayanan & Mitchell 1985)) (see discussion later in text) can alter the dissolution rate or the solubility of drugs. There is no doubt the dissolution rate of different crystal forms vary, and it is also true that the apparent equilibrium solubility will also vary. However, there is only one true equilibrium solubility for any solid in any liquid, all other states being metastable which will ultimately revert to the equilibrium given the appropriate

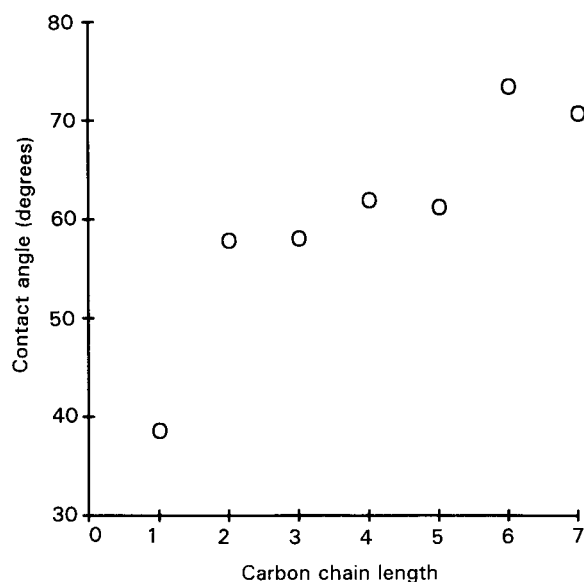


FIG. 2. The contact angle with water as a function of alkyl chain length of the *p*-hydroxybenzoates (reproduced from Forster et al (1991), with permission).

mechanism; this is true irrespective of the initial size, shape or form of the solid (Buckton & Beezer 1992). Although only one equilibrium situation exists, the presence of many metastable states (each with different apparent physicochemical properties) causes much confusion when trying to extract the information on the relative importance of physical form and chemical structure on physicochemical properties.

Despite these reservations, there are clear signs that molecular structure can be correlated with wettability of powders. Sheridan et al (1993b) have shown that the sum of the superdelocalizability indices of hydrogen bonding atoms in a range of different drug molecules correlated well with the contact angle with water for the respective drug powders. The superdelocalizability is a measure of the electron availability of an atom. It follows that the superdelocalizability index of the highest occupied molecular orbital of a molecule provides a guide to its tendency to interact (or react) with other molecules. The relationship between molecular orbital values and surface energy forms part of the discussion on contributions to surface energy in the extensive review by Lee (1993).

The relationship between measured contact angles and the length of the alkyl chain for *p*-hydroxybenzoates shows deviation from linearity (Fig. 2) (Forster et al 1991), showing that the addition of a methylene group to the molecule does not of itself result in an increase in hydrophobicity. There is no direct relationship between wettability and solubility of the alkyl *p*-hydroxybenzoates (Forster et al 1991). However, there are some commonalities. The methyl derivative shows a deviation in response (compared with other members in the series) for both wettability and solubility in hexane. There is also a break in the following measured properties: solubility in water, solubility in hexane, melting point, contact angle with water (Forster et al 1991), and solution thermodynamics

in water, 95% ethanol, 1-octanol and hexane (Beezer et al 1991), between an alkyl chain length of 5 and 6¹ for the *p*-hydroxybenzoates.

The extreme complexity of apparently simple pharmaceutical processes (such as dissolution, which may involve wettability, disintegration and solubility stages) makes any understanding of underlying mechanisms hard to obtain. The application of compensation analysis is a useful approach to studies of structure-activity relationships, and how chemical structure relates to various physical properties, and as such it is surprisingly under-used in pharmaceutical research (see Tomlinson 1983; Vachon & Grant 1987; Buckton & Beezer 1989; Efentakis & Buckton 1990; Buckton & Efentakis 1990; Buckton 1990, 1992; Buckton et al 1991c; Buckton & Tamburic 1992; Tapia et al 1993). A comparison of the thermodynamics of adsorption (wetting) and solution, for a number of barbiturates has revealed that although there is chemical causality for both processes, the structural aspects which relate to wettability differ from those which relate to solubility (Buckton 1990).

The Surface Related to the Product

The most useful application of contact-angle data is to obtain an estimate of the surface energy of the solid. Whereas the contact angle of one liquid on one surface gives an indication of that specific interaction, a calculated surface energy gives a value which is descriptive of the powder surface (rather than an interaction between the powder surface and one test liquid). Theoretically, although not always true in practice (Parsons 1992; Sheridan 1994), the calculated surface energy value should be independent of the liquids that were used to measure the contact angles. A number of different theories have been proposed by which contact angle data can be used to assess solid-surface energy. These include equation of state approaches, which yield a single value for surface energy, and theories which consider surface energies as being best described by component parts. The current theories of the equation of state and that of surface energy components co-exist even though they are totally contradictory. A full, but simple review of surface energy theories has been presented recently (Buckton 1995). Most workers seem to favour the approach of splitting surface energy into component parts in order to describe interaction between essentially polar and non-polar regions of the surface. The early work in this field used two such surface energy components (dispersion and polar), but it has been shown (e.g. van Oss et al (1987), and many subsequent publications, see review by Buckton 1995) that this is an inadequate method of discrimination, as many polar surfaces are in fact monopolar. The concept of monopolar surfaces has been used to explain the presence, and especially the absence, of certain polar

¹ It is interesting to note that the break in properties seen in homologs at an alkyl chain length of 5± is a common occurrence, affecting solid-state properties, solubility, liquid properties, partition and biological response (Buckton et al 1991b). Given the apparent universal application of such observations, it is surprising that comparatively little attention is given to structure-activity relationships for physical phenomena. It is all too often regarded that the word "activity" must be taken to imply "biological response", this is clearly not the case.

interactions, as some systems could not be modelled by simply considering a polar term. In essence, surfaces are considered as having polarity due to Lewis acid or Lewis base interactions. Thus a surface can exhibit polarity by being an electron donor or an electron acceptor. Monopolar surfaces exhibit only one form of polarity (i.e. only electron donor or electron receptor, but not both), it follows that whilst monopoles will exhibit polar interactions, they will only do so when interacting with another surface which is either bipolar or monopolar of the correct type. There will be no capability for interaction between two unmatched monopoles. Despite the fact that the acid-base view of surface energies has now replaced the polar-and-dispersion view (indeed this has been so since the late 1980s), the published work on pharmaceutical systems has largely been based on the early theories. It follows that this review will centre on these early theories due to necessity rather than desirability. Future work must deviate from this trend. It is probable that the older theories have been successful in predicting interactions relating to pharmaceutical problems because many pharmaceutical materials are monopoles of the same sense (i.e. mostly γ^-); this is, however, fortuitous and the use of the outdated theories will fail if materials are considered which are monopoles of the opposite sense. As stated above, a full review of surface energy approaches has been presented elsewhere (Buckton 1995). It is inappropriate to present the basis of the outdated theories of surface energy, but necessary to state that the polar (p) and dispersion (d) components of the surface energy of a solid can be obtained from contact angles measured on that solid with two liquids of known surface tension and polarity. From the calculated surface energy terms for the solid, it is possible to describe the work of cohesion (which is twice the surface energy), and the work of adhesion (W_a) between that solid (subscript 1) and any other phase (subscript 2):

$$W_a = \left[\frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} + \frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} \right] \quad (2)$$

The difference between the work of adhesion between any two phases and the work of cohesion of phase 1 will give the spreading coefficient of phase 1 over phase 2 (λ_{12}). This term describes the interaction between the two phases, as a positive value indicates that spreading will occur (a higher number showing a more favoured interaction), and vice versa in that a negative spreading coefficient will indicate that phase 1 will not spread over phase 2.

For completeness it must be stated that the dispersion component of surface energy is numerically unchanged by using the acid-base theory, but the polar component is different as it is divided into non-additive electron donor and electron receptor components. The dispersive contribution is obtained by measuring a contact angle with a totally non-polar liquid, then the Lewis acid and Lewis base components are obtained for the solid by measuring a contact angle with two different polar liquids (each with known electron donor-electron receptor components, although in reality the true electron donor-electron receptor values are not known, but they are related to values which have been selected for water as an accepted standard). It is then possible to predict interactions between

different phases, and even between two phases in the presence of a third component. Such data treatment is now well developed and will undoubtedly become more widely applied to pharmaceutical problems.

Examples of application of surface energy data to pharmaceutical systems

Surface energy terms, works of cohesion and adhesion, and spreading coefficients can be used to predict the interaction between any two materials. Thus, the examples quoted here do not constitute all combinations that are possible. A full review of these approaches has been given elsewhere (Buckton 1995).

Granulation and tableting. The application in this field of investigation has been pioneered by Rowe (1989a,b, 1990), who has shown that the spreading coefficient of a binder over a drug which is to be wet-granulated will allow the prediction of the most suitable binder to use in the first formulation. It was found that for drugs of low polarity that polyvinylpyrrolidone was predicted to be a better binder than hydroxypropylmethylcellulose, whilst for those of high polarity the opposite was true. These theoretical considerations were confirmed by our own observations (Zajic & Buckton 1990). By considering the granulation and tableting of paracetamol, it was shown (Rowe 1990) that the spreading coefficient of binder over the drug during granulation, correlated with granule and tablet properties (such as granule friability, tablet strength, and tablet capping index). It follows that by use of a library of known physicochemical properties for excipients, and by undertaking physicochemical testing on new drug entities (in this case measuring a contact angle for two liquids on the drug, and then calculating the surface energy terms), that it should be possible to optimize the first development formulation. This forms the most appropriate basis for computer-aided expert systems for formulation, which are currently gaining in popularity (although the physicochemical profile of drug and excipient will include parameters other than just surface energy).

Inhalation systems. There are two main types of inhalation system that are commonly used in general practice. These are metered-dose, and dry-powder inhalers. Metered-dose inhalers are suspensions of drug in a propellant (the propellant is usually a mixture of chlorofluorocarbons, but ozone-friendly alternatives are currently being investigated). These suspensions may be stabilized with surfactants. Dry powder inhalers are either drug alone, or drug with a large carrier particle (usually lactose). The carrier particles are used to adsorb the micronized drug to aid production (e.g. flow properties) and uniformity of dosing. For all inhalers it is necessary for the particles to be less than $5 \mu\text{m}$ otherwise they will not be respirable. This means that there must be no aggregation of particles (and that those systems which use a carrier particle must deaggregate). The role of surface energy in controlling powder behaviour in inhalation systems is especially critical for two reasons. Firstly, the powders must be less than $5 \mu\text{m}$ and hence they will have a large surface area to volume ratio (i.e. the surface area is large and thus surface properties are critical). Secondly, the production of micronized particles necessitates the use of

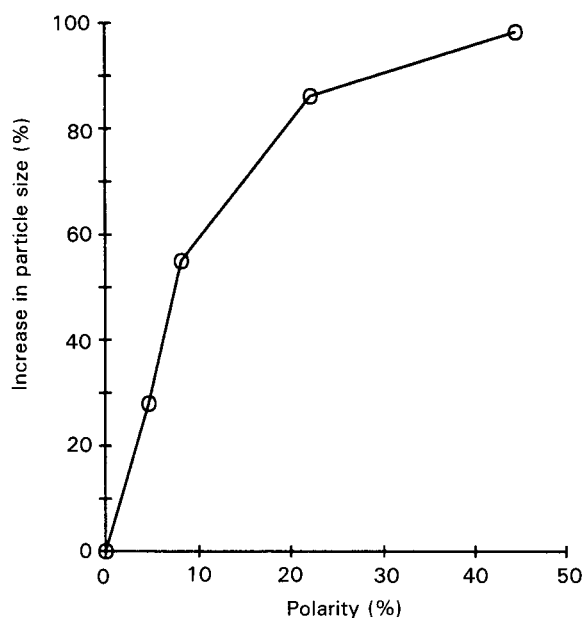


Fig. 3. The extent of aggregation of various model drug powders in a model inhalation aerosol system as a function of the polarity of the model solids (reproduced from Parsons et al (1992b), with permission).

high-energy milling, or similar drastic processing. The effect of high energy processing on powder surfaces is substantial (see below); however, in this section the chemical nature of the surface will be considered.

With regard to metered-dose inhalers, powder surface energy contributes to the ease of dispersion of the powder in the liquid, the tendency for the powder to aggregate in suspension, and the tendency for the powder to adhere to the container walls.

By using five model materials, each of these aspects have been considered with respect to the relevant surface energetic interactions (Parsons et al 1992b). It was found that the ease of dispersion of the model drugs into a chlorofluorocarbon was related to the work of cohesion of the powder. The tendency to aggregate was assessed by measuring the increase in size (which was due to aggregation rather than crystal growth, as it was reversible); this was found to correlate with the polarity of the solids (Fig. 3). The reason for an increase in aggregation with increase in solid polarity is obvious, in that the liquid is non-polar. Finally, the extent of adhesion to the container wall was found to be predictable by considering the work of adhesion to the container (Parsons et al 1992b). In fact, three different container types were considered and, within experimental error, they were superimposable on one exponential plot. It follows that, by use of surface energy terms, it is possible to predict the ease of dispersion, the tendency to aggregate and the losses to the container wall. Furthermore, it is also possible to predict the optimum nature of the container wall that will reduce losses. Optimization of the powder, liquid and container surface energies will allow the production of the most physically stable formulation. Studies on the role of surfactants in such systems are in progress. It is clear that the surface energy of the solid plays a vital role in

the ease of processing and pharmaceutical usefulness of these systems.

With dry-powder inhalers powder surface energy will affect the tendency for the drug to aggregate (cohesion) and to adhere to the delivery device or carrier particle. The interaction between salbutamol sulphate and lactose carriers has been modelled by use of surface energies (Chawla et al 1993). In this work it was clear that the processing history of both the drug and the carrier altered their surface energies, and hence the interaction between the two, and hence the measured amount of material in the respirable fraction (in-vitro study). It is clear that different molecular species will interact with each other in different ways, however, this study also raises the issue of the role of processing on surface energies. It is clear that the same molecular species can behave in a variety of ways in a dosage form simply due to processing-induced changes in its surface energy.

Mucoadhesion. Lehr et al (1993) have considered the binding of polycarbophil to mucus in the presence of fluid. It was shown that the surface energy model yielded a good correlation with mucoadhesive performance. Our own studies (Rilossi & Buckton 1995a) have shown the advantage in considering the mucoadhesive performance in terms of the Lewis acid-Lewis base theory. It has proved possible to explain or to predict the influence of changes in pH on the mucoadhesive behaviour of carbopol.

In a further study (Rilossi & Buckton 1995b) it has been shown that the free energy of interaction between mucin and various polymers correlates well with the mucoadhesive strength. However, separate correlations were seen for ionized and un-ionized polymers with increased mucoadhesive interaction being observed with ionized materials. It will be necessary to correct for ionic interactions if true predictions of mucoadhesive interaction are to be obtained.

It is clear that surface energy terms can be applied to predict and explain interactions between components of a formulation, or between the product and the biological environment. The possible applications are consequently only limited by the imagination and the ability to undertake the necessary experiments.

Demonstration of How Processing Affects the Surface

It has often been noted that changes in processing have a significant influence on the behaviour of dosage forms. Our own interest developed from an (unpublished) observation that an inhalation aerosol remained physically stable except for one batch which needed to be passed through the micronizer twice in order to reach size specification. This batch then aggregated in suspension, although apparently it was identical to all other batches of material. To probe this situation we investigated the effect of different milling processes on the surface nature of a model drug (Buckton et al 1988). This involved utilizing isothermal microcalorimetry to probe the interaction between the processed powder surface and water vapour. The perceived advantage of this technique is that the powder does not need compaction or packing before measurement, and thus the result should give a good indication of the true surface nature. Four different mills were used on the drug (aspirin), either

Table 1. Enthalpy of adsorption of water vapour onto samples of aspirin that had been milled by different techniques. Details of methods and defined standard state are in Buckton et al (1988).

Process	Enthalpy of adsorption (kJ mol ⁻¹)	Particle size (μm)
Vibrating ball	-1.8	13.4
Fluid energy	-1.8	6.7
Hammer	-5.6	14.5
Hammer, then fluid energy	-6.0	6.0
Ball, then fluid energy	-7.4	6.2
Ball	-8.9	12.0

alone or in combination. The results are summarized in Table 1. From the data in Table 1 it can be seen that the interaction of water with the powder surface differed following the variety of processing treatments. Furthermore, the effect of sequential processing is significant. From Table 1 it can be seen that the sample which had been ball-milled had comparatively large size (12 μm) and the most exothermic enthalpy of adsorption, the opposite to that which had been fluid-energy milled. If, however, the ball-milled sample is then passed through the fluid-energy mill (as may happen if the feed size has to be controlled), then the size is reduced to something similar to that which was passed through only the fluid-energy mill (6.2 compared with 6.7 μm), but the surface properties remain rather more like the ball-milled sample (i.e. -7.4 being rather more similar to the ball-milled value at -8.9 than the fluid-energy milled at -1.8 kJ mol⁻¹). Equally, if the hammer-milled sample (large size) is passed through the fluid-energy mill its size is greatly reduced, but the surface remains like that of the hammer-milled sample (enthalpy of adsorption -6 kJ mol⁻¹). This data is indicative of a situation where the total past history of a powder can affect the surface energy, and thus the behaviour in a product. Indeed this seems to fit in with the practical observation that initiated the study.

It is not just milling that alters powder surfaces. As will be seen below, many other unit processes are also important.

Microcalorimetry and excipient (or drug batch) screening. More recently, we have used a vapour flow cell in a microcalorimeter to produce adsorption isotherms of water vapour onto powder surfaces (Sheridan et al 1993a,b). In this study three different sources of lactose were investigated. Two of these sources (Lactochem and Meggle, Wasserburg, Germany) were found to be suitable for use in a product whilst the other supplier's material (DMV, Veghel, The Netherlands) did not work in the product. In principle the three sources were identical (same size, surface area, crystal form), but in practice the product from the three sources was different. In the published study (Sheridan et al 1993a), it was noted that the surface energies as assessed by contact-angle determinations were identical for the three powders, but the calorimetric technique showed a clear differentiation between the bad and good materials. It follows that the calorimetric technique, where the powder is probed by the flow of vapours of varying humidity, offers a significant sensitivity

advantage over contact-angle determinations for powdered systems. The calorimetric approach seems to offer great promise in terms of screening excipient supplies for suitability in a particular product. This could work on the basis that a specific adsorption response would correspond to an excipient that will function in the product, whilst a response outside of the suitable range would represent an excipient that would not be suitable for use. This pass/fail test is potentially of great value; however, there is a need to investigate the molecular basis for the causes of the changes to powder surfaces. One possible reason for changes in surface nature, which may well explain most of the observed variability, is that of changes in surface crystallinity.

Surface Crystallinity

It has long been recognized that processing can induce disorder in apparently crystalline materials. The influences of drying (Huttenrauch & Keiner 1979), spray drying (Mumenthaler & Leuenberger 1991), lyophilization (Pikal et al 1978), mixing (Konno 1990) and tablet compaction (Ahlneck & Alderborn 1989) have all been documented, and it is probable that every other unit process in production can affect the degree of crystallinity of certain materials. The presence of amorphous regions in crystalline solids can be beneficial in terms of enhanced dissolution rate and increased bioavailability, and possibly due to altered interaction with other formulation components. Equally, the amorphous regions can present difficulties such as decreased chemical stability (Pikal et al 1978). Ahlneck & Zografi (1990) have shown that if a material has a small amount of water associated with it, and if that material has a small amount of amorphous content, then the probability is that the bulk of the water will be absorbed into the amorphous region. Thus the apparently insignificant water content will in fact be a huge amount of water in one small area of the sample. Ahlneck & Zografi (1990) describe this as amplification of the effect of water, and show that even small amounts of water can alter molecular mobility in disordered regions and initiate changes which result in physical and chemical instabilities. It follows that there must be great concern over dismissing small quantities of amorphous content, or small amounts of absorbed water, as being too small to matter. The fact is that a small amount of surface disorder may have an enormous influence on product performance.

Measuring small amounts of disorder

The value of a number of techniques in assessing disorder in crystals has been considered recently (Saleki-Gerhardt et al 1994). The techniques considered were X-ray powder diffraction (XRPD), density (helium pycnometry), heats of crystallization by differential scanning calorimetry (DSC) and water vapour sorption. The sample used was sucrose, which was processed in a high-energy mill (to create a partially disordered system) and the results were compared with those obtained for a totally crystalline sample and an amorphous (by lyophilization) sample. Saleki-Gerhardt et al (1994) showed that XRPD, density and heats of crystallization gave a linear relationship between response and %

disorder down to values of about 10% amorphous content, below which they were less reliable. Differences in water sorption between crystalline and partially amorphous samples showed resolution to be as low as 1% amorphous content. It follows that, with the exception of water sorption, the other techniques may not be sensitive enough to detect the small, but critical, amounts of surface disorder that may be induced during processing. It has already been shown above, that isothermal microcalorimetry is a valuable technique for probing differences in wettability of a powder surface, such that changes due to processing can be detected. It is not surprising, therefore, that recent reports have considered isothermal microcalorimetry as a tool to probe surface disorder (Briggner et al 1994; Buckton et al 1995b; Sebhatu et al 1994).

The basis of the isothermal microcalorimetry approach is to store the processed sample in a sealed ampoule in the calorimeter, under conditions which will allow the transition to the thermodynamically stable crystalline state. For many materials this will involve storing at slightly elevated humidities at close to room temperature, whilst for other materials more severe conditions may be required. The humidity can be maintained by sealing the powder in an ampoule with a small tube of a saturated salt solution. A typical response for spray-dried lactose (which appeared to be totally amorphous by XRPD) is shown in Fig. 4. As can be seen, the response is power (which is rate of change of heat) as a function of time, the area under the curve being the total heat given out during the process under study. The characteristics of the response (Fig. 4) are that there is a very small response for wetting in the initial period. This small response is due to the fact that the humidity is generated within the measuring site; thus the response is a composite of evaporation of water and absorption into the powder. As much of the absorption will be similar to condensation, these two responses are almost equal and opposite, hence the small wetting peak. It should be noted that for the experiments described above in which the calorimeter was being used to monitor wetting, the humidity was generated remote from the measuring site, and thus the entire wetting response was measured; hence, totally different information can be obtained from the same instrument by a minor

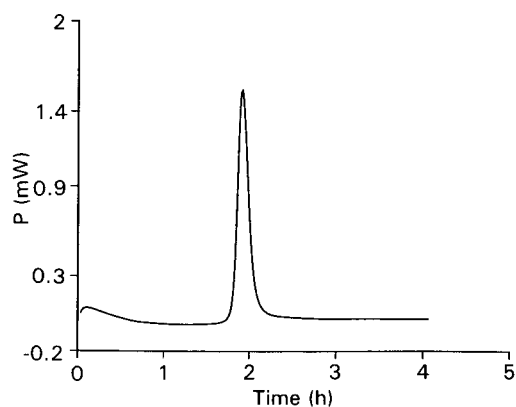


FIG. 4. A typical response for the recrystallization of amorphous lactose as seen by use of isothermal microcalorimetry (reproduced from Briggner et al (1994), with permission). P = power.

redesign of the experiment. Following the small wetting peak was a large sharp response for the recrystallization (this was confirmed by running a sample immediately before and immediately after the response in the XRPD). The sharp peak showed that the recrystallization event was a co-operative process. It is surprising that the powder did not recrystallize gradually from top to bottom of the sample. It might be suspected that the surface layers would saturate, recrystallize, and then water would have to pass through them to reach the lower layers. If such a sequence had occurred, then the response would be a much lower peak power, but a more protracted event. From the response it can be assumed that the water passes through the powder bed, until such time that the entire bed is saturated, before finally causing recrystallization. This model for the co-operative process is further supported by the finding that if the weight of powder is increased, then the lag time before recrystallization is increased (Fig. 5), and equally, if the relative humidity is decreased (by changing the salt solution) then the lag time before crystallization is increased (Briggner et al 1994). If the surface area of the saturated salt solution is altered, the lag before crystallization also changes (increase in area, decrease in lag time). The data presented in Figs 4 and 5 are for a totally amorphous sample of spray-dried lactose; however, if crystalline lactose is fluid-energy milled, it was found that amorphous material was induced in the sample. The extent of the disruption could be quantified by relating the area under the power-time recrystallization peak to that obtained for the amorphous standard (Fig. 6). This quantification reveals that for this material, a high-energy milling process induced more than 7% amorphous material in the sample and that the processing at the highest mill pressures may even induce so much disruption that the effect would be seen by XRPD. There will be many processes which induce less disorder than fluid-energy milling, but which still have very significant effects on product performance. The interesting aspect is to consider the lower limit of detection. By preparing physical mixtures of amorphous lactose and crystalline α -lactose monohydrate, it is possible to probe the detection sensitivity. In doing this, it was found that good reproducibility was seen at 0.6%

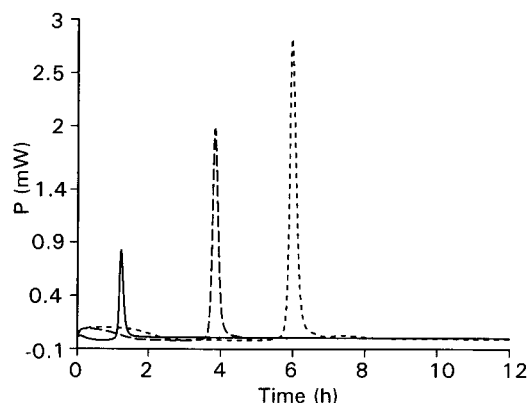


FIG. 5. Responses for the recrystallization of lactose using different sample weights. Key: — 10 mg, - - - 30 mg, - . - . 50 mg. Relative humidity = 85%, temperature = 25°C (reproduced from Briggner et al (1994), with permission). P = power.

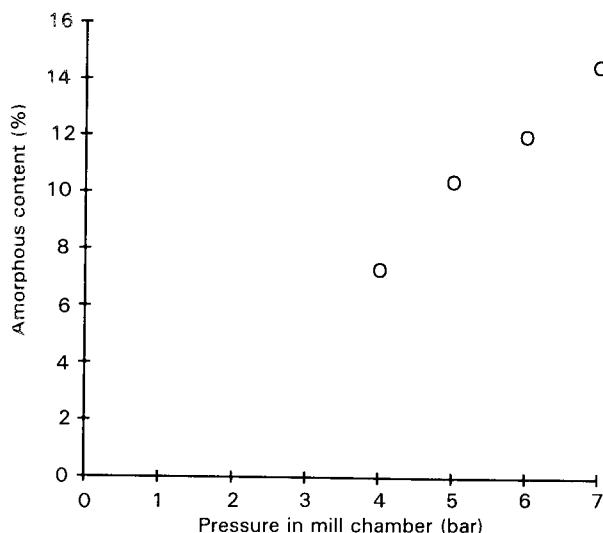


FIG. 6. The amount of amorphous material induced during fluid-energy milling of lactose, when using different air pressures in the mill. Values are determined from the area under the curve of the recrystallization peak obtained by microcalorimetry, with reference to the response for an amorphous standard (reproduced from Briggner et al (1994), with permission).

amorphous material, but that it was starting to be less reliable at 0.3% (Buckton et al 1995b). The exciting prospect is that materials which have as little as 0.5% amorphous content can now be characterized by use of the microcalorimetric technique. This opens up the prospect of understanding the consequences of many changes in processing, and also understanding why these changes sometimes have catastrophic effects on the product.

Under certain conditions, it has been possible to slow the crystallization event to such a stage that multiple peaks are observed (rather than the one smooth response shown in Fig. 4). An example of these multiple peaks is shown in Fig. 7. The peaks in Fig. 7 are probably initially due to the crystallization process starting, which will be initiated by absorbed water giving increased mobility to the molecules in the solid. The molecules will then be able to revert to the thermodynamically stable crystalline form. As the crystallization occurs, the water which caused the event will be expelled. Thus there is an exotherm for the crystallization event, followed by an endotherm for the expulsion of water, followed again by further recrystallization. This is further complicated as the expulsion of water will make the atmosphere in the cell more humid than the equilibrium humidity above the saturated salt solution. This will mean that water will condense into the saturated salt solution (a further exotherm). Thus the processes which occur are complex and, as always, the calorimetric response is a composite of the many thermal events. By careful design of the calorimetric experiment, and by use of other techniques, there is hope that much more fundamental information may be available on crystallization itself. It is worth noting that other materials, such as salbutamol sulphate, behave in a similar manner to lactose.

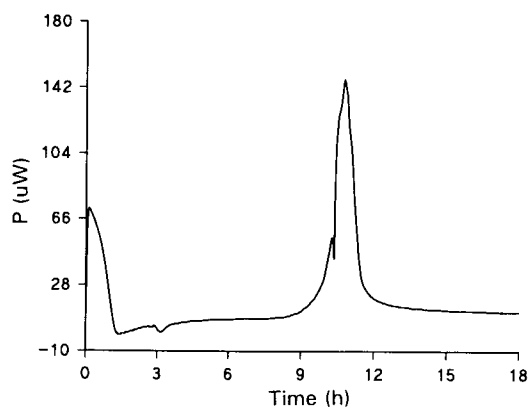


FIG. 7. An example of multiple peaks seen during the recrystallization of spray-dried salbutamol sulphate (taken from Buckton et al 1995c). P = power.

Conclusions

It has been shown that formulations can be optimized by means of surface energy considerations. However, work on the effect of processing on powder surface crystallinity is still in its infancy. Experimental techniques have been unable to address this critical issue until the recent adaptation of the microcalorimetric approach. There can be optimism about future prospects in this area of research. As all materials act and interact at interfaces, the limit of application of interfacial characterization is only limited by the imagination of the investigator and the correct design of experiments. The areas of application include the fields of physical pharmaceuticals and biopharmacy.

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