

Particle Engineering in Pharmaceutical Solids Processing: Surface Energy Considerations

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Abstract: During the past 10 years particle engineering in the pharmaceutical industry has become a topic of increasing importance. Engineers and pharmacists need to understand and control a range of key unit manufacturing operations such as milling, granulation, crystallisation, powder mixing and dry powder inhaled drugs which can be very challenging. It has now become very clear that in many of these particle processing operations, the surface energy of the starting, intermediate or final products is a key factor in understanding the processing operation and or the final product performance. This review will consider the surface energy and surface energy heterogeneity of crystalline solids, methods for the measurement of surface energy, effects of milling on powder surface energy, adhesion and cohesion on powder mixtures, crystal habits and surface energy, surface energy and powder granulation processes, performance of DPI systems and finally crystallisation conditions and surface energy. This review will conclude that the importance of surface energy as a significant factor in understanding the performance of many particulate pharmaceutical products and processes has now been clearly established. It is still nevertheless, work in progress both in terms of development of methods and establishing the limits for when surface energy is the key variable of relevance.

Keywords: Surface energy, contact angle, inverse gas chromatography, pharmaceutical powders, surface properties, powder processing.

INTRODUCTION

The formulation and manufacture of modern pharmaceutical particulate products is a complex and multi-faceted process. Indeed our fundamental understanding of these processes does not meet the needs of industry, especially as more challenging types of powders such as hydrophobic drugs and complex amorphous formulations become more common place. The dominance of solid state dosage forms which involve particulate materials necessitates that interfacial and surface phenomena have an important role to play in determining the quality and performance of both processes and final products. During the past 10 years particle engineering in the pharmaceutical industry has become a topic of increasing importance especially as engineers and pharmacists seek to understand and control a range of key unit manufacturing operations such as milling, granulation, crystallisation, powder mixing and dry powder inhaled drugs. It has now become clear that in many of these particle processing operations, the surface energy of the starting, intermediate or final products can be a key factor in understanding the processing operation and or the final product performance. This review will consider the role played by surface energy in pharmaceutical particle processing operations, and will be preceded by a discussion of the surface energy of pure pharmaceutical solids and experimental methods for its measurement.

SURFACE FREE ENERGY AND THERMODYNAMICS

Our fundamental description of surface free energy follows from the thermodynamic free energy per unit area, γ_{ij} for two phases i and j in contact [1, 2]. From the first law of thermodynamics, the internal energy of a closed system is represented by:

$$dU = TdS - pdV + \sum_{i=1}^c \mu_i dN_i + \gamma_{ij} dA \quad (1)$$

where U is the internal energy, S the entropy, p and T the conditions of pressure and temperature, μ_i the chemical potential of each component, N_i the amount of component i , A the area of the interface and γ_{ij} the interfacial free energy. The interfacial free energy, γ_{ij} is defined as the increase in the internal energy of the entire system per unit increase in interface area at constant volume and entropy of the system under closed conditions, as given in (2):

$$\gamma_{ij} = \left[\frac{\partial G}{\partial A} \right]_{T,P,N_i} \quad (2)$$

The interfacial free energy γ_{ij} may be expressed in terms of the Gibbs free energy (3):

$$\gamma_{ij} = \left[\frac{\partial U}{\partial A} \right]_{S,V,N_i} \quad (3)$$

So for example, the spreading of a liquid i over a solid surface j is determined by their interfacial free energies. At the interface, with a new liquid surface area, A_i will result in the diminishing of the solid surface area, A_j . This change will also cause the creation of the interface surface area, A_{ij} . So for the spontaneous spreading of a liquid i over a solid substrate j , S_{ij} is given by solving the exact differential shown in Eqn 4. Positive values of S_{ij} would indicate a spontaneous spreading of liquid i over solid j . S_{ij} is also known as the spreading coefficient.

$$-\left(\frac{\partial G}{\partial A_i} \right)_{T,P} = S_{i/j} = \gamma_j - \gamma_i - \gamma_{ij} \quad (4)$$

However, commonly the liquid droplet does not fully spread across the entire surface of a solid substrate to form a liquid film. Indeed for many systems such as organic solids, the liquid droplet which exists in the presence of its own vapour, will eventually achieve an equilibrium thermodynamic state whereby a contact angle θ can be defined between the liquid droplet and the solid sub-

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strate. γ_{LV} , γ_{SV} and γ_{SL} represent respectively the liquid surface free energy (commonly called the surface tension for liquids), the solid-vapor surface energy and the solid-liquid surface energy (Fig. 1). The units for surface free energy are mJ m^{-2} , though sometime an equivalent unit mN m^{-1} is used, especially in the case of surface tension measurements. The measurement of the solid surface free energy γ_{SV} for an unknown material is often determined by reference to the liquid wetting characteristics of known liquids as obtained via contact angle measurements.

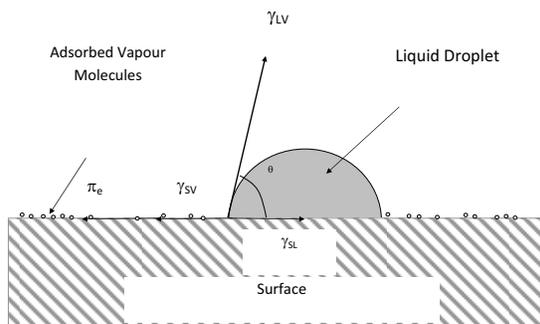


Fig. (1). Sessile drop contact angle schematic for a liquid droplet on a solid substrate with adsorbed vapor film.

Young's equation (5) describes the relationship between the interfacial tensions or free energies of the solid and liquid to the contact angle θ [3]:

$$\gamma_{SV} - \gamma_{SL} = \gamma_{LV} \cos(\theta) \quad (5)$$

The definition for work of adhesion, $W_A = -\Delta G_A$, follows directly from the interfacial free energy:

$$W_A = \gamma_i + \gamma_j - \gamma_{ij} \quad (6)$$

Similarly the work of cohesion, W_C , is defined:

$$W_C = 2\gamma_i \quad (7)$$

Equations (6) and (7) then lead to a key relationship between the work of adhesion, the contact angle and the surface free energy of the contact angle liquid- the Young-Dupre' equation (8) [1]:

$$W_A = \gamma_{LV} [1 + \cos \theta] \quad (8)$$

Sometimes a more detailed equation is provided (9) which takes into account the change in solid-vapour surface energy cause by the presence of adsorbed vapor which exerts a film pressure of π_e . The significant experimental difficulty in measuring π_e means that Eqn (8) is the normally used form.

$$W_A = \gamma_{LV} [1 + \cos \theta] + \pi_e \quad (9)$$

The use of a contact angle liquid with known surface tension properties to determine the surface energetics of an unknown solid state substrate seems a simple enough experimental concept. However, the equations which link these concepts together have only slowly evolved over the past 50 years. The reader is invited to read the excellent and comprehensive review on this topic by Eztler [4]. In this review, we will summarise the major theoretical issues core to this topic, in broadly a historical order.

The determination of the surface energy of solids was pioneered by Zisman who studied the surface energy of polymeric surfaces in the early 1960's at the Naval Research Laboratories [5]. He introduced the essentially empirical concept of the critical wetting tensions γ_c for a solid surface, which was the surface tension of a liquid which just exhibited a contact angle of zero with the solid surface under study. This analysis was based on measuring the contact

angle of a series of liquids with different surface tensions, and thus differing θ 's with the solid of interest, linked with a simple extrapolation, typically graphically to $\theta=0$. Fig. 2 below shows a Zisman plot obtained for morphine sulfate powders by Prestidge and Tsatouhas using a capillary wicking method [6]. The primary limitation of the method is that the differing chemical nature of the interfacial interactions of the contact angle liquids (for example hydrocarbons versus hydrogen bonding liquids like water) with the solid being studied effected the estimates for γ_c obtained. Furthermore, the analysis provides no insight chemically to the interfacial phenomena associated with the wetting event.

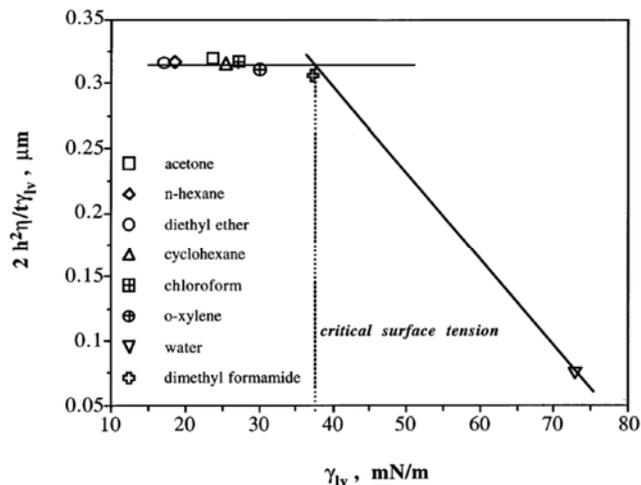


Fig. (2). Morphine sulfate wetting rates as a function of the surface tension of wetting liquids [6].

The Zisman approach proved popular until the 1970's when a number of improved but related methods for surface energy analysis were developed which could be broadly described as semi-empirical in their nature. These developments were driven by the concept developed by Fowkes [7] who advanced the important assumption that the surface tension for many organic materials could be considered to be composed of two independent components; one essentially relating to long range physical forces and another term relating to shorter range chemical forces. Eqn (10) below shows that simple equation where the surface energy or surface tension for a liquid or solid respectively can be considered to be composed of a long range force component due to London van de Waals forces which is commonly referred to as γ^d , as well as a second component which described shorter range forces, originally described as polar forces γ^p . In his original paper, Fowkes considered a wider range of sources for these interactions other than γ^d and γ^p including metallic bonding, induction forces etc for a general material system.

$$\gamma = \gamma^d + \gamma^p \quad (10)$$

The development of Eqn (10) catalysed a number of semi-empirical models for predicting the work of adhesion between a pair of organic material phases. These approaches were based on (i) γ^d and γ^p being treated as independent quantities and (ii) geometric mean approximations based on Berthelot's principle being used to estimate interfacial interactions. Fowkes then allowed thermodynamic terms such as the work of adhesion W_A to be approximated as a simple sum of these independent terms, each relating to a specific type of intermolecular interactions. Owens and Wendt extended Fowkes' equation by grouping the non-bonding London, Debye and Keesom interactions into a similar term which they called dispersive (also recognised as the Lifshitz-van der Waals interactions)

while the remaining terms were grouped as the polar contributions [8]. The Owens-Wendt relationship is also known as the Kaelble Eqn [9] and is given by (11) for a solid-liquid system:

$$\gamma_{SL} = \gamma_{SV} + \gamma_{LV} - 2\sqrt{\gamma_{SV}^d \gamma_{LV}^d} - 2\sqrt{\gamma_{SV}^p \gamma_{LV}^p} \quad (11)$$

This specific approach has been popular because of its simplicity and robustness, with 100's of papers reporting data using this analysis. Practically using two contact angle liquids, commonly water and diiodomethane for whom γ_L^d and γ_L^p are known for both, contact angles for these two liquids on an unknown surface allows γ_S^d and γ_S^p to be determined for this solid.

The next major theoretical development came from Fowkes and Mostafa [10] who shifted the nature of the formalism by which intermolecular forces were split into two independent classes of intermolecular interactions. They considered two specific classes of intermolecular interactions; long range dispersive interactions and short range acid-base interactions; the later term replacing the previous used γ^p term. In the case of the acid-base interactions they proposed the use of the well-established linear free energy relationship developed by Drago [11]; the 4 parameter E&C model. Incorporation of this model into a wetting equation theoretically allowed predictions of the interfacial acid-base free energies of interaction. It is fair to say that despite the sound theoretical basis of this approach, this method did not prove to be popular or useful, mainly because the E&C constants for many contact angle liquids were not known, as well as the lack of reliable estimations for the number of acid-base pair interactions occurring at the interface of interest, a necessary number for using this new theory. A simpler and more useable relationship for acid-base interactions uses the 2 parameter Gutmann donor (DN) and acceptor (AN) number linear free energy relationship which was used by Riddle and Fowkes [12] to generate the acid and base constants for the surface, K_A and K_B . These constants are sometimes reported as acceptor and donor constants for a surface K_A and K_D .

More recently, van Oss *et al.* [13, 14] introduced a refined semi-empirical analysis of acid base interactions, which is given in Eqn (12) below, which considers three independent constants for describing the acid-base and long range interactions; γ^{LW} , γ^+ and γ^- . These parameters describe the long range dispersive, acid and basic surface energies respectively. Unlike previous models this approach introduced an empirical specific acid and basic descriptor for each surface present. However, the van Oss model utilised water as reference materials with the product γ^+ : γ^- equal to unity. This assumption often resulted in an over-basic surface energy parameter estimates. Della Volpe [15] proposed different ratios suggesting that water was not amphoteric but predominantly acidic.

$$\gamma_{SL} = \gamma_{SV} + \gamma_{LV} - 2\sqrt{\gamma_{SV}^{LW} \gamma_{LV}^{LW}} - 2\sqrt{\gamma_{SV}^+ \gamma_{LV}^-} - 2\sqrt{\gamma_{SV}^- \gamma_{LV}^+} \quad (12)$$

In concluding this section it is worthwhile commenting on the limited take up and use of the acid-base models developed in the past 30 years for characterising the surface energy of solid surfaces. The major problems really come from two differing issues. Firstly, and maybe most critically, it is not currently possible to validate using an independent experimental methodology, the theoretical correctness of any the acid-base models summarised here for analysing the interfacial thermodynamics of wetting. It is also not clear whether contact angle and surface tension measurements by themselves give accurate enough estimates for γ^+ and γ^- . Therefore a lack of high fidelity γ^+ and γ^- estimates for the contact angle test

fluids adds further uncertainties in estimating γ^+ and γ^- values for surfaces of interest. Secondly, the assumption implicit in all of the above acid-base models is that the surface of interest is basic and/or acidic and has only one type of acid or base site present. This assumption will be seen in this review to be both unrealistic and overly simplistic, especially for pharmaceutical solid state materials.

MEASUREMENT OF SURFACE ENERGY- CONTACT ANGLE METHODS

Historically the scientific literature on the surface energy of organic materials has been most dominated by studies on polymeric materials, often in the form of films and fibres. In the case of films and other flat sample forms, contact angle techniques have long been the mainstay methods, and these approaches have been in routine use since the work of Zisman and co-workers at NRL in the 1960's [5]. Sessile drop techniques represent the most commonly reported experimental approach for the surface energy determination of solid state films and monolithic solids. Here a droplet of a known liquid which has a surface tension higher than the surface energy of the solid surface of interest is placed on the planar substrate of interest. By imaging the droplet shape profile the contact angle can be estimated. Either by estimating visually the tangent at the three phase contact line or more commonly these days, the Young-Laplace equation is fitted to a digital image of the droplet profile, which in turn allows the contact angle to be measured. Most commonly the advancing contact angle for the liquid is then reported as being representative of the equilibrium contact angle. Though the measurement of contact angles is an intrinsically simple method, there are a number of complicating factors, both in terms of experimental design as well as in data interpretation which researchers need to be cognisant of.

An ideal flat substrate for contact angle study should possess no surface roughness or porosity. The observed experience is that contact angles are not uniquely defined, and that commonly there exist for a specific liquid-solid system a range of stable measurable contact angles, which are characterised by maximum and minimum measurable angles. These are known as the advancing and the receding contact angles respectively, and the difference between these two angles is referred to as contact angle hysteresis. Hysteresis is a function of a number of experimental systems variables including surface roughness and the extent of surface chemical heterogeneity of the solid. The effects of surface roughness and chemical heterogeneity on contact angles are given by the classic papers by Wenzel [16] as well as Cassie and Baxter [17].

The other primary method for contact angle determination is based on wetting force measurements. In this case the substrate of interest, assuming it has a regular geometric shape such as a fibre or a film, can be attached to a sensitive microbalance and the wetting force directly measured when the solid is immersed in the liquid of interest, and the solid pulled through the liquid surfaces. This method forms the basis of the Wilhelmy approach and forces are described by the Eqn (13):

$$F = \gamma_{LV} L \cos \theta \quad (13)$$

where F is the wetting force, γ_{LV} is the surface tension of the test liquid, θ is the contact angle and L the contact length of the liquid with the solid, usually the sample perimeter length. By advancing or receding the three phase contact line of the liquid, advancing and receding contact angles can be measured. This approach is the method of choice for measuring the wetting behaviour of thin fibres. The technique can also be used for thin films and has been adapted for use also with powder compacts. It should however be noted that the formation of powder compacts for either sessile drop or Washburn type experiments carries the risk that the powder

compaction process may result in particle fracture, thus creating new surfaces not representative of the sample at large.

A key condition for measuring an equilibrium wetting property, which is an equilibrium thermodynamic property, is that there should be no significant chemical interactions between the liquid and solid substrate under investigation that might change the properties of either the liquid or the solid substrate during the experiment. In the case of pharmaceutical solids any one of a number of phenomena can seriously invalidate or compromise the equilibrium contact angle determination. Swelling of the substrate as well as dissolution of the substrate can effect both γ_{LV} as well as γ_S , and may even change the topography of the substrate. Chemical reactions, including hydrate or solvate formation can fundamentally compromise the equilibrium nature of the measurement. Some materials will result in liquid absorption into porous substrates, changing the surface to be characterised by the presence of these liquid species.

A further subtle, but not insignificant, constraint is that the probe liquid must have a surface tension greater than the surface energy of the solid to be tested, so as to give a contact angle greater than zero. In general organic materials have surface energies in the range of 35 to 55 mJm⁻², so the list of available test liquids tends to be very limited; water, diiodo methane, ethylene glycol, glycerol and formamide are the ones most commonly used. Probably 95% plus of all contact angle data reported can be attributed to the use of water and or diiodo methane.

The wetting characterisation of porous samples, including powder compacts, is a more complex matter. Most methods in use are based on the classic Washburn Eqn (14) for the capillary rise of a liquid in a network of uniform cylindrical capillaries:

$$v = \frac{r \gamma_{LV} \cos \theta}{2\eta l} \quad (14)$$

Where v describes the rate of penetration of liquid into cylindrical capillaries, γ_{LV} is the surface tension of the test liquid, η is the liquid viscosity and l the depth of penetration, r is the capillary radius and θ is the contact angle. One major limitation of this approach is that few porous solids can be considered to be represented as ensembles of uniform capillaries. Sessile drop techniques can be used for both powder compacts as well as flat substrates which powders have been adhered to and have also both been used to varying levels of success. Both of these methods will be discussed later in this review.

As pharmaceutical products are commonly in the form of particulate materials, the characterisation of their surface energy is challenging as the methods available have complications, and their reactivity towards the contact angle fluids can result in a range of potential non-equilibrium effects. Therefore not surprisingly, alternate methods for determining the surface energy of pharmaceutical powders have been developed including Inverse Gas Chromatography (IGC) and Atomic Force Microscopy (AFM). Of these IGC has attracted the most interest.

SURFACE ENERGY MEASUREMENTS USING ATOMIC FORCE MICROSCOPY

This review has thus far focussed on the more commonly used chemical methods for surface energy determination based on liquid and gas phase probing of a solid surface. During the past 10 years, the use of atomic force microscopy (AFM) to measure surface energy of pharmaceutical solid surfaces has attracted research interest. Louey *et al.* [18] were one of the first groups to report on the surface adhesive forces of pharmaceutical powders using AFM. Dry powder inhaler (DPI) formulations were the focus of this study and the authors used a standard spherical AFM probe which enabled

reproducible adhesional characteristics of the particle surface to be determined. The subsequently estimated surface energies were very low, < 2mJm⁻². Though the specific reasons for such low surface energies were not established, reasons such as particle size, chemical composition of the detaching particle, surface roughness and contact geometry were considered as potential explanations. A subsequent study also on DPI powders was reported by Berard *et al.* [19]. They directly measured using an AFM the adhesional forces between carrier particles (lactose) and drug surfaces, including both crystalline and amorphous forms of zanamivir. Additionally, they reported that the adhesion forces gradually increased with the increasing RH. The authors did not report the surface energy of any of the surfaces studied here.

To estimate the surface energy of a solid using AFM force data, the contact areas need to be estimated as a precursor to estimating the work of adhesion. Such a study was completed by Hooton *et al.* [20] who were the first workers to report works of adhesion for a series of salbutamol sulphate particles using AFM data. A study of AFM contact geometry was also reported by Hooton *et al.* [21] who showed that when considering individual particles, differences in surface chemistry and asperity geometry can lead to drastic changes in adhesion with different humidity conditions. Thus, they argued that the interpretation of the AFM measurement of particle adhesion force needs to take account of these factors if sensible conclusions are to be drawn for pharmaceutical powder systems. Begat *et al.* [22] have also looked at DPI powders and specifically studied how to minimize the variations in contact area between the AFM probe and substrates, by using nanometer smooth crystal surfaces of the drugs and the excipient. This improved uniformity in contact area allowed accurate and reproducible force measurements to be achieved. Cohesive-adhesive force balance graphs were then developed allowing direct comparison of the interaction forces occurring in model carrier-based formulations of salbutamol sulphate-lactose and budesonide-lactose. The use of AFM based force data for pharmaceutical powders has been briefly reviewed by Roberts [23].

Traini *et al.* [24] has used the works of adhesion and cohesion for predicting the suspension stability for pressurised metered dose inhalers powders using AFM, IGC and contact angle data. AFM works of adhesion data did not correlate with γ_S^d based works of adhesion as determined from IGC or contact angle experiments. However, works of adhesion which included polar/acid-base interactions gave more promising correlations with AFM force data. Detailed surface energy data using IGC and AFM have been reported by Davies *et al.* [25] for budesonide particles as well as other model substrates. An unmilled budesonide material displayed surface energy, as determined by AFM of the (002) crystal face of 39-88 mJm⁻². The surface energy of the micronised material as determined by IGC was 68 mJm⁻². The variability in surface energy from AFM, especially apparent for the micronised budesonide was attributed to two factors, intrinsic material variations within a single particle and assumptions present within the contact mechanics model used.

α -lactose monohydrate continues to be one of the most studied materials using IGC. Zhang *et al.* [26] have used AFM to determine γ_S^d of milled and crystalline α -lactose monohydrate. AFM is potentially a very attractive method as it allows the surface energy to be directly related to local surface topology and features. It's downside is the uncertainty in the measurement in terms of spring constant calibration, area of contact, tip radius and the choice of the most appropriate DMT or JKR equation for data analysis, as well as the development of a suitable experimental method for measuring tip-surface interaction forces. When the surface of interest is a particle, these experiments can be especially challenging. In this study the surface energy of crystalline face (0 -1 -1) and a cast amorphous

lactose film was determined to be 23.3 mJm^{-2} and 57.4 mJm^{-2} respectively. This paper demonstrates that AFM can provide localised information from individual faces or within components of heterogeneous powdered samples.

MEASUREMENT OF SURFACE ENERGY- INVERSE GAS CHROMATOGRAPHY METHODS

The recent popularity in the use of inverse gas chromatography (IGC) methods for the surface energy characterisation of powders reflects new scientific developments in the experimental technique as well as a growing appreciation that gas (strictly speaking vapour) adsorption methods can provide a rich and unique understanding of the surface thermodynamic properties of powders not possible using any other method. The history of IGC can be traced back to a number of key research publications in the 1960's and 1970. The reader will find the seminal books by Kiselev and Yashin [27] as well as Conder and Young [28] a very useful background read for this topic and reveal the enormous potential of the IGC method; not just surface energy measurements which is the current topic. Etzler has provided a very detailed and extensive review of surface energy including much detail on both theory and experiment [4]. Grimsey *et al.* have also reviewed some papers on IGC and surface energy effects in 2002 [29].

It is also appropriate to comment on the IGC instrumentation used to measure surface properties. Papers older than about 15 years were all based on home built IGC instruments, with commercial instrument systems appearing in about 2000. The first commercial IGC instrument was the IGC 2000 manufactured by Surface Measurement Systems and was able to measure a wide range of surface properties including the γ_s^d with an automated gas injection systems capable of delivering up to 12 different vapours. In 2012 this system was superseded by the IGC-SEA which allowed IGC to be performed for a series of user selectable fixed surface coverages for all adsorbates. This feature in turn allowed γ_s^d to be determined for specific surface coverages, ie. an isostere method, which in turn allowed surface energy heterogeneity to be quantified. This key development allows more robust and more sensible comparison of IGC data obtained by different groups or researchers as the γ_s^d values can now be directly linked to a specific surface coverage.

IGC experimental methods are vapour adsorption methods, and are conceptually related to the BET surface areas techniques which are in common usage based on gas (nitrogen) adsorption. IGC experiments are however typically conducted at vapor concentrations below that at which monolayer surface coverage occurs, such that the adsorbing molecules behave independently and retention behaviour is thus in the Henry's Law region.

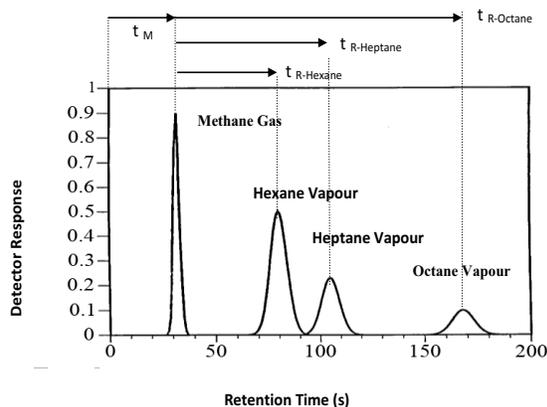


Fig. (3). Series of chromatograms obtained for alkane vapour species interacting with a GC column packed with crystalline fibres.

Fig. 3 above shows four overlaid chromatograms obtained for alkane vapour species interacting with a GC column packed with crystalline fibres at 40°C under conditions of infinite dilution. The quantity t_M is the retention time for an inert non-interacting gas species to sweep through the packed column. This time is known as the experimental dead-time and is typically measured using methane or nitrogen. This retention time t_M when multiplied by the carrier gas flow rate F accurately approximates the dead volume V_M within the system. This dead volume consists of the internal volume of the instrumentation plumbing as well as dead-space within the sample column and its packing.

As the hydrocarbon chain lengths increases of the vapour solute injected, so does the propensity of the solute species to interact with the sample surface via adsorption. This results in increasing retention times for the solute molecules with increase molecular mass and the trend is clearly shown in the peaks shown below for hexane through octane. They direct reflect the stronger molecular interactions of octane vapor for the surface compared say to hexane. The increased residence time in the GC column for the larger alkanes directly results in broader and less intense solute peaks due to increased longitudinal diffusive broadening. The peaks nevertheless maintain their Gaussian shape.

The retention time t_R per unit of sample mass for an adsorbing solute vapour allows the nett retention volume V_N to be determined using Eqn (15):

$$V_N = j \cdot t_R \cdot F \cdot (T/273.15) - j \cdot t_M \cdot F \cdot (T/273.15) \quad (15)$$

where F is the carrier gas flow rate, T is the column temperature, t_M is the dead time and j is a correction term allowing for the pressure changes along the column. The retention process for the solute with the stationary phase is determined by the solute partitioning between the stationary and mobile phases at the relevant temperature, pressure and concentration. For the case in which the retention process is due to solid-vapor adsorption as in the case of surface energy measurements, solute partitioning between the mobile and stationary phases is given by the appropriate adsorption isotherm. At low solute concentrations ($\ll 0.01 \text{ P/P}_0$) the adsorption isotherm is typically linear and this region is commonly described as the Henry's Law region. In this region solute molecules adsorbing onto a surface are independent and nearest neighbor interactions are not significant. Gaussian shaped chromatograms as shown in Fig. 3 result in the case of adsorption in the Henry's Law region. In this linear region of the adsorption isotherm, the nett retention volume V_N may be related directly to the surface area of the sample A and the partitioning coefficient K_S in the case of surface retention of the solute:

$$V_N = A \cdot K_S \quad (16)$$

K_S is also the slope of the adsorption isotherm at infinite dilution and is defined as the ratio of the solute concentration q in the stationary phase to the solute concentration c in the mobile phase:

$$K_S = q/c \quad (17)$$

It is thus apparent that the nett retention volume V_N is directly proportional to the slope of the adsorption isotherm and thus the equilibrium constant for the adsorption process. Consequently standard thermodynamic analysis may be applied to the data. For example, from the temperature dependent partitioning coefficient K_S the heat of adsorption ΔH_A^o using Equation (18) may be determined. Choice of appropriate standard states for the adsorbed species allows both free energies of adsorption ΔG_A^o and entropies of adsorption ΔS_A^o to be determined as well.

$$q_d = -\Delta H_A^o = R \frac{d(\ln K_S)}{d(1/T)} \quad (18)$$

$$\Delta G_A^o = -RT \ln \left[\frac{K_s \cdot p_{s,g}}{\pi_s} \right] \quad (19)$$

$$\Delta S_A^o = \frac{-q_d + \Delta G_A^o}{T} \quad (20)$$

A study of V_N as a function of temperature thus allows a detailed study of surface adsorption thermodynamics to be undertaken using the above equations. Measuring the retention behavior of a series of alkane probes allows the dispersive (long range) van der Waals component of the surface energy of the surface, γ_S^d to be estimated. By measuring the change in retention volume as one increases the molecular size of the alkane probe, the differential free energy of adsorption for an imaginary $-\text{CH}_2-$ species can be determined. Using the assumption that an infinite surface of $-\text{CH}_2-$ groups is equivalent to a polyethylene surface, and with the use of the Fowkes' geometric mean work of adhesion analysis, γ_S^d may be estimated using Eqn 21 :

$$\gamma_S^d = \frac{4}{\gamma_{S-V}} \left[\frac{\Delta G_A^{CH_2}}{N \cdot a_{CH_2}} \right]^2 \quad (21)$$

where N is Avogadro's constant, a_{CH_2} is the area of a $-\text{CH}_2-$ group and γ_{S-V} is the surface energy of polyethylene. This simple ratio measurement was developed by Gray and Dorris [30] has become very popular, not least because there is no need to know the exact surface area for the sample or the cross-sectional area of the adsorbing molecule. Another approach for estimating γ_S^d was reported by Schultz and co-workers [31]. This approach results in a different dependent variable be plotted in the x axis, $a_m \sqrt{\gamma_L^d}$, where a_m is the cross-section adsorption area of the alkane species and γ_L^d is the surface tension of the same alkane liquid. Both are sound methods for γ_S^d data analyses and despite the additional need for accurate estimates for a_m , the Schultz method is more commonly reported.

Both methods typically give the same estimate for γ_S^d to within 1 mJm^{-2} though it has been reported that the Dorris-Gray method does yield more accurate estimates for γ_S^d [32]. In a more extensive evaluation, Shi *et al.* [33] have looked in detail at the relationship between the Dorris-Gray and Schultz methods. They concluded that the Dorris-Gray estimates will always be larger than the Schultz estimates, and that the Dorris-Gray estimates have a more accurate basis.

So though we have discussed details of the analysis of the long range van der Waals forces using alkane vapours, what about the short range forces? These are determined using a number of acid and basic vapour injections, often measured on the samples after the alkane experiments are completed. The solid-vapour retention by acid and base probes by the surface of interest is partially due to the dispersive interactions of the acid/base probes with the surface, and partially due to the acid/base interactions with the surface. Since the dispersive properties of the acid/base probes are well recorded, the retention volume due to acid-base adsorption interactions can be determined, and this is commonly converted into a free energy of specific adsorption; ΔG_A^{sp} . Data is typically reported in one of two main formats. Values of ΔG_A^{sp} for a particular acid or base probe molecule, such as dichloromethane, ethanol or ethyl acetate for example may be directly reported, or this data may be analysed using the Gutmann approach, in which case specific acid and base numbers (K_A , K_B) for the surface maybe reported, or more commonly a ratio of them K_A / K_B is reported. More details on all of

these IGC analyses are provided in the excellent recent review by Mohammadi-Jam and Waters [34].

Until relatively recently, IGC data for estimating γ_S^d was essentially based on a series of injections using alkane probe molecules at infinite dilution injection conditions. This analysis was based on the use of a Henry's Law equation, and therefore assumed that the adsorption isotherm is linear for low surface coverages and implicitly that the surface must therefore be energetically homogeneous. A key implication of this assumption is that retention times, and thus surface energies, are independent of solute injection size. Indeed for virtually all of the research work reported on the characterisation of organic materials such a polymers, and more recently research work on pharmaceutical solids, the assumption that such surfaces must be energetically homogeneous had not been challenged or validated. The advent of a number of wetting papers since 2000 [6, 35-37] has clearly confirmed the surface energy heterogeneity of crystalline pharmaceutical solids. As a result of this work IGC researchers have adopted new experimental methods so as to establish, or not, the surface energy heterogeneity of these solid state materials.

The key reference to this new approach was reported by Ylä-Mäihäniemi *et al.* [32] who introduced the concept of surface energy distributions using an isostere based analysis of IGC data. In this new approach γ_S^d was determined at a number of specific surface coverages (e.g. 0.2% or 2% surface coverage) by a series of vapour injections with the usual alkane probe molecules. This approach takes into account the specific cross-section area of the adsorbing species so that γ_S^d could be estimated for each of these surface coverages. The premise was that adsorption at low surface coverages such as 0.2% surface coverage would sample the higher energy and more active surface sites, on average, than would be sensed by an experiment conducted at 2.0% surface coverage. Fig. 4 below shows schematically this approach.

A refinement of this method for analysing IGC data was proposed by Jefferson *et al.* [38]. Here the authors improve the analysis of surface energy distributions using a numerical model with incorporates a Boltzmann factor into probabilities for the adsorption of differing hydrocarbon species.

WETTABILITY OF PHARMACEUTICAL POWDERS AND CRYSTALS

Early studies on pharmaceutical powder wetting focussed on the capillary rise based liquid approaches. Buckton and Newton [39] determined the critical surface tensions of amylobartbitone powders using a range of liquids and liquid mixtures. Duncan-Hewitt and Nisman [40] comprehensively studied the wettability of an acetaminophen and adipic acid using a range of methods including sedimentation, thin coated films, capillary rise as well as sessile drop measurements on powder compacts and large single crystals. There was a surprising excellent agreement across the measurement approaches, allowing γ_S to be estimated using an equation of state approach.

A study on pharmaceutical powders by Dove *et al.* [41] examined the wetting behaviour of caffeine and theophylline powders using two different contact angle techniques as well as infinite dilution IGC. The authors fabricated thin powder tablets and used a Wilhelmy plate wetting method, as well as determining sessile drop contact angles for very thin layers of powders adhered to glass cover slides using a spray on adhesive. In the case of the Wilhelmy plate data, some significant inconsistencies in the data were reported around very high values of γ_S^d . These anomalies are not surprising considering the complex nature of the topography and porosity

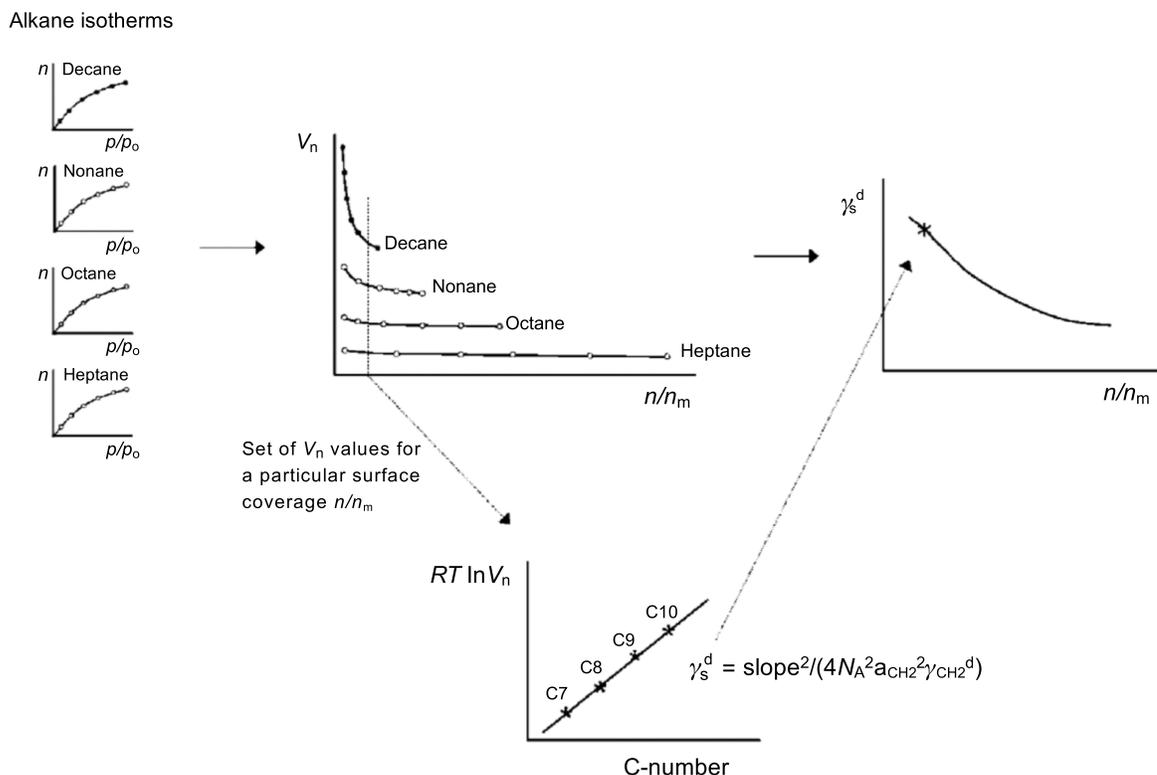


Fig. (4). Schematic diagram of the experimental method for determining the distribution profile for γ_s^d [32].

of the powder plate being studied. The contact angle and surface energy data from the powder coated glass slides seemed to be more reliable, with γ_s^d values of 44.5 and 43.4 mJm⁻² being reported for caffeine and theophylline surfaces respectively. The real concern about this coated glass slide method is the risk that the contact angle data will partially reflect the contact angle of the underlying glue. The authors were able to argue that this did not seem to be a significant effect in their study. In the case of the IGC data, γ_s^d values of 39.9 and 50.8 mJm⁻² being reported for caffeine and theophylline respectively. So though both the IGC and powder coated glass slide contact data gave sensible numbers for γ_s^d , there were still some significant differences in the γ_s^d values reported of between 4 and 8 mJm⁻² between these two methods.

An extensive study of the surface energy of microcrystalline celluloses using capillary wetting and IGC was reported by Steele *et al.* [42]. Despite the potential problems in interpreting capillary wetting data for these water swellable solids, the authors reported surface energies for a range of industrial microcrystalline cellulose powders.

Wettability studies of morphine sulfate powders were reported by Prestidge and Tsatouhas [6] using a capillary rise approach. Reasonably reproducible wetting rates were reported for number of liquids, though sessile drop contact angle experiments on powder compacts were not successful. The Zisman wetting tension was then reported for morphine sulfate and the authors surmised that the relative exposure of different crystal faces plays an important role in controlling the wettability of morphine sulfate powders.

Muster and Prestidge [35] have used a series of crystal facet specific measurements to determine the face-specific structure, chemistry, and wettability of two model pharmaceutical crystals;

N,n-octyl-D-gluconamide (OGA) as well as forms I and III of sulfathiazole (STZ). Direct sessile drop contact angles of water were measured on a number of crystal faces, where sufficiently large enough crystals could be prepared and these experiments were augmented with AFM and ToF-SIMS data. ToF-SIMS molecular fragmentation data confirmed surface compositional differences for different facets of STZ form III and OGA crystals. Contact angle data showed some differences in the facet specific results which were interpreted in terms of face specific surface chemistries.

The surface properties of two crystal habits of celecoxib (CEL), an acicular crystal habit (CEL-A) and a plate-shaped crystal habit (CEL-P) have been reported [43]. Powder wetting data confirmed differences in the wettability and surface energy of these two habits. Enhanced dissolution and pharmaceutical performance of CEL-P was attributed to the presence of more hydrophilic surfaces in this habit compared to CEL-A.

Heng *et al.* have reported a study of the surface energy of a number of API systems using large single crystal contact angle determinations, sessile drops measurements on powder compacts as well as capillary rise experiments using a wetting tensiometer [44]. Contact angle determinations on large macroscopic crystals were found to be the most effective measurement approach and data obtained for aspirin, racemic ibuprofen, S-(+)-Ibuprofen as well as paracetamol forms I and II were reported. They confirmed facet specific contact angle and surface energies for all systems studied. Such rich and reliable data sets on the surface energy of crystal facets could not be obtained with any of the powder based contact angle approaches.

The most detailed study of facet specific surface energies as well as facet surface chemistry for an API was reported by Heng *et al.* [36]. In this study the anisotropic surface energetics and wettability of macroscopic form I crystals of paracetamol were exam-

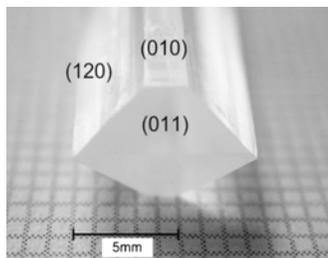
Table I. Paracetamol form I crystals- surface energy, unit crystal cell and OH Group Density [36].

facet	unit cell	unit cell	unit cell	unit cell	no. of	OH group	facet	γ^d	γ^p	γ	γ^p/γ
	length	depth	angle	area							
	(Å)	(Å)	(°)	(Å ²)	groups	(Å ⁻²)					
(201)	14.44	9.4	90	135.7	2	0.0147	(201)	34.9	27.5	62.4	0.44
(001)	12.93	9.4	90	121.5	2	0.0165	(001)	34.4	38.0	72.4	0.53
(011)	11.78	12.93	74.74	146.9	2	0.0136	(011)	33.9	32.7	66.5	0.49
(110)	15.99	7.1	69.31	106.0	1	0.0094	(110)	34.2	20.2	54.4	0.37
(010)	12.93	7.1	64.1	82.59	0	0.0000	(010)	45.1	7.0	52.1	0.13

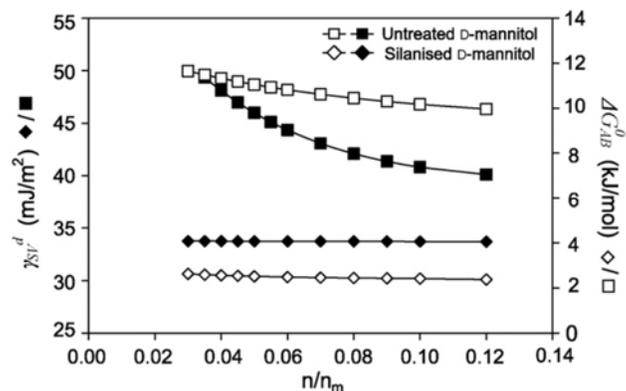
ined in detail, as well as the surface chemical composition of the crystal facets as determined by XPS. Contact angles were determined using a sessile drop method on large macroscopic crystals. Experiments were also conducted using paracetamol saturated water solutions to exclude any dissolution effects on the water contact angle data obtained. Table I above summarises the surface energy data as well as OH group concentrations for each crystal facet. The relative surface polarity for the facets was in decreasing order was (001) > (011) > (201) > (110) > (010) agreeing with the fraction of exposed polar hydroxyl groups as determined using XPS, and correlated with the number of non-hydrogen-bonded hydroxyl groups per unit area present for each crystal facet using known crystal structures. Cleaving form I crystals exposed a more apolar (010) surface with very different surface properties, including a γ_s^d of 45 mJm⁻² which was also much more hydrophobic surface than the other external crystal surfaces. A subsequent paper on forms I and II of paracetamol concluded that the differing polymorphic forms exhibited significant variations in their wetting behaviour for the same Miller indexed faces, though anisotropic surface energetics was reported for both form I and form II crystal surfaces [45].

The wettability of the (001), (100), and (011) crystallographic facets of macroscopic aspirin crystals has been experimentally investigated using a sessile drop contact angle method [37]. The surface energetics were found to be anisotropic and facet dependant, being directly related to the presence of surface carboxylic groups.

A key question which is raised by surface energy characterisation of solids by wetting experiments and by IGC experiments is can this data be compared, and does one obtain the same values for γ_s^d if the work is performed rigorously? This crucial question was answered in 2010 by Ho and co-workers at Imperial College [46]. In their study they used a model hydrophilic excipient, d-mannitol and from it created a model hydrophobic excipient, methyl silanised d-mannitol. These two materials were then produced in both a powdered form as well as in a large single crystal form, allowing both IGC and contact angle analysis to be deployed on the respective sample forms (Fig. 5). For completeness they also looked at the face specific surface chemistry of the primary crystal facets of d-mannitol; (010), (120) and (011).

**Fig. (5).** Macroscopic crystals of β d-mannitol grown from aqueous solution [46].**Table II. Surface energy of untreated and silanised d-mannitol as determined with Owen-Wendt analysis [46].**

Facet	Untreated			Silanised	
	γ_{sv}^d	γ_{sv}^p	γ_{sv}	$\gamma_{sv}^p/\gamma_{sv}$	γ_{sv}^d
(010)	44.1 ± 0.6	12.8 ± 0.3	56.9 ± 0.9	0.23	34.9
(120)	43.3 ± 0.7	18.6 ± 0.4	61.9 ± 1.1	0.30	34.5
(011)	39.5 ± 0.4	35.4 ± 0.7	75.9 ± 1.0	0.47	34.9

**Fig. (6).** γ_s^d and ΔG_{AB}^0 (ethanol) distributions for untreated and silanised d-mannitol [46].

The IGC data in Fig. 6 for the hydrophobic d-mannitol shows γ_s^d to be very constant as a function of surface coverage at 34.5 mJm⁻², whereas the contact angle data summarised in Table II gives γ_s^d to be in the range 34.5 to 35.0 mJm⁻². For the normal hydrophilic d-mannitol, γ_s^d varied between the different facets, ranging from 39 to 44 mJm⁻². The IGC γ_s^d heterogeneity graphs in Fig. 6 shows a maximum value of about 47 mJm⁻², decreasing to a plateau value of about 40 mJm⁻² for high surface coverages. Therefore data for both hydrophilic and hydrophobic d-mannitol gave IGC data which was entirely consistent with the data obtained with contact angles on single crystal facets. XPS confirmed that the (011) facet on normal d-mannitol, which was the most hydrophilic surface, had the highest surface concentration of OH groups.

Ho *et al.* [47] have examined the γ_s^d surface energy of different size fractions of the β form of d-mannitol. The essential premise of the work is that different size fractions of d-mannitol have different crystal aspect ratios, and that resultant exposure of different crystal facets would be reflected by the γ_s^d surface energy distributions measured. Fig. 7 below shows the γ_s^d surface energy distributions as function of size fraction, as well as lines showing the

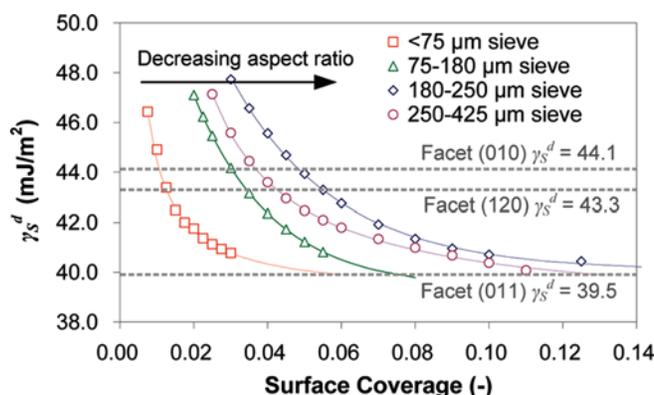


Fig. (7). γ_s^d distributions of d-mannitol obtained with different sieve sizes [47].

surface energy for specific known facets of d-mannitol determined by contact angle studies on large d-mannitol crystals. The work confirmed that γ_s^d surface energy distributions are sensitive to the shape and thus population of crystal facets found in a crystalline powder system.

TRIBOELECTRIC CHARGING OF POWDERS

The triboelectric charging of a powder is a measure of a powder's ability to accept or donate electrons to, or from, another surface with which it is typically in dynamic contact. This phenomenon's presence can manifest itself on processing equipment surfaces or even containers used to store or dispense powders. It is of great practical importance in the pharmaceutical industry and many powder processing operations can suffer from such charging effects. In increasing interest in hydrophobic APIs means that these effects are likely to be more prevalent in the future. Triboelectric charging of powders has been specifically reviewed recently [48].

Ahfat *et al.* [49] reported an early study on powder tribocharging and surface energy for pharmaceutical powders, both excipients and APIs. The surface energies were measured using IGC, as well as by a sessile drop technique where the pharmaceutical powder was adhered to glass slides (as previously reported by Dove *et al.* [41]). γ_s^d and γ_s^p values surface energies were reported from wetting experiments as well as γ_s^d and Gutmann K_A and K_D numbers from the IGC experiment. First order powder tribocharging data was obtained using a Faraday well technique made from stainless steel. It was anticipated that the tribocharging would be ascribable to surface chemical groups present on the particle surfaces and there was some promise that the IGC data using K_A and K_D might prove incitefull. A positive correlation was established between the K_A and K_D and the electrostatic charge measured.

SPRAY DRYING OF SOLIDS

Ohta and Buckton [50] have examined the stability of two amorphous sprayed dried formulations of cefditoren pivoxil both of which exhibited identical T_g 's as determined by DSC. However, the formulations were known to exhibit significant differences in their physical stabilities. Using IGC at infinite dilution, small differences in γ_s^d were observed between the formulations, as well as more significant differences in K_D and K_A for these two formulations which could be ascribed to subtle differences in the acid-base surface chemistry of these two formulations. It was concluded that surface energy descriptors as determined by IGC could be used for studying batch to batch variations in these formulations. However,

the specific relationship between surface property descriptors of powders and their physical stability is a much more complex topic which is currently beyond our current understanding scientifically.

The effect of adding alkylpolyglycoside surfactants to spray dried salbutamol sulphate particles was reported by Columbano *et al.* [51]. Using IGC they determined that γ_s^d values were very similar for all formulations tested, though some small differences in K_D / K_A ratios for some formulations were noted.

WET GRANULATION

Wet granulation is a complex process for particle enlargement which is known to depend on a wide range of properties including particle shape and size, granule packing/porosity, shear forces, powder flow dynamics as well as the wetting a spreading of the binder solution over the powder particles. Despite these complexities, various workers have attempted to identify the specific contribution that powder wetting makes to this process. The importance of particle surface energetics data in optimising wet granulation systems was pioneered by Rowe in the late 1980's [52-54]. Surface thermodynamics for cohesion and adhesion, and specifically the spreading coefficients S_{ij} between substrates and binders solutions were used to inform the selection of binders based on an experimental knowledge of the surface energies of substrates and binders solutions.

Yokoi *et al.* [55] studied the physicochemical properties of wet granulated and spray dried cefditoren pivoxil with various additives. They suggested that difference in acid/base surface chemistry in the different formulations could be measured using IGC, and proposed that different surface chemical groups were present on the particle surface which related to the formulation composition. The importance of the surface free energy in the selection of excipients in the course of a wet-granulation of metronidazole was reported by Tuske *et al.* [56]. Corn starch, lactose, microcrystalline cellulose, hydroxyl-propylcellulose were all considered as potential excipients for formulation with metronidazole. Contact angle data for the excipients allowed the spreading coefficients to be estimated for binder solution spreading. These results were correlated with the friability of the final wet granulated products. When the spreading coefficient of a binder over the substrate is positive, the formation of dense, non-friable pellets can be expected. However, the spreading coefficient results alone did not predict completely the granule properties of complex formulations.

In another study of binder liquid spreading, the wettability of a number of pharmaceutical powders was determined from contact angle data, and the subsequent values for surface energies were then used to determine spreading coefficients. This determination allowed the selection of the most appropriate granulating solvent for a wet granulation process [57]. Predicted granulating solvent performance using solvent-drug spreading coefficients was in good agreement with resulting granules properties, specifically in terms of density, porosity and friability.

A detailed study on the specific effects of particle surface energy and surface chemistry on granule size and granule mechanical properties for high shear wet granulation have been reported by Ho *et al.* [58]. Using standard d-mannitol powder as well as a silanised hydrophobic version of d-mannitol, they produced a series of powder mixtures with identical powder density, particle shape and particle size distributions. IGC established that the silanised and non-silanised powders had very different surface energetics (see Fig. 8). Measurement of the particle size distributions for the final granules produced as well as study of the compressive mechanical properties of the final granules showed significant differences which were ascribed to the wetting phase of the granulation processes (see Fig. 9).

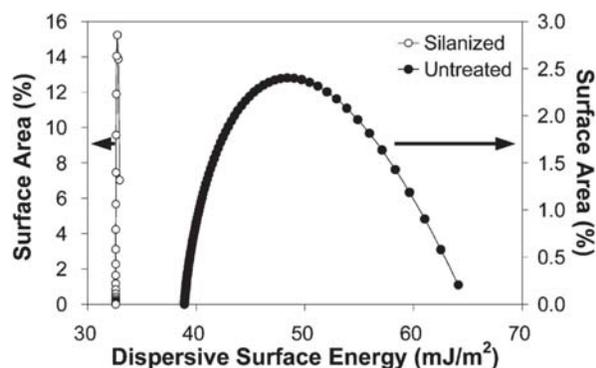


Fig. (8). γ_s^d surface energy heterogeneity distributions measured for d-mannitol [58].

POWDER PREPARATION METHODS

A relatively early study of API milling and crystal surface energy was reported by Heng *et al.* [59]. The effects of milling and particle size on surface energies of form I paracetamol crystals were reported for both particulate as well as macroscopic crystal materials. Milling of form I crystals resulted in fracture along the crystal's lowest attachment energy plane (010), exposing facets of different surface chemistry to that of the native external facets. Milling resulted in the exposure of a more hydrophobic surface for paracetamol form I crystals which becomes increasingly more dominant in its presence with decreasing particle size; indeed γ_s^d for milled samples increased by 20% with decreasing particle size.

A comparison of mannitol particle prepared by differing methods was reported by Tang *et al.* [60] for aerosol delivery applications. Methods used included spray drying, air jet milling as well as a confined liquid impinging jet approach (CLIJ). Table III above shows the significant differences on both γ_s^d and acid/base surface energies reported for these differing types of mannitol. This study, in the context of the current review, highlights how sensitive surface properties are to particle manufacturing method.

Modi *et al.* [61] has reported the effect of crystal habit and milling on the intrinsic dissolution behavior of celecoxib. Celecoxib powder compacts formed from planar crystals exhibited higher wettability than the acicular, milled acicular or milled planar powder compacts. This enhanced wettability manifested itself in much higher levels of acidic surface energy for the planar crystals which was confirmed with higher surface concentrations of nitrogen

Table III. γ_s^d and acceptor and donor indexes (K_A and K_B) of the different mannitol powders at 303 K [60].

Process	γ_s^d (mJm ⁻²)	K_A	K_B
Jet milled	47.9 ± 1.35	0.14 ± 0.02	0.26 ± 0.12
Spray dried	60.3 ± 0.96	0.29 ± 0.04	0.16 ± 0.23
CLIJ	85.3 ± 2.35	0.25 ± 0.05	0.26 ± 0.29

containing species as determined by XPS. These same crystals had an intrinsic dissolution rate which was 20% higher than the 3 other celecoxib samples studied.

Another study of milling and particle shape was reported by Ho *et al.* [62]. They examined both ball milled and unmilled versions of the β form of d-mannitol, and considered differing facture pathways for this material-see Fig. 10. Milling was reported to change crystal aspect ratio which was quantified using dynamic image analysis. Analysis of the surface energy distributions of these powders showed some very clear trends. From Fig. 11, it is clear that γ_s^d is related to the crystal shape of milled d-mannitol. As the BR crystal aspect ratio increases, the γ_s^d profiles display a downward trend toward lower values of γ_s^d . The mean γ_s^d values, as measured from the distributions of surface energy depicted in Fig. 11, decreases from 44.7 to 42.1 mJm⁻² (6% difference) as the aspect ratio increases from 0.39 to 0.48. This reduction in γ_s^d energy was ascribed to the exposure of crystal plane (011) of d-mannitol needles upon milling. This small reduction in the mean values of γ_s^d is rather significant due to the fact that the absolute γ_s^d difference between (010) and (011) is less than 5 mJm⁻². Comparing milled and unmilled d-mannitol powders at the identical aspect ratio, it is clear that the milled materials exhibit consistently smaller particle breadths, implying that milled d-mannitol needles are shorter in length than unmilled d-mannitol.

INHALABILITY OF AEROSOL PARTICLES

There are a number of particle properties which could be expected to control the performance of <5 μ m diameter particles used as active therapeutics for deep lung deposition. Aerosolisation of such powders depends upon range of properties including particle size, topography, shape, density, surface chemistry and surface energy, and this topic with a specific focus on lactose particle has

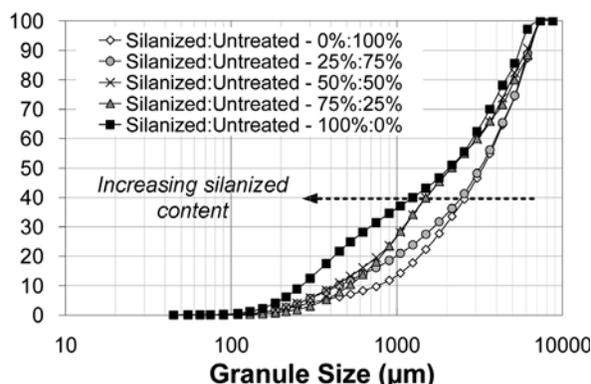


Fig. (9). Cumulative granule size distribution of d-mannitol formulations and the Young's compressive moduli for single 1mm diameter granules for increasing degrees of powder mixture hydrophobicity [58].

silanized d-mannitol content (%)	regression of data to Hertz' model R^2	$E \pm$ standard deviation, number of repeats >20 (GPa)
0	0.6721	0.2053 ± 0.0113 ^d
25	0.9356	0.1620 ± 0.0177
50	0.9164	0.1110 ± 0.0087
75	0.9990	0.1270 ± 0.0339
100	0.9917	0.0789 ± 0.0089

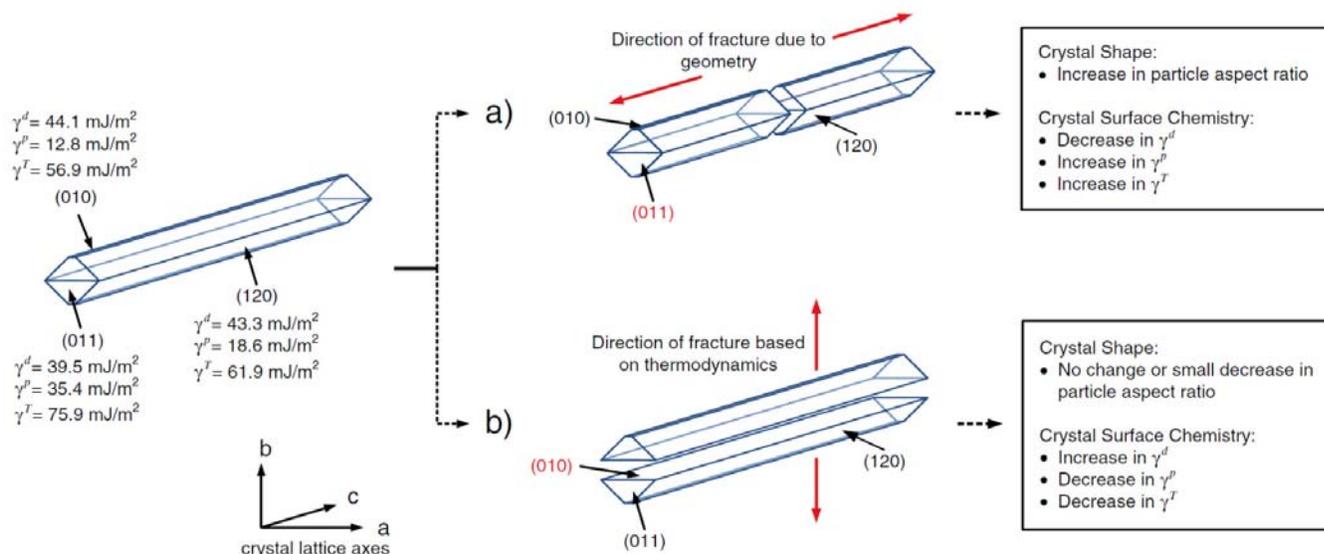


Fig. (10). Diagrams representing the fracture scenarios of d-mannitol with a needle morphology: (a) fracture direction across (011) and (b) fracture direction across (010) [62].

been reviewed by Pilcer *et al.* [63]. Raula *et al.* [64] has examined the aerosol performance for l-leucine coated salbutamol sulphate particles. They concluded that particle surface roughness and particle morphology (buckled or spherical) was more important than γ_s^d , though they did note performance correlations with particle surface acidity.

In a study designed to look at how inhalable particle surface properties could be changed, Davies *et al.* [65] prepared salbutamol sulphate particles via a number of crystallisation routes. This included a traditional cooling crystallisation, an anti-solvent crystallisation as well as crystallisation in the presence of model pulmonary surfactants under carefully controlled conditions. A number of these approaches had a significant impact on the γ_s^d distributions, including most interestingly the anti-solvent crystallisation. This process resulted in a very heterogeneous surface energy distribution, though the surfactant coated particles also had higher γ_s^d distributions compared to most other materials.

MILLING

A large number of studies have reported significant differences in the surface energy of milled pharmaceutical powders. A set of seminal references were published in the mid 1990's by Ticehurst and co-workers on this topic [66-68]. Using IGC they established the changes in γ_s^d for milled of salbutamol-sulphate, *dl*-propranolol hydrochloride and α -lactose monohydrate materials [66]. In the case of industrial salbutamol-sulphate samples they showed that two materials subjected to differing milling regimes differed by a factor of 10 approximately in surface area, with the high surface area material having a γ_s^d of 83 mJm⁻² whilst the low surface area solid had a value less than 1/2 of this. These workers have sensibly packed both IGC samples with the same sample surface area, so that the IGC data represent vapour adsorption measurements at the same surface coverage for both samples. They also established that the acid-base adsorption behaviour of both samples also differed significantly. Using the same experimental approach these workers also studied a series of nominally equivalent batches of α -lactose monohydrate [67]. They concluded that all γ_s^d values were in the range of 40-44 mJm⁻². They did note small changes in the values for

ΔG_A^{sp} for a series of acid-base probes. However, it is unclear if these differences in ΔG_A^{sp} are experimentally significant. Finally, York *et al.* [68] examined 5 sets of *dl*-propranolol hydrochloride powders, including 4 jet milled samples. As particle size decreased from 75 to 8.3 μm , γ_s^d increased from 45 to 61 mJm⁻². Though for 6.6 μm , γ_s^d slightly decreased to 57 mJm⁻²; error bars and uncertainties were not reported, so this difference may or may not be significant. The authors also reported some fairly clear linear trends in ΔG_A^{sp} for dichloromethane and THF adsorption as a function of log particle size. The surface properties determined were discussed in terms of the different crystal facets present on *dl*-propranolol hydrochloride and their attachment energies as predicted by computational models.

An early study on the milling of α -lactose monohydrate and surface energy as determined using IGC was reported by Newell *et al.* [69]. These workers examined differences in γ_s^d due to processing induced disorder so as to understand the effects of disorder on lactose particle surfaces. The milling process created 1% of the amorphous lactose, and γ_s^d was 31.2, 37.1 and 41.6 mJm⁻² for crystalline, spray dried and milled lactose, respectively. However, a physical mixture of crystalline (99%) and amorphous (1%) material had a dispersive surface energy of 31.5 mJm⁻². Newell *et al.* [70] then studied changes in the surface energy of amorphous α -lactose monohydrate as a function of relative humidity. γ_s^d decreased with increasing %RH for amorphous spray dried α -lactose monohydrate, whereas a milled α -lactose monohydrate exhibited the same trends, though the γ_s^d values were about 5 mJm⁻² higher. This study is significant as it establishes that the percentage of amorphous material present implies no information about the distribution of amorphous material in a powder. In this study a mixture of 1% of particles which were purely amorphous was compared to a powder which had the 1% total amorphous content probably spread across the surface of many particles via milling. These two 1% amorphous powders had differing surface γ_s^d values with the 1% physical mixture having effectively the γ_s^d of the unmilled material. This work also serves to remind us that IGC data is most sensitive to the sur-

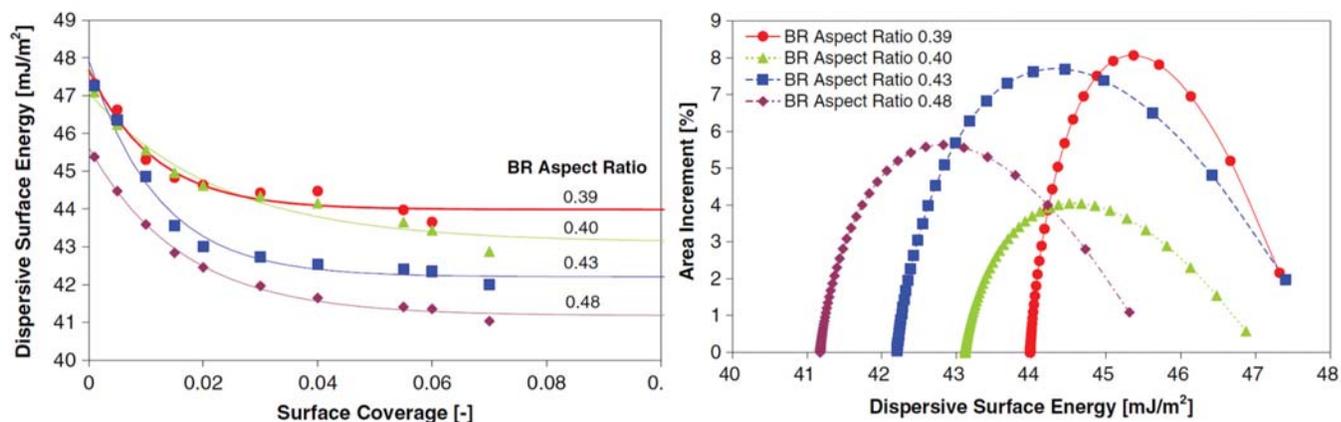


Fig. (11). γ_S^d profiles of milled d-mannitol sieve fractions as a function of bounding rectangular aspect ratios and γ_S^d , obtained by 'area under curve' method, for milled d-mannitol sieve fractions [62].

face area of the sites available for vapour adsorption, not their bulk mass present. That is, IGC is generally a surface based phenomena first and foremost.

The milling of cefditoren pivoxil has been studied by Ohta and Buckton [71]. Material milled for 1 minute had a γ_S^d of 56.2 mJm⁻² whereas γ_S^d decreased to 45.8 mJm⁻² after 30 minutes of milling. γ_S^d for the crystalline starting material was 52.3 mJm⁻². The effect of milling also showed a clear increase in K_D/K_A values with increasing milling time, indicating that the powder surface was becoming more basic during milling. Changes in K_D/K_A with increasing milling time were directly correlated to sample crystallinity- see Fig. 12

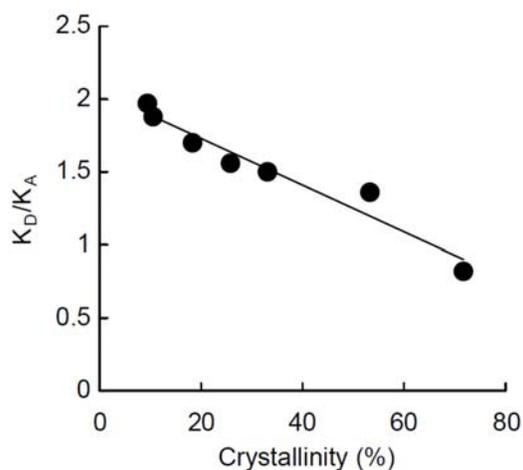


Fig. (12). The relationship between crystallinity and K_D/K_A ratios for cefditoren pivoxil [71].

Das and Stewart have examined the changes in γ_S^d as well as acid-base surface energy distributions for both milled and unmilled indomethacin [72]. They also observed that the γ_S^d surface energy distributions for the milled materials gave higher γ_S^d curves than the as received unmilled material. Significant differences in acid-base surface properties were also reported by the authors for the different material forms.

A study on the surface energy for a series of different milling methods have been reported by Luner *et al.* [73] for succinic acid and sucrose. The specific focus of the study was to identify the impact of high shear wet milling in the presence of different solvents, compared to dry impact milling. Fig. 13 below summaries the major findings of this work. Wet milling created the high surface energy solids followed by the dry milled solids and finally the crystalline starting materials. Sucrose wet-milled in ethanol showed the highest γ_S^d , 90 mJm⁻², which is almost 3-fold higher than that of the unmilled particles. Such significant changes were not expected and as of yet cannot be fully rationalised, though the authors have considered a number of potential explanations.

The surface energy and solubility of ursodeoxycholic acid powders produced following vibratory milling has been reported by Chung *et al.* [74]. Contact angle data indicated that materials which were vibration milled had much higher polar surface energies, and thus surface polarities, compared to both jet milled and as received powders. In general, a correlation between increased drug solubility, decreased crystallinity with increased surface polarity was reported. Gamble *et al.* [75] have investigated the impact of micronisation on the measured surface energy characteristics of Ibipinabant. Micronisation led to an increase in the measured γ_S^d of the drug substance with increasing micronisation energy. The increase in γ_S^d was concluded to be due to the generation of new, higher energy surface sites.

The blending of micronised salbutamol sulphate (SBS) with different concentrations of magnesium stearate (Mgst) and glycerol monostearate (GMS) was followed by co-milling with an air jet mill was recently reported [76]. This method could be used for the surface modification of inhalable drugs particles so as to change inter-particulate forces balance between active ingredient and carrier particles. However, it should be noted that the reliable interpretation of IGC data for such complex multicomponent powder/chemical systems is clearly more problematic due to the multiple potential surface species being sensed. Stank and Steckel [76] concluded that γ_S^d of SBS is lowered using such a process and that the γ_S^d distributions are more homogenous for the co-milled samples (see Fig. 14):

In a recent study Olusanmi *et al.* have examined the detailed powder properties for a set of milled APIs [77]. They showed that API surface energies increased directly with the extent of powder milling. An examination of the powder blending process revealed

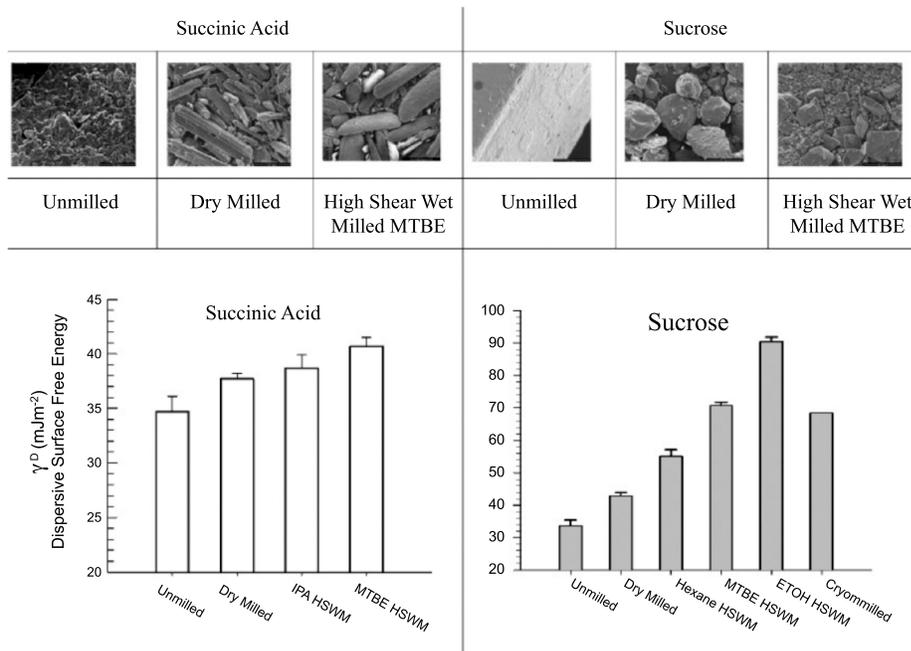


Fig. (13). Surface energy of wet milled succinic acid and sucrose [73].

that the powder wall friction angle was directly correlated with γ_s . It was concluded that the data presented in this study indicates that surface energetics may not be the main factors governing the blending of particulate materials.

POWDER ENGINEERING

The surface properties of magnesium stearate coated α -lactose monohydrate powders as prepared by a mechanical dry processing method was reported by Zhou *et al.* [78]. The untreated and the mechano-fused lactose particles visually appeared very different under SEM, with the mechano-fused materials having a 30% lower BET surface area. γ_s^d surface energy distributions showed some heterogeneity for the mechano-fused lactose particles, with the high coverage γ_s^d being 37 mJm⁻², very close to γ_s^d of pure magnesium stearate; 36 mJm⁻². The untreated materials exhibited a higher but very constant γ_s^d of 45 mJm⁻². Data was also reported for acid-base surface energies, though these estimates seem to be very high. This may be due to using IGC data from low surface coverages to estimate high surface coverage properties. For energetically homogeneous surfaces such an analysis may be acceptable, but for energetically heterogeneous surfaces this could easily lead to overestimates of acid-base properties which are typically very surface coverage dependent. A similar study has been reported by Swaminathan *et al.* [79] for magnesium stearate coated α -lactose monohydrate powders and microcrystalline cellulose (MCC). These authors reported the more conventional single values for γ_s^d of their powders at nominal infinite dilution IGC conditions of 66.8, 41.1 and 40.6 mJm⁻² for MCC, lactose and magnesium stearate respectively. For the MCC-magnesium stearate powder mixtures, γ_s^d changed with blend operating conditions, trending to lower values of γ_s^d similar to plain magnesium stearate with increased mixing times. The authors concluded that γ_s^d could be used a measure of a successful coating process. A word of caution should be added here. For these powder mixtures both excipient and magnesium stearate particles are pre-

sent and therefore changes in γ_s^d measured reflect changes the numbers of the differing surface sites present on which vapour adsorption can occur. In this study this could be because of good blending (when the lubricant was homogeneously dispersed) but could also occur by simply increasing in the surface area of lubricant particles present.

Das and Stewart examined the changes in γ_s^d surface energy distributions for mechano-fused magnesium stearate with α -lactose monohydrate as well as Turbula mixture of the same powders [72, 80]. In both cases γ_s^d distributions for α -lactose monohydrate-magnesium stearate mixtures differed from the original starting materials. Interesting the mechano fused α -lactose monohydrate had a lower γ_s^d surface energy distribution than any other powder including the α -lactose monohydrate and magnesium stearate. This difference was argued to be possibly due to surface group reorientation in the magnesium stearate film which occurred during particle compression/processing. Data was also reported for acid-base surface energies, though these estimates seem to be very high, possible due to the use of low surface coverage data being used. Fig. 15 shows the significant variations in γ_s^d distributions which can result from mechanofusion. The γ_s^d surface energy distributions were found to be consistent with the observed flow behaviour of these surface treated powders

Surface energy distributions have been recently reported for an API powder system coated with two different high surface area SiO₂ powders [81]. This study specifically considers the use of IGC data for binary powder systems and the authors showed that differing γ_s^d distributions were obtained for the uncoated powder, as well as differing API-SiO₂ powder systems. This very detailed study considers the important question as to whether the surface of the API particles is passivated by the presence of the SiO₂ powders. Due to the competing effects of surface energy, number of surface sites present and affinity of the vapour adsorption probes for these differing sites on the γ_s^d distributions obtained, precise inter-

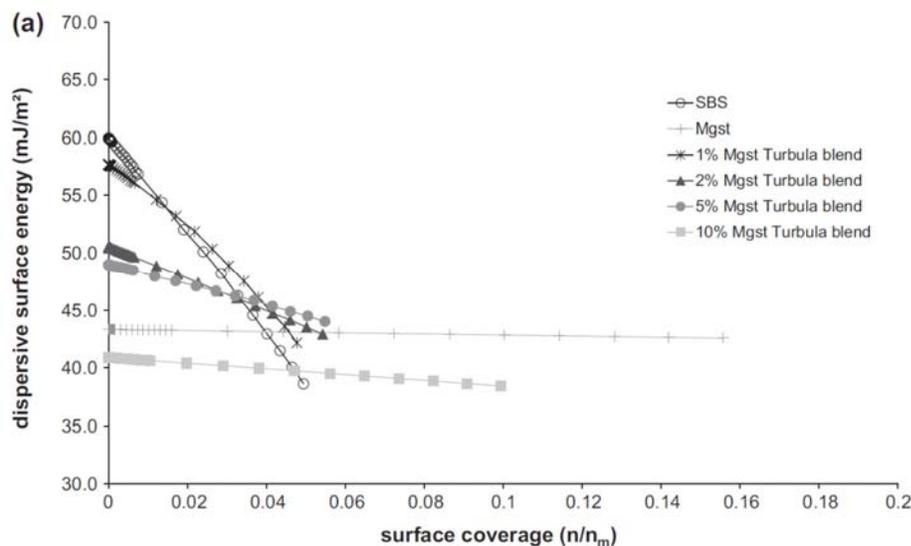


Fig. (14). γ_S^d surface energy distributions, SBS-Mgst co-milled [76].

pretation of such complex phenomena can be challenging. The authors concluded in this case that the API surface was not being passivated by the SiO_2 powders present.

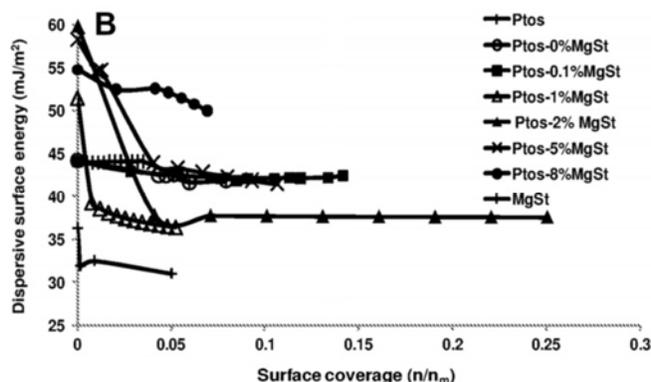


Fig. (15). γ_S^d distributions for Lactose (Ptos) before and after Ptos mechano-fused with 0.1%, 1%, 2%, 5% and 8% magnesium stearate (Mgst) [80].

A key question was recently addressed via a systematic investigation of the influence of dry coating on surface energy of milled pharmaceutical crystals [82]. The observed very high cohesion of milled powders contrast significantly to the improvements observed after dry coating of such materials with nanoparticles. Uncoated micronised ibuprofen showed increased γ_S^d distributions with increasing milling intensity, in contrast, dry-coated milled powders showed a significant reduction in the γ_S^d values. The authors reported that physical mixtures of uncoated micronised ibuprofen and silica exhibited no reduction in surface energy, indicating that dry coating is necessary for the passivation of high-energy sites of ibuprofen created during micronisation. Specifically, dry coatings lead to decreased cohesion and improved flowability because of reduced levels of γ_S^d and the creation of nano scale surface roughness. Detailed surface energy measurements show that an API such as ibuprofen, being crystalline, has higher surface energy as well as increased surface energy heterogeneity as it was made into finer par-

ticles via milling. In contrast, dry coating with nanosilica uniformly reduced the surface energy to a point that the surface energy of 5 μm ibuprofen particles is almost the same as the original 58 μm ibuprofen particles using hydrophobic silica. This silica appears to “quench” high-energy sites and reduce surface energy, which is one of the two major roles played by dry-coated silica. This study highlights the importance of surface energy heterogeneity information as key data in understanding the behavior of complex powder mixtures. Though this conclusion is in direct contrast to that of Gamble *et al.* [79], it highlights the sensitivity of IGC for studying these types of complex powder phenomena.

The flowability of a series of surface treated Al powders have been reported by Jallo *et al.* [83]. In their extensive investigation they looked at surface energy, powder flow, interparticle adhesive forces. Fig. 16 shows the correlation between powder adhesion and acid-base surface energetics they reported.

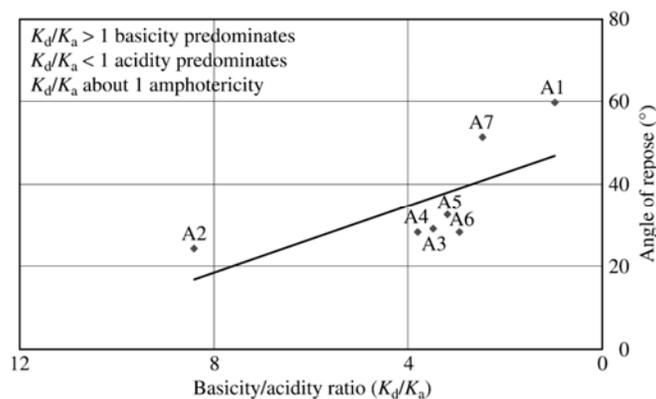


Fig. (16). The relationship between the Angle of Repose and surfaces basicity/acidity. The more basic the aluminum powders, lower the angle of repose which correlated to better flowability [83].

Burnett *et al.* [84] have investigated the effects of quench cooling and ball milling on the surface energy heterogeneity and surface chemistry of crystalline indomethacin (IMC). The surface energy distributions of crystalline, quench cooled and milled IMC samples are shown below in Fig. 16. The quench cooled material was fully

amorphous, whereas the milled and crystalline materials processed no amorphous character. γ_s^d data shows that all IMC samples are energetically fairly heterogeneous, meaning the surface energy changes as a function of surface coverage. Milled IMC is evidently the most active surface with the highest surface energy values and highest surface basicity, having higher γ_s^d values across all surface coverages measured. The quench cooled IMC and crystalline IMC had lower values. Quench cooled and crystalline IMC samples possessed wider variations of γ_s^d , highlighting their more heterogeneous surface chemistry (Fig. 17).

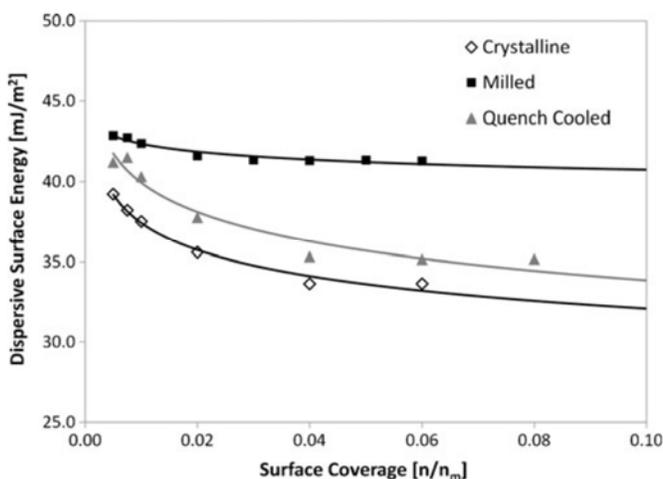


Fig. (17). γ_s^d profiles of three different IMC samples; crystalline, ball milled and melt quenched [84].

Thielmann *et al.* [85] have reported on γ_s^d distributions for milled, recrystallized and as received lactose materials with very similar particle size distributions. Fig. 18 below shows the γ_s^d distributions obtained for the three materials:

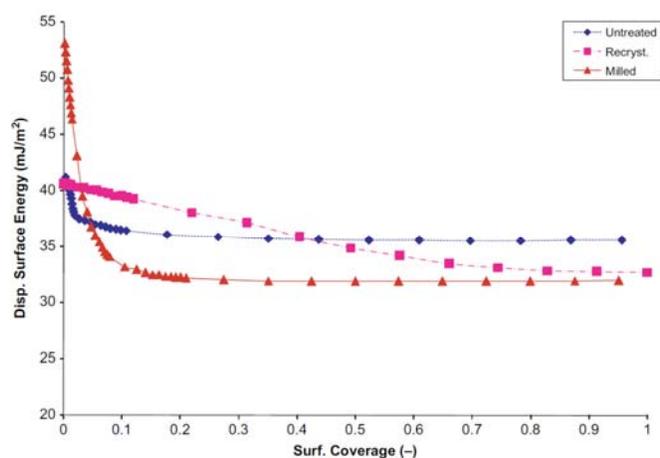


Fig. (18). γ_s^d distributions for crystalline, milled and recrystallised lactose powders [85].

The as received and recrystallized lactose showed a similar values of γ_s^d 's at infinite dilution, though the γ_s^d distributions for the two samples are quite different. For the milled material there is

a shift in the energy distribution of dispersive as well as specific component to higher values, compared to the other two samples. These changes are ascribed to amorphous domains present on the milled crystal surfaces.

Co-crystals are an interesting class of materials which are potential candidates for inhalable drugs. Theophylline co-crystals were prepared with urea (THF-URE), saccharin (THF-SAC) and nicotinamide (THF-NIC) by spray drying by Alhalaweh *et al.* [86]. These powders, as well as some milled materials, were then characterised in terms of the physicochemical properties as well as their inhalation performance when aerosolised from a dry powder inhaler (see Table. IV). Compared to milled theophylline co-crystals, the novel spray dried co-crystals demonstrated considerably lower values of γ_s^d .

Table IV. Surface Energy Properties of Spray Dried (SD) Theophylline Co-crystals and Milled [86].

Material	γ^d (mJ/m ²)	K_A	K_D
SD-THF	41.39±0.42	0.13±0.00	0.02±0.00
SD-THF-SAC	45.70±0.79	0.13±0.00	0.00
SD-THF-Urea	43.23±1.71	0.15±0.00	0.00
SD-THF-NIC	69.98±1.23	0.16±0.00	0.00
Milled THF	60.26±0.42	0.16±0.01	0.00
Milled THF-SAC	49.58±0.20	0.16±0.05	0.00

Facet specific surface energetics of large single crystals of mefenamic acid have been related to the surface energetic profiles of the corresponding powder samples recently by Shah *et al.* [87, 88]. Mefenamic acid crystals with different crystal habits ranging from elongated needles to hexagonal cuboids were obtained by varying the crystallisation conditions. γ_s^d profiles of mefenamic acid powders obtained by IGC for varying crystal habits and were correlated to the relative exposure of different crystal facets. Elongated needle shaped mefenamic acid crystals were found to be about eight times more cohesive as powders relative to hexagonal cube shaped crystals. This powder cohesivity was attributed to the combined effect of differences in the API's surface energy and the surface area Contributions from crystal shape on powder cohesion of mefenamic acid was decoupled from that of surface energy and surface area using a normalisation procedure. Hexagonal cuboid or elongated plate shaped crystals was found to be less cohesive compared to the needle shaped crystals.

OTHER PROPERTIES TRACKED BY SURFACE ENERGY

Hasegara *et al.* [89] have used surface energy and nett retention volume obtained using IGC to follow structural relaxations at the surface of amorphous solid dispersions of indomethacin and PVP. Nett retention volumes decreased by ~15% over a period of 30 hours reflecting changes in the free energy of the system. Traditionally these types of relaxation processes have been successfully evaluated using DSC and isothermal microcalorimetry. These later two approaches measure bulk thermodynamic properties, and specifically enthalpically observable events. By contrast IGC has both a surface focus as well being a technique which measures free energy properties as its primary data set. Structural relaxations clearly pertain to the system moving to a lower free energy state, so the sensitivity of IGC to the surface relaxations is consistent with expectations. IGC showed faster relaxation kinetics to that determined by DSC, indicating that surface relaxations occurred more quickly than bulk relaxations.

A novel use of IGC has been reported by Miyanishi *et al.* [90]. They have followed the surface crystallisation of melt-quenched mixture of crystalline nifedipine and polyvinylpyrrolidone using the

using the nett retention volume for undecane. Though surface energies were not reported here, it is very likely that they too would have been a useful parameter for following the crystallisation kinetics which were then modelled using the Hancock-Sharp and the Avrami-Erofeev equations.

CONCLUSION

It is clear from this review that importance of surface energy is becoming firmly established within the remit of pharmaceutical powders research. Improved experimental methods for measuring surface energy are facilitating this improving understanding of the importance of surface energy in many areas of pharmaceutical powders engineering and formulation. There have been considerable improvement of our understanding within milled materials using IGC methods, and our current understanding of importance of face specific surface chemistry for pharmaceutical solids comes directly from surface energy studies. However, there are many surface properties of powders that are not currently measured reliably such as surface topography or surface charging. We therefore must be realistic and not expect every complex problem in pharmaceutical powder science and engineering to be rationalised simply using surface energy data, but there can be no doubt that it will be an important factor in many cases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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