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Anisotropic Surface Chemistry of Crystalline Pharmaceutical Solids

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ABSTRACT

The purpose of this study was to establish the link between the wetting behavior of crystalline pharmaceutical solids and the localized surface chemistry. A range of conventional wetting techniques were evaluated and compared with a novel experimental approach: sessile drop contact angle measurements on the individual facets of macroscopic (>1 cm) single crystals. Conventional measurement techniques for determining surface energetics such as capillary rise and sessile drops on powder compacts were found not to provide reliable results. When the macroscopic crystal approach was used, major differences for advancing contact angles, θ_a, of water were observed—as low as 16° on facet (001) and as high as 68° on facet (010) of form I paracetamol. θ_a trends were in excellent agreement with X-ray photoelectron spectroscopy surface composition and known crystallographic structures, suggesting a direct relationship to the local surface chemistry. Inverse gas chromatography (IGC) was further used to probe the surface properties of milled and unmilled samples, as a function of particle size. IGC experiments confirmed that milling exposes the weakest attachment energy facet, with increasing dominance as particle size is reduced. The weakest attachment energy facet was also found to exhibit the highest θ_a for water and to be the most hydrophobic facet. This anisotropic wetting behavior was established for a range of crystalline systems: paracetamol polymorphs, aspirin, and ibuprofen racemates. θ_a was found to be very sensitive to the local surface chemistry. It is proposed that the hydrophilicity/hydrophobicity of facets reflects the presence of functional groups at surfaces to form hydrogen bonds with external molecules.

KEYWORDS: Wetting, contact angles, surface chemistry, crystals, physicochemical properties.

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INTRODUCTION

The wetting properties of solids are primarily governed by their surface energetics. Unlike liquid surfaces, solid surfaces cannot be measured by direct surface energy measurement, as a solid surface is rigid. Almost all indirect approaches involve the use of known vapors,[1] liquids,[2] or solids[3] as probes for the solid materials under investigation. In each case, the interaction between the solid and the known external probe may be analyzed in terms of the solid of interest. Accurate and comprehensive knowledge of the surface energetics is vital to improving crystallization techniques and powder processing properties.[4]

Among these approaches, the liquid sessile drop contact angle technique is one of the most common and is sensitive to the outermost molecular layers of the solid surface. The contact angle, which is the angle between the solid surface and the tangent of the liquid drop surface, measured through the liquid phase at the 3-phase (solid-liquid-vapor) contact point, is related to the surface energy of the solid via Young's equation. The solid surface energy is obtained by measuring the contact angles of various reference liquids and performing an appropriate analysis of the data. Wetting behavior and related theories are reviewed elsewhere.[5]

Numerous techniques, depending on the physical form of the material, have been established to determine the surface energies of solids. Conventional methods include sessile drop, capillary rise in a powder bed, air-pressure techniques, Wilhelmy plate, sedimentation volume, film flotation, and vapor probe techniques.[5-8] Most of these traditional methods of characterizing solid materials rely on the sample being packed into a powder bed or column. More recently, atomic force microscopy has also been employed.[9,10]

In this study, both liquid and vapor probe techniques were employed on powdered and macroscopic (>1 cm) crystal samples. For particulate samples, the capillary rise through a powder bed and the sessile drop measurements on powder compacts were evaluated. These are the 2 most frequently used techniques and are thought to be representative of the overall benefits and limitations of powder bed characterization techniques. Vapor probe investigations were conducted using inverse gas chromatography (IGC) operated under infinite dilution conditions. Surface energies obtained from these 2 approaches were then compared with those

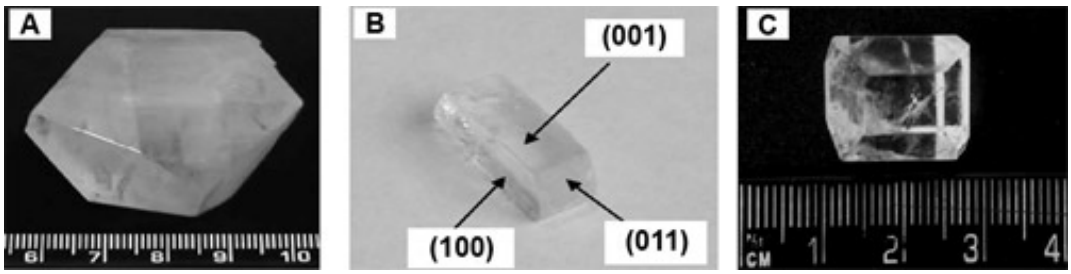

Figure 1. Macroscopic crystals of (a) paracetamol, (b) aspirin, and (c) S-(+)-ibuprofen.

calculated from sessile drop contact angles on macroscopic single crystals. This article has several aims:

- To establish the validity and suitability of experimental methods for determination of surface properties of pharmaceutical solids.
- To measure the wetting behavior of crystalline solids, including polymorphs and racemic compounds, and establish the link between face-specific wetting behavior and localized surface chemistry.
- To determine the effects of manufacturing operations, such as milling, on the surface properties of pharmaceutical solids.

Materials and Methods

Materials

Paracetamol (98% purity) and aspirin >99.5% purity were obtained from Sigma-Aldrich (Poole, UK). Ibuprofen was obtained from Shasun (London, UK), and S-(+)-ibuprofen was obtained from Acros Organics (Geel, Belgium). Methyl alcohol and acetone (>99.9%, Sigma-Aldrich) were used for the preparation of single crystals.

Powder Compact Preparation

Dry powder compacts were prepared with an LR5K mechanical test instrument (Lloyds Instruments, Fareham, UK) with a 20-mm-diameter stainless steel die and punch. Approximately 3 g of powder was poured into the die for compaction, and the assembly was tapped for 1 minute to minimize density fluctuations within the die. The crosshead was lowered at a controlled rate of 5 mm/min, and a series of compacts were prepared with maximum compression forces of 10 kN, 20 kN, 30 kN, and 40 kN. Ejection of the compacts was achieved by applying a corresponding maximum compression force with the crosshead lowered at a constant rate of 5 mm/min. Scanning electron microscope (Jeol Ltd, Herefordshire, UK) images were obtained for the compacts with an accelerating voltage of 20 kV following the gold sputter coating of the samples.

Crystal Growth

Saturated solutions at 20°C were prepared by dissolving paracetamol powder into methanol, and the solutions were stirred until no more solid dissolved. A single seed crystal was then attached to a single aramid fiber (diameter = 10 μm) and suspended in a saturated solution. The saturated solution was then allowed to evaporate slowly over a period of 20 to 30 days, resulting in the growth of a macroscopic single crystal, often greater than 1 cm in length. Crystal images are shown in Figure 1.

The habits of the macroscopic paracetamol single crystals obtained corresponded to those reported in the literature, with major facets of (201), (001), (011), and (110). Crystals were dried under ambient conditions inside an empty beaker before the contact angle measurements were taken. Facet (010), the facet with the lowest attachment energy, was exposed by cleaving the macroscopic crystal perpendicular to the *b*-axis.[11] Advancing contact angles, θ_a, were obtained on freshly cleaved surfaces. The crystallization procedure described here was also tested on several other common pharmaceutical solids. Macroscopic crystal growth was also achieved successfully for aspirin, racemic ibuprofen, S-(+)-ibuprofen, and paracetamol forms I/II. In this article, θ_a for water on macroscopic single crystals of aspirin, racemic ibuprofen, S-(+)-ibuprofen, and paracetamol forms I/II is reported.

Capillary Rise Measurements

The capillary rise of liquid into a powder bed was measured with a tensiometer (K100, Krüss GmbH, Hamburg, Germany). An FL12 Powder Cell (Krüss GmbH) was filled with 1 g of paracetamol powder, and the data were recorded by the Krüss software (version 2.0.1, Krüss GmbH). Experiments were repeated at least 8 times for each liquid probe used.

Sessile Drop Measurements

Contact angles were obtained on powder compacts and on macroscopic single crystals, with at least 8 contact angle measurements being taken for each probe liquid on the samples. Measurement of the contact angles on tablets was performed immediately after compaction. Initial drops of 5 μL were dispensed onto the solid surface and their drop shape profiles fitted automatically. As liquid was continuously added onto the droplet, θ_a was obtained with a Krüss Drop Shape Analysis (DSA 10, Krüss GmbH) instrument. The syringe

remained immersed within the top half of the droplet. Measurements were conducted in open air at 20 ± 2°C with deionized water.

IGC

Particulate samples were packed into presilanated glass columns (4 mm Internal Diameter (ID)) with silanated glass wool end frits. Samples were pretreated at 303 K and 0% relative humidity for 2 hours to remove any residual moisture and solvent. A series of alkane vapors (undecane, decane, nonane, and octane) were selected and used as probes for the dispersive surface free energy. Methane gas was used as a noninteracting probe to determine the dead time of the column. The probes were injected under infinite dilution (4% p/p_0) conditions, and the retention volumes were determined with a peak maximum analysis using an SMS-iGC 2000 (Surface Measurement Systems Ltd, London, UK) instrument. The dispersive component of the surface energy of paracetamol was calculated according to the Schultz et al[12] method using the SMS-iGC analysis software (version 1.2, Surface Measurement Systems Ltd).

X-ray Photoelectron Spectroscopy

X-ray photoelectron (XP) spectra were recorded using a high-vacuum X-ray photoelectron spectroscopy (XPS) instrument (Kratos AXIS HSi, Manchester, UK) equipped with a charge neutralizer and a Mg K_α X-ray source. C, N, and O 1s spectra were acquired at a 40-eV pass energy with 2-point energy referencing employed using adventitious carbon at 285 eV and the valence band. All spectra were Shirley background-subtracted and fitted using a Doniach-Sunjic profile convoluted with a Gaussian/Lorentzian (4:1) mix. Similar line shapes were employed for all C, N, and O 1s components, with respective full width at half maximum (FWHM) of 1.65, 1.69, and 1.76 eV unless otherwise stated. Fitting was performed using CasaXPS Version 2.0.35 software (Kratos, Manchester, UK) using the minimum number of peaks required to minimize the R factor.

Results and Discussion

Capillary Rise

Washburn et al[13] pioneered the wettability characterization of powders. Their analysis was achieved by measuring the liquid penetration rate into a powder bed. This analysis requires that the liquid be nonreactive with the sample and that a range of liquids with differing surface tensions be used. Characterization of powders by the capillary rise method is primarily based on the Washburn equation:

$$h^2 = \frac{r\gamma_{LV}\cos\theta}{2\eta}\cdot t \qquad (1)$$

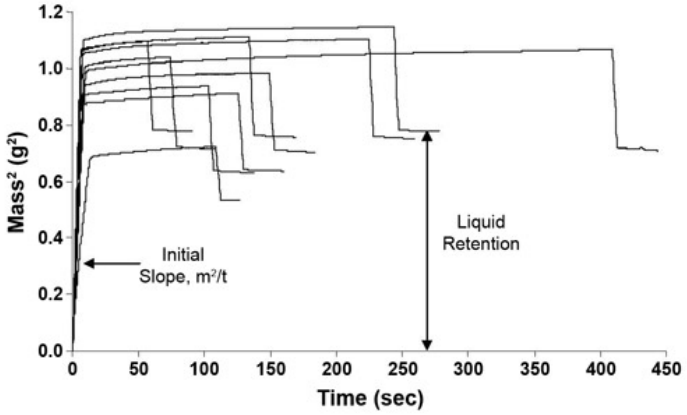

Figure 2. Weight rise curves for n-hexane as a function of time for paracetamol powders.

where h is the distance traversed by the liquid in time t, and r is the effective interstitial pore radius. γ_{LV} and η are the surface tension and viscosity of the liquid, respectively. When the liquid mass gained is measured, the Washburn equation can be expressed as follows[14]:

$$\frac{m^2}{t}\cdot\frac{\eta}{\rho^2} = K\gamma_{LV}\cos\theta \qquad (2)$$

with K, the capillary constant, representing the geometry of the porous network. By plotting the normalized wetting rates, $[\eta/\rho^2][m^2/t]$ versus liquid surface tension, γ_{LV}, one can calculate the capillary constant K and contact angles. K is calculated from the complete wetting case where $\theta = 0$, while the contact angles measured for the partial wetting case are calculated based on the previously obtained K. The capillary rise techniques have also been used to characterize pharmaceutical powders.[8] However, the reproducibility of column packing and the poorly defined effective pore radius have often raised speculation about the accuracy of the experiments. For example, swelling of the bed can change the effective pore radius.[14,15] The wettability of powders can also be evaluated by measuring the air pressure required to halt capillary penetration.[16,17] The applicability of this technique is limited by the same constraints that limit the other capillary techniques.

Figure 2 shows the weight gain curves for the fully wetting case using hexane, a nonpolar probe liquid. Liquid penetration into the bed occurred immediately when the bed was brought into contact with the probe liquid, and the mass increase due to liquid capillary rise occurred over the next several seconds, then plateaued. When no further change in mass was detected, the liquid reservoir was removed from contact with the cell and a drop in mass was observed. This final mass was the total liquid mass uptake or liquid retention by the powder bed. The $[m^2/t]$ was then obtained by fitting the curve and differentiating with respect to time at

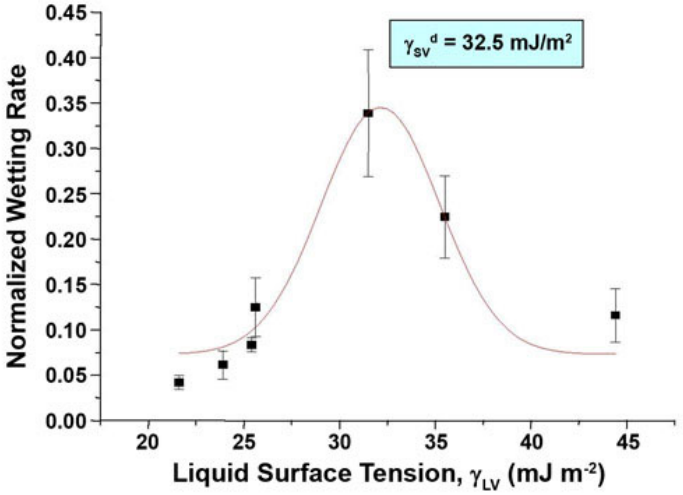

Figure 3. Normalized wetting rates for nonpolar probe liquids for ibuprofen powder bed.

t = 0 seconds. The weight rise curves obtained are very reproducible, especially considering that a new powder sample was used for each measurement. Initial concerns that irreproducible powder packing within the cell would compromise the quality of the data obtained seem to have been unfounded.

The surface energy of the solid particles was obtained by plotting a normalized wetting rates plot, analogous to the classical Zisman approach. To analyze the dispersive surface energy component as measured by the capillary rise method, a normalized wetting rate for nonpolar liquids only was plotted. In the analysis of the dispersive surface energy of paracetamol and ibuprofen powder (Figure 3), only aliphatic hydrocarbon probes were used for the fully wetted section, while both α-bromonaphthalene and diiodomethane were used for the nonwetting part. Each point represented 1 test liquid used, which was then fitted to the Gaussian equation, with the maximum point on the curve giving the dispersive surface energy of the particulate sample. γ_{SV}^{d}, the dispersive surface energy, of paracetamol and ibuprofen was found to be 40.0 mJ/m^2 and 32.5 mJ/m^2, respectively.

IGC

IGC is simply the inverse use of conventional gas chromatography (GC), in which a column is packed with an *unknown* solid sample and *known* vapor probes are injected into the column via an inert carrier gas. The retention time of the probe molecules is recorded by a GC detector, which allows the retention volume and then the partitioning coefficient for the solid-vapor interaction to be determined. From these primary data, a wide range of physicochemical properties of solid materials (eg, surface energies, acid-base functionality of surfaces, diffusion kinetics, solubility parameters, surface heterogeneity, phase transition temperatures) may be determined.[18,19]

To examine the surface energies of pharmaceutical solids, several research groups have studied the infinite dilution retention behavior of organic vapor probes using IGC.[20-22] For infinite-dilution IGC in the Henry's law region, the chromatogram peaks obtained are symmetrical (Gaussian) and V_R^o is given by Equation 3:

$$V_R^o = \frac{j}{m} \cdot F \cdot (t_R - t_o) \cdot \frac{T}{273.15} \qquad (3)$$

where T is the column temperature in Kelvin (K), F is the carrier gas exit flow rate at standard temperature and pressure (STP),t_R is the retention time for the adsorbing probe, t_o is the mobile phase holdup time (dead time), and j is the James-Martin correction. V_R^o can be related to the free energy of adsorption by Equation 4:

$$-\Delta G^o = RT \ ln \ V_R^o + K = N_A \cdot a \cdot W_A \qquad (4)$$

where R is the universal gas constant, K is a constant, N_A is Avogadro's number, a is the cross-sectional area of the adsorbed molecule, and W_A is the work of adhesion.[18] The evaluation of the dispersive component and the acid-base properties of the solid from the retention volumes is described in detail elsewhere.[23]

The surface properties of both paracetamol and ibuprofen powder (as received) were measured by IGC at infinite dilution via pulse injections. The Schultz et al[12] method was used to calculate the dispersive surface energy, γ_{SV}^{d}. The plot of RT lnV_R^o versus a$(\gamma_L^{d})^{1/2}$ shown in Figure 4 for paracetamol and ibuprofen gives γ_{SV}^{d} = 39.8 mJ/m^2 and 31.7 mJ/m^2, respectively.

It is evident that γ_{SV}^{d} values from the IGC technique for paracetamol are similar to those obtained from the liquid capillary rise technique. In a powdered sample, it is expected that the facet with the weakest attachment energy will be preferentially exposed as particle size is reduced. This similarity therefore could be due to the dominance of the weakest attachment energy facet.

It is notable that the IGC technique was able to distinguish small, subtle variations in sample batches.[20] In pharmaceuticals, IGC investigations have included batch-to-batch variations, effects of milling, crystal habits, optical forms, production routes, and effects of humidity on materials properties. A detailed analysis of the γ_{SV}^{d} of milled crystals and unmilled fine crystals grown from different solvents (methanol and acetone), as a function of their particle size, is summarized in Figure 5.[24]

In the case of the single crystals grown from solution, small differences in γ_{SV}^{d} were observed for crystals grown from

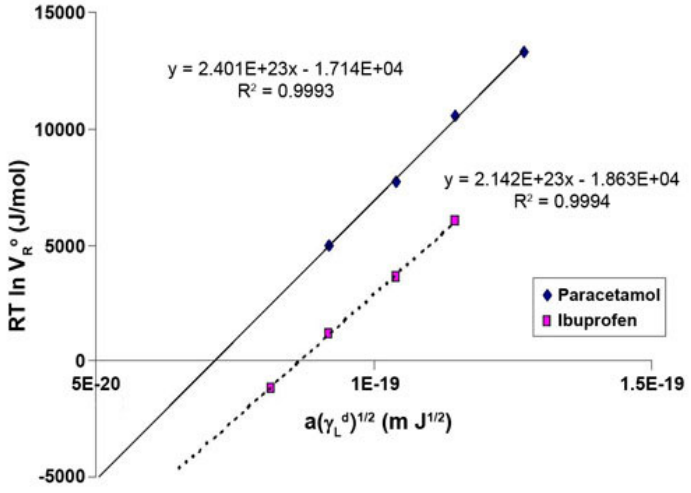

Figure 4. Free energy of adsorption (RT ln V_R) as a function of the dispersive energy of probe vapor, $a(\gamma_L^d)^{1/2}$, for paracetamol and ibuprofen.

methanol and acetone solutions. These γ_{SV}^d values were, however, very similar to those obtained by liquid sessile drop contact angle measurements on the external facets of a macroscopic single crystal.[25] Unlike those of the milled samples, the γ_{SV}^d values of both sets of fine crystals grown from methanol and acetone solution were found to be independent of their particle size. At all size fractions, their γ_{SV}^d values were lower than those of the milled samples. The γ_{SV}^d of facet (010) as measured by diiodomethane contact angles was 45.1 mJ/m^2.[25] This result reconfirms that facet (010) was not initially present in the native crystal and was exposed only upon milling, with increasing dominance as particle size was reduced.

Sessile Drop

Sessile Drop on Compacts

The sessile drop method is a simple, straightforward procedure that is sensitive to the first 10 Å (1 nm) of a surface.[2] A liquid drop is placed on a surface and a tangent aligned at the 3-phase point to obtain the contact angle. To obtain the advancing contact angle, θ_a, the liquid front has to advance over fresh surface, which is achieved by increasing the drop volume slowly. Decreasing the volume allows the receding contact angle, θ_r, to be obtained. While this method is relatively straightforward, having a smooth, flat, and homogeneous surface is ideal. The applicability of this method is further complicated by the existence of contact angle hysteresis, which is defined as the difference between θ_a and θ_r and occurs mainly because of surface roughness and heterogeneity effects.[26]

Contact angle determination of organic powders by the sessile drop method is traditionally performed on powder compacts or tablets. The mechanical fabrication of these powder compacts is known to cause surface deformations,[7] and thus the contact angles measured may not represent the true equilibrium surface energy of the particles. Furthermore, powder compacts have a rough surface topography and are porous, leading to liquid penetration into the tablets as well as swelling effects.

Several researchers have reported sensible and comparable results for powder compacts, with paracetamol giving a surface energy of 46 ± 2 mJ/m^2.[8] However, it was observed here that measured contact angles on powders compacted at 10 kN, 20 kN, 30 kN, and 40 kN were not successful. In this study, the liquid drops of water and diiodomethane placed on compacted tablets penetrated almost immediately upon contact and no equilibrium contact angle was measurable. A time series of liquid drop penetration images on a paracetamol tablet formed under 20 kN compaction pressure are shown in Figure 6. In other studies, it has been reported that dramatic changes in θ for water on paracetamol compacts were observed, with a change in θ from 35° to 0° in 40 seconds.[7] Our study reports that complete penetration of the test liquids occurred within the first 5 seconds, with increasing penetration times for higher compaction pressures. Scanning electron microscopy images (Figure 7) confirmed the obvious conclusion that tablet surfaces are porous, leading to the rapid liquid penetration.

The compacted surfaces studied here also exhibited extensive plastic deformation that was more pronounced at higher compaction pressures, rendering such surfaces unsuitable for characterization. As such, even a measurable θ on a tablet surface might represent the characteristics of not the true equilibrium paracetamol surface but a deformed surface. However, characterization using this method on tablets continues to be reported in the literature, even though doubts have been raised about the validity of such contact angle data.[8] Therefore, results from such approaches should be interpreted with caution. The potential reasons for the poor results obtained here are numerous, but there can be no doubt

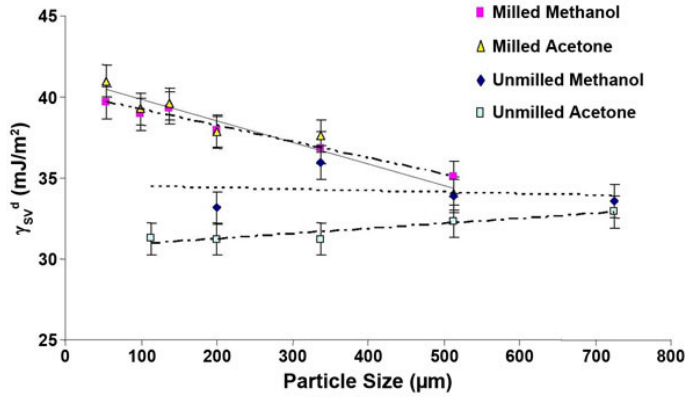

Figure 5. Variation in γ_{SV}^d for milled and unmilled paracetamol crystals as a function of particle size.

Figure 6. Penetration of water droplet into 20 kN paracetamol compacts at (a) 0 ms, (b) 950 ms, and (c) 1950 ms.

that paracetamol did not yield equilibrium θ_a; therefore, such data are clearly invalid for surface energy analysis. The most obvious way of obtaining surfaces large and nonporous for the sessile drop technique is by growing macroscopic-sized single crystals.

Sessile Drop on Single Crystals

The θ_a of probe liquid water on the major facets of form I and form II paracetamol, aspirin, racemic ibuprofen, and S-(+)-ibuprofen crystals is summarized in Table 1. θ_a was found to be facet-specific and dependent on the local surface chemistry. Large variations in θ_a were observed: in the case of water, it was as low as 16° on (001) and as high as 68° on (010) for paracetamol form I single crystals. Similarly large variations in θ_a were observed for all other crystalline systems investigated. Differences in θ_a reflect the specific surface chemical interactions between liquid probes and the solid surface, clearly demonstrating the anisotropic wettability of pharmaceutical crystals. These trends in θ_a were in excellent agreement with surface energetics, surface polarity, XPS surface composition, and crystallographic structures, suggesting a direct relationship between the local surface chemistry and the wetting behavior.[25] We propose that the hydrophilicity/hydrophobicity of facets is significantly dependent on the ability of -OH groups at surfaces to form hydrogen bonds with external molecules in the case of paracetamol (Figure 8).

This anisotropic observation is not limited to paracetamol form I but was also observed for the metastable form II of paracetamol,[27] aspirin,[28] racemic ibuprofen, and S-(+)-ibuprofen single crystals. Variations in the wetting and surface energetics of a pair of organic polymorphic solids (paracetamol form I and form II) were also observed. It is well known that different forms of solid-state polymorphic materials exhibit diverse physicochemical properties,[29] and this study shows that surface properties are also variable. Not only was the wetting behavior found to be anisotropic, but the differing polymorphic forms exhibited significant variations in their wetting behavior for the same Miller-indexed faces.[27]

XPS

XPS is the technique of choice for surface composition analysis for organic materials. XP spectra were recorded on individual facets of the macroscopic single crystals. A detailed analysis of the relative contributions of the functional groups is presented here to qualitatively compare the chemical properties of the facets. High-resolution scans of the C, O, and N 1s XP spectra for paracetamol's most hydrophilic external facets (001) and the weakest attachment energy facet (010) are shown in Figure 8. The relative intensity ratio of (C=O + C-OH):CH_x groups determined from the C 1s spectra varies greatly, being highest for the facet (001) and an order of magnitude lower for the facet (010). This

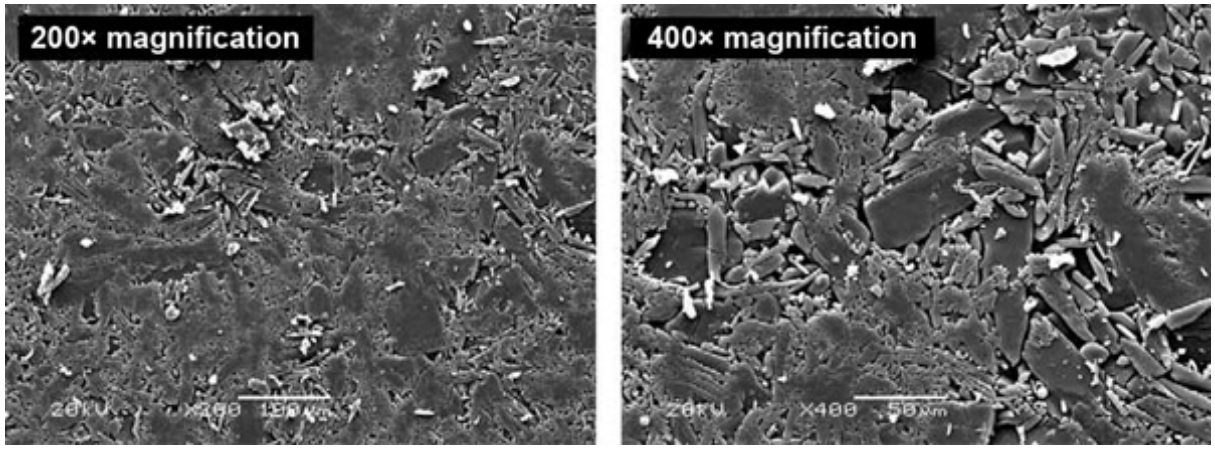

Figure 7. Scanning electron micrographs of paracetamol tablet compacted at 20 kN.

Table 1. θ_a for Probe Liquid Water on Crystalline Facets of Macroscopic Single Crystals

	Advancing Contact Angle, θ_a (Deg)				
Facet	Paracetamol Form I	Paracetamol Form II	Aspirin	Racemic Ibuprofen	S-(+)-Ibuprofen
(201)	38.1 ± 4.6	—	—	—	—
(001)	15.9 ± 3.1	**64.5 ± 3.5***	60.7 ± 3.5	68.5 ± 4.8	64.5 ± 3.9
(011)	29.8 ± 5.7	—	42.9 ± 4.8	46.9 ± 5.5	—
(110)	50.8 ± 4.9	16.6 ± 1.4	—	—	48.4 ± 4.0
(010)	**67.7 ± 2.5***	17.9 ± 2.5	—	—	—
(100)	—	—	**52.9 ± 2.5***	**77.2 ± 4.0***	**70.7 ± 3.1***

*Bolded data are values for the weakest attachment energy facet. (—) indicates that no such facet was present in the macroscopic crystal.

demonstrates that there are significant differences in the distribution of surface groups over the different facets of paracetamol crystals and that these differences are manifested in the anisotropic wetting behavior noted previously.[25,30] The predicted surface polarity of paracetamol facets determined by XPS based on the relative intensity ratio is proposed to decrease in the order (001) > (011) > (201) > (110) > (010), which is in excellent agreement with contact angle analysis. XPS data have successfully shown the influence of surface chemistry at specific planes of a complex organic crystalline material in governing wetting behavior.

Three different techniques were used in this study: the sessile drop contact angle technique, the capillary rise, and a vapor sorption technique. While the theoretical and experimental difficulties associated with these techniques do not need to be enumerated here, several conclusions may be drawn as follows: the sessile drop technique has long been considered the most surface-sensitive technique. With the inability to measure contact angles of droplets on individual particles, compaction of powders to a form a tablet was thought to provide an alternative substrate for measurement. Such tablets are typically prepared under high pressure but have been found to have deformed surfaces. Our paracetamol compacts were also rough and porous, causing the drops to penetrate into the tablets within a few seconds of liquid contact, resulting in no equilibrium θ_a being obtained. One main conclusion here is that powder compacts are unsuitable for the reliable evaluation of surface chemistry of complex organic solids, as has been previously noted by other works.

For macroscopic single crystals, measured θ_a's were found to differ on all facets examined and were attributed to the variations in local surface chemistry and molecular orientation at the surface. Such comprehensive information about the solid surface properties may prove to be invaluable in improving our understanding of pharmaceutical solids, and the reliable nature of this approach provides a rich level of surface chemical detail for crystalline pharmaceutical

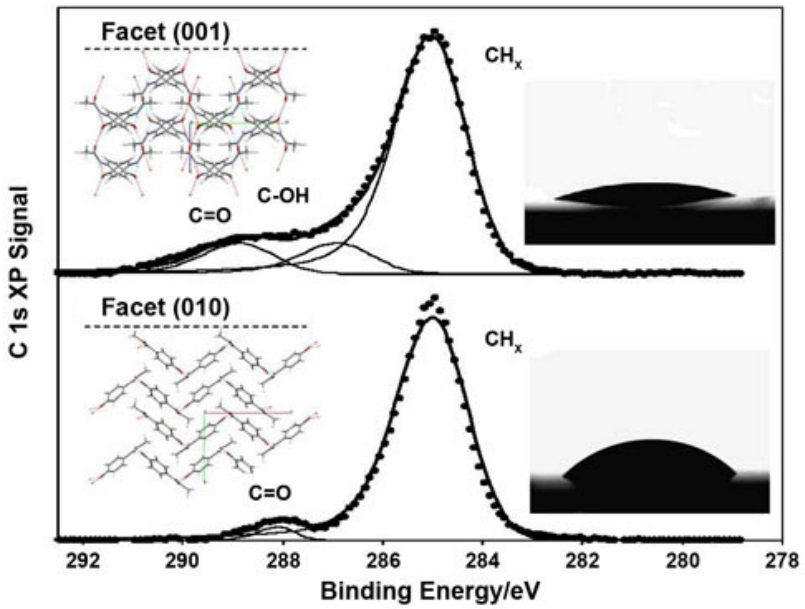

Figure 8. C 1s X-ray photoelectron (XP) spectra and crystal structure (a) top—facet (001), and (b) bottom—facet (010) of form I paracetamol crystal. (Inset: water droplets on crystalline facets.)

solids never previously observed using data obtained from compacts or using capillary methods.

For the commercial paracetamol powders, measurements by both the capillary rise and IGC techniques were found to be in reasonable agreement. However, the results obtained from the capillary rise method should be treated with caution, as the Washburn analysis employs numerous assumptions. The large errors encountered here do not allow small variations in particle properties to be reliably distinguished. Thus, macroscopic crystalline samples are the preferred method.

Though it may not always be viable to grow macroscopic crystals, our experience has been that this task, though time-consuming, is not as daunting as expected. In the more likely event that powdered samples need to be analyzed, a technique for characterization of powdered samples must be chosen. Vapor sorption techniques such as IGC are recommended because the interactions between a gaseous probe and a solid surface are better understood and the experimental techniques are certainly more robust. IGC has been reported to be able to differentiate between the effects of subtle production, processing, and environmental conditions on powders.

CONCLUSIONS

The wetting behavior of crystalline pharmaceutical solids is anisotropic, and θ_a was found to be very sensitive to the local surface chemistry. Conventional measurement techniques for evaluation of particulate surface energetics would at best reveal an average property, perhaps that of the dominant facet. Characterization of macroscopic pharmaceutical crystals using a sessile drop technique reveals a rich mosaic of information on crystal facets, including facet-dependent wettability for a wide range of solids. Milling of crystalline solids exposes the weakest attachment energy facet, and the facet's dominance increases with decreasing particle size, successfully determined by IGC. This facet is also found to be the most hydrophobic.

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