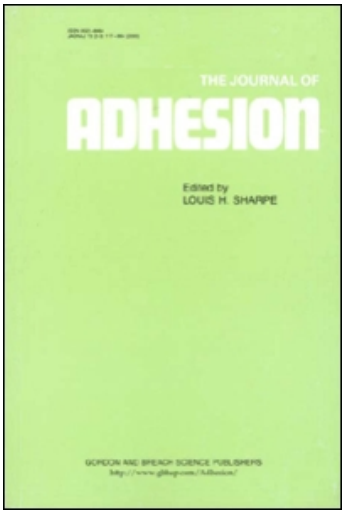

The Journal of Adhesion

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713453635

Wetting Behavior of Ibuprofen Racemate Surfaces

Raimundo Ho[a]; Jerry Y. Y. Heng[a]; Sarah E. Dilworth[b]; Daryl R. Williams[a]
[a] Department of Chemical Engineering, Imperial College London, South Kensington Campus, London, United Kingdom [b] Pharmaceutical and Analytical R&D, AstraZeneca, Macclesfield, Cheshire, United Kingdom

To cite this Article Ho, Raimundo , Heng, Jerry Y. Y. , Dilworth, Sarah E. and Williams, Daryl R.(2008) 'Wetting Behavior of Ibuprofen Racemate Surfaces', The Journal of Adhesion, 84: 6, 483 — 501
To link to this Article: DOI: 10.1080/00218460802161517
URL: http://dx.doi.org/10.1080/00218460802161517

The Journal of Adhesion, 84:483–501, 2008

ISSN: 0021-8464 print/1545-5823 online
DOI: 10.1080/00218460802161517

Taylor & Francis
Taylor & Francis Group

Wetting Behavior of Ibuprofen Racemate Surfaces

Raimundo Ho[1], Jerry Y. Y. Heng[1], Sarah E. Dilworth[2], and Daryl R. Williams[1]
[1]Department of Chemical Engineering, Imperial College London, South Kensington Campus, London, United Kingdom
[2]Pharmaceutical and Analytical R&D, AstraZeneca, Macclesfield, Cheshire, United Kingdom

The wetting behavior and detailed surface energetics of a racemate crystalline system were measured via contact angle measurements and inverse gas chromatography at finite concentrations. The advancing contact angles for water, diiodomethane, formamide, and ethylene glycol were measured on specific facets for racemic ibuprofen and S-(+)-ibuprofen single macroscopic crystals, and were found to be facet dependent for both systems. This observation demonstrates that variation in molecular orientation within the crystal lattice results in variations in exposed surface chemistry for differing facets, which results in anisotropic wetting behavior as previously reported. Surface free energy profiles of the ibuprofen racemates determined using a novel inverse gas chromatography method showed that powder samples (75–150 μm *particle diameter) exhibited relatively homogeneous surface energies, with similar values of* $\gamma_{SV}{}^{d}$ *to those obtained by the contact angle analysis. These results lead us to conclude that ibuprofen exhibited a low level of surface heterogeneity, with the dominant facet of these powders exhibiting a low* $\gamma_{SV}{}^{d}$*, with high energetic sites estimated to be* $<3\%$ *of exposed available surface.*

Keywords: Contact angle; Crystals; Heterogeneity; Inverse gas chromatography; Optical isomers; Surface chemistry; Surface free energy; Wetting

Received 18 October 2007; in final form 26 March 2008.
One of a Collection of papers honouring John F. Watts, the receipient in February 2008 of *The Adhesion Society Award for Excellence in Adhesion Science, Sponsored by 3M*.

Address correspondence to Daryl R. Williams, Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK. E-mail: d.r.williams@imperial.ac.uk

INTRODUCTION

Mirror images of molecules which do not superimpose or have planes or centres of symmetry are termed as enantiomers. Such molecules are capable of rotating the plane of light to the left or right, depending on the enantiomorphic form, denoted by the R and S convention. Crystallization of enantiomers can lead to one of the following, the optically active R or S crystals or, in the case of a mixture of the correct proportions, a racemic compound. Racemism can also be exhibited by a mechanical mixture of two enantiomers of equal proportion, and is termed as conglomerates. In this paper, the detailed surface energetics of an ibuprofen racemic compound and the S-(+)-ibuprofen enantiomer crystals are reported for the first time.

Ibuprofen [2-(4-isobutylphenyl)propionic acid] possesses an asymmetric carbon which gives rise to its chirality. The racemic ibuprofen has quite different thermodynamic properties compared with the S-(+)-ibuprofen. Perlovich *et al*. [1] reported that heats of sublimation of the racemic form and S forms of ibuprofen were 116 and 108 kJ/mol, respectively. This difference is indicative that the former is the thermodynamically more stable form.

Recrystallization of ibuprofen from solution has resulted in various crystal habits being created, with crystals possessing a higher aspect ratio being formed from non-polar solvents. X-ray diffraction studies have revealed similar diffraction patterns for these habits, thus excluding polymorphic modifications during crystallization [2]. Prismatic shaped crystals often possess more favorable tabletting and particulate flow properties as opposed to the needle shaped crystals [3–5]. It has been proposed that these differences in crystal habits are directly due to the variations in the solid-liquid interactions which occur between the crystal and the solution from which they are crystallized [6]. A strong relationship illustrating the importance of these differences in intermolecular interactions is demonstrated by the variable dissolution rates of different ibuprofen crystal habits [7].

An ibuprofen molecule consists of a carboxylic acid group, a benzene ring, and a methyl terminated group. Hence, it may interact with external molecules *via* both dispersive and polar intermolecular interactions. The arrangement of these constituent groups results in the molecule having one hydrophobic end whilst the other end is very hydrophilic (Figure 1).

The surface energies of particulate materials directly influence their adhesive behavior and, consequently, their ability to flow, mill, compact, agglomerate, or be dispersed as solid state materials [8]. Wetting studies with probe liquids are often employed to evaluate

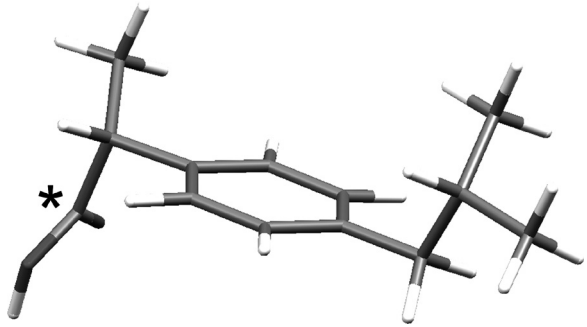

FIGURE 1 Ibuprofen molecule with (*) denoting the chiral centre.

the surface properties of solids by measuring the liquid contact angle [9], which is related to the solid's surface energies *via* Young's equation [10] and various semi-empirical analyses [11–13]. The experimental measurement of the wetting behavior of particulate systems faces numerous experimental and theoretical limitations. It has, therefore, been proposed that these conventional techniques should be abandoned in favor of characterization of large single crystals which provide much better quality of surface chemical information [14].

The wetting literature for organic solids for the past 50 years has been dominated by studies on polymer-based materials [15]. The general observation is that organic solids exhibit isotropic wetting behavior, though our intuitive expectation would be that this assumption should be false for crystalline solids. Our recent work has shown that anisotropic surface chemical behavior for pharmaceutical crystalline solids is the norm, and this could well explain the wide variation in surface properties reported for pharmaceutical crystalline solids [16–18], as well as some of the variability experienced in powder-based processing operations of these types of powders.

EXPERIMENTAL

Materials

Ibuprofen [2-(4-isobutylphenyl)propionic acid] (Shasun, London, UK) and S-(+)-Ibuprofen [(2S)-2-[4-(2-methylpropyl)phenyl]propionic acid] (Acros Organics, Geel, Belgium) were used without further purification. HPLC grade acetone (>99.9% purity, Sigma-Aldrich, Poole, UK) was used for the preparation of macroscopic crystals.

Preparation of Macroscopic Ibuprofen Crystals

Macroscopic single crystals were grown which allowed the direct determination of the facet specific wettability of racemic ibuprofen and S-(+)-ibuprofen. These macroscopic crystals were prepared by slow solvent evaporation from a saturated acetone solution. A single seed crystal was suspended using a single aramid fiber (diameter = 10 μm) in the saturated solution without stirring. The solvent was allowed to evaporate slowly at 20°C over a period of 20–30 days, resulting in crystal growth which ultimately culminated in macroscopically large crystals (length > 1 cm). Their crystal habit is shown in Figure 2. Crystals were dried under ambient conditions before conducting contact angle measurements.

The reported crystal structure of ibuprofen was refined at 100 K and determined by single-crystal pulsed neutron diffraction [19]. Ibuprofen racemate crystallizes in the monoclinic form with four (z = 4) molecules in each unit cell and of $P2_1/C$ space group. The unit cell parameters are as follows: a = 14.397 Å, b = 7.818 Å, and c = 10.506 Å with $\beta = 99.7^\circ$ and were obtained from Cambridge Structural Database (CSD). S-(+)-ibuprofen also crystallizes in the monoclinic form, but with unit cell parameters of a = 12.456 Å, b = 8.036 Å, and c = 13.533 Å with $\beta = 112.86^\circ$ [20].

The unit cell parameters for the systems were used to calculate their interplanar spacing and dihedral angles for facet identification. Crystallographic structure at specific facets was generated from these input files obtained from CSD using mercury (version 1.2.1, CCDC, Cambridge, UK). The structures for racemic ibuprofen and S-(+)-ibuprofen at specific facets are shown in Figures 3 and 4, respectively.

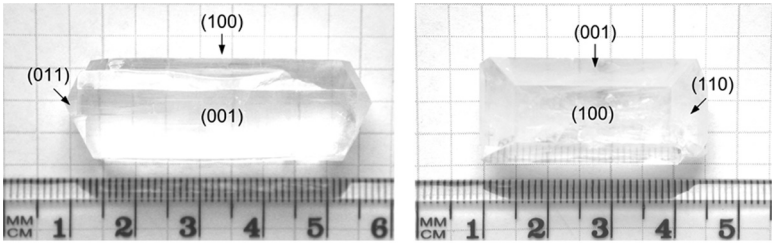

FIGURE 2 Macroscopic crystals of (a) racemic ibuprofen and (b) S-(+)-ibuprofen.

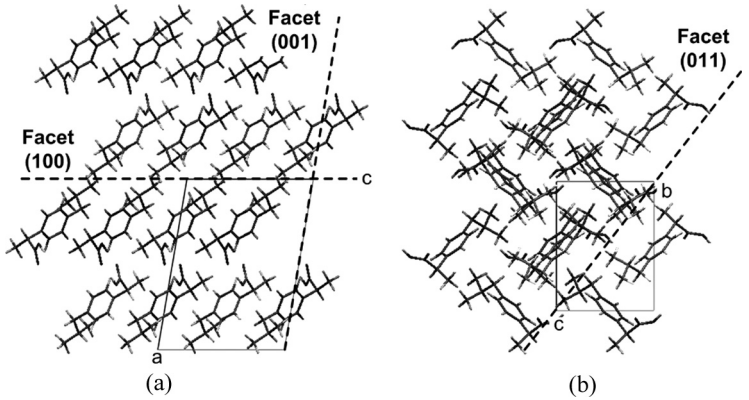

FIGURE 3 Crystallographic structure of racemic ibuprofen crystals viewed along (a) b-axis and (b) a-axis.

Contact Angle Measurement

The advancing contact angles, θ_a, for diiodomethane (>99%, Acros Organics, Geel, Belgium), deionized water, formamide (>99.5%, Acros Organics), and ethylene glycol (>99%, Sigma-Aldrich, Poole, UK) were measured on all available facets of racemic ibuprofen and S-(+)-ibuprofen crystals with a Krüss drop shape analyser (DSA 10, Krüss GmbH, Hamburg, Germany). A minimum of 20 droplets on more than five single crystals were determined for each system. Diiodomethane was purified by passing through chromatographic columns packed with silica (Merck KGaA, Darmstadt, Germany) and alumina (Sigma-Aldrich, Poole, UK).

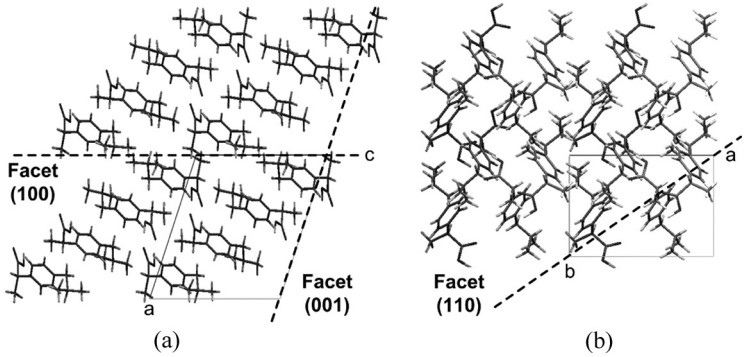

FIGURE 4 Crystallographic structure of S-(+)-ibuprofen crystals viewed along (a) b-axis and (b) c-axis.

Inverse Gas Chromatography (IGC)

IGC experiments were conducted using an iGC 2000 (Surface Measurement Systems, London, UK) with a flame ionisation detector. Racemic and S-(+)-ibuprofen powders from a 75–150 μm sieve fraction, which were obtained by sieving the powders (as received) using a test sieve shaker through a series of stainless steel test sieves (Pascall Engineering, Suffolk, UK), were packed into standard pre-silanised iGC columns (300 × 4 mm ID) with silanised glass wool at each end. Columns were filled with 1.6–1.8 g of material and then conditioned *in-situ* in the iGC with helium purge at 20 sccm for 2 h at 303 K to remove physisorbed water. Following pre-treatment, pulse injections using a 0.25 ml gas loop at 30°C were performed. A series of purely dispersive n-alkane vapour probes (undecane, decane, nonane, octane, heptane) (HPLC grade, Sigma-Aldrich, Poole, UK) were injected at 0.03, 0.05, 0.10, 0.25, 0.50, 0.60, 0.70, 0.80, and 0.95 p/p_0 to determine adsorption isotherms, and net retention volumes, V_R^0, were determined using peak maximum (PM) analysis. A polar probe, ethanol (99.7–100% v/v, Merck KGaA, Darmstadt, Germany), was injected at the same series of concentrations to probe non-dispersive interactions. Methane gas was injected at 0.10 p/p_0 to determine column dead time. Helium, at a flow rate of 10 sccm, was used as the carrier gas for all injections. V_R^0 and adsorption isotherms were calculated using SMS-iGC Analysis Macros (version 1.2, Surface Measurement Systems, London, UK). BET surface area was determined by standard nitrogen adsorption technique (Tristar 3000, Micromeritics, Dunstable, UK).

RESULTS AND DISCUSSIONS

Contact Angle Measurement

The sessile drop contact angle method is a simple, straightforward procedure for measuring wettability which is sensitive to the first 10 Å (1 nm) of a surface [21]. A liquid drop is placed on the surface of interest and a tangent is prescribed at the three-phase contact point to obtain the contact angle. These experimental measurements are usually performed optically with the use of computer programs to fit drop profile dimensions to a Laplacian equation of the drop shape. A flat solid sample area of only a few square millimeters is required and small quantities of probe liquid (μL) are sufficient to obtain contact angle data. The probe liquid should be non-reactive with the solid surface and have a low volatility. In order to obtain the advancing contact angle, θ_a,the liquid front has to advance across fresh surface and this is achieved by increasing the drop volume slowly. Decreasing the

volume allows the receding contact angle, θ_r, to be measured. Contact angle determination of complex organic solids using the sessile drop method is commonly performed on powder compacts or tablets. However, the fabrication of powder compacts under high pressures is reported to cause surface deformation [22] and, thus, such contact angles measured may, therefore, not represent the true equilibrium surface energy of the particles. The macroscopic crystal approach described in this work contains no such limitation.

Whilst the sessile drop method is relatively straightforward experimentally, a surface which is smooth, flat, and homogenous is ideally required. Without these attributes, the applicability of this method is further complicated by the existence of the contact angle hysteresis [23–26], which is defined as the difference between the θ_a and the θ_r. This phenomenon occurs mainly due to surface roughness and chemical heterogeneity of the surface [27–29], though a complete understanding of this hysteresis has proven to be an elusive goal. We have established that though surface roughness and crystal dissolution are potential problems for the measurement approach outlined above, both of these factors have negligible effects on the anisotropic wetting behavior as experimentally observed [16]. Though crystal dissolution in water might have been a specific issue for the case for paracetamol crystals, it is believed that such effects will be even less apparent for a hydrophobic drug such as ibuprofen, which is almost non-soluble in water (molar solubility at $25^{\circ}C = 0.552 \times 10^{-4}$ mol/L) [30].

The inability to measure contact angles directly on individual powder particles is due to the small size of powder particles, normally $<100\,\mu m$ in diameter. This limitation can in theory be overcome by the use of very small droplets, but small droplets vaporize quickly due to their high Laplacian pressure. The use of larger surfaces (millimeter scale) seems, however, to be a more feasible option. One possible way of obtaining surfaces large enough for the sessile drop technique is by growing macroscopic sized single crystals, an approach proven successful by our group [16–18]. Such smooth and flat facets are ideal surfaces for the sessile drop method. This new and novel method has been investigated extensively for various crystalline systems [31], with the racemate system behavior reported here for the first time.

Racemic Ibuprofen

θ_a of diiodomethane, water, formamide, and ethylene glycol obtained for racemic ibuprofen single crystals are shown in Table 1. θ_a of diiodomethane were found to be highest at 45.5° on facet (100) and

TABLE 1 θ_a (°) for Specific Crystalline Facets of Ibuprofen Crystals

	Facet	(100)	(001)	(110)	(011)
Racemic ibuprofen	Diidomethane	45.5 ± 3.0	36.9 ± 3.5	–	35.0 ± 3.4
	Water	77.2 ± 4.0	68.5 ± 4.8	–	46.9 ± 5.5
	Formamide	41.3 ± 6.7	19.0 ± 2.5	–	16.9 ± 1.6
	Ethylene glycol	70.6 ± 4.3	35.4 ± 5.1	–	–
S-(+)-Ibuprofen	Diidomethane	31.2 ± 3.0	38.4 ± 2.7	39.5 ± 3.5	–
	Water	70.7 ± 3.1	64.5 ± 3.9	48.4 ± 4.0	–
	Formamide	11.2 ± 3.5	16.5 ± 4.3	17.4 ± 2.7	–
	Ethylene glycol	26.7 ± 4.5	48.1 ± 3.4	23.7 ± 5.4	–

about 36°, approximately 20% lower, on facets (001) and (011). Water contact angles showed a large variation over the three facets with the highest θ_a on facet (100), followed by (001) and (011), with the θ_a 40% lower, whereas formamide and ethylene glycol contact angles showed similar trends. As reported for other crystalline solids [16–18], anisotropic wetting behavior is also observed here for ibuprofen crystals.

The crystallographic structure of ibuprofen facets (100), (001), and (011) are shown in Figure 3. For facets (100) and (001), the carboxylic functionality is not available to form hydrogen bonds at the surfaces of these facets. The carboxylic functionality forms a pair of hydrogen bonds (by donating and accepting) with an adjacent molecule's carboxylic functionality resulting in the formation of an intermolecular dimer. Although this group appears to be closer to the surface at facet (001), this apparent proximity did not translate to an enhanced level of hydrophilicity, possibly due to the presence of very stable dimer complexes which provide no accessible hydrophilic sites.

Although θ_a for water on facets (100) and (001) were similar within experimental errors, θ_a for diiodomethane differed. Winn and Doherty [32] calculated the attachment energies for various facets of crystalline ibuprofen and reported the lowest value for facet (100). This concurs very well with the calculated total surface energies summarized in Table 2. Assuming that the two facets had almost identical polar components (based on contact angles of water), the difference between these two faces is due to dispersive surface energy (γ_{SV}^d) variations. The γ_{SV}^d of facet (100), which is the predicted lowest attachment energy facet, was found to be about 17–21% lower than γ_{SV}^d for facets (001) and (011).

The crystallographic structure of facet (011) is shown in Figure 3. θ_a for water and formamide on this face were found to be lower than for facets (100) and (001). On this facet, the carboxylic functionalities do

TABLE 2 Surface Energy (mJ/m^2) for Racemic Ibuprofen Using the Classical Owens-Wendt Approach

Facet	γ_{sv}^d	γ_{sv}^p	γ_{sv}	$\gamma_{sv}^p/\gamma_{sv}$
(100)	33.4 ± 0.5	4.6 ± 0.2	38.0 ± 0.8	0.122
(001)	42.1 ± 0.6	7.3 ± 0.3	49.4 ± 1.0	0.149
(011)	40.0 ± 0.6	18.9 ± 0.6	58.9 ± 1.2	0.322

not form hydrogen bonded dimers and, thus, may contribute to hydrogen bonding interactions at the surface.

Based on the θ_a results for water, an order of hydrophilicity for racemic ibuprofen crystalline facets can be proposed which is:

$$(011) > (001) > (100).$$

From the θ_a data for diiodomethane, an order of the van der Waals type of interactions for racemic ibuprofen crystalline facets can be proposed:

$$(011) = (001) > (100).$$

S-(+)-Ibuprofen

θ_a of diiodomethane, water, formamide, and ethylene glycol for S-(+)-ibuprofen single crystals are shown in Table 1. θ_a of diiodomethane were found to be about 40° on facets (001) and (110) and about 30°, approximately 25% lower, on facet (100). Water contact angles were found to be different on all three facets with the lowest values of θ_a on facet (110), followed by (001) and (100). Formamide and ethylene contact angles were also very different for the three facets.

Like the racemic ibuprofen crystals, the carboxylic functionality of the ibuprofen molecule forms hydrogen bond pairs *via* a dimer conformation. No hydrogen bonding potential at the surface of facets (100) and (001) is evident as shown in the crystallographic structure of ibuprofen (Figure 4). On the other hand, the crystallographic structure of facet (110) suggests that carboxylic functionality present may be able to participate in the interactions with external molecules at the surface.

The S-(+)-ibuprofen single crystals were observed to be rather brittle and to fracture easily at both the (100) and (001) planes. However, to our best knowledge, there have been no reported studies on the mechanical properties of S-(+)-ibuprofen crystals. Therefore, a prediction of the fracture purely based on its known crystallographic structure can be offered. Due to the similarities between the two

mirror image molecules, the unit cell for both racemic and S-(+)-ibuprofen are also very similar. One would, therefore, be inclined to predict that their fracture planes may also be similar or the same. The racemic crystalline ibuprofen has a weakest attachment energy facet at its (100) plane and this assumption will be adopted for the S-(+)-ibuprofen crystalline structure. In this study, it has been observed that the θ_a of water is found to be the highest on facet (100) and this observation concurs well with our hypothesis that the weakest attachment energy facet for crystalline pharmaceutical solids is the most hydrophobic surface. This observation has been reported for other crystalline systems investigated [31].

Based on the contact angle results of probe liquid water, an order of hydrophilicity for S-(+)-ibuprofen crystalline facets can be proposed which is:

$$(110) > (001) = (100).$$

From the θ_a data for diiodomethane, it can be proposed that the order of the van der Waals type of interactions for S-(+)-ibuprofen crystalline facets is:

$$(100) > (001) = (110).$$

Surface Energy Measured by Contact Angle

The calculated surface energies as determined by the classical Owens-Wendt analysis are shown in Table 2 for racemic ibuprofen crystals. This analysis considers the total surface energy to consist of two independent surface energy components: a dispersive (γ_{SV}^{d}) and a polar (γ_{SV}^{p}) component. Though more contemporary and refined analyses exist, where the polar interactions are described more appropriately as acid-base interactions which include hydrogen bonding, the simplicity and robustness of this classic analysis makes it still a useful first order model. Facets (100) and (001) possessed almost identical polar surface energies, with facet (100) being marginally lower. On the other hand, facet (011) is about twice as polar, confirming the presence and contribution of the carboxylic functionality at the specific surface.

The calculated surface energies for S-(+)-ibuprofen are shown in Table 3. The total surface energies of both facets (100) and (001) also appear to be almost identical, as in the case of racemic ibuprofen, with only small differences in both the dispersive and polar components. Our results show that (100) and (001) facets have the lowest surface energies and we would predict that these should exhibit the weakest

TABLE 3 Surface Energy (mJ/m^2) for S-(+)-Ibuprofen Using the Classical Owens-Wendt Approach

Facet	γ_{SV}^d	γ_{SV}^p	γ_{SV}	$\gamma_{SV}^p/\gamma_{SV}$
(100)	46.6 ± 0.6	5.7 ± 0.2	52.3 ± 0.8	0.110
(001)	38.4 ± 0.5	9.2 ± 0.3	47.6 ± 0.8	0.194
(110)	35.4 ± 0.6	18.6 ± 0.5	54.0 ± 1.1	0.344

attachment energies, though no modelling data currently exist to test this hypothesis. Interestingly, facet (110) is also about twice as polar based on γ_{SV}^p compared with the other two facets, confirming the presence and contribution of the carboxylic functionality to that facet's surface properties.

Although the surface energetics for racemic ibuprofen and S-(+)-ibuprofen are very similar, the largest differences are found in θ_a for diiodomethane, formamide, and ethylene glycol between facets (100) for both forms. However, these differences in θ_a disappear when comparing facets (100) and (011) for the racemic form and facets (100) and (110) for the S-(+)-ibuprofen—θ_a all agree within the experimental errors.

Perlovich *et al*. [1] applied computer simulation to predict crystal lattice energies of racemic ibuprofen and S-(+)-ibuprofen using force field models developed by Mayo *et al*. [33] and Gavezzotti and Filippini [34]. The computed crystal lattice energetic data indicated that the van der Waals interaction energies contributes more in the total packing energy of S-(+)-ibuprofen crystal compared with the racemic form. These same calculations concluded that the hydrogen bonding interaction energies correspond to 25 to 32% of the total computed lattice energy, with virtually all of the other energies being due to van der Waals interactions for both forms. The average hydrogen bonding contribution to the computer crystal lattice energies for both forms of ibuprofen is 28%. Our surface energy calculations shown in Tables 2 and 3 give the fraction of surface energy due to polar/hydrogen bonding to be in the range of 11 to 35% of the total surface energy, depending upon the facet and form considered. The simple arithmetic average of all surface energy due to polar/hydrogen bonding gives a global average of 21% which is not inconsistent with the computed lattice energies.

Although the results of the computational methods correlate usefully with experimental contact angle measurements, it may be premature to conclude that the crystal lattice energies alone may be directly applicable to predict adhesion and wetting behavior. The

value of surface free energy is not only reflective of whether a functional group is present, but also its lability and, therefore, whether the functional group can participate in intermolecular interactions. This case is highlighted by the carboxylic groups present close to the surface of facet (001) for racemic ibuprofen, as described earlier.

In the current work, it appears that both racemic and S-(+)-ibuprofens have relatively similar wetting behavior. Hydrophobicity/hydrophilicity trends are similar on the similar indexed facets, *i.e.*, similarly indexed facets on racemic ibuprofen are just as hydrophobic or hydrophilic as the facet on S-(+)-ibuprofen. This might appear to contradict an earlier conclusion for paracetamol polymorphs forms I and II which shows that the wetting behavior of similarly indexed facet may not be the same [17]. In the case of the racemates of ibuprofen, the crystal lattice, the unit lengths and β are relatively similar. Furthermore, the two forms of ibuprofen also have the same hydrogen bonding between the carboxylic groups forming dimers, unlike the case of paracetamol, which is reported in detail elsewhere [16]. This further illustrates the importance of surface chemistry, the availabilities of functional groups, and the orientation of these molecules in the crystal in determining the wetting behavior of organic crystalline solids.

IGC Analysis

The use of IGC in the pharmaceutical industry is increasingly recognised, and the technique has been widely applied in adhesion and wettability studies on pharmaceutical materials [35,36]. IGC can be used to determine surface free energy of solid powders, and a general review of the various applications can be found in [37]. The major advantage of IGC in determining surface energy is that it overcomes problems in relation to surface roughness, porosity, inhomogeneity, and morphological change of sample as may be encountered with methods such as atomic force microscopy, contact angle, and capillary rise method. In the normal measurement method for $\gamma_{SV}{}^{d}$, IGC is operated in the infinite dilution regime when small concentrations of alkane vapours are injected into the sample column to probe material surface properties. These low concentrations of adsorbates tend to interact with the higher energy sites on the material surface; therefore, only a very small portion of the surface is characterised, typically $<0.5\%$. Recently, an analysis has been developed for the determination of surface energy profiles by IGC in which up to 70%

of the surface sites are characterised [38]. In the current work, the surface energetic data obtained from contact angles on macroscopic crystal facets is compared with these IGC surface energy profile measurements.

The principle of this new approach is based on an adsorption isostere methodology, and requires the measurements of adsorption isotherms for a range of alkanes at a series of finite concentrations. Detailed description of the theory and method of measurements can be found in [38] and [39]. This approach can also be applied to determine the distribution profile of the specific free energy of desorption, ΔG^0, and, in theory, the profiles of acidity constant, K_A, and basicity constant, K_B, as described by Gutmann [40]. By conducting a series of IGC measurements at finite concentrations. Thielmann *et al*. [39] have successfully measured the γ_{SV}^d distribution profiles of untreated, amorphous, and recrystallized lactose, and were able to show that the decrease in γ_{SV}^d with increasing surface coverage is less pronounced in the recrystallized lactose sample than in the milled and untreated samples, suggesting that the recrystallized material is energetically more homogenous. It was also possible to distinguish between differences in ethanol specific free energies of desorption of the samples. This approach has also been successfully applied recently to the characterization of mannitol powders [36].

Surface Energy Profiles Measured by IGC

The determination of surface energy profile of a particulate sample relies on a plot of net retention volume, V_R^0, as a function of surface coverage, n/n_m. In practice, V_R^0 can be determined at higher surface coverage by increasing the probe vapour partial pressure to finite concentration conditions such that a much greater number of surface sites can be probed. Detailed derivation of V_R^0 *versus* n/n_m plots is reported in [38]. In infinite dilution measurement, γ_{SV}^d of the solid can be determined by applying the approach of Dorris and Gray [41] using a combination of alkane probes at a single injection concentration, but this measured value of γ_{SV}^d cannot be related to any particular surface coverage. By calculating γ_{SV}^d using a combination of alkanes at different surface coverages from the V_R^0 *versus* n/n_m plot, a map of γ_{SV}^d as a function of surface coverage can be determined.

Figures 5 and 6 illustrate V_R^0 *versus* n/n_m for the 75–150 μm sieve fractions of racemic and S-(+)-ibuprofen, respectively. It can be noticed that V_R^0 for different vapour probes are almost constant, within experimental errors, with increasing surface coverage. The trends

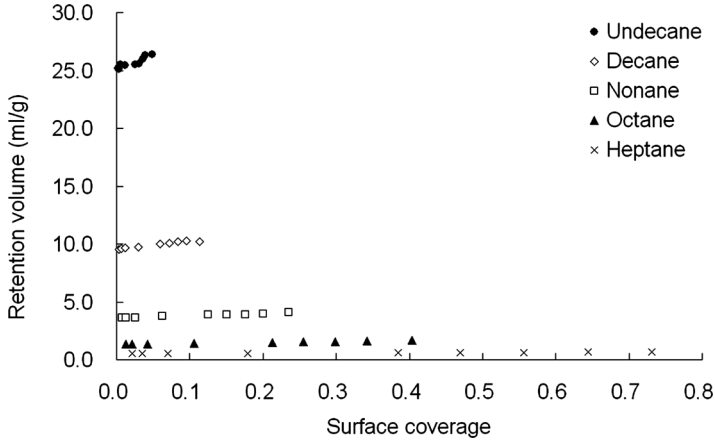

FIGURE 5 Net retention volume against fractional surface coverage for racemic ibuprofen.

in the net retention volume observed here are very different from those of the α-lactose samples previously reported by Thielmann *et al*. [39]. It is generally recognised that real solid material may exhibit broad surface energy distributions which can be due to presence of impurities, different types of crystal facets, growth steps, crystal edges, surface pores, local degree of crystallinity, and surface functional groups [42,43]. A hydrophilic excipient such as crystalline

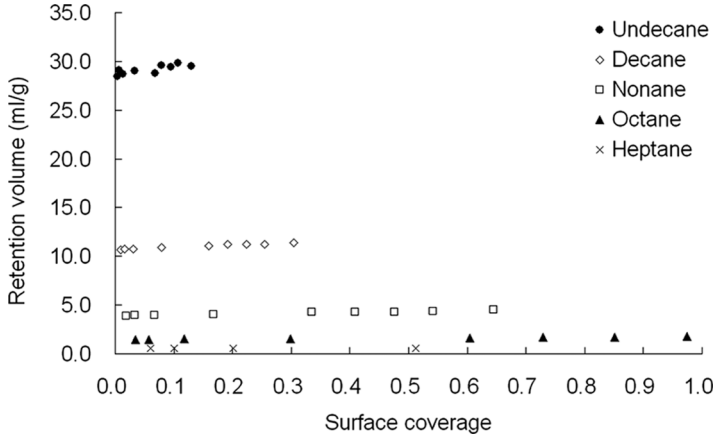

FIGURE 6 Net retention volume against fractional surface coverage for S-(+)-ibuprofen.

lactose has multiple facets and may also possess amorphous domains due to processing conditions such as milling [44]; therefore, it is plausible that the surface energy of such materials is heterogeneous. Similarly, racemic ibuprofen and S-(+)-ibuprofen with anisotropic crystal surface energies as reported here would also be expected to exhibit some level of heterogeneity but, interestingly, γ_{SV}^{d} profiles for racemic and S-(+)-ibuprofen were found here to be relatively homogeneous (Figure 7). The negligible change in V_R^0 with increasing coverage for the two ibuprofen samples implies a relatively constant γ_{SV}^{d}. For racemic ibuprofen, over 97% of the surface has a γ_{SV}^{d} of approximately 33 mJ/m^2, whereas over 96% of surface has a γ_{SV}^{d} of approximately 35 mJ/m^2 for S-(+)-ibuprofen. It is interesting to note that, for each material, the γ_{SV}^{d} value measured by IGC closely resembles that of the crystal facet with the lowest γ_{SV}^{d}, *i.e.*, facet (100) in the case of racemic ibuprofen and facet (110) in the case of S-(+)-ibuprofen, as obtained *via* contact angle measurements reported in the previous section. Although our contact angle studies showed that γ_{SV}^{d} on various indexed crystal facets are different, these have not been translated to the overall surface energy profiles for particulate ibuprofen. One could propose that the percentage of higher energy sites was below 3–4% of the total surface for both materials, and was outside the detection limit of the current experimental methodology. Or possibly, that the powders tested in the current study possess a very large fraction of the lowest γ_{SV}^{d} facets due to minimization of surface

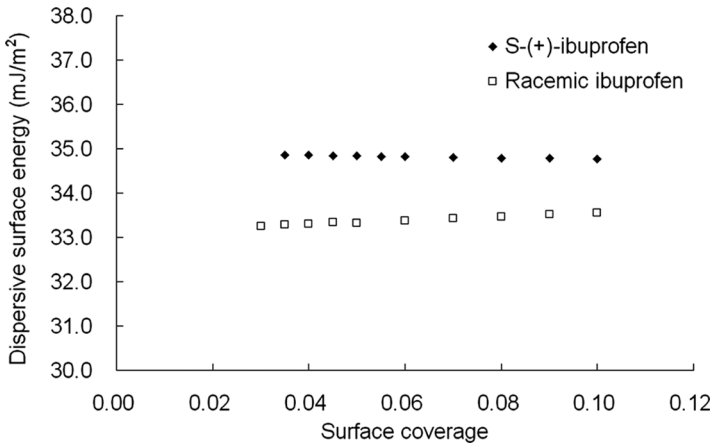

FIGURE 7 Dispersive surface energy distribution for racemic ibuprofen and S-(+)-ibuprofen.

energies as a result of crystallization, as postulated by Gibbs' theorem for crystal growth [45].

The polar interactions of a powder sample can be characterized by IGC using a polar adsorbate such as ethanol. If the sample is capable of dispersive and polar interactions, the adsorption of polar adsorbate gives rise to an additional interaction term and, hence, the V_R^0 can be considered to consist of a dispersive as well as a polar component. The specific free energy of desorption can then be determined from V_R^0. The distribution profiles of ΔG^0 (ethanol) for racemic and S-(+)-ibuprofen are shown in Figure 8. The heterogeneity in ΔG^0 for both samples is relatively more pronounced than that in $\gamma_{SV}{}^d$ as mentioned above, which is to be expected by stronger, more specific adsorption processes. Despite the similarity in ΔG^0 between both samples, ΔG^0 for the S-(+)-enantiomer is slightly greater than that for the racemate, consistent with the higher $\gamma_{SV}{}^p$ reported in Tables 2 and 3. These results from IGC further support the observation that both racemic and S-(+)-ibuprofens have relatively similar wetting behavior.

It is concluded that advanced IGC and single crystal contact angle techniques are powerful and complementary methods for characterizing solids with different surface properties as demonstrated in the case of lactose (heterogeneous surface) and ibuprofen (homogeneous surface), and allows the quantification of the surface energetics and wetting properties of complex organic solids.

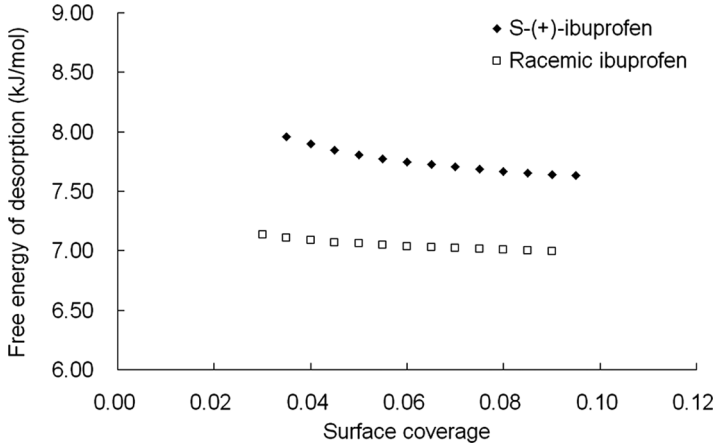

FIGURE 8 Distribution of free energy of desorption of ethanol for racemic ibuprofen and S-(+)-ibuprofen.

CONCLUSIONS

This study compares the facet specific surface energetics for macroscopic crystals of a racemate system with the surface energetic profiles for the corresponding powdered crystals. The contact angle measurements using water, diiodomethane, formamide, and ethylene glycol for racemic and S (+) enantiomer ibuprofen single crystals, at specific crystalline facets, are reported, and the wettability of ibuprofen (racemic and S enantiomer) single crystals was found to be anisotropic. θ_a of water differs by up to 40% for various specific crystal facets. On those facets where the carboxylic functionality is able to form hydrogen bonds, a significant hydrophilic behavior was observed. The hydrophilicity order for racemic ibuprofen and S-(+)-ibuprofen, respectively, as determined by contact angles with water are:

$$(011) > (001) > (100)$$

$$(110) > (001) = (100).$$

θ_a of diiodomethane on facets for racemic ibuprofen and S-(+)-ibuprofen were similar. Overall, the portions of the surface energy ascribed to hydrogen bonding based on calculated surface energies are, on average, consistent with those predicted by computational modelling of the hydrogen bonding component of lattice energies. Surface energy profiles were also measured by IGC at a series of finite concentrations *via* pulse injections of n-alkanes and ethanol. These results further supported the findings that both racemic and S-(+)-ibuprofens exhibit relatively similar wetting behavior with similar γ_{SV}^{d} results to that obtained from the direct wetting measurements. IGC also showed that these commercial powders are relatively homogeneous with the suggestion that one crystal facet dominated a majority of total external surface.

ACKNOWLEDGMENTS

The authors would like to acknowledge the use of the Engineering and Physical Sciences Research Council's. Chemical Database Service at Daresbury and R.H. would also like to acknowledge the financial support of AstraZeneca UK.

REFERENCES

[1] Perlovich, G. L., Kurkov, S. V., Hansen, L. K. R., and Bauer-Brandl, A., *J. Pharm. Sci.* **93**, 654–666 (2004).

[2] Di Martino, P., Beccerica, M., Joiris, E., Palmieri, G. F., Gayot, A., and Martelli, S., *J. Cryst. Growth* **243**, 345–355 (2002).

[3] Garekani, H. A., Sadeghi, F., Badiee, A., Mostafa, S. A., and Rajabi-Siahboomi, A. R., *Drug Dev. Ind. Pharm.* **27**, 803–809 (2001).
[4] Rasenack, N. and Muller, B. W., *Drug Dev. Ind. Pharm.* **28**, 1077–1089 (2002).
[5] Rasenack, N. and Muller, B. W., *Int. J. Pharm.* **244**, 45–57 (2002).
[6] Cano, H., Gabas, N., and Canselier, J. P., *J. Cryst. Growth* **224**, 335–341 (2001).
[7] Rasenack, N. and Muller, B. W., *Int. J. Pharm.* **245**, 9–24 (2002).
[8] Duncan-Hewitt, W. and Nisman, R., *Contact Angle, Wettability and Adhesion*, (VSP, Utrecht, 1993), pp. 791–811.
[9] Good, R. J., *Surface and Colloid Science*, (Plenum Press, New York, 1979), pp. 1–29.
[10] Young, T., *Philosophical Transactions of the Royal Society of London* **95**, 65–87 (1805).
[11] Fowkes, F. M., *Ind. Eng. Chem.* **56**, 40–52 (1964).
[12] Owens, D. K. and Wendt, R. C., *J. Appl. Polym. Sci.* **13**, 1741–1747 (1969).
[13] van Oss, C. J., Good, R. J., and Chaudhury, M. K., *Langmuir* **4**, 884–891 (1988).
[14] Heng, J. Y. Y., Bismarck, A., and Williams, D. R., *AAPS PharmSciTech* **7**, Article 84 (2006).
[15] Wu, S., *Polymer Interface and Adhesion*, (Marcel Dekker, New York, 1982).
[16] Heng, J. Y. Y., Bismarck, A., Lee, A. F., Wilson, K., and Williams, D. R., *Langmuir* **22**, 2760–2769 (2006).
[17] Heng, J. Y. Y. and Williams, D. R., *Langmuir* **22**, 6905–6909 (2006).
[18] Heng, J. Y. Y., Bismarck, A., Lee, A. F., Wilson, K., and Williams, D. R., *J. Pharm. Sci.* **98**, 2134–2144 (2007).
[19] Shankland, N., Wilson, C. C., Florence, A. J., and Cox, P. J., *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **53**, 951–954 (1997).
[20] Hansen, L. K., Perlovich, G. L., and Baver-Brandl, A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **59**, 01357–01358 (2003).
[21] Kwok, D. Y. and Neumann, A. W., *Surface Characterization Methods: Principles, Techniques and Applications*, (Marcel Dekker, New York, 1999).
[22] Buckton, G., *Contact Angle, Wettability and Adhesion*, (VSP, Utrecht, 1993), pp. 437–451.
[23] Schwartz, L. W. and Garoff, S., *Langmuir* **1**, 219–230 (1985).
[24] Lam, C. N. C., Kim, N., Hui, D., Kwok, D. Y., Hair, M. L., and Neumann, A. W., *Colloids Surf. A* **189**, 265–278 (2001).
[25] Lam, C. N. C., Wu, R., Li, D., Hair, M. L., and Neumann, A. W., *Adv. Colloid Interface Sci.* **96**, 169–191 (2002).
[26] Extrand, C. W. and Kumagai, Y., *J. Colloid Interface Sci.* **191**, 378–383 (1997).
[27] Nakae, H., Inui, R., Hirata, Y., and Saito, H., *Acta Mater.* **46**, 2313–2318 (1998).
[28] Hazlett, R. D., *Contact Angle, Wettability and Adhesion*, (VSP, Utrecht, 1993), pp. 173–181.
[29] Bartell, F. E. and Shepard, J. W., *J. Phys. Chem.* **57**, 211–215 (1953).
[30] Garzon, L. C. and Martinez, F., *J. Solution Chem.* **33**, 1379–1395 (2004).
[31] Heng, J. Y. Y., *Anisotropic Surface Properties of Crystalline Pharmaceutical Solids*, (University of London, London, 2006).
[32] Winn, D. and Doherty, M. F. *AICHE J.* **46**, 1348–1367 (2000).
[33] Mayo, S. L., Olafson, B. D., and Goddard, W. A., *J. Phys. Chem.* **94**, 8897–8909 (1990).
[34] Gavezzotti, A. and Filippini, G., *Theoretical Aspects and Computer Modeling of the Molecular Solid State*, (John Wiley & Sons, Chichester, U.K., 1997), pp. 61–97, 237.
[35] Grimsey, I. M., Feeley, J. C., and York, P., *J. Pharm. Sci.* **91**, 571–583 (2002).

[36] Ho, R., Heng, J. Y. Y., Dilworth, S. E., Hinder, S. J., Watts, J. F., and Williams, D. R., (in preparation).
[37] Heng, J. Y. Y., Pearse, D. F., Wilson, D. A., and Williams, D. R., *Solid State Characterization of Pharmaceuticals*, (ASSA International, Danbury, 2006).
[38] Ylä-Mäihäniemi, P. P., Heng, J. Y. Y., Thielmann, F., and Williams, D. R., *Langmuir* (submitted).
[39] Thielmann, F., Burnett, D. J., and Heng, J. Y. Y., *Drug Dev. Ind. Pharm*. **33**, 1240–1253 (2007).
[40] Gutmann, V., *Coord. Chem. Rev*. **2**, 239–256 (1967).
[41] Dorris, G. M. and Gray, D. G., *J. Colloid Interface Sci*. **77**, 353–362 (1980).
[42] Jaroniec, M. and Madey, R., *Physical Adsorption on Heterogeneous Solids*, (Elsevier, Amsterdam, 1988), pp. 4–5.
[43] Villieras, F., Michot, L. J., Bardot, F., Chamerois, M., Eypert-Blaison, C., Francois, M., Gerard, G., and Cases, J. M., *Comptes Rendus Geoscience* **334**, 597–609 (2002).
[44] Descamps, M., Willart, J. F., Dudognon, E., and Caron, V., *J. Pharm. Sci*. **96**, 1398–1407 (2007).
[45] Gibbs, J. W., *Thermodynamics*, (Yale University Press, New Haven, 1948), Vol I.