

# Interactions of water with the surfaces of crystal polymorphs

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## Abstract

The purpose of this study is to investigate the interactions of water adsorption on the surfaces of different crystal forms of the same drug. The energy of interaction between water vapor and the surfaces of the two crystal polymorphs has been investigated as a function of temperature and water activity. One of the adsorbents, the metastable form of the monotropically related pair used here, showed greater adsorptive capacity in terms of both the amount of water uptake as well the integral heat of adsorption. However, the specific heat of adsorption values revealed that even though the surface of the thermodynamically stable crystal adsorbs less water, water molecules are actually more strongly bound when adsorbed on the surface of the stable crystal form. This means that the metastable crystal form adsorbs a greater amount of more weakly bound water. Conversely, the thermodynamically stable form, presents on its surface a smaller number of stronger adsorption sites for water. This study also shows that the crystalline character of the surfaces of the two polymorphs, shown as quantifiable differences in their surface interactions, is maintained despite the presence of any crystal defects incorporated upon milling.

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## 1. Introduction

The study of the interactions between powders is of great interest to various industrial applications. The mixing, dispersion and deposition properties of powders, as well as the physical stability of powder blends, are critical to many processes, as is the case in the pharmaceutical and food industries. Particles in a powder or powder blend interact with each other at the level of their surfaces. Powder behavior is, to a large extent, a reflection of the energetics of the interaction between the surfaces of powder particles. Therefore, the surface properties of powders constitute a determining factor in their behavior during processing. Leusen (1994) has pointed out that the interaction energy should be “controlled” by exploiting interfacial properties of the powders in order to improve powder properties. Such type of control requires the ability to make quantitative comparisons regarding the interactive properties of powdered materials. The chemical composition of a material plays a definite role on the

nature and magnitude of the interactions of that material with others. In many instances, however, controlling or manipulating the properties of materials such as powders is limited to physical means, i.e., without a change in the chemistry involved. This brings up the question about the extent to which the physical attributes of material alone can alter the energetics of its interactions with other substances.

In this report, the energetics of surface interactions of two different crystal polymorphs is investigated. The chosen powders are therefore organic crystals identical chemical composition, i.e., the powders are different physical forms of the same chemical entity. The organic compound selected is an active pharmaceutical substance, a leukotriene D<sub>4</sub> (LTD<sub>4</sub>) antagonist. The powders used in the study have been treated in such a way as to minimize, as much as possible, the effect of geometrical factors such as the particle size distribution and the specific surface area of the powders. The goal in this study is to investigate how differences in physical arrangements of the same organic molecule manifest themselves in the energy of interaction of the corresponding surface. The working hypothesis is that the differences in surface properties obtained by preparing the materials in different molecular arrangements (crystal modifi-

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cations) are quantifiably different by means of the study of their interactions with a common probe. Such differences should, in turn, be relatable to the differences in the macroscopic properties of the corresponding powders. The difference in response that distinct surfaces of identical chemical composition present upon exposure to a common perturbation, such as the interaction with a probe molecule, provides a quantitative measure of the differences in energy between the corresponding materials. A suitable probe for this purpose is the vapor of a solvent, chosen as the adsorbate, for studying its interaction with the different types of surface. Water was selected as the probe for this study. Water plays a central role in many pharmaceutical situations because of its biological importance, ubiquitous nature and common use in pharmaceutical processing.

A number of methods are currently available for the analysis of surface properties. Among these are interfacial contact angle measurements (Buckton and Newton, 1986; Egawa et al., 1992), microcalorimetry (Berlin et al., 1971; Bystrom, 1990; Angberg et al., 1992; Briggner et al., 1994; Sebbatu et al., 1994; Bakri, 1997), water sorption isotherms (Hendrisken et al., 1995; Stubberud et al., 1995; Otsuka et al., 1988; Saleki-Gerhardt et al., 1994), inverse gas chromatography (IGC) (York, 1994; Ticehurst et al., 1994; Hancock et al., 1997; Feeley et al., 1998; Grimsey et al., 2002), atomic force microscopy (AFM) (Danesh et al., 2000) and molecular orbital indices modeling (Sheridan et al., 1995). Each method has specific advantages and limitations in terms of its methodology, complexity and applicability, all of which may affect the usefulness of individual measurements. The techniques listed above are, nonetheless, often complementary in the information they provide, and when used in combination, analysis techniques can provide a more complete description of the properties and behavior of powder surfaces than any individual technique could. In this report, microcalorimetry and water adsorption measurements are used in combination, in order to study the differences in surface energetics between the powders of two crystal modifications of the LTD<sub>4</sub> compound. The use of thermodynamic parameters as practical indicators for the assessment of differences in surface energetics provides an objective means to explore how intermolecular interactions ultimately manifest themselves at the macroscopic level, affecting the behavior of the bulk powder.

## 2. Materials and methods

A pharmaceutical organic compound (LTD<sub>4</sub>, Hoffmann-La Roche, Nutley, NJ, USA) was selected to make the two types of powder to be used as adsorbents. The chemical structure of LTD<sub>4</sub> is shown in Fig. 1. The compound is highly hydrophobic, practically insoluble in water. The LTD<sub>4</sub> compound can be prepared as two different crystal forms, A and B. The two

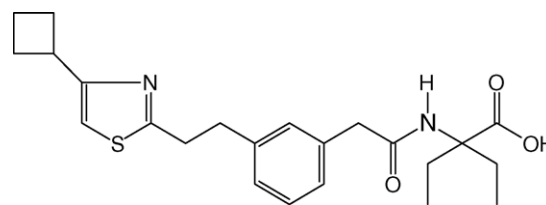


Fig. 1. Chemical structure of LTD<sub>4</sub>.

Table 1  
Physicochemical properties LTD<sub>4</sub> polymorphs A and B

Property	Polymorph	
	A	B
Absolute density (g ml <sup>-1</sup> )	1.260	1.290
Melting point (°C)	163	167
ΔH <sub>m</sub> (J g <sup>-1</sup> )	275	300
Water solubility (μg ml <sup>-1</sup> )	1.23	0.86

polymorphs are monotropically related and form B is the thermodynamically stable form. One important aspect is that both crystal forms are kinetically very stable, i.e., they can stay indefinitely without undergoing any solid phase transition, even when exposed to physical stress such as that generated during milling. Table 1 shows physicochemical properties for the two polymorphs. The corresponding unit cell parameters of their crystals are provided in Table 2. Crystallization yields crystals with different habit and considerably different particle size for each of the two forms. Form A is produced as large small (200–600 μm long) needles, whereas form B is produced as large (0.5–1 mm) prisms. Therefore, the obtained crystals of the two forms were milled in a fluid energy mill (4 in. Sturtevant Microniser), and subsequently, sieved in order to obtain the two crystal forms with similar particle size distributions as well as similar specific surface areas. Fig. 2 shows electron microscopy (SEM) images as well as the particle size distributions for the two crystal forms used in this study. The data on the particle size distribution and specific surface area of the powders used in this study are summarized in Table 3.

### 2.1. Water uptake measurements

Water sorption experiments were carried out in a dynamic flow vapor sorption apparatus (Model SGA 100, VTI Corporation, Hialeah, FL, USA). Samples of each of the two adsorbents were placed in the instrument sample chamber and their moisture uptake was measured as a function of relative humidity (RH). Water sorption isotherms for both powders were carried out at 20 °C, 25 °C, 35 °C and 45 °C. The sample size for each run was approximately 50 mg.

Table 2  
Crystal unit cell parameters for polymorphs A and B of LTD<sub>4</sub>

Crystal form	Z	a (Å)	b (Å)	c (Å)	β	Volume (Å <sup>3</sup> )	Volume per molecule (Å <sup>3</sup> molecule <sup>-1</sup> )	Space group
A	4	18.018	6.916	18.182	92.15	2264	566	P2 <sub>1</sub> /a
B	4	6.930	23.059	13.606	96.55	2160	540	P2 <sub>1</sub> /n

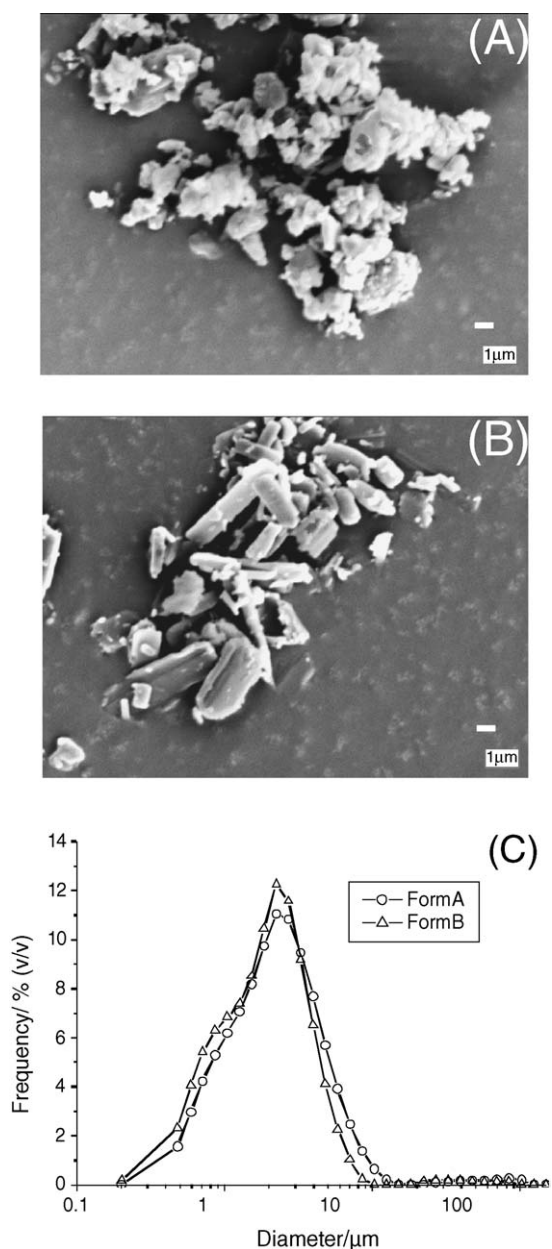


Fig. 2. Powders of two polymorphs of LTD<sub>4</sub>. (A) SEM photograph of polymorph A (micronized) powder; (B) SEM photograph of polymorph B (micronized) powder; (C) particle size distribution (laser diffraction) of the two physical forms used in this study.

### 2.2. Isothermal microcalorimetry

The heat of adsorption of water vapor onto each of the two crystal forms was measured under varying RH conditions

Table 3  
Particle size and surface area data for the two powders used in this study

Form	Particle size distribution (μm)			Specific surface area (m <sup>2</sup> g <sup>-1</sup> )
	D(v, 10)	D(v, 50)	D(v, 90)	
A	5.8	2.4	0.9	8.18
B	4.7	2.2	0.8	7.38

using an isothermal heat conduction microcalorimeter (Thermal Activity Monitor, TAM, Thermometric AB, Sweden). The integral heats of adsorption were measured using a TAM instrument fitted with a Thermometric RH perfusion ampoule (accessory Model 2255) adapted with Kalrez o-rings. The relative humidity above the solid samples was controlled as originally described by Bakri (1993). For the calorimetric determinations, an accurately weighed sample of approximately 30 mg of the powder was placed in a 4 ml stainless steel sealed ampoule. Prior to the analysis, the sample was dried overnight under dry nitrogen flow (~0% RH) until a signal of zero heat flow was attained in the calorimeter. With every run, a blank experiment was conducted under identical conditions using an equal but empty ampoule. The calorimetric adsorption experiments were conducted at four temperatures: 20 °C, 25 °C, 35 °C and 45 °C. The incoming relative vapor pressure of water was set to increase in 10% increments up to 100%. With every increase in RH, a positive response was recorded until equilibrium was re-established (i.e., zero heat flow). The time integral of the recorded heat flow trace corresponds to the heat evolved for the process under study. The area under the curve of each adsorption peak was calculated using Origin<sup>TM</sup> version 5.0 software (Microcal, MA, USA).

### 2.3. Specific surface area

The surface area of the powders was measured by the BET gas adsorption isotherm method. An automated BET Sorptometer (Porous Materials Inc., Ithaca, NY) using a BET method for analysis to determine the surface area of the different powders of the drug. An accurately weighed sample of powder of approximately 2 g was placed into the glass loop of the instrument and the filled loop was then submerged into liquid nitrogen. Prior to the actual measurement, the samples were gas purged in the glass loop by subjecting them to vacuum during 24 h. After the purging step, nitrogen sorption was performed in multi-point mode in order to determine the specific surface area of the powders.

## 3. Results and discussion

Water uptake results are presented in Fig. 3. Form A adsorbs greater quantities of water than form B under all conditions of temperature and relative humidity investigated. Such an effect is clearly observable from Fig. 3, especially at higher RH values. The figure also shows that the variability is significantly greater for form A than for form B, particularly at 25 °C and 35 °C. In contrast, the water uptake data for form B shows very little variability at all temperatures investigated. These results suggest greater heterogeneity on the surface of the thermodynamically metastable form (A).

Results for water adsorption obtained by isothermal microcalorimetry at the different temperatures and RH conditions are shown in Fig. 4. Adsorption of water vapor on form A evolves a greater amount of heat than in the case of adsorbent B under all conditions of temperature and relative humidity investigated. This effect, again, is most noticeable at the higher RH levels. At the three lower temperatures (20 °C, 25 °C and 35 °C), form A shows a sharp increase in heat of adsorption as function

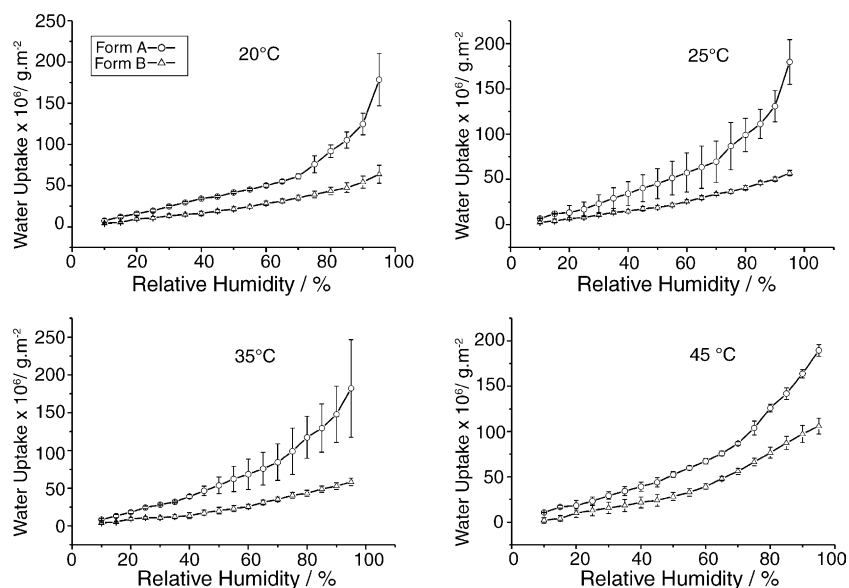


Fig. 3. Water uptake isotherms for the two crystal forms at different temperatures.

of relative humidity at RH values above  $\sim 80\%$ . Form B shows also a similar sharp increase at high RH, but in this case, the sharp increase is only observed at  $25^\circ\text{C}$ . It is noteworthy that for each of the two adsorbents, the heat of adsorption reaches the highest values at  $25^\circ\text{C}$  in comparison with the other temperatures.

Figs. 3 and 4 clearly show that the two crystal surfaces are measurably different in their ability to interact with water. Polymorph A shows greater adsorption capacity in terms of both water uptake and the corresponding heat of adsorption, under all temperature and relative humidity conditions investigated in this study. It is pertinent to note that the crystal form with the lower integral heat of adsorption, B, is also the more stable thermodynamic phase. The results shown in Figs. 3 and 4 are therefore

consistent with a situation in which the crystal form with higher free energy at its core (i.e., the metastable form) exhibits also greater free energy at its surface. A less stable solid phase is expected to have greater number of energetic (active) sites that favor water sorption (Zografi and Tam, 1976).

In order to enable more detailed comparisons between the two adsorbent phases, an alternative mode for data presentation would be helpful. All the information relative to the uptake of water and the corresponding heat evolved upon water adsorption, by each of the two crystal forms, is contained in Figs. 3 and 4, respectively. Data presentation in the form of isotherms, however, may not be the optimal format for purposes of comparison. The use of isobars offers an alternative, more convenient means

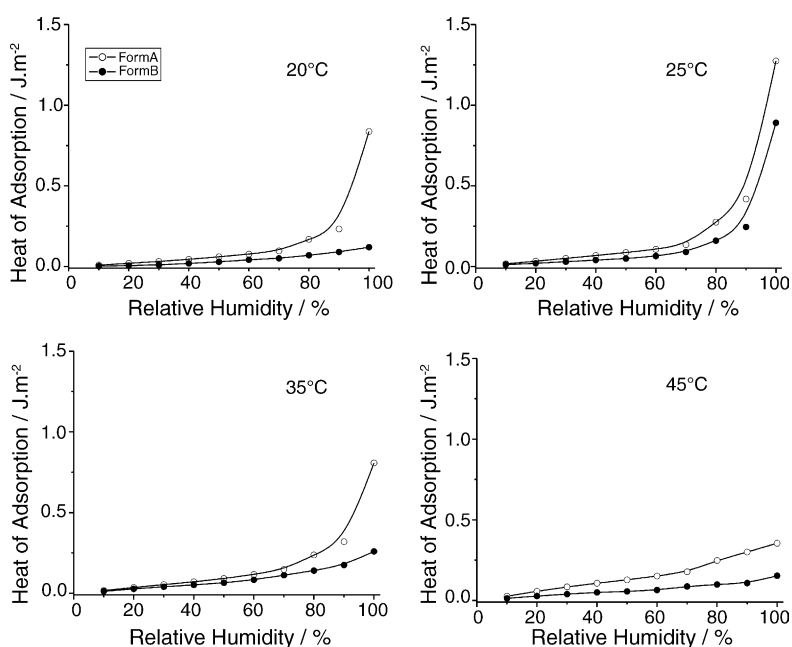


Fig. 4. Integral heat of adsorption for water onto the two crystal forms, as a function of relative humidity, at different temperatures.



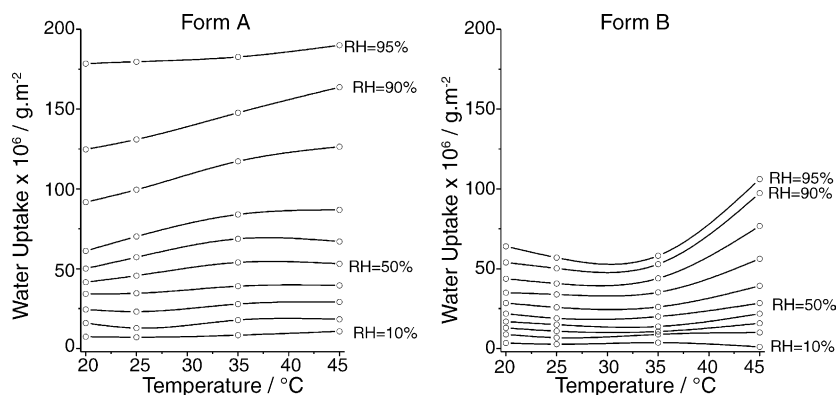


Fig. 5. Water uptake data presented as relative isobars for the two adsorbents.

of presenting the same data for comparison purposes. Presentation of adsorption data in the form of isobars is very useful because it makes it visually simple to separate the effects of temperature from those of relative humidity when comparing the adsorptive properties of different materials.

Fig. 5 shows the same sorption data as in Fig. 3, but in the form of isobars, specifically, as *relative isobars*, i.e., as lines of constant partial pressure of water vapor (relative humidity). Each line in Fig. 5 corresponds to a constant level of RH, the lines are termed relative isobars because each line corresponds to a constant value of water vapor pressure *relative* to the water saturation pressure at the same temperature (i.e., constant water activity). The relative isobars presented in Fig. 5 correspond to water activity values ranging from 10% (bottom) to 95% (top), with 10% increments between 10% and 90% RH. Thus, moving vertically through Fig. 5 (constant temperature) from one isobar to another, corresponds to a *linear* increase in the water activity. Such linear increase in water activity is in turn accompanied by a directly proportional increase in the concentration of water vapor in the environment surrounding the powder sample. This means, for example, that a change from the 20% isobar to the 40% RH isobar, at constant temperature, corresponds to a doubling of the water activity resulting, in turn, from a doubling in the concentration of water molecules present in the vapor phase. In addition to being linear, such an isothermal increase in the vapor phase activity of water also represents a degree of freedom in terms of Gibbs phase rule, since it is controlled directly by the observer.

In contrast, moving *along* a relative isobar (increasing temperature), also corresponds to an increase in the water concentration in the vapor phase, but without an accompanying increase in water activity. In this case, the vapor phase water concentration increases with temperature due to the increase in saturation concentration with temperature, but the ratio between the concentration of water molecules in the vapor phase and the corresponding saturation concentration remains constant. It is important to point out that the concentration of water molecules along a relative isobar does not represent a degree of freedom in the sense of Gibbs phase rule; along a relative isobar, the vapor phase water concentration is fixed by the temperature. Another important consideration is that a raise in temperature produces a non-linear increase in the water concentration present in the vapor phase.

The differences in water uptake between the two crystal forms are clearly observable in Fig. 5. The figure also shows details about the differences between the two materials that are not readily observable in Fig. 3. The adsorption capacity of form A shows more significant variations in the vertical direction, whereas the variability in adsorption for form B is more pronounced as a function of temperature (horizontally). At high relative humidity values, the increase in water uptake by form A is disproportionate with the increase in relative humidity. The vertical spread of relative isobars observed for form A is an indication of the greater degree of surface heterogeneity on this form. A perfectly homogeneous surface would show a vertical spread of lines in direct proportion to the spread of the corresponding relative humidity values. Fig. 5 shows that the relative isobars are more proportionately distributed in the case of form B. However, in this case an increase in water uptake is clearly observable at the highest temperature investigated (45 °C). At 45 °C, form B shows signs of surface heterogeneity similar to those observed with form A at lower temperatures. Because the mechanism of water adsorption is hydrogen bonding, which is significantly weakened with increasing temperature, the excess sorption with temperature has to be the result of the increased collision frequency of the water vapor molecules onto the crystal surface and other water molecules.

The microcalorimetric data of Fig. 4 is presented as relative isobars in Fig. 6. Unlike the different profiles obtained from water uptake, the heat evolved upon the adsorption of water results in patterns of similar shape for the two adsorbents. The presence of a threshold value at about 70% RH is clear for both crystal forms. Relative humidity conditions of 70% and higher give place to a significant increase in the heat of adsorption for the two polymorphs. The increased heat of adsorption above 70% RH peaks at about 25 °C, for the two crystal forms. It is evident from Figs. 5 and 6 that the peaks observed in the heat of adsorption (Fig. 6) do not correspond, for either adsorbent, to an accompanying peak in water uptake (Fig. 5). This means that any feasible explanation for the observed bell shaped increase in the heat of adsorption in Fig. 6 must exclude an accompanying increase in water adsorption. A consistent and likely explanation for the presence a peak in the heat adsorption, is the presence of interactions between the water molecules adsorbed on the surface. Adsorbed molecules have some degree of two dimensional

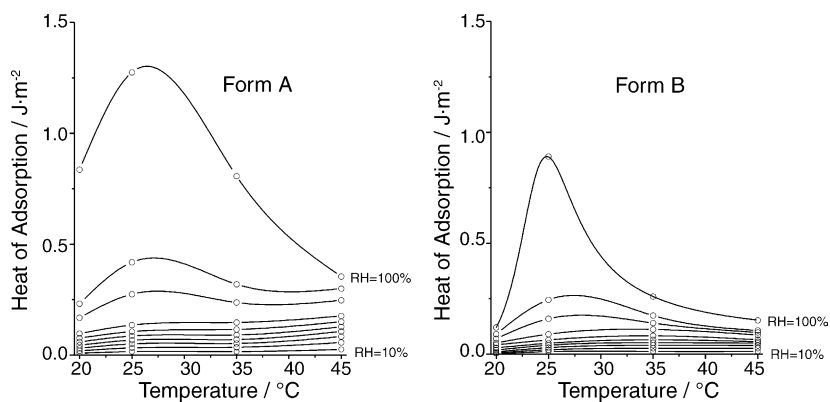


Fig. 6. Heat of adsorption data presented as relative isobars for the two adsorbents.

mobility and exhibit the behavior of non-ideal gases (Adamson, 1990). At sufficiently high surface concentrations, adsorbed molecules can interact and form clusters. The formation of this type of aggregates would produce an exothermic signal without accompanying additional adsorption, as was observed in this study. Cluster formation by adsorbed water molecules has been observed in activated carbons (Salame and Bandoz, 1999). In those cases, formation of water clusters takes place under fairly low humidity conditions, such that surface phenomena control the sorption process at relative humidities as low as 30% or even less. The preceding account could also explain why the excess heat of adsorption peaks at a particular temperature (25 °C in the present case). The formation of clusters on the crystal surface requires the adsorbed molecules to have certain degree of mobility. This situation implies that clusters will be formed by adsorbed water molecules that are not very strongly bound. Raising temperature will hinder cluster formation of adsorbed water molecules. On the other hand, if the temperature is too low (recall that saturation pressure decreases with decreasing temperature), insufficient density of adsorbed molecules would also prevent

cluster formation. The data in Figs. 5 and 6 suggest that the optimal temperature for adsorbed cluster formation is about 25 °C for the two polymorphs of this study.

Figs. 5 and 6 show that the two crystal forms are quantitatively different in their interactions with water in terms of both their adsorption capacity as well as the heat evolved upon the adsorption of water. One relevant question is how these measurable differences manifest themselves in the energetics of interaction of the probe molecule with each of the surfaces involved. Figs. 5 and 6 are greatly informative in differentiating between the two adsorbents. However, the information in these figures is still somewhat limited because both water uptake and energy of adsorption are given relative to the amount of adsorbent present (expressed as surface area). In order to establish the inherent differences in surface energetics between the two types of surface, it would be more informative to look into the energy evolved when a water molecule “lands” on one type of surface versus the other. By combining the water uptake and calorimetric data, it is possible to assess the strength of the interaction between the adsorbed water molecules and the different surfaces. Fig. 7

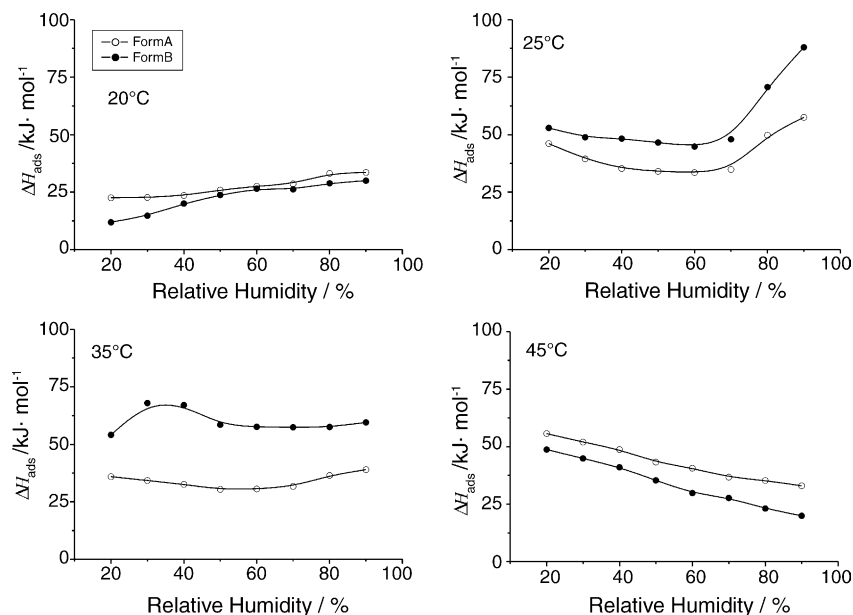


Fig. 7. Specific heat of adsorption for water on each of the two different crystal forms, as a function relative humidity, at different temperatures.

combines the information presented in Figs. 5 and 6. This figure shows the specific heat of adsorption, i.e., the heat of adsorption relative to the amount of water adsorbed instead of to the amount (surface) of crystalline adsorbent present. The specific heat of adsorption is more informative about the energetics of sorption. The specific heat of adsorption centers on the adsorbate and the energy evolved upon water adsorption, without the questionability of whether a unit surface area of form A is truly equivalent to a unit area of form B. Since the two crystal forms used in this study adsorb small amounts of water, calculation of specific heats of adsorption values were restricted to the 20–90% RH range, where sorption measurements are most reliable. The data in Fig. 7 point toward a fundamental difference between polymorphs A and B. At 25 °C, both the total heat of adsorption and the amount of water adsorbed are greater for form A than for form B. However, the specific heat of adsorption is greater for form B. This result is strong indication of a very different type of interactive surface in each case. More water can adsorb onto surface A than on surface B, but this happens by the adsorbate occupying a greater number of sites on the crystal surface of A that are, in terms of their interaction with water, actually weaker than the adsorption sites on the surface of form B. In the range of temperatures typical of pharmaceutical processing, form A thus exhibits a greater ability to interact with water through a greater number of weaker interactions on its surface than those present on form B. In physical terms, this situation corresponds to something very much like an energetic equivalent to surface “fuzziness” in the case of the surface of form A. A crude but useful analogy on these lines would be to visualize the surface of particles of form A, as consisting of a material such as Velcro®. In contrast, the surface of polymorph B would be analogous to a material covered with snap press buttons. Site by site, the interactions of the fuzzy surface are weaker, but they are more numerous and have less restrictive orientation requirements. The net effect is that a fuzzy surface will result in greater cumulative adhesion energy for the particle as a whole. It is noteworthy that in order to attain similar particle size distribution for the two polymorphs, it was form B the material subjected to the more energy intensive milling process, since it consisted of substantially larger crystals. However, form A is the one that exhibits the more energetically heterogeneous surface, based on the interactions with water.

The foregoing discussion brings forth the question of which one of the two crystalline adsorbents, A or B, has the more hydrophobic (or hydrophilic) surface. In terms of the amount of water adsorbed, form A can be considered more hydrophilic (or less hydrophobic). However, in terms of affinity (strength of the interaction), the surface of form B has greater affinity for water molecules. A comparison of the interaction of the two surfaces with a hydrophobic probe would give useful information regarding this question. The sorption instrument and the calorimeter were both setup to run adsorption measurements with the two crystal forms using heptane vapor as the adsorbate at 25 °C. The vapor uptake, integral heat of adsorption and specific heat of adsorption data for the two crystal forms are plotted in Fig. 8. Up to  $P/P^0 \sim 0.8$ , form B shows greater values for all three parameters. It is important to point out that the specific heat of

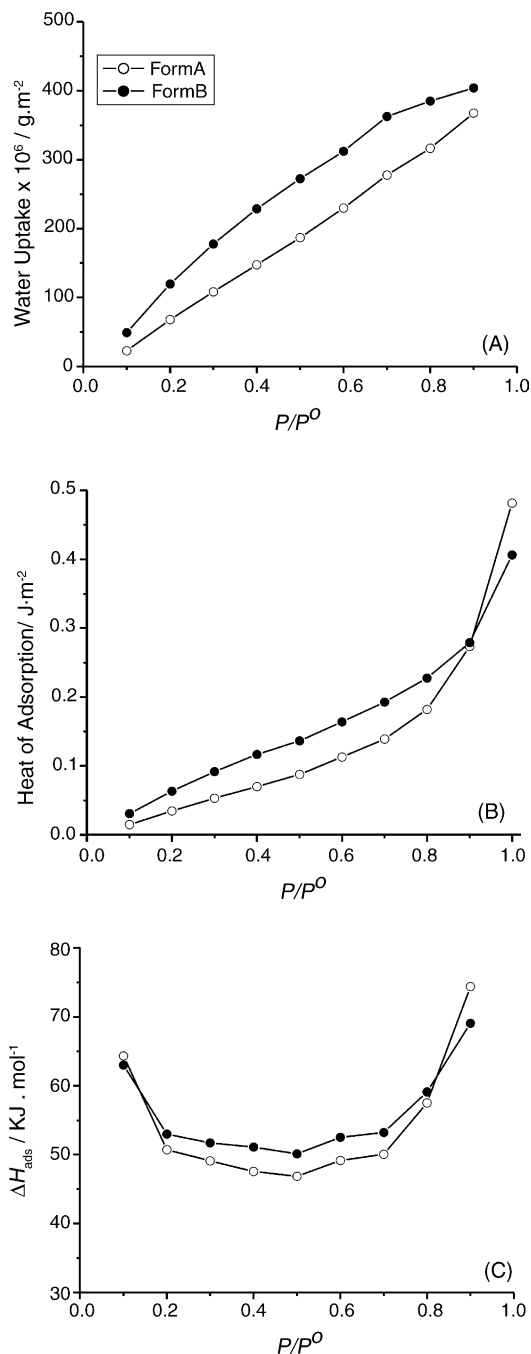


Fig. 8. Adsorption of heptane on the two crystal forms. (A) Vapor uptake isotherm; (B) integral heat of adsorption; (C) specific heat of adsorption.

adsorption for water and heptane are both higher for polymorph B. Crystals have different faces, and each face can exhibit different chemical and physical properties. The existence of sorption sites of different nature (acidic, basic, oxidizing and reducing) on the same material surface has been established for inorganic crystals. Some inorganic polymorphs exhibit different adsorptive properties due to different nature and density of adsorption sites on their surface, which in turn is the direct result of their different crystal structures (Bachiller-Baeza et al., 1998). A similar argument would explain the greater strength for both hydrophilic and hydrophobic interactions observed with form B.

It is noteworthy from Fig. 8 that the adsorption of heptane by form A gives an essentially straight line. Although the data are limited, such a profile suggests some level of uniformity in the energetic distribution of hydrophobic adsorption sites for this polymorph. It is interesting to point out that in its interaction with water, form A exhibits greater level of heterogeneity on its surface than form B, whereas in its interaction with a hydrophobic probe such as heptane, the surface of form A does not seem to exhibit the same degree of heterogeneity.

#### 4. Conclusions

Crystal polymorphs are distinctly different materials of identical chemical composition. The different spatial arrangements of the same molecule produce physicochemical differences that manifest themselves on the surface of the corresponding crystals. Water adsorption experiments were conducted to probe the surface properties of two polymorphs of an organic compound of pharmaceutical relevance. The surfaces of the two crystal forms investigated in the present study, are energetically different to sufficient degree, as to allow direct and reliable measurements of their interaction with a common probe such as water. The fact that the powders used in this study were both milled materials deserves further discussion. The physical stress that the milling process imparts on the crystals produces defects on their surfaces, thus affecting their powder properties (Feeley et al., 1998, 2002; Mackin et al., 2002a). There is a widespread notion that the milling of powders completely obliterates the crystalline character of their surfaces. However, while there is a significant amount of published work on methodologies for assessing the presence and levels of amorphous regions on processed powders (Briggner et al., 1994; Giron et al., 1997; Mackin et al., 2002b; Brodka-Pfeiffer et al., 2003; Price and Young, 2005), there is remarkably little published work aimed at investigating whether milling actually effaces the crystalline character of powder surfaces. In some cases, milling has been reported to result in a powder surface that resembles that of the amorphous material (Newell et al., 2001). In other instances however, milling produces powders whose surfaces are not very different from those of the unmilled crystalline material (Tong et al., 2002). The results of the present study indicate that the differences between the two milled materials investigated, are primarily due to the fact that they are different crystal forms. The fact that the specific heat of adsorption of two adsorbates as different as water and heptane, is greater in both cases for the same polymorph (B), can only be explained by a highly structured arrangement of the drug molecules on the adsorbing surface. In other words, by the crystalline nature of the surfaces involved. For the polymorphic system used in this study, the difference in adsorption properties between the two forms is primarily a reflection of their different crystalline structure. Moreover, infinite dilution studies using inverse gas chromatography (Carvajal, 2001) provide further evidence for this argument. These results do not imply that the milled powders used in this study are free of surface defects, because they certainly have them. But for the powders studied here, the different crystalline attributes of their surfaces predominate in determining their surface properties.

The two materials investigated in this study showed measurable differences in the extent of water sorption, specific heat of adsorption as well as in the level of heterogeneity of their surfaces. The combined use of vapor sorption measurements and microcalorimetry proved to be a powerful tool capable of revealing critical differences in the interactive properties of the two types of surface investigated. The combination of techniques provides details about the two surfaces that clearly differentiate them. Form A exhibits a greater number of weaker active sites for water on its surface compared with form B. Conversely, the surface of form B exhibits stronger binding sites for water, but these are more limited in number. The type of adsorptive behavior shown by form A was interpreted as analogous to (energetic) surface fuzziness. It is interesting to note that the atomic force microscopy studies on the surface of cimetidine polymorphs have shown that only for one of the two physical forms of this compound, adsorbed water (as a function of relative humidity) alters the AFM-obtained image of the corresponding surface (Danesh et al., 2000). It seems therefore that for certain crystalline structures, the boundary between the layer of adsorbed water and the crystal surface itself is somewhat blurred.

The results from water adsorption experiments in this study indicate that the surface of form A is somewhat more heterogeneous than that of form B. However, from the adsorption of a non-polar, non-hydrogen bonding adsorbate such as heptane, the surface of polymorph A seems rather homogeneous, even more so than the surface of form B. These findings indicate that surface heterogeneity is better viewed as an energetic concept, rather than a topological one. It is clear that at the molecular level, the best description of a surface would be given by an account of its interactions.

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