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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.

Keywords: Water activity; Water uptake; Water interactions; Moisture sorption; Isothermal microcalorimetry; Vapor sorption; Crystal surface; Polymorphs; Water–solid interactions; Surface energetics

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_4 (LTD_4) 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_4 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

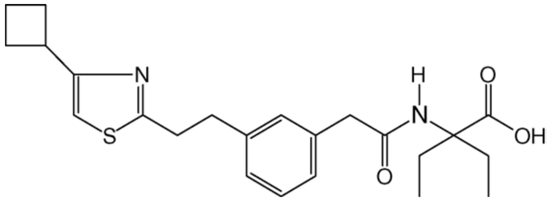

Fig. 1. Chemical structure of LTD_4.

Table 1
Physicochemical properties LTD_4 polymorphs A and B

Property	Polymorph	
	A	B
Absolute density ($g\,ml^{-1}$)	1.260	1.290
Melting point (°C)	163	167
ΔH_m ($J\,g^{-1}$)	275	300
Water solubility ($\mu g\,ml^{-1}$)	1.23	0.86

A pharmaceutical organic compound (LTD_4, Hoffmann-La Roche, Nutley, NJ, USA) was selected to make the two types of powder to be used as adsorbents. The chemical structure of LTD4 is shown in Fig. 1. The compound is highly hydrophobic, practically insoluble in water. The LTD_4 compound can be prepared as two different crystal forms, A and B. The two 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_4

Crystal form	*Z*	*a* (Å)	*b* (Å)	*c* (Å)	*β*	Volume (Å^3)	Volume per molecule (Å^3 molecule^{-1})	Space group
A	4	18.018	6.916	18.182	92.15	2264	566	$P2_1/a$
B	4	6.930	23.059	13.606	96.55	2160	540	$P2_1/n$