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Inverse gas chromatography a tool to follow physicochemical modifications of pharmaceutical solids: Crystal habit and particles size surface effects

M.G. Cares-Pacheco[a,*], R. Calvet[a], G. Vaca-Medina[b,c], A. Rouilly[b,c], F. Espitalier[a]

[a] Université de Toulouse; Mines Albi, UMR CNRS 5302, Centre RAPSODEE; Campus Jarlard, F-81013 Albi cedex 09, France
[b] Université de Toulouse; INP-ENSIACET, LCA, 310130 Toulouse, France
[c] INRA; UMR 1010 CAI, 310130 Toulouse, France

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ABSTRACT

Powders are complex systems and so pharmaceutical solids are not the exception. Nowadays, pharmaceutical ingredients must comply with well-defined draconian specifications imposing narrow particle size range, control on the mean particle size, crystalline structure, crystal habits aspect and surface properties of powders, among others. The different facets, physical forms, defects and/or impurities of the solid will alter its interaction properties. A powerful way of studying surface properties is based on the adsorption of an organic or water vapor on a powder. Inverse gas chromatography (IGC) appears as a useful method to characterize the surface properties of divided solids.

The aim of this work is to study the sensitivity of IGC, in Henry's domain, in order to detect the impact of size and morphology in surface energy of two crystalline forms of an excipient, D-mannitol. Surface energy analyses using IGC have shown that the α form is the most energetically active form. To study size and shape influence on polymorphism, pure α and β mannitol samples were cryomilled (CM) and/or spray dried (SD). All forms showed an increase of the surface energy after treatment, with a higher influence for β samples (γ_s^d of 40–62 mJ m^{-2}) than for α mannitol samples (γ_s^d of 75–86 mJ m^{-2}). Surface heterogeneity analysis in Henry's domain showed a more heterogeneous β-CM sample (62–52 mJ m^{-2}). Moreover, despite its spherical shape and quite homogeneous size distribution, β-SD mannitol samples showed a slightly heterogeneous surface (57–52 mJ m^{-2}) also higher than the recrystallized β pure sample (~40 mJ m^{-2}).

1. Introduction

Pharmaceutical solids must comply with well-defined specifications in terms of bioavailability, solubility, toxicity and stability. Nowadays, the requirements are more and more draconian, imposing narrow particle size range, control on the mean particle size, crystalline structure, crystal habits aspect and surface properties of powders, among others. A large set of operations is developed to answer these requirements. The processes for producing fine powders (around micrometer) are varied as melt quenching, grinding, freeze-drying, spray drying, crystallization, antisolvent precipitation, milling, and supercritical fluids. Depending upon the nature of the active pharmaceutical ingredients (APIs), it is known that the preparation method influences the physical stability and crystallization behavior. The impact of these processes on solid phase transformations may lead to the formation of a metastable or an amorphous form, or a mixtures of various crystalline forms including other hydrates (or solvates). These changes are desired for certain stages of the formulation or for some use properties of the API, but sometimes can also have undesirable effects on the solid.

Inverse gas chromatography (IGC) appears as a tool to study the changes on surface properties in order to highlight process influences to assess drug delivery systems performance. Mechanical operations are the most studied processes to determine pharmaceutical solids surface's behavior. Most authors described an increase of the dispersive component of the solid surface energy, γ_s^d, after mechanical grinding (Table 1). This increase is generally attributed to the exposure of specific crystal facets that present different chemical groups, the formation of higher energy zones such as crystal defects, dislocations and/or to solids state transformations (Chamarthy et Pinal, 2008; Feeley et al., 2002;

* Corresponding author.
E-mail address: gcares@mines-albi.fr (M.G. Cares-Pacheco).

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Nomenclature

a_s (m^2/g)	Specific surface area of the solid
d (n,0.5) (μm)	Number median diameter
D [υ,0.5] (μm)	Median volume diameter
Δg_{ads} (J/mol)	Molar free energy variation for an isothermal adsorption of probe molecules
m (g)	Sample mass
n (mol)	Desorbed mole number
n_{ads} (μmol/g)	Adsorbed mole number per gram of solid
n_m (mol)	Monolayer capacity or number of adsorbed moles corresponding to a monolayer
P (Pa)	Vapor pressure or partial pressure
P_{sat} (Pa)	Saturation vapor pressure
T (K)	Temperature
T_c (K)	Column temperature
t_N (min)	Net retention time
V_N (cm^3)	Net retention volume
W_{adh} (J/m^2)	Work of adhesion when adsorption occurs
n/n_m (–)	Surface coverage

Greek symbols

γ_l^d (J/m^2 or N/m)	Liquid surface energy (or surface tension)
γ_s^d (J/m^2 or N/m)	Dispersive component of solid surface energy
γ_s (J/m^2 or N/m)	Total surface energy of a solid
γ_s^{sp} (J/m^2 or N/m)	Specific component of solid surface energy
θ_s (–)	Surface coverage

Table 1
An overview of the influence of particles size reduction over the surface properties of pharmaceutical ingredients by IGC.

Pharmaceutical solid	γ_s^d	Reference
Acetaminophen	↑	Trowbridge et al. (1998) Heng et al. (2006)
Cefditoren pivoxil	↓	Ohta and Buckton (2004)
DL-propanolol hydrochloride	↑	York et al. (1998)
Felodipine	↑	Chamarthy and Pinal (2008)
Griseofulvine	↑	Chamarthy and Pinal (2008) Feng et al. (2008) Otte and Carvajal (2011)
	↓	Otte et al. (2012)
Ibipinabant	↑	Gamble et al. (2012)
Indomethacin	↑	Planinsek et al. (2010) Lim et al. (2013)
Lactose	↑	Ahfat et al. (2000) Feeley et al. (2002) Newell and Buckton (2004) Thielmann et al. (2007) Shariare et al. (2011) Brum and Burnett (2011) Jones et al. (2012)
Mannitol	↑	Ho et al. (2012)
Salbutamol sulfate	↑	Ticehurst et al. (1994) Feeley et al. (1998)
Salmeterol Xinofoate	↑	Tong et al. (2001, 2006) Das et al. (2009)
Sucrose	↑	Surana et al. (2003) Hasegawa et al. (2009) Luner et al. (2012)
Succinic acid	↑	Luner et al. (2012)

Feng et al., 2008; Heng et al., 2006; Ho et al., 2012; Newell and Buckton, 2004).

1.1. Surface energy, particles size and surface chemistry

Due to the anisotropic nature of powders, the exhibition of new crystal faces under milling can change the acidic/basic character of the solid depending on the functional groups present in the exposed facets. Heng et al. (2006) highlighted the anisotropic nature of form I paracetamol crystals. The confrontation of sessile drop and IGC, allowed them to conclude that grinding leads to a fragmentation of the facet (0 1 0), which possesses the weakest attachment energy and exhibits the large γ_s^d. Thus, after milling the γ_s^d of the samples increased, showing a more hydrophobic surface, with decreasing particle size.

York et al. (1998) were interested in the milling of DL-propranolol hydrochloride. The evolution of γ_s^d showed to depend on the particles size. During milling the surface becomes increasingly more energetic (γ_s^d from 45 to 61 mJ/m^2 for particles 75–16.5 μm) until reached a plateau followed by a small fall in γ_s^d for the finest powder (<10 μm). The authors concluded that the increases in γ_s^d, and in Δg_{ads} using CH_2Cl_2 as probe molecule, are due to a fragmentation releasing the dominant crystal face, which posses the lowest attachment energy and is rich in naphthalene groups. Attrition might become significant as milling intensity increase releasing faces having OH groups, naphthalene and Cl^- ions.

Trowbridge et al. (1998) highlighted that acetaminophen size reduction from 30 to 10 μm leaded to an increase of γ_s^d from 50.9 to 61.3 mJ/m^2 and to an increase of Δg_{ads} from 327 to 506 J/mol, using chloroform as probe molecule. Milling also increases the hydrophobic and basic character of acetaminophen surface. This results are in agreement with those obtained by molecular modeling which established that milling leads to the exposure of the crystal facet (0 1 0) which contain an hydrophobic methyl group, a benzene ring and a carboxyl group, both basic.

Ohta and Buckton (2004) studied surface energetic changes of cefditoren pivoxil, a cephalosporin antibiotic, as consequence of milling. After grinding in a vibration mill, the authors found a decrease in the γ_s^d according to the grinding time, from 52.3 mJ/m^2 before milling to 45.8 mJ/m^2 after 30 min of grinding with a decrease in solid crystallinity. In addition, the authors have shown a decrease in the solid acidic character with an increased on its basicity. These effects are attributed to the exposure of carbonyl groups, which have an electron donating nature.

Luner et al. (2012) studied by IGC the impact of high shear wet milling (HSWM) and dry milling (DM) on the surface properties of two pharmaceutical compounds, succinic acid and sucrose. Physicochemical characterization of both samples showed that bulk properties were unaffected by wet and dry milling while surface properties analyses showed an increase of solids dispersive surface energy after DM and HSWM. Succinic acid samples, γ_s^d = 35 mJ/m^2, exhibit minor differences between dry milled and wet milled samples, 40 ± 2 mJ/m^2, attributed to minimal impact of cleavage and the exposure of crystal facets with similar atomic surface arrangements. For HSWM sucrose, the polarity of the solvents used during wet milling influenced γ_s^d of the milled samples from 55 to 71 to 91 mJ/m^2, for hexane, methyl tertiary butyl ether and ethanol respectively while dry milled samples exhibit a γ_s^d of 44 mJ/m^2. Differences between dry and wet milling processes were attributed to the attrition mechanism in presence of solvent.

Reducing particle size may also be necessary for the API to reach the target organ, particularly when the drug administration is by