Physicochemical characterization of D-mannitol polymorphs: The challenging surface energy determination by inverse gas chromatography in the infinite dilution region

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

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

A B S T R A C T

Nowadays, it is well known that surface interactions play a preponderant role in mechanical operations, which are fundamental in pharmaceutical processing and formulation. Nevertheless, it is difficult to correlate surface behaviour in processes to physical properties measurement. Indeed, most pharmaceutical solids have multiple surface energies because of varying forms, crystal faces and impurities contents or physical defects, among others.

In this paper, D-mannitol polymorphs (α, β and δ) were studied through different characterization techniques highlighting bulk and surface behaviour differences. Due to the low adsorption behaviour of β and δ polymorphs, special emphasis has been paid to surface energy analysis by inverse gas chromatography, IGC. Surface energy behaviour has been studied in Henry's domain showing that, for some organic solids, the classical IGC infinite dilution zone is never reached. IGC studies highlighted, without precedent in literature, dispersive surface energy differences between α and β mannitol, with a most energetically active α form with a γ_s^d of 74.9 mJ·m^{-2}. Surface heterogeneity studies showed a highly heterogeneous α mannitol with a more homogeneous β (40.0 mJ.m^{-2}) and δ mannitol (40.3 mJ.m^{-2}). Moreover, these last two forms behaved similarly considering surface energy at different probe concentrations.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Active pharmaceutical ingredients, APIs, must comply with well-defined specifications in terms of bioavailability, stability, toxicity, purity, morphology, stability, size, etc. Most of these substances can exist in several solid-state forms: polymorphs, pseudo-polymorphs, solvates/hydrates or amorphous forms depending on the generation, growth and formulation conditions. This diversity of solid forms requires a thorough understanding of solid-state phenomena that may occur in pharmaceutical engineering. Each of these forms has a different crystalline structure, and hence, different physicochemical properties. In the pharmaceutical field, the consequences related to polymorphism, habitus, surface state and particle size distribution does not relate only to APIs but also to excipients. Moreover, excipients play a key role in manufacturability but also in API's dissolution and bioavailability. Solid surface properties such as size, shape and powder agglomeration are also known to impact dissolution behaviour, compactability, aerosol performance and surface energetics among others (Ho et al., 2012; Tang et al., 2009).

Thus, to ensure a high quality to these organic solids, it is essential characterizing the solid-state forms, both in qualitative and quantitative ways. Characterization can be approached by a wide variety of analytical techniques. Over the last decade, the most frequently used solid-state techniques have been in decreasing order, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), infrared spectroscopy (IR) and microscopy (Chieng et al., 2011). Most authors use at least two characterization techniques; however, all these methods give information at different levels or different depths within the solid and not especially on the surface. These days, it is well known that surface interactions play a fundamental role in mechanical operations such as grinding, milling and compaction, processes

* Corresponding author. Tel.: +33 5 63 49 32 26; fax: +33 5 63 49 30 25.
  E-mail address: gcares@mines-albi.fr (M.G. Cares-Pacheco).

Nomenclature

$\mathcal{A}$ (m²)	Surface area of solid in contact with the adsorbed phase
A_{ads} (J)	Helmholtz free energy of the adsorbed phase
a_g (m²/molecule)	Area occupied by an adsorbed probe molecule
a_s (m²/g)	Specific surface area of the solid
F_{ads} (J)	Free energy of the adsorbed phase
F_s (cm³STP/min)	Carrier gas flowrate at the exit of the column at 273.15–K and standard pressure
ΔG_{ads} (J)	Gibbs free energy variation for isothermal adsorption of n_{ads} moles of probe from n_g moles in gas phase initially
Δg_{ads} (J/mol)	Molar free energy variation for an isothermal adsorption of probe molecules
Δg_{CH_2} (J/mol)	Molar free energy variation for an isothermal adsorption of a methylene group
j (−)	James–Martin correction factor
K (m)	Henry's constant
m (g)	Sample mass
n_{ads} (mole)	Adsorbed mole number
N_a (molecules/mol)	Avogadro number
n_g (moles)	Number of gas moles
n_m (moles)	Monolayer capacity or number of adsorbed moles corresponding to a monolayer
n_{sol} (moles)	Solid mole number
P (Pa)	Vapour pressure
P_2 (Pa)	Vapour pressure of a pure component in equilibrium with its adsorbed phase at a spreading pressure π_2
R	Perfect gas law constant, 8314 J K⁻¹ mol⁻¹
S_{ads} (J/K)	Entropy of the adsorbed phase
T (K)	Temperature
T_c (K)	Column temperature
t_N (min)	Net retention time
t_0 (min)	Dead time
t_R (min)	Retention time
V_{ads} (m³)	Volume of the adsorbed phase
V_N (cm³/g)	Net retention volume
W_{adh} (J/m²)	Work of adhesion when adsorption occurs

Greek symbols

γ_c (J/m² or N/m)	Critical surface energy of a solid (used in Zisman theory)
γ_l^d (J/m² or N/m)	Liquid surface energy (or surface tension)
γ_s^d (J/m² or N/m)	Dispersive component of solid surface energy
γ_s (J/m² or N/m)	Total surface energy of a solid
γ_s^p (J/m² or N/m)	Polar component of solid surface energy
$\gamma_{CH_2}^d$ (J/m² or N/m)	Dispersive component of surface energy of a methylene group
θ (°)	C angle of a liquid on a solid
θ_s (−)	Surface coverage
μ_{ads} (J/mol)	Chemical potential of the adsorbed phase
μ_g (J/mol)	Chemical potential of the gas phase
π (J/m²)	Spreading pressure of the adsorbate per unit surface area of solid
π_2 (J/m²)	Spreading pressure of the adsorbate in equilibrium with its vapour phase at P_2
φ (J/mol)	Change in internal energy per mole unit of adsorbent due to the spreading of adsorbate

commonly used in pharmaceutical formulations but also in storage stability. Indeed, an important physicochemical property of solids is the surface energy because it reflects interfacial interactions between the solid and its environment. It seems, therefore, of utmost importance to examine and quantify the surface properties of a solid.

Organic solids are definitely complex systems. The complexity is related to the anisotropic nature of crystalline solids. In fact, it has been demonstrated that each face of a crystal or defects present in the solid structure has different surface properties generally attributed to different proportions of the functional groups exposed on it (Heng et al., 2006; Ho et al., 2010). Thus, a single value that represents the surface energy of a powder may be at best, a mean value.

A quite large number of methods have been used in the literature to determine surface energy on pharmaceuticals solids; contact angle, vapour adsorption techniques and atomic force microscopy (AFM). The most common methods are those that relate, directly or indirectly, surface energy to the contact angle formed between a liquid and a solid: spreading, capillary rise, Wilhelmy plate and heat of immersion. The limitations of these methods have been well reviewed but, even if the surface energy values obtained from contact angle measurements are somewhat inaccurate, the mean values obtained have been successfully correlated to functionality or end-use properties (Buckton, 1995; Buckton and Gill, 2007).

Nowadays, the study of the anisotropic surface properties of a solid goes through the investigation of solid–vapour interactions. In fact, wettability measurements are based on the interaction between a liquid and a solid surface. This leads to a macroscopic average of the surface energy, which is sensitive to surface roughness, porosity, packing structure and tortuosity of the porous material. On the contrary, gas–solid interactions give access to microscopic variations of the surface structure. Indeed, the study of the interactions between isolated gas molecules and the solid of interest will be sensitive to local variations of the surface at a molecular scale. Different characterization techniques are implemented based on vapour adsorption–desorption onto/from a solid, which are aimed to give information on specific surface area, porous structure and distribution (Rouquerol et al., 1999). The mechanisms of surface coverage and/or pore filling can be described by the study of a sorption isotherm. Indeed, the overall shape of the isotherm is governed by the gas–solid interactions, the solid's pore structure and temperature. A sorption isotherm relates the adsorbed vapour amount to the vapour concentration surrounding the solid in equilibrium conditions. Different parameters can be measured to determine an adsorption isotherm: the vapour pressure, the sample mass and the retention time. Each of these properties gives rise to a class of analytical techniques; manometric, gravimetric or chromatographic. However, very few are exploited to give surface energetic information; for that purpose, the two main techniques commonly used are dynamic vapour sorption (DVS) (Storey and Ymén, 2011) and inverse gas chromatography (IGC) (Ho and Heng, 2013; Mohammadi-Jam and Waters, 2014).