Journal of Pharmaceutical Sciences 106 (2017) 1538-1544

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

The Pressure-Temperature Phase Diagram of Metacetamol and Its Comparison to the Phase Diagram of Paracetamol

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ARTICLE INFO

Article history:
Received 15 November 2016
Revised 11 January 2017
Accepted 2 February 2017
Available online 10 February 2017

Keywords:
calorimetry
crystal polymorphism
physical characterization
phase behavior
topological phase diagram
thermodynamics
solid state
thermal expansion
physical stability

ABSTRACT

Understanding the polymorphic behavior of active pharmaceutical ingredients is important for formulation purposes and regulatory reasons. Metacetamol is an isomer of paracetamol and it similarly exhibits polymorphism. In the present article, it has been found that one of the polymorphs of metacetamol is only stable under increased pressure, which has led to the conclusion that metacetamol like paracetamol is a monotropic system under ordinary (= laboratory) conditions and that it becomes enantiotropic under pressure with the I-II-L triple point coordinates for metacetamol $T_{I\text{-}II\text{-}L}$ = 535 ± 10 K and $P_{I\text{-}II\text{-}L}$ = 692 ± 70 MPa. However, whereas for paracetamol the enantiotropy under pressure can be foreseen, because the metastable polymorph is denser, in the case of metacetamol this is not possible, as the metastable polymorph is less dense than the stable one. The existence of the stability domain for the less dense polymorph of metacetamol can only be demonstrated by the construction of the topological phase diagram as presented in this article. It is a delicate interplay between the specific volume differences and the enthalpy differences causing the stability domain of the less dense polymorph to be sandwiched between the denser polymorph and the liquid. Metacetamol shares this behavior with bicalutamide and fluoxetine nitrate.

Introduction

Metacetamol

Metacetamol is an isomer of the well-known drug paracetamol and is also known as 3-acetamidophenol or *N*-(3-hydroxyphenyl) acetamide. The chemical structure is provided in Figure 1. Its crystalline dimorphism has been demonstrated by McGregor et al., who recently published the structure of a new polymorph, form II, which is monoclinic with space group $P2_1$. They also confirmed the structure of the known polymorph, form I, which is orthorhombic with space group $Pna2_1$.[1,2]

The present study has been carried out in the framework of a more general study on the pressure-temperature (P-T) behavior of polymorphism in small organic molecules and in particular in active pharmaceutical ingredients (APIs). Often, polymorphism of active ingredients is tested by a few calorimetric measurements by differential scanning calorimetry (DSC) and transition temperatures are reported with the accuracy of the equipment stated in the manual. In an ideal world, this approach would certainly be viable, but often the system exhibits more complicated behavior, which only becomes apparent when multiple measurements at multiple heating rates are carried out. For example, the API may be decomposing or the solid-solid transition of an enantiotropic system may depend on the heating rate of the DSC measurements.[3-5] It implies that it is often wise to establish the best possible representation of the phase behavior of an API including its behavior under pressure. The latter parameter is important, because thermodynamics is consistent. The phase behavior under pressure must coincide with that observed under "ordinary conditions" (i.e., conditions where the system is free to set its own pressure as in a DSC for example). High-pressure phase transition measurements can therefore be used for verification. In other cases, high-pressure data may even be used to find transition temperatures that are not observed by measurements under "ordinary conditions," as was the case for paracetamol[6,7] and other systems.[5,8] Measurements will always depend on kinetic factors

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http://dx.doi.org/10.1016/j.xphs.2017.02.003
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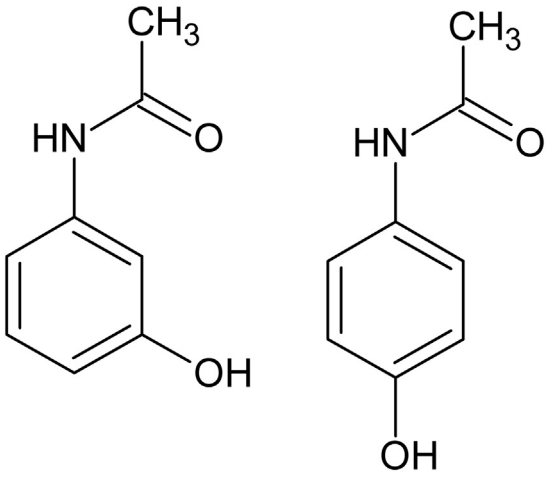

Figure 1. Chemical structure of metacetamol (left-hand side) (*N*-(3-hydroxyphenyl) acetamide), $C_8H_9N_2O_2$, M = 151.16 g mol^{-1}, and for comparison on the right-hand side, the chemical structure of paracetamol.

(also high-pressure measurements for that matter, but the response of the system may be different), but the thermodynamic behavior of a system only depends on the differences in Gibbs energy between the phases. The most obvious reason to use high-pressure measurements is to study the response of an API to pressure, because during tableting and grinding it will be subjected to changing pressure. In particular for monotropic systems such as paracetamol, the fact that a second polymorph exists, but with an unknown stability domain, essentially obliges the scientist in pre-formulation to investigate, where the solid-solid transition is located as a function of pressure and temperature, because one would like to know whether a sudden transition into the metastable form by processing the API under pressure is likely or not.

The objective of this article was to establish the topological and experimental P-T phase diagram of the dimorphism of metacetamol. Data at ordinary pressure and experimental measurements under pressure have been obtained. In the case of its isomer paracetamol, the topological approach had led to the correct prediction of the experimental P-T phase diagram that was obtained a few years later.[6,7] Because paracetamol and metacetamol are closely related isomers, a comparison will be made between their phase diagrams.

Available Data From the Literature

The melting point of form I and its melting enthalpy have been determined by Perlovich et al[9]: $T_{I\rightarrow L}$ = 416.2 K, $\Delta_{I\rightarrow L}H$ = 24.6 kJ mol^{-1} (= 163 J g^{-1}). They determined its vapor pressure too in the range from 344.5 K to 397 K, which can be summarized as:

$$\ln P_{I\rightarrow V}/\mathrm{Pa} = 33.0(\pm 0.4) - 13188(\pm 138)/(T/\mathrm{K}) \quad (1)$$

Unfortunately, McGregor et al.,[1] who used DSC to determine the temperatures of fusion of forms I and II and reported onsets at 420.5 K and 400 K, respectively, did not mention the melting enthalpies. However, they did provide the recorded DSC curves on heating and on reheating of the same specimen and therefore the surface areas of the melting peaks of the 2 forms could be determined. The surface ratio of 1.19 equals the ratio $\Delta_{I\rightarrow L}H/\Delta_{II\rightarrow L}H$, leading to an estimate of $\Delta_{II\rightarrow L}H$ = 137 J g^{-1} using the known value of $\Delta_{I\rightarrow L}H$ previously found by Perlovich et al.[9] A summary of the calorimetric results can be found in Table 1.

The specific volume for both polymorphs can be found in Table 1. Using the limited temperature-dependent data and assuming a linear relationship, the following 2 expressions for the specific volume as a function of the temperature can be found:

Table 1
Crystallographic and Calorimetric Data Available in the Literature for the 2 Known Polymorphs of Metacetamol

Temperature/K	Form I, Orthorhombic, Pna2$_1$ v_I/cm^3 g^{-1}	Form II, Monoclinic, P2$_1$ v_{II}/cm^3 g^{-1}	Ref
120	0.72586	0.72943	1
298	–	0.75453	1
293	0.75635	–	2
Polymorph	**T_{fus}/K**	**Δ_{fus}H/J g^{-1}**	**Ref**
Form I	416.2	162.74	9
	420.5	–[a]	1
	420.6 ± 1.0	190.6 ± 4.6	This work
Form II	400	–[a]	1
	399.4 ± 1.0	156.6 ± 4.5	This work

No numeric enthalpy data have been reported in ref 1.
[a] From ref 1, the ratio between the areas of the 2 melting peaks has been estimated to be 1.19 using the reported DSC curves.

$$v_I \Big/ \mathrm{cm^3 g^{-1}} = 0.70471 + 0.00017624 \cdot \mathrm{T/K} \quad (2)$$

$$v_{II} \Big/ \mathrm{cm^3 g^{-1}} = 0.71251 + 0.00014101 \cdot \mathrm{T/K} \quad (3)$$

From these 2 expressions, also the expansivity coefficients α_V can be obtained ($v = v_0 \cdot (1+\alpha_V \cdot T)$). For $\alpha_{V,I}$, it leads to 2.50 × 10^{-4} K^{-1} and for $\alpha_{V,II}$ 1.98 × 10^{-4} K^{-1} can be found. Both expansivity coefficients are close to the average value of about 2 × 10^{-4} K^{-1} found for molecular solids[10-19] and APIs.[20-23] However, a closer study of the 2 expressions 2 and 3 and the data in Table 1 demonstrates that although form I appears to be denser at low temperature, it exhibits the largest thermal expansion ($\alpha_{V,I} > \alpha_{V,II}$) and at room temperature its density is actually less than that of form II. This creates a thermodynamic dilemma, because 2 polymorphs with distinct internal energies due to the different interactions between the molecules can hardly lead to the same specific volume without encountering a discontinuity (i.e., phase equilibrium). This thermodynamic inconsistency is most likely due to the different x-ray diffraction equipment used for the measurement at 293 K.

If one were to construct the topological P-T phase diagram of metacetamol, it will be necessary to determine the volume inequality between the 2 phases unequivocally. In addition, reliable calorimetric data are a necessity, and if possible a comparison with an experimentally obtained P-T phase diagram would be welcome.

Materials and Methods

Metacetamol was purchased from Sigma-Aldrich with a purity higher than 97%. It was used as such after verification by X-ray diffraction that all peaks could be ascribed to polymorph I.

High-resolution x-ray powder diffraction measurements using the Debye-Scherrer geometry and transmission mode were carried out with a vertically mounted INEL cylindrical position-sensitive detector (CPS-120) with 4096 channels (0.029°—2θ angular step). Monochromatic Cu-Kα_1 (λ = 1.54056 Å) radiation was selected by means of an asymmetrically focusing incident-beam curved quartz monochromator. The generator power was set to 35 kV and 35 mA. Measurements as a function of temperature were taken by means of a liquid nitrogen 700 series Cryostream Cooler from Oxford, UK Cryosystems. External calibration by means of the cubic phase $Na_2Ca_3Al_2F_4$ and cubic spline fitting was used to convert the measurement channels into 2θ. Peak positions were determined using