



Raman spectroscopy of racemic ibuprofen: Evidence of molecular disorder in phase II

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ABSTRACT

Low- and high-frequency Raman experiments in the 5–200 cm⁻¹ and 600–1800 cm⁻¹ ranges were carried out in the crystalline and amorphous states of ibuprofen. Low-frequency investigations indubitably reveal the existence of a molecular disorder in the metastable phase (phase II), through the observation of quasielastic contribution below 30 cm⁻¹, and the absence of phonon peaks in the Raman susceptibility which mimics the density of vibrational states of an amorphous state. High-frequency Raman spectra indicate a local order in phase II similar to that in the glassy state. Both dynamic and static molecular disorder could contribute to the Raman signatures of the disorder in crystalline phase II. Raman investigations suggest that phase II can be considered as a transient metastable state in the devitrification process of ibuprofen upon heating from a far from equilibrium state toward the stable phase I.

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1. Introduction

The detailed knowledge on the polymorphism of pharmaceuticals has important consequences for the production of drugs. First, polymorphic varieties can have different physical properties, e.g. different solubilities, that can lead to drastically different bio-availabilities of two forms. Second, during the processing (milling, spray drying, lyophilization, tablet compaction, etc.) and the storage of pharmaceutical compounds, various degrees of disorder in the form of crystal defects can be generated. Disordered materials are inherently metastable and will tend to convert into a more thermodynamically stable crystalline form. In this context, investigating the degree of disorder or thermodynamic stability of pharmaceutical materials is crucial in their formulation, storage and processing. Ibuprofen, 2(4-isobutylphenyl) propanoic acid, is a frequently used non-steroidal anti-inflammatory drug. It is currently available as a racemic compound of S(+)-ibuprofen and R(–)-ibuprofen, the (S+) conformation corresponding to the pharmacologically active form (Adams et al., 1976). Despite the evidence of different crystal morphologies (Lee et al., 2006; Nada et al., 2005; Rasenack and Muller, 2002a,b), only one crystalline phase

(phase I) was identified until the recent detection of a metastable phase (phase II) from X-ray diffraction and differential scanning calorimetry investigations (Dudognon et al., 2008). The metastable state was formed after rapid quench of the melt at 143 K, i.e. well below the glass transition temperature ($T_g \approx 228$ K, Johari et al., 2007), isothermal annealing during 1 h and heated at 258 K. At this temperature, undercooled liquid isothermally transforms toward the new metastable phase II. Structural determinations of the metastable (Derollez et al., 2010) and stable (Connell, 1974; Shankland et al., 1997) phases lead to similar molecular organizations in cyclic dimers via hydrogen bonding in a monoclinic unit cell with the same space group ($P2_1/c$). The structural organization of ibuprofen molecules in phases I and II are plotted in Fig. 1. The main difference between the two structural descriptions results in the orientation of hydrogen bonding between two enantiomers, perpendicular to dimer chains linking the different chains in the stable phase I, and in the direction of dimer chains in phase II. These two different kinds of molecular association can explain the stronger cohesion between dimer chains in phase I, and hence a cell volume in phase II 5% larger than that in phase I at the same temperature (258 K). It was reported that, given the abnormally high value obtained for the overall Debye–Waller factor, it was kept fixed during structural refinements of phase II (Derollez et al., 2010). It can be also found in the structure determination a significant difference between reliability factors obtained for the (Le Bail) profile fitting of the diffraction pattern (~8%) and for the Rietveld refinements (~14%) including the fit of Bragg peak intensities associated

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