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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.

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 bioavailabilities 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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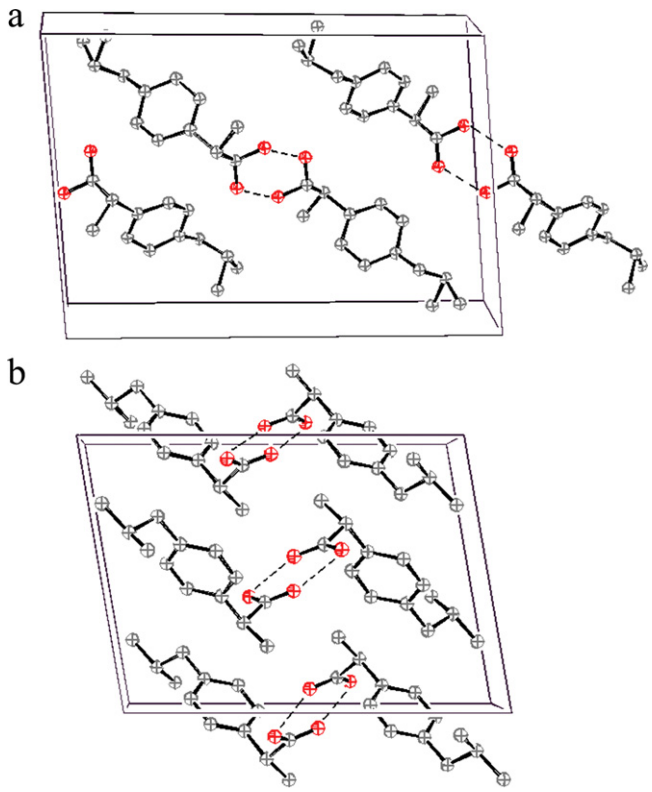

Fig. 1. Representation in the (a and b) plane of the molecular organization and the unit cell of ibuprofen. (a) In phase II, from Derollez et al. (2010). (b) In phase I, from Shankland et al. (1997).

to the atomic positions. These abnormal features in the structural refinement of phase II suggest the existence of a positional atomic disorder not considered in the refinement of the structural model. The analysis of the dynamics of the different states of ibuprofen is needed to give a better structural description and a better insight into stability conditions of phase II. It was shown that low-frequency Raman spectroscopy can clarify structural description in different molecular disordered systems (Hédoux et al., 2011a, 2004, 2006). Consequently, Raman investigations were carried out in the different states of racemic ibuprofen.

2. Materials and methods

2.1. Materials

Racemic ibuprofen, 2(4-isobutylphenyl) propanoic acid, was purchased from Sigma Chemical Company (lot No. 026H1368), with a purity of 99.8% and used without further purification.

2.2. Raman spectroscopy

2.2.1. Experimental procedure

Raman spectra were recorded in the 5–200 cm^{-1} range, in VV + VH geometry to obtain non polarized light-scattering spectrum under a scattering angle $\theta = 180°$, using the 514.5 nm line of a mixed argon–krypton Coherent laser. The spectrometer is composed of a double monochromator comprising four mirrors characterized by a focal length of 800 mm, and a spectrograph. The entrance and exit slits are opened and kept to 200 μm, determining for the incident radiation a resolution of nearly 2 cm^{-1} in the low-frequency range. It is the monochromator which prohibits the exciting line from entering the spectrograph field. The well-adapted positioning of the monochromator with respect to the spectrograph and the choice of experimental conditions (incident radiation, slit width) allow a rejection of exciting light down to 5 cm^{-1}. The spectrometer is equipped with a liquid nitrogen cooled charge coupled device detector. Temperature control of the sample was provided by an Oxford nitrogen-flux device which keeps temperature fluctuation within 0.1 K. Two series of experiments were performed. (i) The first set of experiments was carried out on a small volume of sample (~0.002 cm^3) placed into a Lindemann glass capillary (Ø = 0.7 mm). In this case a thermal history rigorously similar to that used to analyze phase II by X-ray diffraction (Derollez et al., 2010; Dudognon et al., 2008) was imposed to the sample, i.e. the powder was melt at 373 K and cooled down to 143 K at 6 K/min where the sample was annealed for 1 h. Some cracks were clearly observed below 160 K, via the deviation of the laser beam through the cylindrical container and a turbidity of the under-cooled liquid. The sample was then heated at 260 K for analyzing the isothermal transformation of the under-cooled liquid toward phase II. The small volume of sample analyzed requires an acquisition time of 10 min. (ii) In the second set of experiments, a greater amount of Ibuprofen powder (~0.4 cm^3) was loaded in a hermetically sealed spherical pyrex cell. The large analyzed scattering volume (~0.4 cm^3) provides Raman spectra of high quality compared to the set of experiments (i), and allows us to record low-frequency Raman spectra in the 5–200 cm^{-1} range in 2 min. In this case, the sample was quenched from 360 K down to 190 K, i.e. more than 40 K below T_g by shifting the sample located in hot air stream (360 K) into the regulated nitrogen flux (190 K) of the Oxford device. Some cracks were observed at higher temperature (~190 K) than in the first set of experiments. The temperature is then increased (6 K/min) from 190 K up to 260 K (32 K above the glass transition temperature), for isothermal annealing. The isothermal transformation of the under-cooled liquid was investigated from the analysis of the temporal dependence of the low-frequency spectrum. Raman investigations have been also carried out in the 600–1800 cm^{-1} spectrum were intra-molecular vibrations can be detected and used to analyze the local order.

2.2.2. Analysis of Raman spectra of molecular compounds

Raman spectroscopy gives the original opportunity to analyze the three kinds of molecular motions existing in the organic molecular compounds, in the framework of the rigid body model. (i) The internal motions, corresponding to vibrations within the molecule, (ii) the semi-internal (or semi-external) motions usually corresponding to very large amplitude rotations of a group of atoms within the molecule or the whole of the molecule, and (iii) the external motions associated to intermolecular and collective vibrations, named lattice vibrations or phonons in the crystalline state, and consisting in a vibrational density of states in the solid amorphous state. The pronounced contrast between strong covalent intramolecular interactions and soft van der Waals intermolecular attractions or hydrogen bonding association is reflected in the Raman spectra by a spectral gap between external and internal peaks. However, in disordered molecular systems the low-frequency Raman intensity results from the overlapping contributions of semi-external motions, associated with the quasi-elastic (QES) intensity, and external or collective motions (Hédoux et al., 2006, 2011b). Internal modes are sensitive to the local molecular organization. A broadening of Raman bands generally reflects the existence of different molecular configurations or orientations at equivalent sites in a crystal (Denicourt et al., 2003). On the other hand, it was shown that low-frequency Raman investigations make possible to detect, and identify crystalline features in the early stages of crystallization (Denicourt et al., 2003; Hédoux et al., 2009), and to discriminate the emergence of crystalline features in disordered states from structural changes in the local order of amorphous states (polyamorphism) (Hedoux et al., 2001; Hédoux