European Journal of Pharmaceutical Sciences 77 (2015) 48–59

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

The interplay between the paracetamol polymorphism and its molecular structures dissolved in supercritical CO_2 in contact with the solid phase: *In situ* vibration spectroscopy and molecular dynamics simulation analysis

Roman D. Oparin [a,*], Myriam Moreau [b], Isabelle De Walle [b], Marco Paolantoni [c], Abdenacer Idrissi [b], Michael G. Kiselev [a]

[a] G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences (RAS), Akademicheskaya str. 1, Ivanovo 153045, Russia
[b] Laboratoire de Spectrochimie Infrarouge et Raman (UMR CNRS A8516), Université Lille 1 Sciences et Technologies, 59655 Villeneuve d'Ascq Cedex, France
[c] Dipartimento di Chimica, Biologia e Biotecnologie, Università degli Studi di Perugia, via Elce di Sotto 8, I-06123 Perugia, Italy

ARTICLE INFO

Article history:
Received 1 February 2015
Received in revised form 8 May 2015
Accepted 15 May 2015
Available online 28 May 2015

Keywords:
Conformational polymorphism
Supercritical fluids
In situ infrared spectroscopy

ABSTRACT

The aim of this paper is to characterize the distribution of paracetamol conformers which are dissolved in a supercritical CO_2 phase being in equilibrium with their corresponding crystalline form. The quantum calculations and molecular dynamics simulations were used in order to characterize the structure and analyze the vibration spectra of the paracetamol conformers in vacuum and in a mixture with CO_2 at various thermodynamic state parameters (p,T). The metadynamics approach was applied to efficiently sample the various conformers of paracetamol. Furthermore, using *in situ* IR spectroscopy, the conformers that are dissolved in supercritical CO_2 were identified and the evolution of the probability of their presence as a functions of thermodynamic condition was quantified while the change in the crystalline form of paracetamol have been monitored by DSC, micro IR and Raman techniques. The DSC analysis as well as micro IR and Raman spectroscopic studies of the crystalline paracetamol show that the subsequent heating up above the melting temperature of the polymorph I of paracetamol and the cooling down to room temperature in the presence of supercritical CO_2 induces the formation of polymorph II. The *in situ* IR investigation shows that two conformers (Conf. 1 and Conf. 2) are present in the phase of CO_2 while conformer 3 (Conf. 3) has a high probability to be present after re-crystallization.

1. Introduction

Polymorphism of the drug compounds is one of the important problems in pharmaceutical science and the screening of polymorphism is a hardly solving problem, because of the many control parameters (Llinàs and Goodman, 2008). A full understanding of the kinetics of transformation between the various polymorphs of bioactive molecules requires the knowledge and the characterization of these polymorphs. The polymorphism of a drug substance or excipient can have a profound impact on its properties such as biological action, production and formulation. An insufficient understanding of the change between the polymorphic forms of a drug results in problems encountered during the processing or the storage stages. Paracetamol is a model drug which exhibits potential for re-crystallization into different polymorphic forms. It has five polymorphs, two of them are stable (Espeau et al., 2005), the third one is unstable (Gaisford et al., 2010), the fourth and fifth ones were recently discovered using high pressure (Smith et al., 2014), however no confirmation from other work is found in the literature. The first polymorph of paracetamol has monoclinic structure, while the second one is characterized by orthorhombic structure (Ivanova, 2005). Since conformations of paracetamol molecules at different polymorphic forms are only slightly different from each other, the crystalline paracetamol is one of the representatives of packing polymorphism. (Burgina et al., 2004; Ivanova, 2005; Wilson, 1997). Paracetamol was a subject of many studies whose aim is the rationalization of its thermal behavior. In these studies, the initial form of paracetamol (whose

Abbreviations: DSC, differential scanning calorimetry; IR, infrared; NMR, neutron magnetic resonance; SS NMR, solid state neutron magnetic resonance; SCF, supercritical fluid; HTHP, high pressure high temperature.

* Corresponding author.

http://dx.doi.org/10.1016/j.ejps.2015.05.016
0928-0987/

origin/history was not all the time specified) underwent a heating–cooling stages and the structure was characterized using X-ray (de Wet et al., 1998; Di Martino et al., 1997; Nichols and Frampton, 1998; Szelagiewicz et al., 1999), and DSC (de Wet et al., 1998; Di Martino et al., 1997, 1996; Hancock and Shamblin, 2001; Kauffman et al., 2008; Nichols and Frampton, 1998; Szelagiewicz et al., 1999), while the chemical structure was identified using vibration IR- (Di Martino et al., 1997; Moynihan and O'Hare, 2002; Wang et al., 2002) and Raman- (Ayala, 2007; Kauffman et al., 2008; Moynihan and O'Hare, 2002; Nanubolu and Burley, 2012; Szelagiewicz et al., 1999) spectroscopy as well as NMR (Brittain, 1997; Moynihan and O'Hare, 2002) spectroscopy. In addition to these techniques, hot stage optical microscopy was used to follow the time changes of the optical images during the heating–cooling process (de Wet et al., 1998; Di Martino et al., 1997; Nichols and Frampton, 1998; Szelagiewicz et al., 1999). Although there is a convergence about the existence of the three polymorphs of paracetamol (polymorph IV and V were reported only in one paper) and the transformation between them, the careful analysis of the published data shows that the occurrence of these transformation remains far from being predicted or monitored, and even coherently described (Espeau et al., 2005). Indeed there are still uncertainties about the reproducibility of the results obtained by the various authors both in terms of the kinetics and the crystal structure of the produced/processed paracetamol. Furthermore, the analysis of the published data converges to point out that there are many parameters that have a determinant effect on the process of formation of paracetamol polymorphs. These parameters include the rate of heating–cooling (de Wet et al., 1998), the sample preparation (the information of which is lacking in many publications) and the operating conditions around the initial paracetamol sample (covered/sealed/hermetic with a control of the head-space of the sample, or uncovered/open air sample). Qi et al. for instance (Qi et al., 2008) suggest that the re-crystallized form of paracetamol may be dependent on the nature of the head-space gas. The presence of oxygen or other component in the air or trace of moisture at the head-space of the initial paracetamol sample resulting in a greater preponderance for the formation of meta-stable polymorphs (Kachrimanis et al., 2008).

The aim of the present paper is to study the changes between the various polymorphic forms of paracetamol by controlling the external parameters particularly at the interface of the initial paracetamol solid sample. The challenge is to reach the reproducibility of the re-crystallization behavior both in terms of the kinetics and the polymorph forms of the processed initial paracetamol sample. The strategy is to use supercritical fluids (SCF) technology (Yasuji et al., 2008). In the pharmaceutical industry the use of SCF and especially supercritical carbon dioxide is a promising alternative to replace processes such as extraction, drying and crystallization while more effectively controlling particle size and crystal polymorph (Careno et al., 2012). Carbon dioxide can replace environmentally toxic solvents as acetone, carbon tetrachloride, dimethylsulfoxide and so on, in process that although expensive purification procedure is used the final product contain low but still dangerous concentration of these toxic solvents (Llinàs and Goodman, 2008). Kordikowski et al. (2001) reported the crystallization of sulfathiazole polymorphs using supercritical carbon dioxide as anti-solvent. Authors did not find any difference in between using liquid or supercritical carbon dioxide. Obtaining the products with the required polymorphism also becomes possible when using SCF solvents. A new polymorph of didanosine was obtained by Bettini and Menabeni (2010) from the supercritical anti-solvent process. The new polymorph was characterized by means of 1D and 2D multinuclear (1H, 13C, 15N) SS NMR. The particle size of the new crystalline phase was reduced by varying the anti-solvent density through a pressure increase. Rodrigues et al. (2011) introduced atomization of supercritical anti-solvent induced suspensions as a new anti-solvent technique which is potentially enabling a better control of the crystallization. The role of solute concentration has been studied in the work performed by Bouchard and Jovanović (2008). The results show that it is possible to selectively produce the metastable β-glycine and α-glycine at low and high solute concentrations, or at high and low ethanol concentrations, respectively.

In the present paper, we use supercritical CO_2 as medium to control the content of the paracetamol in the $scCO_2$ phase in contact with the solid form. Paracetamol was used as a model compound in order to show that by varying the external parameters of a state it is possible to control formation of various polymorphic modifications in its crystalline phase. For the experiment, the surrounding space around the sample is filled with CO_2, in a sealed high pressure high temperature vessel (optical cell or a reactor). The study of the heating–cooling stages of paracetamol and then the transformation between the various paracetamol polymorphs in supercritical CO_2 is helpful in several aspects:

(i) The initial paracetamol is only in contact with the CO_2 medium at controlled thermodynamic conditions (p,T). The temperature is changed from 70 °C to 180 °C (that is slightly above the melting one). These changes are accompanied by the change of pressure between 187 bar and 517 bar. This allows studying the effect of thermodynamic conditions on the transformation between the various polymorph forms of paracetamol. Furthermore, the CO_2 can be removed easily from the sample and no residual carbon dioxide will remain incorporated in the final paracetamol sample. This will ensure to reduce the impact of moisture on the kinetic stability of the produced polymorph of paracetamol.

(ii) More interestingly, the presence of CO_2 at the interface of the solid sample allows monitoring the paracetamol molecules that are dissolved in CO_2. This makes it possible to analyze the equilibrium between the paracetamol molecules in the solid and fluid (dissolved in CO_2) phases. This constitutes the main advantage of our approach. It allows us to monitor the structural changes of the solid form and to identify the molecular structures that are dissolved in supercritical CO_2.

2. Materials and methods

2.1. Materials

The paracetamol (99% purity) was purchased from Sigma–Aldrich (A7085 Sigma-Aldrich). The CO_2 gas (99,99% purity) was purchased from "Linda Rus".

2.2. Experimental methods

A schematic diagram of the experimental setup is presented in Fig. 1. (Oparin et al., 2014) The initial monoclinic form of paracetamol (referenced here after to *Init*) was placed in the bottom part of optical high-pressure-high-temperature (HPHT) cell and then the cell was pumped out in order to remove all residuals of water and other air components. After that the setup was filled by dry CO_2 through a stainless steel capillary connected to a manual pump containing pressurized CO_2 and allowing the adjustment of the pressure. The temperature was monitored thanks to four cartridge heaters disposed in its body in which two thermocouples were also placed for the regulation and the control of the temperature with an accuracy of about ±1 °C. As shown in the left side of Fig. 1 the collected IR spectra correspond to the paracetamol molecules that are dissolved in $scCO_2$ phase.