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Crystallization kinetics and molecular mobility of an amorphous active pharmaceutical ingredient: A case study with Biclotymol

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ABSTRACT

The present case study focuses on the crystallization kinetics and molecular mobility of an amorphous mouth and throat drug namely Biclotymol, through differential scanning calorimetry (DSC), temperature resolved X-ray powder diffraction (TR-XRPD) and hot stage microscopy (HSM). Kinetics of crystallization above the glass transition through isothermal and non-isothermal cold crystallization were considered. Avrami model was used for isothermal crystallization process. Non-isothermal cold crystallization was investigated through Augis and Bennett model. Differences between crystallization processes have been ascribed to a site-saturated nucleation mechanism of the metastable form, confirmed by optical microscopy images. Regarding molecular mobility, a feature of molecular dynamics in glass-forming liquids as thermodynamic fragility index m was determined through calorimetric measurements. It turned out to be around $m = 100$, describing Biclotymol as a fragile glass-former for Angell's classification. Relatively long-term stability of amorphous Biclotymol above T_g was analyzed indirectly by calorimetric monitoring to evaluate thermodynamic parameters and crystallization behavior of glassy Biclotymol. Within eight months of storage above T_g ($T = T_g + 2\,^{\circ}C$), amorphous Biclotymol does not show a strong inclination to crystallize and forms a relatively stable glass. This case study, involving a multidisciplinary approach, points out the importance of continuing looking for stability predictors.

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1. Introduction

In the pharmaceutical industry, crystalline active pharmaceutical ingredients (API hereafter) and/or excipients have been so far preferred for the formulation of drugs because of stability concerns (Singhal and Curatolo, 2004). However, a number of pharmaceutical ingredients are prompt to get amorphized and it has been demonstrated that amorphous API can result in a significant enhancement of dissolution (Gupta et al., 2004) and biodisponibility (Serajuddin, 1999) with reference to the crystallized solid. Thus, development of drugs in the amorphous state offers an interesting route and has motivated a strong interest in the last decades (Bhugra and Pikal, 2008; Hancock and Zografi, 1997). Amorphous APIs can be prepared through various established ways: supercooling of the melt (Laitinen et al., 2013; Wojnarowska et al., 2010), high-energy milling (Willart and Descamps, 2008), rapid precipitation from a solution (spray drying) (Tajber et al., 2009), hot melt extrusion (Lakshman et al., 2008) or desolvation (Saleki-Gerhardt et al., 1995). Nevertheless, preparation method as well as thermal and mechanical treatments employed during formulation of the drug have been shown to affect the life expectancy of the amorphous API (Patterson et al., 2005), which is a significant concern from a pharmaceutical perspective. Instability of the amorphous state compared to the crystalline state arises from a higher molecular mobility contributing sometimes to spontaneous recrystallization processes (Bhardwaj et al., 2013; Zhou et al., 2002). Molecular mechanisms governing the kinetic stability of amorphous API remains unclear as a large number of experimental factors may impact the process of crystallization such as temperature, pressure or exposure to humidity (Yu, 2001). These mechanisms need to be clarified in order to design reliable formulation processes (Morris et al., 2001).

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Several researchers have attempted to understand and somehow to predict the life expectancy of organic amorphous compounds by looking for a correlation between crystallization tendency of different glass formers with molecular mobility and thermodynamic properties of the amorphous state. Stability was first correlated with the difference between glass transition and the storage temperature (Hancock and Shamblin, 2001; Zhou et al., 2007). It is recognized that storage well below T_g (usually 50 K) could prevent crystallization and ensure a physically stable drug during its shelf-life (Capen et al., 2012). Storage conditions could also be defined in terms of the Vogel temperature T_0 (obtained from the Vogel–Fulcher–Tammann equation) regularly assigned as a hypothetical thermodynamic temperature at which molecular mobility is regarded to be close to zero.

Ongoing researches emphasize that molecular mobility could be a factor to account for life expectancy (Andronis and Zografi, 1997; Kothari et al., 2014; Shamblin et al., 1999). However, it appears that molecular mobility is often compound specific and its reduction does not systematically improve the stability (Bhardwaj and Suryanarayanan, 2012; Zhou et al., 2002). Further attempts to determine amorphous stability were made through depth analysis of other parameters such as configurational thermodynamic parameters (entropy, enthalpy). Zhou et al. (2002) suggest that the key parameter should be the configurational entropy while Marsac et al. (2006) established a correlation with configurational enthalpy. Mahlin et al. (2011) for their part, applied statistical metrology (glass transition and molecular weight measurements) in order to predict the stability of various compounds (Mahlin et al., 2011).

In parallel to this, several authors have indicated that assessing quantification of crystallization behavior could also be considered through measures of glass-forming ability (Baird et al., 2010; Graeser et al., 2009). Simple parameters have been highlighted such as the reduced glass transition temperature (T_{rg}) (Kauzmann, 1948) and temperature difference ($T_{crys,ons} - T_g$), where $T_{crys,ons}$ is the onset temperature of crystallization (Lu et al., 2000). Good glass formers, i.e. intrinsically inclined to become amorphous upon solidification by cooling, appear to possess a chemical structure related to a wide molecular weight or/and a poor molecular symmetry as many adjustable torsion angles (Mahlin et al., 2011). Moreover, good glass formers seem also to be inclined to a wide free energy difference between crystalline and amorphous states (Baird et al., 2010).

Recently, fragility introduced by Angell (1985, 1991) has been considered as a worthwhile parameter regarding life expectancy of amorphous API systems (Gupta et al., 2004; Grzybowska et al., 2010). Glass formers defined as “fragile” exhibit a rapid molecular mobility variation at the vicinity of T_g unlike “strong” glass formers. It was recently depicted for polymeric systems as “a key parameter for observing modifications of the relaxation environment of macromolecules” (Evans et al., 2013). In this idea, several recent studies have been carried out on the influence of several parameters on fragility index of polymers: microstructure modification (Delpouve et al., 2014), nanostructuration (Arabeche et al., 2014), nanofillers addition (Crétois et al., 2013; Saiter et al., 2013), nanoconfinement (Yin et al., 2012), on a 20-million-year-old amber (Zhao et al., 2013; Zhao and McKenna, 2014), on metallic glasses (Ikeda and Aniya, 2010; Wei et al., 2014), on self-assembled-molecules (Dhotel et al., 2013, 2015; Scott et al., 2008). Similarly, Kunal et al. (2008) highlighted the concept of packing efficiency of glass-forming materials (Kunal et al., 2008). According to this approach, movement limitations of individual repeated units of the material will lead to an inefficient packing ability and in this way to a higher fragility. Recent years have witnessed an increasing exploitation of fragility concept as it allows to classify glass-forming API/excipients based on dynamics differences (Brás et al., 2014). High fragility index of amorphous systems has been associated with a higher free energy. Thus, a higher physical stability could be expected for strong glass formers compared to fragile glass formers. However, it is worth pointing out that there are exceptions from the above theory and none of them can be considered nowadays as a general rule of thumb. Indeed, some fragile glass-formers do not correlate with crystallization tendencies of pharmaceuticals (Adrjanowicz et al., 2012). It has been highlighted that in the supercooled liquid state, on the basis of a panel of three antibiotics (azithromycin, clarithromycin, and roxithromycin) exhibiting a fragile glass-forming behavior ($m \approx 120$), only clarithromycin crystallizes below T_g. A recent study conducted on amorphous paroxetine hydrochloride showed that in contrast to a high fragility ($m = 107$), a stable glass of this drug can be obtained (Pina et al., 2015). Moreover, it has been highlighted that quantification of relaxation time and fragility index can also be subject to a misinterpretation (Johari and Shanker, 2010). A straightforward conclusion could not be drawn since all key factors have to be recognized, analyzed and put in perspective through multivariate analysis. Thus, due to the limited number of active pharmaceutical ingredients analyzed, no interrelationship between complex processes involved in stability has been highlighted.

In view to contribute to this challenging inquiry, we characterized the amorphous state of Biclotymol, an active pharmaceutical ingredient which possesses antiseptic properties and is used for the treatment of otolaryngology infections. Biclotymol, 2,2′-methylenebis(4-chloro-3-methylisopropylphenol), can be esteemed as a multidisciplinary model compound since it presents a favorable polymorphism as well as a glass transition temperature close to room temperature. Herein, we report our investigation on the kinetics of crystallization and molecular dynamics of this amorphous drug performed through temperature-resolved X-ray powder diffraction (TR-XRPD), differential scanning calorimetry (DSC) and hot stage microscopy (HSM). The relevancy of fragility index, recently considered as an indicator of life expectancy of amorphous APIs, is discussed.

2. Materials and methods

2.1. Materials

Biclotymol crystalline powder ($C_{21}H_{26}Cl_2O_2$, $M_w = 381.32$ g/mol), was kindly provided by Pharmasynthese (Inabata Group) and was used without further purification. X-ray diffractogram of commercial Biclotymol was recorded and reveals a completely crystalline form in agreement with Rantsordas et al. (1978).

2.2. Differential scanning calorimetry (DSC)

DSC experiments were performed using a PerkinElmer 8500 apparatus equipped with a refrigerated cooling system. Small sample masses of 5 ± 0.5 mg were enclosed into sealed standard aluminum pans to improve thermal conductivity and ensure that powder will follow the imposed thermal variations. Baseline was calibrated from $-15\,^{\circ}C$ to $160\,^{\circ}C$ with the scanning rate of 5 K/min used in the experiments. Prior to measurement, two standards as benzophenone and indium were used for temperature and enthalpy calibrations. The atmosphere of the analyses was regulated by a nitrogen flux (20 mL/min). The PerkinElmer Pyris Software was used for data processing.

2.3. Thermogravimetric analysis (TGA)

TGA analyses were performed using a Netzsch TG 209 apparatus. Baseline has been calibrated from $30\,^{\circ}C$ to $500\,^{\circ}C$ with a

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