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The slow relaxation dynamics in active pharmaceutical ingredients studied by DSC and TSDC: Voriconazole, miconazole and itraconazole

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ABSTRACT

The slow molecular mobility of three active pharmaceutical drugs (voriconazole, miconazole and itraconazole) has been studied by differential scanning calorimetry (DSC) and thermally stimulated depolarization currents (TSDC). This study yielded the main kinetic features of the secondary relaxations and of the main (glass transition) relaxation, in particular their distribution of relaxation times. The dynamic fragility of the three glass formers was determined from DSC data (using two different procedures) and from TSDC data. According to our results voriconazole behaves as a relatively strong liquid, while miconazole is moderately fragile and itraconazole is a very fragile liquid. There are no studies in this area published in the literature relating to voriconazole. Also not available in the literature is a slow mobility study by dielectric relaxation spectroscopy in the amorphous miconazole. Apart from that, the results obtained are in reasonable agreement with published works using different experimental techniques.

1. Introduction

The wide dissemination of the amorphous materials in the pharmaceutical (Levine, 2002; Yu, 2001) and food industries (Roos, 2008; Slade and Levine, 2002) requires a deeper investigation of the nature and the stability of the glassy state. It is a growing conviction among the pharmaceutical scientists that the amorphization is a good way to improve the oral bioavailability of new drugs poorly soluble in water. The use of amorphous drugs is however limited by the glass instability (tendency to crystallization). There is a general belief that a comprehensive understanding of the molecular mobility in amorphous materials allows a reliable prediction of the amorphous stability. As a consequence, in the pharmaceutical area much of the literature on the amorphous solid state is focused on the study of the relationship between molecular mobility and chemical and physical stability (Shamblin et al., 1999). Correlations have been found between the thermodynamic and kinetic properties and the observed amorphous stability of drug substances (Graeser et al., 2009). Furthermore, it is known that the cooperative mobility is responsible for instability (Kothari et al., 2014) and good correlations were found between the relaxation time of the α-relaxation and the crystallization onset time in amorphous pharmaceuticals (Bhardwaj et al., 2013). It was also shown that the slow secondary relaxations (Johari-Goldstein) can facilitate the main mobility even if they are not directly the cause of the amorphous instability (Bhattacharya and Suryanarayanan, 2009) and there is even slight evidence about the destabilizing role of the fast secondary motions (Paladi and Oguni, 2003; Xu et al., 2013).

The problem of the drug administration in the amorphous state is not however resolved by the mere knowledge of their molecular mobility. Many drugs, as voriconazole and miconazole studied in the present work, have T_g below room temperature, so that they are not good candidates to be delivered in the pure amorphous solid form. On the other hand, progress in drug design has been accompanied by an increase in molecular complexity and by a decrease in solubility of the active pharmaceutical ingredients (API). Therefore, the formulation of strategies to improve the solubility of poorly water-soluble APIs is of great importance (Singh et al., 2011; Williams et al., 2013). One of them is to deliver the drug in the form of an amorphous solid dispersion (ASD) (He and Ho, 2015) where the maximum solubility advantage occurs if the drug is present as a single phase in the amorphous state. In ASDs the carriers are often hydrophilic polymers (cellulose derivatives, poly(ethyleneglycol) and poly(vinylpyrrolidone) for

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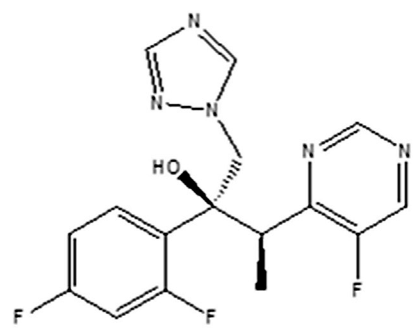
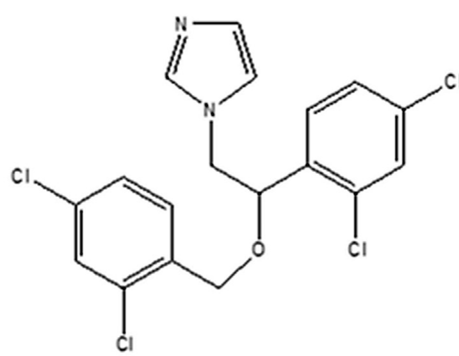
example) that are reported to enhance the solubility of the drug acting as a mechanical substratum for amorphous stabilization, reducing the mobility of the drug due to the high viscosity of the system and to the drug-polymer interactions. The comparison of data from the study of the mobility in the ASD with data on the mobility in the pure drug and in the pure polymer will help the understanding of the differences between the mobility of the molecule in the pure drug and in the ASD. Such studies are up to now very scarce in the literature (Yuan et al., 2014). Let us also note that the relative crystallization tendency of drugs from amorphous solid dispersions seems to depend on the relative crystallization tendency of the pure drugs (Marsac et al., 2006). We thus believe that the study of the mobility in the pure amorphous substances remains relevant beyond a mere academic interest.

This work is part of a recently launched research program on the study by thermally stimulated depolarization currents (TSDC) of the slow molecular mobility in low molecular weight glass formers with pharmaceutical interest (Correia et al., 2001; Diogo and Moura Ramos, 2015; Mora et al., 2014; Moura Ramos et al., 2005), focusing now on voriconazole, miconazole and itraconazole. These are three azole antifungal agents used to treat a variety of fungal infections that work interfering with the formation of the fungal cell membrane resulting in the death of the fungus. The molecular mobility of these pharmaceutical ingredients will be studied in the amorphous solid state using thermally stimulated currents (TSDC) and differential scanning calorimetry (DSC) as experimental techniques. The results obtained will be compared, when possible, with those published in the literature and obtained by other



(a)



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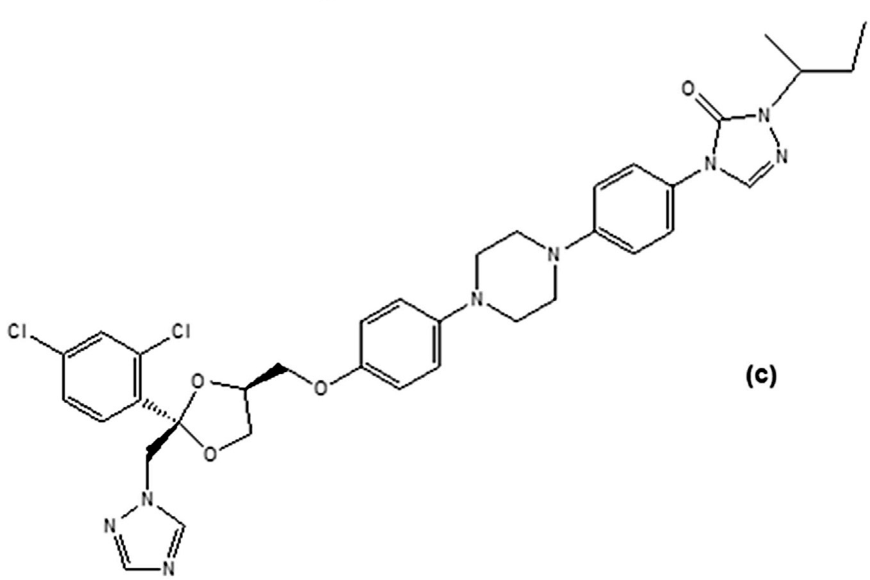

(c)

Fig. 1. Chemical structures of voriconazole (a), miconazole (b) and itraconazole (c).