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Research paper

Impact of low molecular weight excipient octaacetylmaltose on the liquid crystalline ordering and molecular dynamics in the supercooled liquid and glassy state of itraconazole

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ABSTRACT

Different experimental and theoretical techniques were applied to investigate basic physical properties of very stable and homogeneous solid dispersions formed by itraconazole and octaacetylmaltose. Differential scanning calorimetry as well as semi-empirical calculations have indicated that liquid crystalline ordering in itraconazole was completely suppressed in the binary mixtures. Molecular dynamics studies with the use of broadband dielectric spectroscopy have shown that the width of the structural relaxation process becomes smaller and fragility drops in solid dispersions with respect to the pure itraconazole. Moreover, the dynamics of secondary relaxation processes was affected by acetylated maltose. As demonstrated, β- and γ-secondary modes shift to higher and lower frequencies, respectively. On the other hand, aging experiments revealed that isostructural relaxation times in the glassy state become systematically longer with the addition of modified carbohydrate. This is a very important finding in the context of the current discussion on the factors affecting physical stability of easily crystallizing APIs. It seems that beside intermolecular interactions and local reorientation, the global mobility might control the crystallization of amorphous solid dispersions. Finally, we have demonstrated that itraconazole in binary mixtures dissolves faster and to greater extent with respect to the crystalline and amorphous form of this API.

1. Introduction

The amorphous active pharmaceutical ingredients (APIs) have attracted a particular interest in the pharmaceutical industry because they are characterized by higher apparent solubility and faster dissolution rate when compared to their crystalline counterparts [1]. Consequently, bioavailability of drugs having dissolution-rate limited absorption can be significantly enhanced [2–4]. One should also note that recent reports demonstrate better tableting properties of disordered APIs with respect to the crystalline ones [5]. However, despite various advantages, they are thermodynamically unstable and may undergo recrystallization over the time course of processing and storage, losing their key properties [6,7].

Abbreviations: acGLU, acetylated glucose; acMAL, acetylated maltose; acSUC, acetylated sucrose; AGV, Adam-Gibbs-Vogel; API, active pharmaceutical ingredient; BDS, Broadband Dielectric Spectroscopy; CEL, celecoxib; CM, Coupling Model; DSC, Differential Scanning Calorimetry; HPMC, hydroxypropyl methylcellulose; ITZ, itraconazole; JG, Johari–Goldstein; KWW, Kohlrausch-Williams-Watts; LC, liquid crystalline; PEG, polyethylene glycol; PPGs, polypropylene glycols; PVP, polyvinylpyrrolidone; PVP/VA, vinylpyrrolidone vinyl acetate; RH, relative humidity; T_g, glass transition temperature; VFT, Vogel–Fulcher–Tammann; XRD, X-ray diffraction.

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The physical instability is the major disadvantage of amorphous APIs. Many studies have shown a correlation between the recrystallization tendencies of such materials with molecular mobility, thermodynamic properties, molecular interactions, moisture content, and the way how the amorphous state is generated [7–16]. It should be noted that a lot of efforts have been done to understand the connection between physical instability of amorphous pharmaceuticals and their molecular mobility. However, this issue seems to be very complex since the crystallization depends on many different factors [7,8,13–16].

Herein, it is also important to note that molecular mobility comprises both global and local motions. The global relaxation, called in literature the structural or α-process, governs liquid–glass transition and it is responsible for the relaxation of the molecular structure and the viscous flow. Below the glass transition temperature, T_g, it becomes too slow, hence structural dynamics cannot be monitored by any spectroscopic technique. On the other hand, in this region of temperatures secondary relaxation (or relaxations) usually emerges. Based on the current knowledge one can divide secondary processes into two groups, i.e. [17–19] (i) modes originating from the motions of some small parts of molecules, governed by the intramolecular potential barrier and (ii) modes of intermolecular character related to the motions of the whole molecule.

A relation between molecular mobility (also local) and crystallization tendencies of amorphous substances below the glass transition temperature is often considered [17,20–25]. Many investigators claim, that β-process plays an important role in controlling physical stability of given API [13,17]. In this context one can remind the paper by Oguni et al. Based on the optical microscopy, dielectric and calorimetric data of crystal growth in 3,3′-dimethoxy-4,4′-bis(2,2-diphenylvinyl)biphenyl, *o*-terphenyl, salol and triphenylethylene they concluded that the crystallization below T_g is controlled by the relaxation time of the β-process rather than the α-one [21-24]. In turn, Vyazovkin et al. by using DSC method have studied glassy indomethacin aged at 273 and 263 K for periods of time up to 109 and 210 days, respectively [26]. The authors related a crystallization process of this API to the secondary relaxation which becomes visible in dielectric loss spectra at T = 263 K. Moreover, Grzybowska et al. have shown, that physical instability of the glassy celecoxib (CEL) is related to the β (JG)-secondary relaxation [17].

It is worth noting, that only few research has been done to understand the role of the structural relaxation process in the crystallization below T_g [23,25]. It is related to the difficulties in precise and direct determination of the α-relaxation time deep in the glassy state. Of course, there are some theoretical approaches that enable us to evaluate structural relaxation times in the glassy state. One can mention the modified Adam-Gibbs-Vogel (AGV) equation proposed by Hodge [27]. However, since it was derived to describe dynamics in non-equilibrium glassy state it correctly provides α-relaxation times only for freshly prepared glasses. As aging proceeds, structural relaxation times are expected to change, approaching equilibrium values [28].

Very recently Casalini and Roland proposed new fast and accurate experimental method to determine τ_α in the glass [29]. It is based on monitoring changes of the β-relaxation with physical aging. Then obtained data are used to evaluate the α-relaxation dynamics below T_g. Previously this approach was used to calculate the structural relaxation times deep in the glassy state in different materials (sucrose, trehalose, hydroxyl-(OH-) and amino-(NH2-) terminated polypropylene glycols (PPGs) of varying molecular weight, telmisartan) [30–32].

In this paper, we investigate the impact of small molecular excipient-octaacetylmaltose (acMAL) on the local and global dynamics in the glassy state of itraconazole (ITZ) (Fig. 1), which is a broad-spectrum triazole antifungal agent of poor solubility and bioavailability [33,34].

Our recent findings have revealed that intermolecular interactions between indomethacin and acetylated saccharides are mainly responsible for long-term stability of API in the binary amorphous mixtures [35,36]. Herein, we demonstrate that except of molecular interactions the structural relaxation may play a key role in controlling crystallization ability of produced dispersions. Detailed molecular dynamics studies as well as aging experiments have indicated that long term stability of dispersion formed between ITZ and octaacetylmaltose might be related to the exceedingly long timescale of the global mobility in the glassy state of examined samples. This issue seems to be crucial for further design and the development of pharmaceutical formulations containing amorphous APIs. Better understanding of these phenomena may give an opportunity to optimize the storage conditions of disordered APIs and consequently prevent from recrystallization. Another very interesting point of our studies concerns the impact of excipient on the liquid–crystalline ordering reported for ITZ.

2. Materials and methods

2.1. Materials

Itraconazole [IUPAC Name: (2R,4S)-rel-1-(butan-2-yl)-4-{4-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl) piperazin-1-yl]-phenyl}-4,5-dihydro-1H-1,2,4-triazol-5-one), $C_{35}H_{38}Cl_2N_8O_4$, M_w = 705.64 g/mol] and octaacetylmaltose (acMAL, $C_{28}H_{38}O_{19}$, M_w =678.6 g/mol), octaacetylsucrose (acSUC, $C_{28}H_{38}O_{19}$, M_w = 678.6 g/mol) and pentaacetylglucose (acGLU, $C_{16}H_{22}O_{11}$, 390.34 g/mol), having purities greater than 98%, were obtained from Sigma Aldrich and used as received. The chemical structures of all compounds are displayed in Fig. 1.

2.2. Methods

2.2.1. Preparation of amorphous systems of itraconazole with acetylated saccharides

The amorphous ITZ, acMAL, acSUC, acGLU and ITZ–acMAL, ITZ–acSUC, ITZ–aGLU binary systems with different weight ratios of both components were prepared by the quench cooling technique in the temperature and humidity controlled glovebox (PLAS LABORATORIES Inc. 890-THC-DT/EXP/SP) at the assured relative humidity RH < 10%. In order to obtain the homogeneous ITZ-acetylated saccharide mixtures, first we thoroughly mixed crystalline powders of both compounds in appropriate proportions in a heat-resistant glass vial. The weight of powder mixtures was about 0.5 g. Then we put the magnetic stir bar into the vial with the mixture. Afterward, the crystalline samples were melted in the vial on the hot plate magnetic stirrer (CAT M 17.5) at T = 443.15 K. The temperature inside the vial was controlled by using Pt-100 sensor. After the crystalline dispersions of ITZ with acetylated saccharides were fully melted we transferred them from a hot to cold metal plate. The amorphous samples obtained in this way were analyzed immediately after the preparation.

2.2.2. Differential Scanning Calorimetry (DSC)

Calorimetric measurements of amorphous form of ITZ, acMAL, acSUC, acGLU and binary mixtures of ITZ with acetylated saccharides were taken with double-furnace, using double-furnace Mettler–Toledo DSC apparatus (Mettler–Toledo International, Inc., Greifensee, Switzerland) equipped with a liquid nitrogen cooling accessory and a HSS8 ceramic sensor (heat flux sensor with 120 thermocouples). Temperature and enthalpy calibrations were