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Research Paper

Changes in dynamics of the glass-forming pharmaceutical nifedipine in binary mixtures with octaacetylmaltose

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ABSTRACT

Some molecular glass-formers can crystallize in the glassy state, some of which are van der Waals molecules and some are pharmaceuticals. The molecular mechanism responsible for this glass-to-crystal mode of crystallization is of interest to the glass transition research community as well as to the pharmaceutical industry because the effect is detrimental to stability of amorphous form of the drugs stored below the glass transition temperature. Two prominent models have been proposed for the molecular mechanism. In the homogeneous nucleation-based crystallization model, the molecular mechanism is the secondary relaxation, and the other model assumes that the molecular process responsible for crystal growth in the glassy state is from the local molecular motions. Crystal growth requires motion of the entire molecule, and in the glassy state the only such local molecular motion is engendered by the secondary relaxation of the Johari–Goldstein (JG) kind. While the JG secondary relaxation is the crux in the two models of glass-to-crystal growth, it has not been found in the glassy state of the pharmaceuticals studied so far. The examples include 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY), indomethacin (IMC) and nifedipine (NIF). In the absence of any evidence of the JG secondary relaxation, the conundrum is that the two models of glass-to-crystal growth cannot be validated. It turns out these pharmaceuticals all have structural α-relaxations with narrow frequency dispersion. Empirically, glass-formers with narrow α-dispersion have JG secondary relaxation with weak relaxation strength, not well separated from the α-relaxation, and hence cannot be resolved. Theoretically, the narrow width of the α-dispersion is due to weak intermolecular coupling. In this article we enhance the intermolecular coupling of NIF by mixing with octaacetylmaltose to enhance the intermolecular coupling of NIF. In this way we have successfully resolved the JG secondary relaxation in the dielectric loss spectra of the NIF component in the glassy state, and validated the two models of glass-to-crystal growth.

1. Introduction

Molecular dynamics of glass-forming pharmaceuticals occupy the attention of the pharmaceutical research community as well as the glass transition research community. The pharmaceutical community is concerned with the task of enhancing the stability of amorphous pharmaceuticals against crystallization [1–11].

The question needed for an answer is the identity of the relaxation process in the amorphous solid pharmaceuticals which is instrumental for crystallization in the bulk and on free surfaces [12]. If identified, one would like to know how to modify the relaxation by physical or chemical means in order to reduce its efficacy in causing crystallization. The physical and chemical structures of the pharmaceuticals are often distinctly different from the ordinary glass-formers studied by the glass transition research community. Thus, the glass-forming pharmaceuticals offer more a variety of glass-forming substances for studying the molecular dynamics relevant for glass transition.

Abbreviations: acMAL, octaacetylmaltose; CM, Coupling Model; DSE, Debye–Stokes–Einstein; GC, glass-to-crystal; HN, Havriliak–Negami; IMC, indomethacin; JG, Johari–Goldstein; KWW, Kohlrausch–Williams–Watts; *m*, isobaric fragility; NIF, nifedipine; ROY, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile; T_g, glass transition temperature; VFT, Vogel–Fulcher–Tammann.

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An example is nifedipine, the drug for treatment of hypertension. Crystallization is a problem of stability of amorphous nifedipine stored below T_g, the glass transition temperature. Present are fast modes of crystal growth directly from the glass-to-crystal (GC) mode occurring in the bulk [13] and at the free surface [12]. Fast crystal growth in the glassy state was found earlier in several non-pharmaceutical glass-formers such as *o*-terphenyl by Oguni and coworkers [14]. They proposed the homogeneous nucleation-based crystallization model whereby crystal growth in the glass is affected by the coalescence of homogeneous crystal nuclei onto an existing crystal surface at a rate determined by the secondary relaxation. Another model proposed by Sun et al. is solid-state crystal growth by local mobility [15]. This model assumes that the molecular process responsible for crystal growth in the glassy state originates from the 'local molecular motions'. In the glassy state of small molecular glass-formers, 'local molecular motions' are the secondary relaxations broadly classified in two types [16]. The secondary relaxation involving an isolated part of the molecule (e.g. trivial rotating motion of the CH_3 group or side groups of some polymers) is usually faster than that involving the entire molecule. In many cases it is referred to as the γ-process [9–11,17]. The latter, designated the Johari–Goldstein (JG) β-relaxation in Ref. [16], is universal and has properties strongly connected to that of the structural α-relaxation, and hence it is fundamentally important.

Sun et al. did not specify which kind of secondary relaxations is associated with the 'local molecular motions' in their model. Neither this was done for the secondary relaxation in the homogeneous nucleation-based crystallization model of Oguni and coworkers [18,19]. Notwithstanding, the JG β-relaxation is the candidate because intuitively crystal growth requires motion of the entire molecule. There is no ambiguity in the case of *o*-terphenyl and toluene considered by Oguni and coworkers [19], because there is only a single secondary relaxation in these semi-rigid or totally rigid molecules, which is of the JG kind [16]. For the pharmaceuticals studied so far for crystal growth in the glassy state, the situation is far from clear. The examples include 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) [20], indomethacin (IMC) [21] and nifedipine (NIF) [22]. No secondary relaxation is resolved in the broadband dielectric spectra of ROY at ambient pressure [20]. There is a fast γ-relaxation evident from the dielectric loss spectra in IMC, but its relaxation time is pressure insensitive, and hence not the JG β-relaxation according to one of the criteria [16]. A secondary relaxation of nifedipine was found deep in the glassy state [23], but its relaxation time at T_g is more than 3 orders of magnitude shorter than the JG β-relaxation time, τ_{JG}, estimated from the primitive relaxation time, τ_0, of the Coupling Model [16]. There are reports of slowing down of crystal growth of NIF in the glassy state by mixing it with low concentration of polymers [13,24]. The degree of slowing down of crystal growth was found to correlate well with the T_g of the neat polymer, suggesting that the mobility of polymer chains is an important factor. Another study of reduction of the crystal growth rate in the liquid state with addition of large concentration of modified carbohydrates including octaacetylmaltose (acMAL) has suggested the cause is the intermolecular interactions of NIF with the modified carbohydrate [25]. Despite the advances, no direct evidence of the presence of JG β-relaxation came out from these studies.

The dilemma present to this date is that despite the JG β-relaxation is supposed to play the critical role in crystal growth in the glass according to the two prominent models, we have no direct evidence of its existence in ROY, IMC and NIF. The frequency dispersion of the α-relaxation in all these pharmaceuticals is rather narrow possibly due to weak intermolecular interaction. It is well established empirically as well as theoretically [26,27] that the separation of the JG β-relaxation from the α-relaxation is an increasing function of the width of the dispersion of the α-relaxation. The narrow α-dispersions of the three pharmaceuticals means small separation of the JG β-relaxation from the more intense α-relaxation, making it difficult to be observed. In this article, we enhance the intermolecular interaction of nifedipine by mixing it with high concentration of acMAL having higher glass transition temperature than NIF. The α-relaxation of the NIF component in the mixture is broadened in response to the enhanced intermolecular interaction in the mixture, and the JG β-relaxation of NIF appears in the spectra for the first time. The result confirms that the JG β-relaxation does exist in nifedipine, and validates the basis of the two models proposed to account for crystal growth in the glassy state of these pharmaceuticals.

2. Experimental section

2.1. Materials

Nifedipine (NIF, IUPAC Name: 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{17}H_{18}N_2O_6$, M_w = 346.34 g/mol) and octaacetylmaltose (acMAL, $C_{28}H_{38}O_{19}$, M_w = 678.6 g/mol), having purities greater than 98%, were obtained from Sigma Aldrich and used as received. The molecular structures of the studied compounds are shown in Fig. 1.

2.2. Methods

2.2.1. Preparation of amorphous systems of nifedipine with octaacetylmaltose by quench cooling

The amorphous nifedipine (NIF), octaacetylmaltose (acMAL) and binary systems NIF–acMAL with different weight ratios of NIF to acMAL 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 NIF–acMAL binary mixtures, first we thoroughly mixed crystalline powders of both compounds in appropriate proportions in a heat resistant glass vial (weight of powder mixture was about 0.5 g). After that we put the magnetic stir bar into the vial with the mixture. Next, the crystalline components 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 mixture NIF–acMAL was fully melted it was transferred from the hot plate to a very cold metal plate. The amorphous samples obtained in this way were analyzed immediately after the preparation. We investigated three mixtures of nifedipine and octaacetylmaltose with different weight ratios of the former to the latter (Table 1).

2.2.2. Differential scanning calorimetry (DSC)

Standard differential scanning calorimetry measurements of amorphous nifedipine and octaacetylmaltose, as well as NIF–acMAL

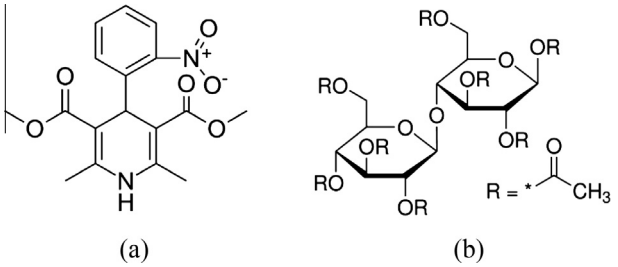

Fig. 1. Chemical structures of nifedipine (a), and octaacetylmaltose (b).