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Research paper

Studying of crystal growth and overall crystallization of naproxen from binary mixtures

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ABSTRACT

Broadband dielectric spectroscopy (BDS) and differential scanning calorimetry (DSC) were applied to investigate the molecular dynamics and phase transitions in binary mixtures composed of naproxen (NAP) and acetylated saccharides: maltose (acMAL) and sucrose (acSUC). Moreover, the application of BDS method and optical microscopy enabled us to study both crystallization kinetics and crystal growth of naproxen from the solid dispersions with the highest content of modified carbohydrates (1:5 wt ratio). It was found that the activation barriers of crystallization estimated from dielectric measurements are completely different for both studied herein mixtures. Much higher E_a (=205 kJ/mol) was obtained for NAP-acMAL solid dispersion. It is probably due to simultaneous crystallization of both components of the mixture. On the other hand, lower value of E_a in the case of NAP-acSUC solid dispersion (81 kJ/mol) indicated, that naproxen is the only crystallizing compound. This hypothesis was confirmed by X-ray diffraction studies. We also suggested that specific intermolecular dipole-dipole interactions between active substance and excipient may be an alternative explanation for the difference between activation barrier obtained for NAP-acMAL and NAP-acSUC binary mixtures. Furthermore, optical measurements showed that the activation energy for crystal growth of naproxen increases in binary mixtures. They also revealed that both excipients: acMAL and acSUC move the temperature of the maximum of crystal growth towards lower temperatures. Interestingly, this maximum occurs for nearly the same structural relaxation time, which is a good approximation of viscosity, for all samples. Finally, it was also noticed that although naproxen crystallizes to the same polymorphic form in both systems, there are some differences in morphology of obtained crystals. Thus, the observed behavior may have a significant impact on the bioavailability and dissolution rate of API produced in that way.

1. Introduction

When the liquid is cooled down from the melting temperature two different scenarios are possible: (i) liquid may form a crystalline solid or (ii) it may reach a glassy state. While the crystalline state is characterized by a long-range order, the amorphous one is described by an atomic disorder. The latter phase can be formed upon cooling a liquid with sufficiently high cooling rate to avoid nucleation of material. In this context it should be mentioned that currently there is quite intensive debate on the role of different factors (kinetic and thermodynamic ones, chemical structure, symmetry) in predicting which scenario, crystallization or glass formation prevail upon cooling of the given liquid.

Crystallization is a typical first order phase transition. It is composed of two major events: (i) nucleation and (ii) crystal growth [1,2]. The former step is related to the stochastic spontaneous formation of small crystalline nuclei made of few molecules in the liquid. It plays a decisive role in controlling formation of given crystal structure. A parameter, that is often used to characterize this stage of crystallization is the nucleation rate, N (unit: $m^{-3}\,s^{-1}$). It is

Abbreviations: acMAL, acetylated maltose; acSUC, acetylated sucrose; API, active pharmaceutical ingredient; BCS, biopharmaceutics classification system; BDS, broadband dielectric spectroscopy; CNT, classical nucleation theory; DSC, differential scanning calorimetry; E_a, activation barrier of crystallization; E_{cg}, activation barrier for crystal growth; GT, Gordon-Taylor; HN, Havriliak-Negami; m, isobaric fragility; MD, molecular dynamics; NAP, naproxen; NSAID, nonsteroidal anti-inflammatory drug; T_g, glass transition temperature; T_m, melting temperature; TOP, two order parameter; VFT, Vogel-Fulcher-Tammann; XRD, X-ray diffraction.

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defined as the number of formed crystal nuclei per unit of volume and time. The latter step of crystallization (crystal growth) occurs after the barrier to nucleation has been overcome. Then, the nuclei grow to form crystals of at least microscopic size. A measure of the growing of crystal surface of the critical nuclei is crystal growth velocity G (unit: m s^{-1}). The second stage of crystallization is generally described by three models: (i) normal growth, (ii) two-dimensional growth and (iii) growth mediated by screw dislocations [3].

As widely reported in the literature, the progress and essential physics of crystallization can be discussed within the Classical Nucleation Theory (CNT) [3,4]. According to this approach, fluctuations give rise to the appearance of a small nucleus of a new phase initiating the creation of an interface between liquid and solid phases. For a spherical nucleus, the total free energy cost (ascribed as the driving force, ΔG) to form a spherical crystallite with radius r is defined by:

$$\Delta G = -\frac{4}{3}\pi r^3 n_s \delta\mu + 4\pi r^2 \gamma, \quad (1)$$

where n_s is the number density of particles in the solid, $\delta\mu$ is the difference between the liquid and solid chemical potentials and γ is the interfacial free energy per unit area. While, the first part of Eq. (1) is related to the volume, the second one is the surface term. With an increase of the cluster size, the total free energy goes through the maximum at a critical size ($r_c = 2\gamma/(n_s\delta\mu)$) and the height of the free energy barrier is given by:

$$\Delta G^C = 16\pi\gamma^3/3(n_s\delta\mu)^2. \quad (2)$$

$\delta\mu$ can be approximated by [5]:

$$\delta\mu = \Delta H_f(1 - T/T_m), \quad (3)$$

where ΔH_f is the enthalpy of fusion and T_m is the melting temperature. Overall crystallization is considered as the interplay between the nucleation rate, N and crystal growth velocity, G. These quantities are basically determined by: (i) the driving force, ΔG; (ii) the interfacial free energy, γ and (iii) the diffusivity, D_T. One can add that ΔG can be easily obtained from experimental data [6,7]. On the other hand, the determination of the γ parameter is more complex. Although, it can be obtained experimentally with the use of many different techniques [8,9]. Recently, many researchers have also estimated this parameter for simple systems composed of hard spheres, Lennard-Jones particles or metal atoms from molecular dynamics (MD) simulations [10–12]. However, it should be mentioned that the determination of γ from simulations remains challenging.

Furthermore, assuming the validity of Stokes-Einstein relation, the third parameter, D_T, is often replaced by the shear viscosity $\eta(D_T \propto 1/\eta)$ [5]), which in turn is connected to the structural (α) relaxation time via the Maxwell's relation (these quantities are roughly proportional) [13]. However, as shown in literature such replacement is questionable due to possible decoupling between diffusion and structural relaxation at certain temperature T_B (usually $T_B = 1.2\ T_g$) [3,14,15]. It is worthwhile to mention that the decoupling between D_T and η usually correlates with the fragility, m (i.e. the more fragile the liquid, the greater decoupling is observed) [15,16]. In this context, one can also recall the Two Order Parameter (TOP) model proposed by Tanaka [17,18]. According to this approach, crystallization and the liquid-glass transition can be controlled by two parameters: (i) kinetic factor and (ii) energetic frustration. While the former is connected with the viscosity, the latter is related to the bond order parameter, S, and can be expressed in variation of fragility. TOP model predicts the lower frustration for more fragile liquids, $S \rightarrow 0$. Therefore, the higher value of m indicates the greater crystallization tendency of glass-formers.

Moreover, few years ago crystallization kinetics versus viscosity was studied by Ediger et al. [19]. The authors reported the following relation between both quantities:

$$\mu_c = \eta^{\xi}, \quad (4)$$

where ξ is an exponent lying in the range ($0 \leqslant \xi \leqslant 1$) which depends systematically on the fragility of the liquid. They showed that the lower value of the exponent, the greater decoupling between viscosity and translational diffusion and hence the crystallization process becomes preferred.

In literature, one can find many papers devoted to crystallization studies of active pharmaceutical ingredients (APIs), especially those from II or IV group according to the Biopharmaceutics Classification System (BCS) [20–27]. However, they mainly focus on crystallization from the glassy state. An example of active substance prepared in the amorphous form, which easily crystallizes regardless of the thermodynamic conditions is naproxen (class II of BCS) [28,29]. It is a nonsteroidal anti-inflammatory drug (NSAID), commonly used for the reduction of moderate to severe pain, fever, inflammation and stiffness. It is worth mentioning that only few papers in literature describe the crystallization of amorphous NAP. In this context, one can remind very recent paper by Sibik et al. [29]. Authors demonstrated that naproxen crystallizes very easily well below the glass transition temperature (T_g). Moreover, the strong correlation between molecular dynamics related to JG secondary relaxation and the physical stability of studied pharmaceutical was established. One can also mention papers by Lim et al. [30] and Zhu et al. [31], where physical properties and stability of NAP mixed with various matrices were studied.

In this paper, we investigate the crystallization of naproxen from binary mixtures with acetylated sucrose and acetylated maltose by means of dielectric spectroscopy and optical microscopy. It was shown that the activation energy (E_a) of crystallization estimated from the former technique differs significantly for both systems. Moreover, additional calorimetric and X-ray diffraction measurements indicated that high value of E_a estimated for NAP-acMAL mixture might be caused by simultaneous crystallization of modified maltose, which affects the overall crystallization barrier. It is worth noting that in the binary system composed of modified sucrose, naproxen was the only component undergoing crystallization. Another plausible reason for the higher E_a in case of NAP-acMAL mixture may be stronger dipole-dipole interactions occurring in the system. Further optical studies enabled us to determine both the rates and activation barriers for the crystal growth. It was found that E_{cg} increases in both studied herein mixtures. What is more, the maximum in crystal growth rate, although shifts towards lower temperatures with addition of given carbohydrate, occurs for nearly the same τ_α. Finally, it was also shown that although the same polymorph of API grows in the studied temperature range, the morphology of the formed crystal is slightly modified. This observation may have significant implication for the modification of dissolution and bioavailability properties of naproxen.

2. Materials and methods

2.1. Materials

Naproxen, [IUPAC name: (2S)-2-(6-methoxy-2-naphthyl)propanoic acid], $C_{14}H_{14}O_3$, M_w = 230,259 g/mol, 99% purity, was supplied by Chemat. Octaacetylmaltose (acMAL, $C_{28}H_{38}O_{19}$, M_w = 678.6 g/mol) and octaacetylsucrose (acSUC, $C_{28}H_{38}O_{19}$, M_w = 678.6 g/mol) having purities greater than 98%, were obtained from Sigma Aldrich and used as received. The chemical structures of all compounds are shown in Scheme 1.