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Highly stable glasses of celecoxib: Influence on thermo-kinetic properties, microstructure and response towards crystal growth

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ABSTRACT

Celecoxib, an anti-inflammatory drug widely used as a pharmaceutical product, is known for its poor ability to form a glass and its high tendency towards crystallization. Here, we report the preparation of vapor-deposited ultrastable glasses of Celecoxib with an onset temperature of the glass transition 20 K above its conventional value and a high thermodynamic stability. The time required for the loss of molecular anisotropy is 3 orders of magnitude higher than the time scales required for the alpha relaxation. We also report the influence of the stability of the glass on the surface crystallization at temperatures below the glass transition temperature. The growth of surface crystals is 30% faster in conventional glasses prepared from the liquid than in highly stable glasses.

1. Introduction

Pharmaceutical products are typically formed by crystalline drugs that are poorly water-soluble and show limited bioavailability [1]. On the contrary, amorphous forms show improved solubility [2]. However, their limited stability hinders widespread commercialization. Unfortunately, the amorphous state has higher energy than the crystalline state and may undergo crystallization during processing, storage and use of the product. Therefore, amorphous materials with enhanced stability could be the basis of a new generation of pharmaceutical drugs. Traditionally, the two ways to obtain very stable glasses were by reducing the cooling rate, though this approach is limited by the onset of crystallization, and by aging the glass at temperatures below the glass transition temperature, a very slow kinetical process. In addition, crystallization can be activated if Johari-Goldstein relaxation mechanisms are active at the aging temperature [3]. Very recently, a new methodology to prepare highly stable glasses has emerged [4] and now it is well consolidated within the scientific community. This methodology employs physical vapor deposition at deposition temperatures slightly below the glass transition temperature, Tg, i.e. $T_{dep} = 0.8$–0.9Tg, as a route to obtain thin film glasses with a remarkable enhancement of their kinetic and thermodynamic stability. Glasses grown in these conditions rival in stability with natural ambers aged during millions of years [5]. This behavior was initially observed for 1,3-bis-(1-naphthyl)-5-(2-naphthyl)benzene (TNB) [6] and indomethacin (IMC) [4], but later on it has been corroborated for many other organic molecules such as toluene [7], ethylbenzene [7] or even mixtures of cis/trans-Decalin [8], in what seems to be a general trend for organic molecules [9]. This methodology has been successfully extended to produce highly stable polymers [10] and metallic glasses [11,12].

Besides the enhancement in thermodynamic and kinetic stability, vapor-deposited ultrastable glasses exhibit other remarkable properties when compared to the conventional glass, such as higher thermal stability [13], higher density [14], lower thermal expansion coefficient [15] and a growth front transformation mechanism into the liquid that initiates at free surfaces [16,17]. A striking property observed in thin film highly stable glasses of certain molecules is the existence of molecular anisotropy that produces a low-q extra peak in X-ray diffraction patterns [18–20] and birefringence in ellipsometric experiments [14,15].

The primary goal of this paper is to analyze the feasibility of preparing highly stable glasses of a poor glass former such as celecoxib, CXIB. This molecule, largely used as a nonsteroidal anti-inflammatory drug, shows a prompt tendency to crystallization, inhibiting commercialization in the amorphous form [2]. We determine the kinetic and thermodynamic stability of the molecule by differential scanning calorimetry, DSC. Our results indicate that it is indeed possible to form ultrastable thin film glasses of this molecule and that the optimum substrate temperature is around 0.85 Tg, in agreement with a number of previous reports on other molecules [4]. We also use synchrotron X-ray diffraction to monitor the evolution of the anisotropic molecular packing during annealings

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above Tg. Comparison to calorimetric data allows establishing a link between the loss of anisotropy and the primary relaxation in the glass. The influence of stability on the crystallization of the glass is examined comparing the crystal growth rate between a highly stable glass and a conventional glass cooled from the liquid. Remarkably, even though the crystallization is apparently driven by surface diffusion mechanisms, we do observe a difference as a function of stability.

2. Experimental method

Celecoxib glassy films were deposited by evaporation at a growth rate of 0.2 nm/s in a UHV chamber with a base pressure of 3×10^{-8} mbar. The material was evaporated at its melting temperature using an effusion cell from CREATEC. The deposition rate was followed in-situ during evaporation by a microbalance placed inside the chamber. A liquid nitrogen cold trap was installed in order to improve the vacuum quality. The temperature of the substrate was controlled by means of a temperature controlled socket. Celecoxib crystalline powder with purity higher than 98% was acquired from Haihang Industry Co., Ltd. and was used without further treatment.

DSC measurements were performed in a Perkin Elmer DSC7. Films around 1.5 μm thick were deposited on aluminum foil, which was folded and introduced in the DSC aluminum pan. In this way, it was possible to measure samples with a total mass around 1 mg. The thermal treatment consisted in most of the cases on two consecutive heating ramps from 283 K up to 356 K. Both heating and cooling ramps were performed at 10 K/min. Thus, the first heating curve corresponds to the as-deposited glass and the second, to a slow cooled sample (note: by conventional glass or slow cooled glass we mean hereafter a glass that has been cooled from the liquid at 10 K/min). The conversion of the power raw data from the calorimetric measurements to heat capacity has been performed by base line subtraction and the imposition of the specific heat of the glass and the liquid [21] before and after the glass transition for a particular mass.

Ultrastable films of CXIB of ~40 μm were structurally characterized by means of wide angle X-ray scattering, WAXS, at the NCD line of ALBA synchrotron radiation light source. The films were deposited on 7×7 mm^2 pieces of Si wafer and placed in a Linkam stage which allowed acquisition of the diffraction profiles during isothermal treatment in N_2 atmosphere. Organic molecules have small scattering factor and long acquisition times are usually required to obtain reasonable X-ray spectra. In order to maximize the signal from the celecoxib layer we selected a transmission geometry with the beam (780×160 μm^2) crossing the sample parallel to the substrate. In this configuration, reasonable spectra with high signal-to-noise ratio were collected in 30 s. A shutter protected the sample during off periods, minimizing X-ray beam/sample interaction. Careful calibration experiments carried out at ambient T and slightly below Tg indicated that no apparent damaging (in terms of visual inspection and by the constancy over time of the absolute intensity of the low-q X-ray diffraction peak) was observed in the conditions of the experiment. A photon flux of 10^{12} ph/s was used during the experiments.

Surface crystallization was followed by measuring the size of surface crystals on both ultrastable and conventional thin film glasses (thickness ~5 μm). The latest were prepared by heating the ultrastable glass films above the glass transition temperature and cooling them down at 10 K/min, immediately after. A Linkam stage was used to keep the samples at constant temperature, 318 K, during crystallization. The experiments were carried out under ambient air with 50% relative humidity. Selected crystals were followed in-situ with an optical microscope for several hours.

3. Results and discussion

We analyze the dependence of stability on deposition temperature by preparing samples at temperatures ranging from 0.65Tg to 0.92Tg, where Tg = 326 K corresponds to the glass transition temperature of a conventional glass of CXIB. Fig. 1 shows the specific heat curves of seven glasses obtained at different substrate temperatures. The position and the area of the endothermic peak, corresponding to the glass transition, change as a function of the deposition temperature. We evaluate the onset temperature by extrapolation of the glass heat capacity and its intersection with the line representing the rise in specific heat, as schematically shown for the sample grown at 0.85Tg. The shallow increase of heat capacity prior to the definition of the calorimetric peak is due to the initial transformation of the glass to a supercooled liquid from the free surface [22]. The evolution of the onset of the glass transition temperature, T_{on}, with T_{dep} is represented in Fig. 2b. A maximum in T_{on}, which indicates a maximum in kinetic stability, occurs at deposition temperatures between 0.8 and 0.9Tg. The thermodynamic stability as a function of deposition temperature is analyzed through the evolution of the fictive temperature, T_f. We have used the procedure described by Moynihan et al. [23] to calculate T_f. Basically, the limiting fictive temperature is determined by the intersection temperature between the enthalpy of the liquid and the enthalpy of the glass, which are obtained by integrating the specific heat as a function of the temperature. As can be seen in Fig. 2a, glasses grown at temperatures between 0.8 and 0.9Tg have a minimum in T_f, and therefore a maximum in thermodynamic stability. Equivalent results have been obtained for many other organic molecules [6–9,24–26].

In order to obtain glasses with such kinetic and thermodynamic stability it would be necessary to submit the conventional glass to very long aging times or to cool down the liquid at very slow cooling rates. While the first option is not feasible in the laboratory time scale, the second option would not produce a glass but a crystal, since the necessary cooling rates are in general much lower than the critical cooling rate [27], Qr. For instance, from our DSC measurements, we infer a Qr for CXIB around 0.5–1 K/min, when cooling the sample from the melting temperature. An estimation of the equivalent cooling rate associated with a certain fictive temperature can be carried out by extrapolating the Arrhenius relation between the scaled cooling rate Q/Qs and the fictive temperature T_f/T_f^S [28]. Fig. 3 shows the normalized fictive temperatures of bulk glasses obtained experimentally by cooling the liquid at different rates. For the normalization, we have used the fictive temperature of the conventional glass (Qs = −10 K/min). The equivalent cooling rates of the glassy films are obtained from the extrapolation of the Arrhenius fit of the experimental data on the basis of their fictive temperature. For the more stable glass (deposited at 0.85Tg), the equivalent cooling rate is of the order of 10^{-4} K/min, four orders of magnitude lower than the critical cooling rate for crystallization.

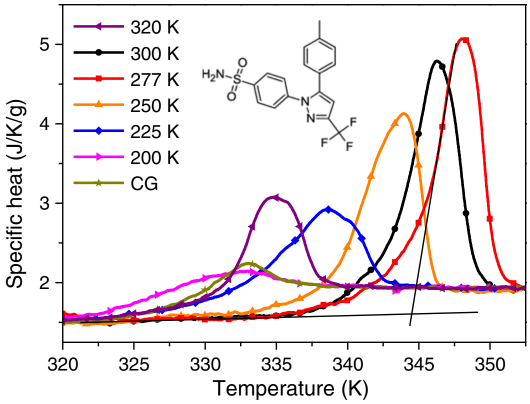

Fig. 1. Specific heat curves obtained by DSC at 10 K/min corresponding to CXIB films deposited at different temperatures. In all cases the films were deposited at 0.2 nm/s and the deposition temperatures are indicated in the legend of the graph. CG corresponds to a glass obtained from cooling the liquid at 10 K/min (conventional glass). The method for determining the onset temperature is indicated on the red curve (T_{dep} = 0.85Tg). The inset shows the molecular structure of CXIB.