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Collective relaxation dynamics and crystallization kinetics of the amorphous Biclotymol antiseptic

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ABSTRACT

We employ dielectric spectroscopy to monitor the relaxation dynamics and crystallization kinetics of the Biclotymol antiseptic in its amorphous phase. The glass transition temperature of the material as determined by dielectric spectroscopy is $T_g = 290 \pm 1$ K. The primary (α) relaxation dynamics is observed to follow a Vogel–Fulcher–Tammann temperature dependence, with a kinetic fragility index $m = 86 \pm 13$, which classifies Biclotymol as a relatively fragile glass former. A secondary relaxation is also observed, corresponding to an intramolecular dynamic process of the non-rigid Biclotymol molecule. The crystallization kinetics, measured at four different temperatures above the glass transition temperature, follows an Avrami behavior with exponent virtually equal to $n = 2$, indicating one-dimensional crystallization into needle-like crystallites, as experimentally observed, with a time-constant nucleation rate. The activation barrier for crystallization is found to be $E_a = 115 \pm 22$ kJ mol^{-1}.

1. Introduction

Pharmaceutically active molecules and active pharmaceutical ingredients (API's) are generally stored in solid form, either as crystalline or amorphous (glassy) powders. Compared to the crystalline form, the amorphous form of API's offers the advantage of a higher solubility (Gupta et al., 2004) and bioavailability (Serajuddin, 1999). The amorphous glass state has however the disadvantage of being thermodynamically unstable against the nucleation of crystalline phases (Bhardwaj et al., 2013; Zhou et al., 2002). The microscopic mechanisms governing the kinetic stability of amorphous API remains unclear, and the crystallization kinetics appears to be determined by a large number of factors such as preparation method, thermal and mechanical treatments employed during formulation (Patterson et al., 2005), storage temperature, application of pressure or exposure to humidity (Yu, 2001). It is generally found that storage well below the glass transition temperature T_g (*e.g.*, at $T_g - 50$ K) prevents crystallization of the amorphous state and thus ensures a physically stable drug during its shelf-life (Capen et al., 2012; Pogna et al., 2015). In general, the thermal energy and the molecular mobility below T_g are considered to be too low to produce the rearrangements necessary for the nucleation of the crystalline phase, although some authors have proposed that the secondary Johari–Goldstein relaxation (considered as the primitive relaxation) can provide enough mobility to activate the crystallization process. (Adrjanowicz et al., 2012a) A recent study (Schammé et al., 2015) on Biclotymol, 2,2′′-methylenebis(4-chloro-3methylisopropylphenol), an antiseptic used for mouth, throat and pulmonary infections, has shown that it can be stored in its amorphous form during months also several degrees above the T_g of the material, *i.e.*, at temperatures at which the material is in the supercooled liquid state and the molecular mobility is slow but not negligible. Motivated by this finding, we present here an experimental study of the recrystallization of Biclotymol from its supercooled state at four different temperatures, by means of broadband dielectric spectroscopy, a well-established technique to investigate crystallization kinetics in API's (Adrjanowicz et al., 2010, 2012b; Kaminski et al., 2011). We find in particular that crystallization takes place on the timescale of hours even at moderate temperatures ($T_g + 14$K), and that therefore temperature control is critical to preserve the amorphous state. Moreover, we study in detail the fragility of this glass-forming API and the crystallization mechanism. Crystallization can be well described by the Avrami law with integer exponent n equal to 2, corresponding to one-dimensional growth of needle-like crystallites, as experimentally observed, with a time-independent nucleation rate.

Abbreviations: VFT, Vogel–Fulcher–Tammann.

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2. Material and methods

Biclotymol powder of medicinal grade was provided by Bouchara–Recordati (France) and used as received. The sample batch was the same as in our previous work (Céolin et al., 2008). Differential scanning calorimetry measurements were carried out in the temperature range between 250 and 450 K with heating or cooling rates 10 K min^{-1}, using a Q100 calorimeter from TA-Instruments. The value of the melting temperature determined by calorimetry was used as a check that the quality of the sample had not deteriorated.

Dielectric measurements were carried out in parallel-plate capacitor configuration with a Novocontrol Alpha analyzer. The sample was initially melted above 400 K and inserted in the molten state inside a home-made stainless steel capacitor specially designed for liquid samples, with plates separated by silica spacers. The capacitor was held at high enough temperature to ensure that the sample remained liquid during the filling, and was then mounted in the dielectric spectroscopy setup. For the measurements of the molecular dynamics (those of Fig. 1), 50 μm diameter spacers were used to achieve a higher capacitance, while for isothermal crystallization measurements (Figs. 3 and 4) 100 μm diameter spacers were employed, to avoid any effect due to geometrical constraints on the sample. The probed temperature range was between 115 K and 350 K, and dielectric measurements were carried out in the frequency (f) range from 10^{-2} to 10^{8} Hz. Most measurements were carried out between 10^{-2} to 5×10^{6} Hz using a Novocontrol Alpha analyzer. Few measurements were carried out between 10^{6} and 10^{8} Hz to probe the secondary relaxation dynamics above the glass transition temperature. For these high-frequency measurements a HP4291 impedance analyzer was employed in reflectometry geometry, with the sample capacitor mounted at the end of a coaxial cable.

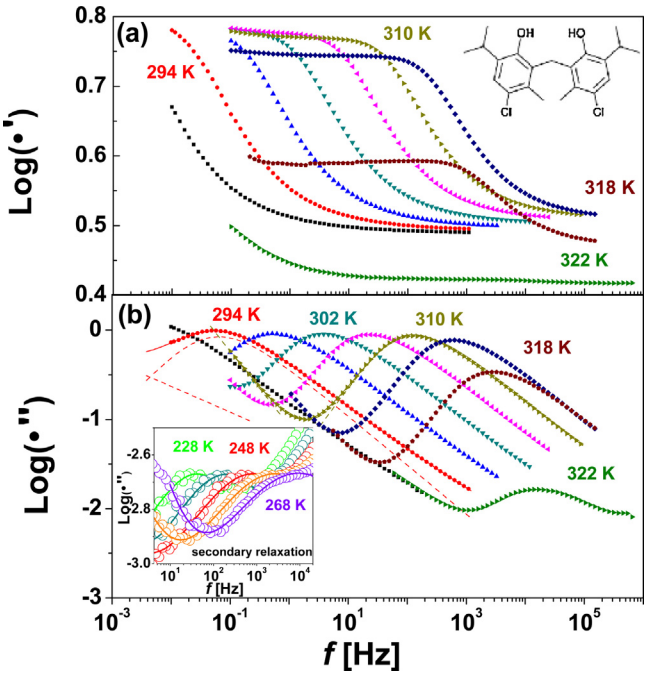

Fig. 1. Permittivity spectra $\varepsilon'(f)$ (a) and loss spectra $\varepsilon''(f)$ (b) of Biclotymol between 290 and 322 K every 4 K. In (b), continuous lines are fits assuming a Havriliak–Negami profile of the primary α relaxation, on top of a conductivity background proportional to inverse frequency (both contributions are shown as dashed lines). For clarity, the fit results and fit components are displayed only for the temperatures of 294 and 310 K, and only some of the measured spectra are shown. Inset to (a): molecular structure of Biclotymol. Inset to (b): selected loss spectra $\varepsilon''(f)$ of Biclotymol below T_g (every 10 K between 228 and 268 K), where a secondary relaxation is visible (markers), fitted with a Cole–Cole function plus a background mimicking the high-frequency tail of the α relaxation feature (the fits are displayed as continuous lines).

In all measurements, the sample was initially re-melted inside the capacitor and then cooled down as fast as possible to below T_g to avoid crystallization. All measurements of the primary α relaxation were measured while heating up for the same reason, and for isothermal crystallization measurements the measuring temperature was reached by heating as fast as possible from T_g (see Section 3). Temperature control of the capacitor and thus of the sample was achieved with a nitrogen-gas flow cryostat. The typical maximum heating/cooling rates were not higher than 15 K/min.

Dielectric spectroscopy yields the complex permittivity ε of the sample as a function of f. Dynamic relaxation processes are visible as broad peaks in the so-called loss spectra (semi-logarithmic plots of the imaginary part of $\varepsilon''(f)$ of the complex permittivity), in correspondence of which a step-like decrease is observed in the real part $\varepsilon'(f)$ as the real and imaginary parts of ε are related by Kramers–Kronig transformations (Kremer and Schönhals, 2003). Biclotymol exhibited two dynamic processes, namely a collective primary relaxation at lower frequency (α process) and a secondary dynamics at higher frequency. The primary relaxation feature was fitted with a Havriliak–Negami function, superposed to a background proportional to reciprocal frequency that mimicked the conductivity contribution to the loss spectra. The analytic expression of the Havriliak–Negami function is (Havriliak and Negami, 1966, 1967):

$$\varepsilon_{HN}(f) = \varepsilon_\infty + \frac{\Delta\varepsilon}{\left(1+(i2f\tau_{HN})^{\beta}\right)^{\gamma}}, \quad (1)$$

where $\Delta\varepsilon = \varepsilon_s - \varepsilon_\infty$ is the dielectric strength (equal to the step variation of ε', and proportional to the density of molecules taking part in the relaxation process), and ε_∞ and ε_s are the high-frequency and static low-frequency limits of the real permittivity. The parameters β and γ, called Havriliak–Negami exponents, lie in the range from 0 to 1 and are related with the shape and asymmetry of the relaxation time distribution; finally, τ_{HN} is a fitting parameter from which the characteristic time τ_α at which the dielectric loss of the primary relaxation process is maximum is obtained as:

$$\tau_\alpha = \tau_{HN}\left(\sin\frac{\beta\pi}{2+2\gamma}\right)^{-1/\beta}\left(\sin\frac{\beta\gamma\pi}{2+2\gamma}\right)^{1/\beta}. \quad (2)$$

The secondary relaxation processes was fitted as a Cole–Cole function, commonly employed for secondary relaxations (Kremer and Schönhals, 2003), which is a special case of the Havriliak–Negami function with $\gamma = 1$. In such case, it may be seen from Eq. (2) that the characteristic relaxation time τ_s of the secondary process is directly the value of the Cole–Cole fit parameter, namely $\tau_s = \tau_{CC} = \tau_{HN}(\gamma = 1)$. For the fit of the spectra of the secondary relaxation, a background proportional to reciprocal frequency was also added, to reproduce the high-frequency tail of the α process.

3. Results and discussion

Fig. 1 shows the real (a) and imaginary (b) part of the complex relative dielectric permittivity of Biclotymol in its supercooled liquid (amorphous) state, as measured upon heating from low temperature (only the data between T_g and $T_g + 32$ K are shown; the molecular structure of Biclotymol is shown as an inset to Fig. 1(a)). A clear primary relaxation is observed, visible as a peak in the imaginary permittivity (b) and as a corresponding decrease in the real permittivity (a). The primary relaxation corresponds to the