Combining Dielectric and Thermal characterization techniques for studying the molecular dynamics of a pharmaceutical drug: S-ibuprofen

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In the pharmaceutical industry one of the concerning problems in the applicability of drugs is related to the poor solubility exhibited by crystalline phases. Recently the use of the disordered amorphous state as an alternative to the crystalline one has gained a growing interest. In fact, it is well known that a solid amorphous material has a higher molecular mobility *versus* the crystalline counterpart, thus presenting a faster dissolution and improved solubility. Therefore, the bioavailability of a pharmaceutically active substance in the amorphous form can be desirably enhanced relatively to the corresponding ordered crystalline solid.

However, it is very important for any application involving solid amorphous materials to have in mind that, in this form, they are out-of-equilibrium. Consequently, they are unstable: the allowed molecular rearrangements will tend to reestablish the equilibrium by a complex process known as physical ageing which involves a decrease of enthalpy and specific volume. Moreover, the physical instability can be manifested for example as recrystallization of the material. Because of this, it is very important to characterize the molecular mobility in the amorphous form in order to predict the stability of the substance.

Ibuprofen is a non-steroidal worldwide used pharmaceutical compound which belongs to the category of 2-arylpropanoic acid, showing analgesic, antipyretic and anti-inflammatory properties. Commonly, it is commercially available as a racemic crystalline compound of S-(+)-ibuprofen and R-(-)-ibuprofen. The S-(+) conformation corresponding to the pharmacological active form is the aim of the present work based on Differential Scanning Calorimetry (DSC) and Dielectric Relaxation Spectroscopy (DRS) complementary measurements; results will be compared with those previously published for the racemic compound [1].

DSC was used to establish the experimental conditions for obtaining the S-(+)-ibuprofen in the amorphous form. After melting the crystalline starting material ($T_m = 52°C$) by heating to 80 ºC, a cooling rate of 10 ºC.min^{-1} down to -130 ºC was enough to avoid crystallization: no exothermic peaks were observed in the thermogram and a clear heat capacity jump, signature of the glass transformation (conversion from the supercooled liquid to the solid amorphous) was detected. On the subsequent heating ramp at 10 ºC.min^{-1}, the onset of the glass transformation was determined at the glass transition temperature, $T_g = -46°C$, with a variation in the heat capacity of 0.39 J(g.ºC)$^{-1}$; on further heating to 80 ºC, S-ibuprofen persists in the supercooled metastable amorphous state (cold-crystallization and subsequent melting were not observed). Lower cooling rates were also tested (≥ 2 ºC.min^{-1}) with no observation of melt-crystallization. Thus, similarly to the racemic compound ($T_m = 74°C$; $T_g = -47°C$), S-ibuprofen can be classified as a very good glass-former.

The molecular mobility in the amorphous ibuprofen, both in the glass and supercooled liquid, was studied by using DRS. In this technique, a sinusoidal electric field is applied over the sample given rise to a dipolar polarization. The way how this polarization is lost after removal the field is characteristic of the material and it can be quantify by the relaxation time (τ) directly related to the molecular mobility. In DRS, the relaxation time is obtained from the variation of the dielectric permittivity as a function of the frequency of the applied electric field, at a given temperature: $\tau = 1/(2\pi f_m)$, where f_m is the frequency of the maximum of the dielectric loss peak (see Figure 1).

Isothermal dielectric spectra of S-(+)-ibuprofen were taken on cooling from 80 ºC to -120 ºC

and on subsequent heating, in the same temperature range. As observed from the DSC measurements, on cooling, no melt-crystallization was observed in spite of the fact that isothermal data acquisition corresponds to very low rates (less than 0.1 ºC.min^{-1}) - a full amorphous solid was thus obtained. Figure 1 displays the isothermal spectra of permittivity (dielectric loss) obtained on heating the glassy sample, in the temperature range where the main relaxation, the α-process associated to the dynamic glass transition, is detected. Besides the expected shift to higher frequencies of the peak in ε´´ with the temperature increase (due to the increment of molecular mobility), an abrupt decrease in the intensity is detected above -5 ºC, leading to the total extinction of the α-peak at 3 ºC, *i.e.*, the dipolar moment is completely lost. This is a clear indication of the occurrence of cold-crystallization of the sample. A similar behaviour was observed for racemic ibuprofen [1]. Besides the α-relaxation, a lower intense process (secondary relaxation) was detected in the low temperature (high frequency) range (below T_g).

As is typical for many glass formers, the temperature dependence of the relaxation times of the α-process is clearly non-Arrhenian being well described by the Vogel-Fulcher-Tamman (VFT) equation $\tau = \tau_\infty \, exp[B/(T - T_0)]$ [2] with parameters: $\tau_\infty = 2.7 * 10^{-4} s$, $B = 1359\ K$ and $T_0 = 187.7\ K$. The dynamical glass transition temperature, estimated from these parameters and considering the relaxation time at T_g of 100 s, has a value of $T_g = -47.3°C$, in very good agreement with that obtained from calorimetric measurements.

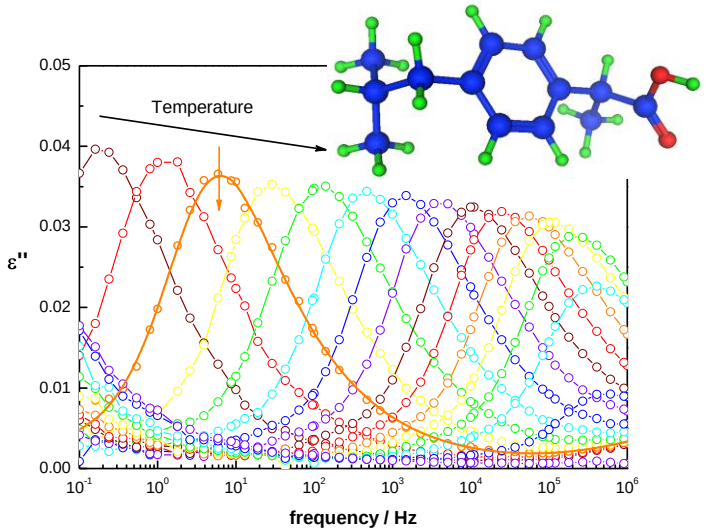

Figure 1. Dielectric loss spectra for the S-(+)-ibuprofen taken on heating: only isothermal data from -42 to 3 ºC every 3 degrees are represented. For spectrum at -36 ºC, the solid line represents the curve fitted and the arrow indicates the position of f_m. Inset: chemical structure of the molecule.

An interesting parameter that reflects the departure from the Arrhenius behaviour is the fragility index, $m = \left[\partial log(\tau)/\partial\left(T_g/T\right)\right]_{T=T_g}$ [3]. For this compound, the value obtained was 93 (identical to the racemic compound), which in accordance with the Angell's classification is an indication of a fragile material.

Concerning the secondary relaxation, the relaxation times exhibit an Arrhenius temperature dependence with a low value of the activation energy: this is typical of more localized motions probably inside the molecule. However, a more detailed study of this relaxation will be done in order to clarify the molecular origin.

In conclusion, relating to the ibuprofen racemic compound, S-(+)-ibuprofen doesn't show significant differences in relation to the glass transition temperature and the temperature dependence of the relaxation times of the main relaxation process.

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