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The slow molecular dynamics in amorphous probucol

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ABSTRACT

The slow molecular mobility in the active pharmaceutical ingredient probucol was studied by Thermally stimulated depolarisation currents (TSDC) in the temperature region between −130 and 50 °C. The distribution of relaxation times was characterized for the secondary relaxations and for the glass transition relaxation. Based on aging results we were able to draw distinctions between the fast secondary relaxation on the one hand, and the slow-β or Johari–Goldstein relaxation on the other. The steepness index of probucol was calculated from the temperature dependent relaxation time of the glass transition and using methods based on the influence of the scanning rate on the glass transition signal (in DSC and TSDC). The obtained values show some scattering but they are in the frontier between the fragile and strong behaviors.

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1. Introduction

Probucol is a pharmaceutical ingredient with diversified pharmacological properties, and the history of its clinical applications is reported in the literature [1]. To synthetize, let us underline its use as a lipid regulating agent, and its pronounced anti-oxidant and anti-inflammatory properties. It has also been shown to protect and amend heart and vascular disorders, and to have beneficial effects on neural and synaptic plasticity in brain aging as well as combating common Alzheimer disease through its cholesterol lowering effect [2].

Probucol is an extremely lipophilic substance, with very low water solubility. The use of the amorphous formulations of drugs and excipients to improve solubility, accelerate dissolution and promote therapeutic activity, i.e., as a means of improving bioavailability, is of increasing interest all the more since a large percentage of new drugs have a low aqueous solubility [3–5]. However, an amorphous solid is in a non- equilibrium state, i.e., there is a thermodynamic driving force for the amorphous phase to crystallize (devitrify) over time due to the fact that the amorphous solid has a higher free energy compared to its crystalline forms. Moreover, the absence of long range order and the lower strength of the intermolecular interactions in the amorphous compared to the crystalline state, lower the energy barriers that are to be overcome for physical and chemical transformations of the glass. In this context, the physical and chemical stability of the glass, both during the processing operation and during storage, is of critical importance, and the knowledge of the molecular mobility is crucial to preclude the molecular processes that destabilize the amorphous substance. In fact, molecular motions in amorphous materials can influence both chemical and physical processes, and the temperature dependent relaxation time, that can be measured experimentally, is a fundamental parameter. Furthermore, due to the dynamically heterogeneous nature of the amorphous state, the molecular motions in glassy materials are distributed, in energy as well as in entropy. As a consequence, we need to understand what regions of the distribution are more relevant to trouble the stability of the amorphous pharmaceutical ingredients.

In contrast to many amorphous active pharmaceutical ingredients, no systematic studies on the molecular mobility of probucol are found in the literature. In the present work we report the results of an investigation using the experimental technique of Thermally Stimulated Depolarization Currents (TSDC), which provides quantitative information on the distribution of relaxation times of the different slow motional modes. The low equivalent frequency ($\sim 10^{-4}$ Hz) of the TSDC technique makes it highly sensitive, with an enhanced resolution power of the different relaxation processes. As a consequence of this feature, the secondary relaxations appear most often in the TSDC spectra as a very broad peak, well separated from the main relaxation. Dielectric relaxation spectroscopy, with its very wide frequency

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range of ∼14 decades, is a powerful and widely used dielectric technique [6,7]. TSDC is not so widely used, but it is a complementary dielectric technique that proved to be helpful in the study of the slow mobility. The most important advantage of TSDC is the possibility, using the partial polarization procedure, of experimentally resolve a broadly distributed relaxation process into its narrowly distributed relaxation modes; this enables the calculation of the temperature dependent relaxation time, $\tau(T)$, associated to a very narrow distribution of motional modes.

2. Experimental

2.1. Sample preparation

Probucol, (chemical structure in Fig. 1), molecular weight MW = 516.844 g mol^{-1}, CAS [23,288-49-5], displays two polymorphic forms [8]; the most stable has a melting point in the vicinity of T_m = 125 °C [8–10]. Our probucol samples were from Sigma–Aldrich, product n° P9672, and were used without further purification. The as received sample melts with an onset at $(T_m)_{on}$ = 125.9 °C and a maximum rate at $(T_m)_{max}$ = 127.1 °C, melting enthalpy $\Delta_{fus}H$ = 61.9 J g^{-1} = 32.0 kJ mol^{-1}, which closely agree with other published values [10], and indicates that it corresponds to the most stable polymorph of crystalline probucol [8] and emphasizes the high purity of the sample.

The amorphous solid form of probucol was prepared inside the TSDC apparatus (see below) under helium atmosphere, by melting a pellet of the crystal (thickness of ≅ 0.2 mm) at 135 °C, and cooling from the isotropic liquid. The substance displayed excellent glass forming ability, with a wide supercooled liquid temperature region and high thermal stability against crystallization. On the other hand, the preparation conditions above indicated (helium atmosphere and melting above 100 °C) ensure a very low water content of the sample.

2.2. Differential scanning calorimetry (DSC)

The calorimetric measurements were performed with a 2920 MDSC system from TA Instruments Inc., (USA). The samples of ∼5–10 mg were introduced in aluminum pans. The measuring cell was continuously purged with dry high purity helium gas at a flow rate of 30 mL/min. An empty aluminum pan, identical to that used for the sample, was used as the reference. Cooling was achieved with a liquid nitrogen cooling accessory which permits automatic and continuous programmed sample cooling down to −150 °C (123 K). The baseline was calibrated by scanning the temperature domain of the experiments with an empty pan. Additional details on the calibration procedures, including temperature and enthalpy, are given elsewhere [11].

2.3. Thermally stimulated depolarization currents (TSDC)

Thermally Stimulated Currents (TSC) experiments were carried out with a TSC/RMA 9000 spectrometer (TherMold Partners, Stamford, CT, USA) covering the temperature range between −170 and +400 °C. The melting point of indium was used in order to calibrate the instrument at different linear rates, from −20 K min^{-1} to +20 K min^{-1}. The configuration of the cell is a parallel plate capacitor with an effective area of ∼38 mm^2. The sample, with a thickness of 0.2 mm, was placed between the two electrodes, and immersed in an atmosphere of high purity helium (1.1 bar). Our samples were studied in the temperature interval from −130 °C up to +40 °C, and several baselines were performed (experiments obtained by heating the depolarized sample) to verify that no singular electric event (space charge effects for example) was present on the studied temperature range. The physical background of TSC is presented in a variety of review articles [12–15], which can be useful for the reader not familiar with this experimental technique.

The TSDC technique is adequate to probe slow molecular motions (1–3000 s). The fact that the relaxation time of the motional processes is temperature dependent, and becomes longer as temperature decreases, allows to make it exceedingly long (freezing process) compared with the timescale of the experiment. In order to analyse specific regions of the TSDC spectrum the partial polarization (PP) procedure, also called fractional polarisation, is often used (see Appendix for a short description of a TSDC experiment). Two important parameters in a TSDC experiment are the polarisation temperature, T_P, at which the polarising electric field is turned on, and the temperature $T_P' < T_P$ at which the field is turned off (see Fig. 2).

The difference $T_P' - T_P = \Delta T$ is the width of the polarization window of the experiment. If it is wide, the retained polarization (and of course the current peak that is the result of a TSDC experiment) will correspond to a complex set of energy distributed motional modes. Oppositely, the PP experiment where the polarizing field is applied in a narrow temperature interval, allows probing more narrowly distributed relaxation modes. In the conceptual limit of a very narrow polarization window, the experimental depolarisation current peak is supposed to correspond to a single mode of relaxation [16] . In the present work, and in most of our previous ones, we use polarisation windows two degrees wide, and we tacitly assume that this window isolates single relaxation processes. This assumption is based on the observation that similar partial polarization experiments with polarization windows of 0.5, 1 or 2 degrees lead to similar results.

The discussion of the methods for TSDC data treatment and of the nature of the information provided by the TSDC technique are presented elsewhere [17] in a detailed and comprehensive way

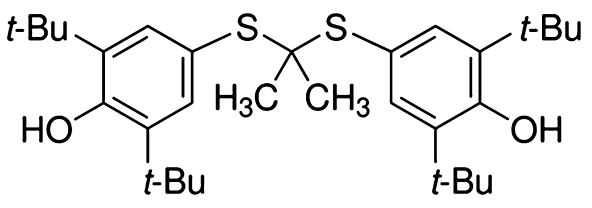

Fig. 1. Chemical structure of probucol.

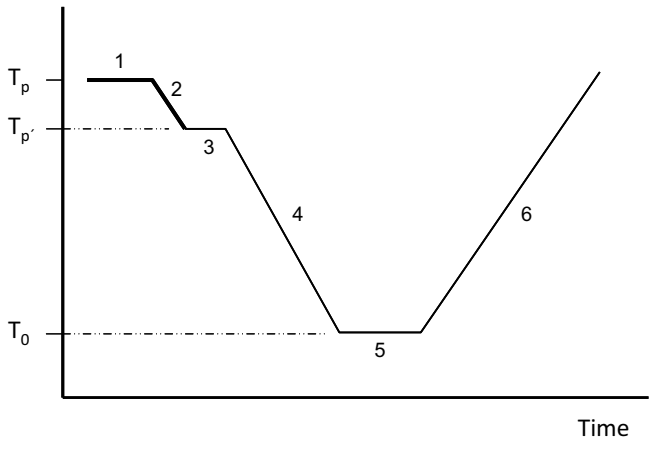

Fig. 2. Experimental protocol in the form of a temperature-time diagram for a thermostimulated depolarization currents experiment. The width of the polarising window is $\Delta T = T_P - T_P'$. In a partial polarization (PP) experiment it is typically between 0 and 5 °C. The electric field is on in steps 1 and 2 (thicker lines). The depolarisation current is measured during the constant rate heating process (step 6).

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