Thermochimica Acta 623 (2016) 29–35

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Differential scanning calorimetry and thermally stimulated depolarization currents study on the molecular dynamics in amorphous fenofibrate

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ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form 1 October 2015
Accepted 9 November 2015
Available online 12 November 2015

Keywords:
Amorphous pharmaceuticals
Molecular mobility
Fragility index
DSC
TSDC
Thermal analysis
Relaxation time

ABSTRACT

The slow molecular mobility of the active pharmaceutical drug fenofibrate is studied by differential scanning calorimetry (DSC) and thermally stimulated depolarization currents (TSDC). The general kinetic features of the secondary relaxations and of the main relaxation, in particular their distribution of relaxation times, were determined by TSDC. Different experimental procedures were used to determine the fragility index by DSC and the obtained results were discussed. The TSDC fragility is in very good agreement with the value obtained by dielectric relaxation spectroscopy (DRS), and all the DSC, TSDC and DRS values indicate that fenofibrate is a very fragile liquid. Given that this means a strong aging sensitivity, we profited from this property to evaluate the influence of physical aging on the fragility values determined by TSDC. From the results of experiments designed to achieve this goal we can conclude that this influence can be considered as negligible.

1. Introduction

The science of the glassy state and of the glass transition attracted great interest and met considerable development in recent decades [1–4]. The amorphous solid state is particularly important in pharmaceutical research and this importance arises, among other things, from the fact that the amorphous form displays higher solubility and dissolution rate compared to the crystal, and hence potentially a higher bioavailability [5–7]. However, the advantages of the amorphous state may get lost if it displays poor physical stability, i.e. if it tends to crystallize during the processes of manufacture and storage. As a consequence, a considerable research effort was focused on finding correlations between the thermodynamic and kinetic properties and the observed amorphous stability of drug substances [8]. In this context, the probable coupling between the molecular mobility and the stability of amorphous phases is receiving an increasing attention [9,10]. It is known that the glass transition mobility is responsible for instability [10], but some local molecular motions (Johari–Goldstein) are precursors of the glass transition, so that they can facilitate the main mobility even if they are not directly the cause of the amorphous instability [9]. Limited evidence also exists about the destabilizing role of the fast secondary motions [11,12]. The kinetic characterization of the secondary relaxations, the faster ones as well as the Johari–Goldstein relaxation, is thus essential to permit finding the conditions for higher stability of the glassy state.

In the present work we continue our previous study by thermally stimulated depolarization currents (TSDC) of the slow molecular mobility in low molecular weight glass formers with pharmaceutical interest [13–15], focusing now on fenofibrate. This is a pharmaceutical drug that is used to lower the cholesterol levels in patients at risk of cardiovascular disease. It reduces the low-density lipoprotein (LDL), the very low-density lipoprotein (VLDL) and triglyceride levels and, at the same time, it increases high-density lipoprotein (HDL) concentrations. Its crystalline form is poorly soluble in water and the amorphous state of this drug substance is easily obtained by different procedures including cooling from the melt.

The main and the secondary mobilities in amorphous fenofibrate have been recently studied by dielectric relaxation

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http://dx.doi.org/10.1016/j.tca.2015.11.012
0040-6031/

spectroscopy (DRS) [16]. TSDC is a dielectric related technique that is also suitable to study the slow molecular mobility in the amorphous solid state. The secondary relaxations can be studied by both dielectric techniques directly below the glass transition temperature. However, while DRS provides average values of the distribution of activation energies, TSDC affords information about the extent of such a distribution. In the case of the α-relaxation, while TSDC watches it directly at the temperatures of the glass transformation, DRS most often sees the main relaxation at temperatures in the metastable liquid. Furthermore, while the low equivalent frequency of TSDC leads to an enhancement of the resolution power of the different relaxations, the very wide frequency range of dielectric spectroscopy constitutes an enormous advantage of this experimental technique. These are reasons, among others, that make thermally stimulated depolarization currents a very useful complementary tool to dielectric relaxation spectroscopy [9,17].

2. Experimental

2.1. Materials

Fenofibrate, IUPAC name propan-2-yl 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoate, (CAS number 49562-28-9), was purchased from Sigma–Aldrich (purity ≥ 99%) and was used without further purification. The empirical formula is $C_{20}H_{21}ClO_4$, and the molecular weight is 360.83 g mol^{-1}. The chemical structure is presented in Fig. 1.

2.2. Techniques

2.2.1. 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 aluminium pans. The measuring cell was continuously purged with dry high purity helium gas at a flow rate of 30 mL min^{-1}. An empty aluminium 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 [18]. As will be resumed below, the most important thermal events we observed in the DSC thermogram of fenofibrate are the melting peaks of two polymorphs located at 74.4 °C (polymorph II) and 81.6 °C (polymorph I) and a glass transition signal with an extrapolated onset at −17.5 °C (on heating at 10 °C min^{-1}).

2.2.2. Thermally Stimulated Depolarization Currents (TSDC)

Thermally stimulated current experiments were carried out with a TSC/RMA spectrometer (TherMold, USA) covering the range from −170 °C to +400 °C. For these measurements a tablet of the crystalline powder was prepared in the form of a compressed disc of ~0.5 mm thickness, shaped under the pressure of ~735 MPa, was dried in a vacuum oven for two hours at a temperature of ~(T_{fus} − 20). After cooling to room temperature, the sample was placed inside the TSDC apparatus between the electrodes of a parallel plane capacitor with effective area of ~38 mm^2, and immersed in a high purity helium atmosphere (1.1 bar). The sample was then heated to 10° above the melting temperature, left isothermally for five minutes, and the amorphous state was obtained by fast cooling (~20 °C min^{-1}) down to temperatures well below T_g.

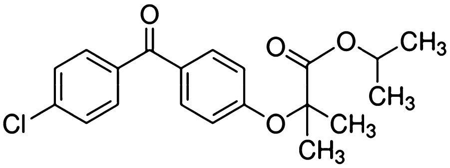

Fig. 1. Chemical structure of fenofibrate.

The TSDC technique is adequate to probe slow molecular motions (1–3000 s). The fact that the relaxation time increases as temperature decreases allows making it exceedingly long (freezing process) compared with the timescale of the experiment; this constitutes the basis of the TSDC technique.

In order to analyse specific regions of the TSDC spectrum the partial polarization (PP) procedure, also called thermal windowing, is often used. 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 Section 1 of the Electronic Supplementary Materials for a description of a TSDC experiment and particularly of the PP procedure). The difference $T_{P'} - T_P$ 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 polarization window is narrow, allows probing more narrowly distributed relaxation modes. In the present work, and in most of our previous ones, we use polarisation windows 2° wide, $\Delta T = 2$ °C, and we tacitly assume that this window isolates single relaxation processes. This hypothesis is based on the observation that similar partial polarization experiments with polarization windows of 0.2°, 1° or 2° lead to essentially to the same results. The experimental result of an experiment with small ΔT is a relatively narrow depolarization peak that can be analyzed in order to obtain the kinetic features of the corresponding mobility. The heating rate was $q = 4$ °C min^{-1} for all the experiments shown. This heating rate is low enough to ensure an equilibrium depolarization process and, as will be shown at the end of this work, high enough to minimize aging effects on the depolarization current intensity, $I(T)$.

The explanations of the physical background of TSDC, of the usual experimental procedures, of the methods for data treatment and of the nature of the information provided are presented in different publications [19–21], and a concise and comprehensive explanation is available in the electronic supplementary materials attached to the present article.

3. Results and discussion

3.1. Differential Scanning Calorimetry

3.1.1. General results

In all our calorimetric experiments fenofibrate never crystallized on cooling from the equilibrium melt (cooling rates between 1 and 20 °C min^{-1}, starting from 10° to 20° above the melting temperature), but a broad cold crystallization was often observed on heating, with an onset at 30–35 °C and a maximum rate at ~60 °C. The signals of the exothermic cold crystallization and of the endothermic melting processes partially coalesced. Two polymorphs were found, as reported before, with melting peaks located at 74.4 °C (polymorph II) and 81.6 °C (polymorph I), in good agreement with literature [22]. We were not able to determine the melting enthalpy of the metastable polymorph (II) because, between the melting peaks of the two polymorphs I and II, the heat flow line shows an exothermic event that seems to indicate that the melting of polymorph II is immediately followed by recrystallization of its melt into polymorph I, which in turn melts on further