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Original Article

Molecular dynamics of amorphous pharmaceutical fenofibrate studied by broadband dielectric spectroscopy ☆

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ABSTRACT

Fenofibrate is mainly used to reduce cholesterol level in patients at risk of cardiovascular disease. Thermal transition study with the help of differential scanning calorimetry (DSC) shows that the aforesaid active pharmaceutical ingredient (API) is a good glass former. Based on our DSC study, the molecular dynamics of this API has been carried out by broadband dielectric spectroscopy (BDS) covering wide temperature and frequency ranges. Dielectric measurements of amorphous fenofibrate were performed after its vitrification by fast cooling from a few degrees above the melting point (T_m=354.11 K) to deep glassy state. The sample does not show any crystallization tendency during cooling and reaches the glassy state. The temperature dependence of the structural relaxation has been fitted by single Vogel–Fulcher–Tamman (VFT) equation. From VFT fit, glass transition temperature (T_g) was estimated as 250.56 K and fragility (m) was determined as 94.02. This drug is classified as a fragile glass former. Deviations of experimental data from Kohlrausch–Williams–Watts (KWW) fits on high-frequency flank of α-peak indicate the presence of an excess wing in fenofibrate. Based on Ngai's coupling model, we identified the excess wing as true Johari–Goldstein (JG) process. Below the glass transition temperature one can clearly see a secondary relaxation (γ) with an activation energy of 32.67 kJ/mol.

1. Introduction

To increase the solubility and bioavailability of the poorly water soluble crystalline drugs is a challenge to modern pharmaceutical scientists. One of the promising methods for improving solubility and bioavailability of poorly water soluble crystalline drugs is to prepare them in the amorphous form. Amorphous form of pharmacologically active materials is very important because this form has enhanced thermodynamic properties, having high internal energy, solubility, bioavailability, dissolution rate, better compression characteristics and greater therapeutic activity than the corresponding crystalline counterpart [1–4]. However, amorphous systems are physically and chemically unstable and therefore show crystallization tendencies.

Recent studies on various amorphous pharmaceutical drugs show that molecular mobility above and below the glass transition temperature (T_g) plays an important role in the devitrification of the drugs. The knowledge about the molecular dynamics of the drugs in the amorphous phase is very important for safety storage in order to obtain the maximum shelf-life and stability [5–8].

Fenofibrate had been chosen as a model drug for the current study. It is a fibric acid derivative which has greater high density lipoprotein cholesterol (HDL-CH) rising and greater low density lipoprotein cholesterol (LDL-CH) lowering action than other fibrates [9]. To the best of our knowledge, this will be the first attempt to describe the dielectric relaxation study of amorphous fenofibrate.

For this it is essential to have a better understanding of molecular dynamics in supercooled and glassy state of this API. In the present study, we used differential scanning calorimetry (DSC) for thermal transition analysis and observed that fenofibrate is a very good glass former. Based on DSC study, dielectric measurements of this API were carried out by broadband dielectric spectroscopy (BDS) as an investigative tool to study the molecular dynamics of amorphous systems in a wide range of frequencies ($f=10^9$–10^{-2} Hz) at different thermodynamic conditions (P, T). Recently this technique has been successfully applied to study the molecular dynamics of various amorphous pharmaceuticals [10–12]. To get a clear picture of hydrogen bonding in the crystalline and amorphous state of fenofibrate, infrared (IR) spectroscopy was used.

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2. Material and methods

2.1. Material

Fenofibrate, a white crystalline powder CAS no. 6271-86-2, was supplied by Sigma Aldrich with purity ≥99%. The drug was crystalline in nature as confirmed by the sharp diffraction patterns of the PXRD result, which is depicted in Fig. 1. Its chemical structure is presented in Fig. 2. Obtained material was used as received without further purification.

2.2. Methods

2.2.1. Image analysis system (IAS)

Image analysis was used to investigate micro- and macro-specimens objectively to provide information regarding the microstructure, quantity, size, area, shape and phase analysis. Images were captured using light optical microscope and analyzed using image analysis software. This technique can be applied in the field of material science, biological science, pharmaceutical science, etc. Particle size of fenofibrate was taken by dispersing the sample in water.

2.2.2. DSC

A DSC instrument (821^e Mettler-Toledo GmbH) operated with STAR^e software version 9.1 and equipped with an intracooler was used for the thermal transition studies. The instrument was calibrated by using indium for temperature and specific heat. Fenofibrate of 3.1540 mg was analyzed under dry nitrogen purge (50 mL/min) in a sealed pinhole aluminum pan. The sample was heated from room temperature to 91 °C and held for 3 min; it was cooled to −50 °C and held for 5 min; and again it was heated to 91 °C. During the entire process a constant heating and cooling rate of 10 °C/min was used. Thermograms were collected during heating. Melting point (T_m) was determined as the onset of the endothermic peak, whereas glass transition temperature (T_g) was measured as the onset of the glass transition.

2.2.3. Fourier transform infrared (FTIR) spectroscopy

The IR spectra of crystalline and amorphous samples were collected on a Perkin Elmer (model: Synthesis Monitoring System) and Nicolet instruments corporation USA (Model MAGNA), respectively.

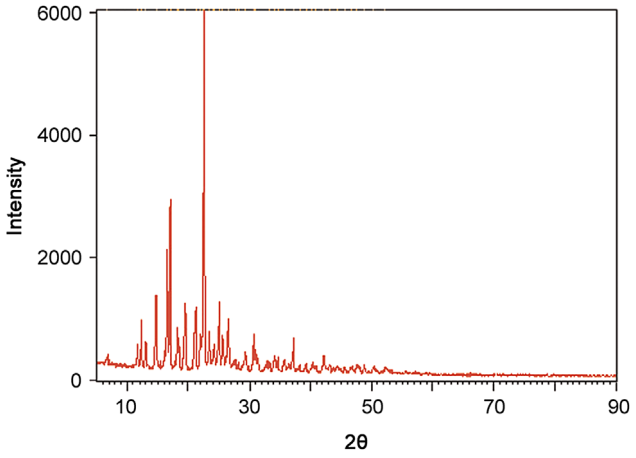

Fig. 1. XRPD pattern of crystalline fenofibrate.

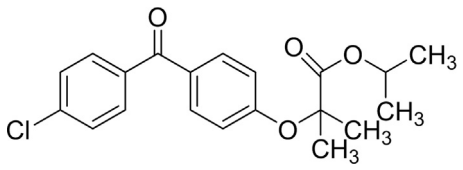

Fig. 2. The chemical structure of fenofibrate.

2.2.4. BDS

Isobaric dielectric measurements at ambient pressure were carried out using Novo-Control GMBH alpha dielectric spectrometer covering a frequency range from 10^{-2} to 10^7 Hz. Temperature was controlled by using a nitrogen gas cryostat with temperature stability better than 0.1 K. The tested sample was placed in a measurement capacitor made of stainless steel (diameter: 30 mm, gap: 0.20 mm). Teflon was used as the spacer. Dielectric measurements of fenofibrate were performed after its vitrification by fast cooling (10 K/min) from a few degrees above the melting point (T_m=354.11 K). The temperature measurements were carried out from 123.15 K to 305.15 K in different steps. However, the sample did not crystallize during cooling from the melting temperature.

3. Results and discussion

3.1. Particle size

Particle size of fenofibrate was analyzed by IAS and the maximum size was found to be 9.95 μm and the minimum was found to be 1.91 μm. The details of analysis are presented in Table 1.

3.2. Thermal studies

The onset glass transition was observed at 254.15 K, which is considered as the glass transition temperature (T_g) of fenofibrate. The onset melting of the sample was observed at 354.11 K, which is melting temperature (T_m) of the sample. No crystallization was observed either cooling below T_g or subsequent heating up to melting point. These results were in good agreement with those reported by Baird et al. [13] and Zhou et al. [7]. Thermodynamic quantities obtained from the current work and from the literature are listed in Table 2. The obtained thermogram of fenofibrate is presented in Fig. 3.

3.3. Spectroscopic investigation of hydrogen bonding

The spectra of fenofibrate showed different strengths of hydrogen bonding (Fig. 4A and B). Two carbonyl peaks were seen in the crystalline and amorphous fenofibrate, one from the C=O, and the other from the methyl ester carbonyl group. Crystalline fenofibrate showed two peaks at 1729.53 cm^{-1} and 1651.48 cm^{-1}, respectively. But in the amorphous form two peaks were seen at 1728.25 cm^{-1} and 1654.22 cm^{-1}, respectively. Because of the hydrogen bond formation the carbonyl peak position shifted to a lower wave number. In the amorphous phase, only one carbonyl group took part in the hydrogen bond formation by a downward shift of 1.28 cm^{-1}. The other peak shifted by value of 2.74 cm^{-1} to a higher peak position. The upward shifted in the position of the C=O group suggests that the hydrogen bond in the crystalline

Table 1
Class interval and number of particles of fenofibrate.

ID class	Class interval (μm)	No. of particles
1	0–2	280
2	2–4	777
3	4–6	371
4	6–8	163
5	8–10	79
6	10–12	0