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Molecular dynamics in liquid and glassy states of non-steroidal anti-inflammatory drug: Ketoprofen

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ABSTRACT

Ketoprofen is a well known nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin. The molecular mobility of amorphous ketoprofen has been investigated by broadband dielectric spectroscopy (BDS) covering wide temperature and frequency range. Multiple relaxation processes were observed. Besides the primary α-relaxation, one secondary relaxation, γ-have been identified. The γ-process visible in the dielectric spectra at very low temperature is non-JG relaxation, and has an activation energy E = 37.91 kJ/mol typical for local mobility. Based on Ngai's coupling model smaller n or a larger Kohlrausch exponent $(1-n)$ of the α-relaxation associated with larger τ_β (T_g). In the case of ketoprofen we conclude that the secondary relaxation (β) emerging from intermolecular motions, is hidden under the dominant α-peak. The temperature dependence of the relaxation time of the α-process can be described over the entire measured range by a single Vogel–Fulcher–Tammann (VFT) equation. From VFT fits, the glass transition temperature (T_g) was estimated as 267.07 K, and a fragility or steepness index m = 86.57 was calculated, showing that ketoprofen is a fragile glass former. Our differential scanning calorimetry (DSC) study shows that ketoprofen is a non-crystallizing compound. To confirm the hydrogen bond patterns of ketoprofen FTIR spectroscopy was applied in both crystalline and amorphous phases. Solubility test performed at 37 °C proved that amorphous phase is more soluble than the crystalline phase.

1. Introduction

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin (Tripathi, 2008). Among the pharmaceutical drugs about 40% are found to be poorly water soluble, which results in inadequate bioavailability (Lipinski, 2002). In order to induce the effect of the drug fully, the dose of the used drug will be kept in higher level during manufacturing. To improve the bioavailability and solubility of active pharmaceutical ingredients (APIs) is a challenging task of a pharmaceutical scientist. Dantuluri et al., pointed out that nanocrystalline solid dispersion (NCSD) is a best alternative for poorly water soluble drugs. NCSDs can be prepared by annealing of amorphous solid dispersion to increase the solubility and bioavailability (Dantuluri et al., 2011; Gupta et al., 2004; Hancock and Zografi, 1997; Hancock and Parks, 2000; Shawn et al., 2005).

Amorphous solids are characterized by short range order and have different physical properties than that of their crystalline equivalent; they have high internal energy, enthalpy and specific volume. Because of these reasons they have enhanced dissolution rate and bioavailability, but their higher molecular mobility will reduce the shelf life of the amorphous drug during processing and storage i.e., there is greater tendency for devitrification of the drug (Alie et al., 2003; Gupta and Bansal, 2005; Yu, 2001; Makower and Dye, 1956). Moreover it is easier to make tablets out of amorphous pharmaceuticals and can avoid the use of excipients, which is used for making the drugs into tablet form (Kaminski et al., 2010).

Recent reports shows that molecular mobility is responsible for the instability of the amorphous phase (Aso et al., 2000; Bhugra and Pikal, 2007; Grzybowska et al., 2010; Shamblin et al., 1999; Zhou et al., 2002). Significant amount of molecular mobility has been reported even 25 K below the glass transition temperature (T_g) which results in slow crystallization of indomethacin (Andronis and Zografi, 1998; Imaizumi and Nambu, 1980). This shows that storage of an amorphous drug below T_g is not safe to avoid crystallization. Because of this reason preparation of the drugs in the amorphous form for commercial use is very limited, even though it is economical (Kaminski et al., 2010; Zhou et al., 2008).

In amorphous state different relaxation phenomena can be observed due to the increase in viscosity when temperature decreases.

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α-relaxation is found to be present above T_g and considered as the slowest one due to the cooperative rearrangement of molecules (Wu, 1991). In the case of ibuprofen a less intense process named as Debye process was observed at frequencies lower than that for the α-process (Brás et al., 2008). Below T_g various other relaxations, often called the secondary relaxations are observed (Capaccioli et al., 2008; Shahin Thayyil et al., 2008). So it is important to understand the molecular dynamics in the glassy state of this pharmaceutical system for getting predictable stability.

We have used differential scanning calorimetry (DSC) to find the glass forming ability of this sample. DSC is used to study thermal properties of drugs in the crystalline and amorphous form (Crowley and Zografi, 2001; Hancock and Parks, 2000). Broadband dielectric spectroscopy (BDS) is an effective tool to probe the molecular dynamics in the molten, supercooled, and glassy states of APIs in a wide range of frequencies ($f = 10^9$ to 10^{-2} Hz), at different thermodynamic conditions (P, T) and was recently employed in pharmaceutical research (Brás et al., 2008; Johari et al., 2005; Sailaja and Shain Thayyil, 2012).

The present study gives an insight to the molecular mechanism involved in the amorphous state of this anti-inflammatory drug ketoprofen, which is selected as a model compound for our study over a wide temperature (193.15–343.15 K) and frequency range (10^{-2} to 10^7 Hz). The complete relaxation spectra show α-relaxation above T_g and one secondary relaxation γ below T_g. The BDS investigations were complemented with DSC, infrared spectroscopy, to get the clear picture of molecular dynamics. To the best of our knowledge, this is the first attempt to describe the molecular mechanisms of amorphous ketoprofen.

2. Materials and methods

2.1. Material

Ketoprofen, a white crystalline powder was purchased from Sigma Aldrich (purity ⩾98%). Ketoprofen is chemically described as (RS) 2 – (3-benzoylphenyl)-propionic acid. Its empirical formula is $C_{16}H_{14}O_3$ and molecular weight is 254.28 g mol^{-1}. The chemical structure is shown in Fig. 1. The purchased material was used without further purification.

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC)

Calorimetric response of the sample was measured using a DSC instrument (821^e Mettler-Toledo GmbH) operating with STAR^e software version 9.1 and equipped with an intra cooler. The instrument was calibrated using indium. The sample of 4.5530 mg was analyzed under dry nitrogen purge (50 ml/min) in a sealed pinhole aluminum pan. The sample was heated from room temperature to 110 °C and held for 5 min, subsequently it was cooled to (−50 °C) and held for 15 min, then it was again heated to 115 °C and a constant heating and cooling rate of 10 °C/min was used. Thermograms were collected during heating. Melting point was determined as onset of the endothermic peak, whereas T_g was measured as the onset of the glass transition.

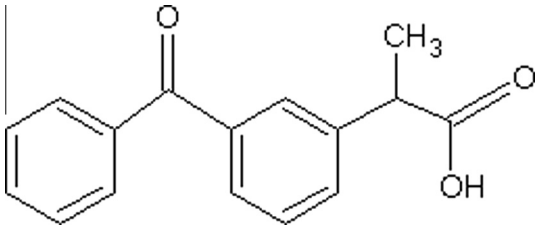

Fig. 1. The chemical structure of ketoprofen.

2.2.2. Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were collected on a FTIR microscope (Perkin Elmer, Model: Synthesis Monitoring System) for amorphous system and FTIR (Nicolet instruments corporation USA Model MAGNA 550) for crystalline state.

2.2.3. Broadband dielectric spectroscopy (BDS)

The complex dielectric function $\varepsilon^*(f) = \varepsilon'(f) - i\varepsilon''(f)$ (f = frequency, ε' = real part, ε'' = imaginary part of permittivity) of ketoprofen was measured at ambient pressure using Novo-Control GMBH alpha analyzer (Hundsangen, Germany) over a wide frequency range of 10^{-2} to 10^7 Hz. The temperature was controlled by nitrogen gas cryostat with temperature stability better than 0.1 K. The sample was placed between two stainless steel electrodes of the capacitor with a gap of 0.20 mm and diameter 30 mm. Teflon was used as the spacer. In order to study the molecular dynamics of the sample in the supercooled and glassy state, the sample was held for 20 min at 383 K slightly above T_m to ensure complete melting. Dielectric measurements were performed after its vitrification by fast cooling (10 K/min) from a few degrees above the melting point. The dielectric spectra were collected in a wide range of temperature from 193.15 K to 343.15 K in different steps: 193.15–263.15 K in steps of 10 K, whereas in temperature range from 263.15 K to 303.15 K in steps of 2 K, 303.15–323.15 K in steps of 4 K and from 323.15 to 343.15 K in steps of 10 K.

2.2.3.1. Data analysis. Dielectric spectra were analyzed using WinFIT V3.2 program provided by Novocontrol. The equation used is Havriliak–Negami (HN) function (Havriliak and Negami, 1967; Brás et al., 2008; Kalinovskaya and Vij, 2000; Wojnarowska et al., 2010) together with an ionic conductivity term:

$$\varepsilon^*(\omega) = \varepsilon' - i\varepsilon'' = -i\left(\frac{\sigma_0}{\varepsilon_0\omega}\right)^N + \left[\varepsilon_\infty + \sum_k \left(\frac{\Delta\varepsilon}{(1+(i\omega\tau_{HNk})^{\alpha_{HNk}})^{\beta_{HNk}}}\right)\right] \quad (1)$$

The first term denotes the conductivity effects ($\sigma_0/\varepsilon_0\omega$) and added to the imaginary part of the fit function, σ_0 is the conductivity due to the translational motion of the ions and ε_0 is the dielectric permittivity of vacuum. After a fit is complete the conductivity term can be subtracted from fit function of the measured data. N is the exponent related to the ionic conductivity of the sample which is due to the mobility of ions. Second term is the HN function. Where k sums over different relaxation processes, ω is the angular frequency, τ_{HN} is the characteristic relaxation time which is related to the frequency of maximal loss f_{max}, ε is the dielectric strength, ε_∞ the high frequency limit of the real part $\varepsilon'(\omega)$; α_{HN}, β_{HN} are the shape parameters. For secondary relaxation process, $\beta_{HN} = 1$, and the HN function reduces to Cole–Cole function. The relaxation time τ can be calculated by using the equation given below:

$$\tau = \tau_{HN} \times \left[\sin\left(\frac{\alpha_{HN}\pi}{2+2\beta_{HN}}\right)\right]^{-1/\alpha_{HN}} \left[\sin\left(\frac{\alpha_{HN}\beta_{HN}\pi}{2+2\beta_{HN}}\right)\right]^{1/\alpha_{HN}} \quad (2)$$

2.2.4. Solubility measurement

Solubility measurements of crystalline and amorphous ketoprofen were performed at 37 °C in ethanol which is found to be the solvent of ketoprofen according to Indian Pharmacopoeia (2010).