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Molecular mobility in the supercooled and glassy states of nizatidine and perphenazine

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ABSTRACT

The dielectric properties of two pharmaceuticals nizatidine and perphenazine were investigated in the supercooled liquid and glassy states by broadband dielectric spectroscopy. Two relaxation processes were observed in both the pharmaceuticals. The relaxation process observed above the glass transition temperature is the structural alpha relaxation and below the glass transition temperature is the gamma relaxation of intramolecular origin. The Johari-Goldstein beta relaxation coming from the motion of the entire molecule is found to be hidden under the structural relaxation peak in both the pharmaceuticals.

1. Introduction

Amorphous state plays an important role for increasing the solubility and hence the bioavailability of pharmaceutical drugs. This state is having high free energy, dissolution rate and increased solubility than that of the crystalline counter-part. However, the amorphous state is susceptible to crystallization and this undesirable effect limits the storage time of the pharmaceutical while remaining in the glassy state. The molecular mechanism responsible for the glass-to-crystal mode of crystallization is important to know. There are two models for the molecular mechanism of crystallization. One is the homogeneous nucleation-based crystallization model whereby crystal growth in the glass is affected by the coalescence of homogeneous crystal nuclei onto an existing crystal surface at a rate determined by the secondary relaxation (Hikima et al., 1998). Another model proposes that the molecular process responsible for crystal growth in the glassy state is from the local molecular motions (Sun et al., 2008). In the glassy state of small molecular glass-formers, local molecular motions are the secondary relaxations broadly classified in two types (Ngai and Paluch, 2004). Faster secondary relaxation involves the intramolecular motion of a part of the molecule is usually referred to as the γ-process. The slowest secondary relaxation involves motion of the entire molecule, and is referred to as the Johari-Goldstein (JG) β-relaxation in ref. (Ngai and Paluch, 2004).

The JG β-relaxation is related to the primitive relaxation of the Coupling Model (CM) (Ngai, 1998; Ngai, 2003; Ngai, 2011). Since the primitive relaxation is universal and has properties strongly connected to that of the structural α-relaxation, so is the JG β-relaxation. The two models of glass-to-crystal crystallization both did not specify which kind of secondary relaxation is operative and associated with either the local molecular motions. Notwithstanding, the JG β-relaxation has to be the mechanism because intuitively it is clear that crystal growth requires motion of the entire molecule. Thus, for fundamental understanding of glass transition as well as applications, it is relevant to study the molecular dynamics of pharmaceutical in the supercooled and glassy states by characterizing the structural α-relaxation, and all the secondary relaxations including the JG β-relaxation. The results help in evaluating the instability of the amorphous pharmaceuticals towards crystallization. Based on the thermal studies by differential scanning calorimetry on these active pharmaceutical ingredients (Pajula et al., 2010) these drugs were classified as non-crystallizing compounds, that did not crystallize during the cooling and the subsequent heating treatment. In this paper we report the results of a study of the molecular mobility of two pharmaceuticals nizatidine and perphenazine in the supercooled and glassy states by broadband dielectric spectroscopy. The two active pharmaceutical ingredients are highly polar and convenient to show about the same molecular dynamics and mobility even though they have very different chemical structures. The frequency dispersion of the α-relaxation is narrow and the JG β-relaxation is too close to be resolved, like found in many different pharmaceuticals recently published (Sailaja

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et al., 2013., Sailaja et al., 2016., Paluch et al., 2016). It is a comprehensive collection of the dielectric relaxation data of the molecular dynamics. In practically all Vander Waals molecular glass-formers including many pharmaceuticals found is the strong anti-correlation between the width of the α-loss peak at or near the glass transition temperature T_g and the polarity of the molecule. In other words, larger the dielectric relaxation strength $\Delta\varepsilon(T_g)$ of the system, narrower is the α-loss peak or larger the fractional exponent β_{KWW} in the Kohlrausch-Williams-Watts correlation function of the α-relaxation. This remarkable property is explained by the contribution from the dipole-dipole interaction potential $V_{dd}(r) = Dr^{-6}$ to the attractive part of the intermolecular potential, making the resultant potential more harmonic. Our dielectric relaxation data of nizatidine and perphenazine are used to critically test this anticorrelation.

2. Materials and methods

2.1. Nizatidine

It is described as *N*-(2-[(2-[(dimethylamino) methyl] thiazol-4-yl) methylthio] ethyl) -*N*- methyl -2-nitroethene-1, 1-diamine and molecular weight is 331.46 g. mol^{-1}. Its empirical formula is $C_{12}H_{21}N_5O_2S_2$. Off white crystalline powder [CAS NO 76963-41-2] purchased from Sigma Aldrich (Fluka) was used without further purification. The chemical structure is presented in Fig. 1.

Nizatidine is a commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). Its bioavailability is about 70%.

2.2. Perphenazine

A white crystalline powder CAS NO 58-39-9 was purchased from Sigma Aldrich. It is chemically described by 2-[4-[3-(2chloro-10H-phenothiazin-10-yl) propyl]piperazin-1-yl]ethanol. Its empirical formula is $C_{21}H_{26}ClN_3OS$ and molecular weight is 403.97 g. mol^{-1}. The chemical structure is presented in Fig. 2. The purchased material was used without further purification.

Perphenazine is a typical antipsychotic drug. It has an oral bioavailability of approximately 40% and used to treat psychosis and the manic phases of bipolar disorder.

2.3. Broadband dielectric spectroscopy (BDS)

Dielectric measurements of nizatidine were performed after its vitrification by fast cooling (10 K/min) from 10 K above the melting point ($T_m = 405.36$ K) and held isothermally for 10 min. However the sample does not crystallize during cooling from the melting temperature. The dielectric measurements were carried out from 123.15 K to 373.15 K in different temperature steps from the glassy state to the supercooled liquid state. Dielectric measurements of perphenazine were performed after its vitrification by fast cooling (10 K/min) from 10 K above the melting point ($T_m = 367.12$ K) and held isothermally for 10 min. However the sample does not crystallize during cooling from the melting temperature. The dielectric measurements were carried out from 123.15 K to 307.15 K in different steps of increase in temperature.

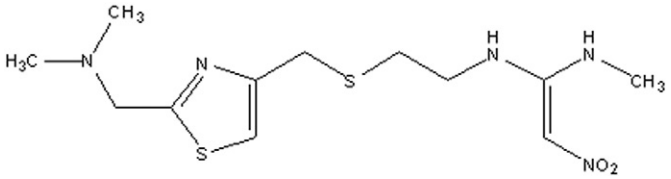

Fig. 1. The chemical structure of nizatidine.

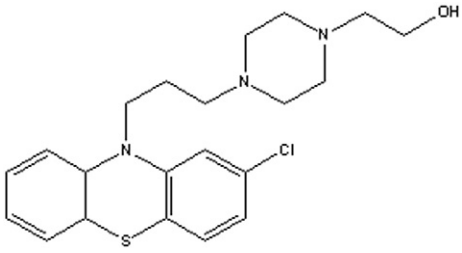

Fig. 2. The chemical structure of perphenazine.

3. Results and discussion

3.1. Nizatidine

We have measured the real $\varepsilon'(f)$ and imaginary $\varepsilon''(f)$ part of the complex dielectric response $\varepsilon^*(f) = \varepsilon'(f)\text{-}i\varepsilon''(f)$ over a wide temperature range i.e., between 123.15 K and 373.15 K. The dielectric loss spectra (i.e., ε'' plotted as a function of frequency f) are shown in Fig. 3. Dielectric loss spectra collected in the supercooled liquid state exhibits α-relaxation and dc-conductivity, associated with translational motion of ions. However, the most prominent feature visible in Fig. 3(a) is strong

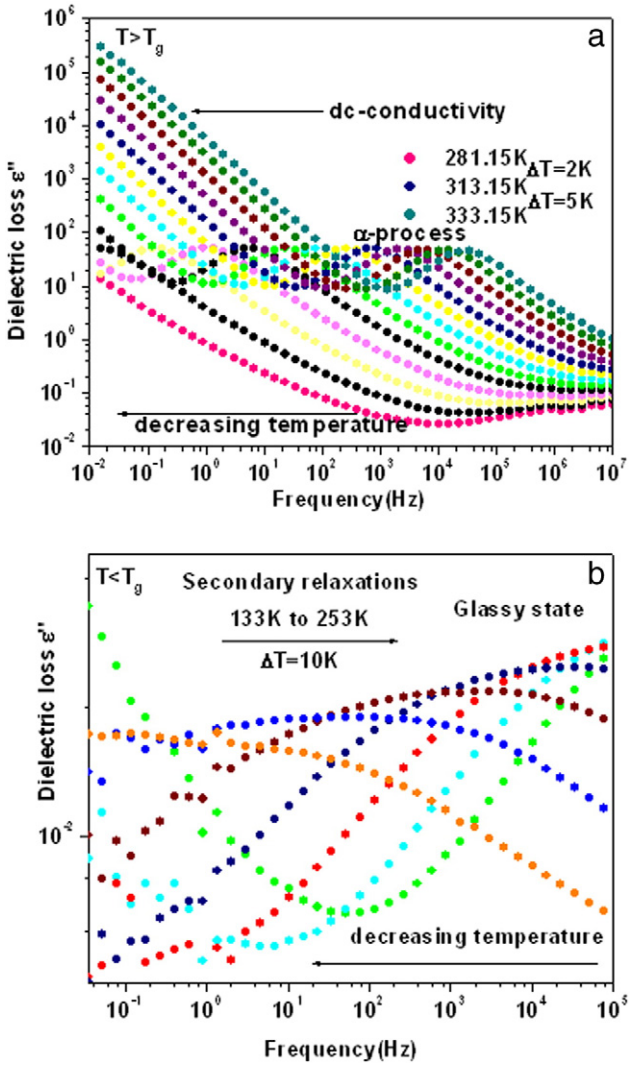

Fig. 3. The dielectric loss of nizatidine at temperatures, (a) above T_g and (b) below T_g. Structural relaxation is predominant at temperatures above T_g and secondary relaxation is predominant at temperatures below T_g.