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Relaxation Dynamics of Amorphous Dibucaine Using Dielectric Studies

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Abstract. Using broadband dielectric spectroscopy the molecular mobility of dibucaine is investigated in the supercooled liquid and gassy states, over a wide temperature range for some test frequencies. Above the glass transition temperature T_g, the presence of structural α- relaxation peak was observed due to the cooperative motions of the molecule and upon cooling frozen kinetically to form the glass. The secondary relaxation process was perceivable below T_g due to localized motions. The peak loss frequency of α-relaxation process shows non-Arrhenius behavior and obeys Vogel-Fulcher-Tammann equation over the measured temperature range whereas the β- process shows Arrhenius behavior.

Keywords: Molecular mobility, Glass transition temperature, Broadband dielectric spectroscopy.
PACS: 77.22.Gm, 64.70.P-

INTRODUCTION

Investigating the molecular dynamics of amorphous pharmaceutical is very important for proposing an alternative way to achieve better solubility and bioavailability *via* oral route. One of the unique features of molecular dynamics of glass-forming systems is the continuous and dramatic increase of the structural relaxation time from values of the order of picoseconds in the liquid state to hundreds of seconds in the vicinity of the glass transition temperature. Drugs prepared in the amorphous forms are characterized by better bioavailability and solubility than their crystalline counterparts [1]. But the amorphous pharmaceuticals can quickly revert to their crystalline forms since supercooled and glassy states are thermodynamically unstable [2] and hence the stability of the amorphous phase against the physical and chemical degradation is a crucial issue to be addressed to determine the applicability of the amorphous active pharmaceutical ingredient (API) for practical application. Crystallization in amorphous materials can be triggered by the intermolecular relaxation modes [3] and these relaxations are very important in determining the shelf life of amorphous pharmaceuticals.

It is well accepted that broadband dielectric spectroscopy (BDS) is a useful tool for studying molecular dynamics in amorphous pharmaceuticals because of the rotational degrees of freedom enjoyed by supercooled and glassy materials. The relaxation properties over a very wide range of frequencies at different thermodynamic conditions (T, P) can be monitored using this technique.

EXPERIMENTAL

Dielectric relaxation spectroscopy probes the interaction of a macroscopic sample with a time dependent electric field. The resulting polarization is expressed by the frequency-dependent complex permittivity which characterizes the relaxation dynamics of the molecules within the sample.

Dibucaine with purity ≥ 99% was purchased from Sigma Aldrich, USA and used as received without further purification. Amorphous dibucaine was prepared by cooling the melt with very high cooling rate to avoid crystallization. Dielectric measurements were carried out using Novocontrol Alpha analyzer. The sample cell is made up of a parallel plate

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capacitor separated by silicon fiber spacers of 50 micron diameter with an empty cell capacitance of approximately 100 pF and the sample is filled between the plates. The temperature is controlled using dry nitrogen-flow in the Novocontrol Quatro cryosystem (-170°C – 125°C). The sample was heated to few degrees above the melting point and cooled rapidly to -170^{0}C. Dielectric spectra for different frequencies were measured during heating of the sample from deep glassy state.

Dibucaine is an amino amide local anesthetic and is used to treat pain and itching caused by minor burns, insect bites, sun burn and other minor skin irritations.

RESULTS AND DISCUSSIONS

The chemical formula of dibucaine (IUPAC name: 2-Butoxy-N- [2-(diethylamino) ethyl] -4-quinoline carboxamide) is ($C_{20}H_{29}N_3O_2$) and molecular weight is 343.46g/mol. This compound belongs to the quinoline carboxamides. These are quinolines in which the quinoline ring system is substituted by one or more carboxamide groups. The chemical structure of dibucaine is given below, in figure 1.

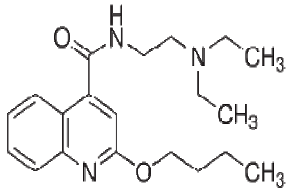

FIGURE 1. Chemical structure of dibucaine.

The sample was earlier studied by Fukuoka *et.al* with DSC and they reported T_g to be 246 K, T_m = 336 K and T_g/T_m = 0.73 [4]. From the dielectric studies we got the glass transition temperature, $T_g \approx 239$ K. Temperature variation of dielectric loss *ε"* at test frequencies 10 Hz, 100 Hz, 1 kHz, 10 kHz, and 100 kHz is shown in figure 2.

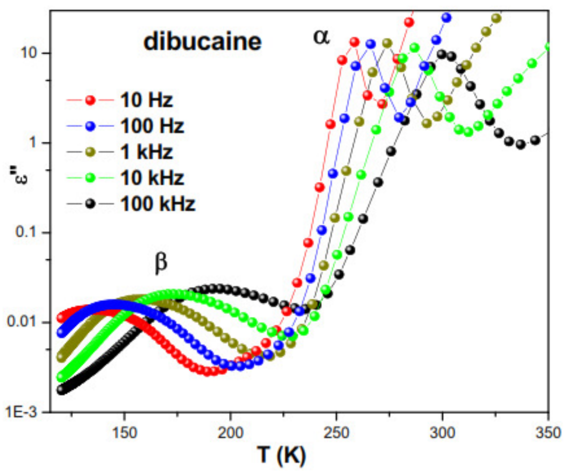

FIGURE 2. Variation of *ε"* with temperature.

Molecular dynamics of super cooled liquids are usually characterized by motions occurring on different length and time scales. Mainly there are two kinds of motions, of which, the α -relaxation process, observed near the glass transition reflects the molecular rearrangements of a cooperative character and is directly related to the liquid-glass transition. As temperature decreases and the glassy state is reached, different types of local motions occur. These are generally termed as secondary relaxations. The increase in loss at higher temperatures above the α-process is due to conductivity which increases with temperature in an Arrhenius fashion. The variation of real part of dielectric permittivity *ε'* for the same test frequencies is shown in figure 3.

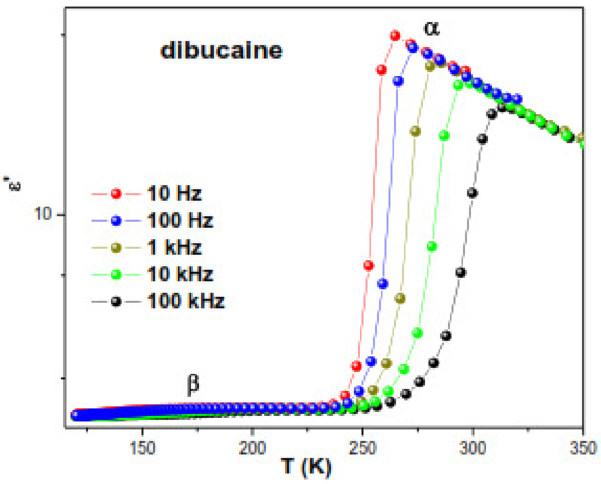

FIGURE 3. Variation of *ε'* with temperature.

The α-process slows down more rapidly on approaching the glass transition and kinetically freezes at T_g. This is due to the rapid increase in viscosity at T_g. As the temperature increases, the α-relaxation peak is rapidly shifted to higher frequency region. Another characteristic feature of α- relaxation is the deviation of temperature dependence from the Arrhenius behavior. This non-Arrhenius temperature dependence and non-exponential relaxation pattern are the most prominent features of the α- relaxation [5]. In experiments with fragile glasses, temperature dependence of the α- relaxation time can be described empirically with the Vogel-Fulcher-Tamman (VFT) law [6].

$$f_{m,\alpha} = f_{0,\alpha} e^{\left(\frac{-B}{(T-T_0)}\right)}. \qquad (1)$$

where T_0 is the Vogel-Fulcher temperature which indicates the divergence of the relaxation time at infinite viscosity corresponding to the complete blocking of the structural relaxation, $f_{0,\alpha}$ is a constant and B=E/R, where E corresponds to the activation energy. The above parameters for dibucaine are $\log f_0(\text{Hz}) = 10.89$, $B = 1526.07$ and $T_0 = 188.54$K. From the VFT fit we also got the glass transition temperature $T_g = 236.97$ K and the activation energy for α- process, $E_\alpha = 12.69$ kJ/mol and the fragility index m = 66.96. The VFT Temperature T_0 is very close to the Kauzmann temperature T_K at which entropies of supercooled liquid and solid become equal [7].

Dielectric loss spectra corresponding to the secondary relaxations appears as broad peaks, more often symmetric and slowly moving to lower frequencies on decreasing temperature [8]. At temperature below the glass transition temperature where the structural relaxation moved out the frequency interval of the measurement, the temperature dependence of the secondary β-relaxations is usually described by the Arrhenius equation

$$f_m = f_0 e^{\left(\frac{-E}{RT}\right)}. \qquad (2)$$

R is the universal gas constant ($R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$), f_0 is the relaxation frequency at high temperature and E is the activation energy. The parameters from Arrhenius fit are $\log f_{0,\beta} = 13.91$ and $E_\beta = 31.53$ kJ/mol.

At microscopic level, two different kinds of mechanisms contribute to the secondary relaxation processes. One is due to the dynamics of molecular subunits (intra-molecular origin) which can move independently from the whole molecule. Second one is due the dynamics of the whole molecule (intermolecular origin) known as Johari Goldstein (JG) β- relaxation and is argued to be the universal characteristic of glass transition [9]. In some glass formers, JG β-relaxation is unresolved and is hidden between the intense α-relaxation and faster non-JG secondary γ-relaxation and while in some glass formers no secondary relaxation is observed, but an excess wing is appeared at the high- frequency tail of the α- peak.

CONCLUSIONS

The molecular dynamics of amorphous dibucaine were investigated in its supercooled and glassy states over a broad temperature range at frequencies 10 Hz, 100 Hz, 1 kHz, 10 kHz, and 100 kHz. The study revealed the different relaxation processes and their characteristics.

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