

Molecular Dynamics in Amorphous Atropine and Tolnaftate

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Abstract

During the development of new pharmaceutical products in amorphous form, the molecular mobility of amorphous active ingredients has to be characterized in detail. Here, using broadband dielectric spectroscopy, the molecular mobility in supercooled liquid and glassy states of two pharmaceuticals namely atropine and tolnaftate have been studied. The dielectric permittivity and loss spectra of glassy and ultraviscous states of the above two pharmaceuticals have been measured for some test frequencies over a wide temperature range. Above the glass transition temperature T_g , the presence of the structural α -relaxation peak was observed which shifts towards lower frequencies as the temperature decreases and kinetically freezes at T_g . The secondary relaxations perceivable below the glass transition temperature is due to intramolecular modes and are usually designated as β , γ and δ etc. are clearly observed in the ϵ'' spectra of atropine, while in tolnaftate no secondary relaxation processes is observed in the loss spectra, but an excess contribution to the high-frequency tail of the α -peak, called excess wing is observed. The α -process shows non-Arrhenius behavior for both the samples. The dielectric relaxation time increases on cooling according to the Vogel-Fulcher-Tammann equation. The secondary relaxation process shows Arrhenius behavior.

Keywords: Amorphous pharmaceuticals, Broadband dielectric spectroscopy, Molecular dynamics.

Introduction

In the pharmaceutical industry, the characterization of drugs is very important. Several multitude analytical techniques are used for this purpose. The pharmaceutical industry is aiming to achieve drug preservation and administration via amorphous form because amorphous pharmaceuticals have the superiority in preservation, drug delivery, bioavailability and other advantages. Most of the water insoluble active pharmaceutical ingredients (APIs) exhibit low bioavailability. Thus in order to induce pharmaceutical effects, the dose of the used drug has to be increased which in turn results in the increase of the side effects of the pharmaceuticals. This can be avoided by the preparation of the pharmaceuticals in its amorphous form. Amorphous API has better solubility properties with body fluids and has higher bioavailability comparing to its crystalline counterpart. In many cases, the drug absorption time is four to five times faster than the crystalline form. Increasing the bioavailability of pharmaceutical compounds by solubility/dissolution enhancement is extremely important to the pharmaceutical industry. Bioavailability improvements that can be attained by using an amorphous form of a drug present a more significant challenge in pharmaceutical industry¹. But the amorphous systems are not thermodynamically stable and they can revert to their crystalline form.

One of the major issues to be avoided during the preservation of amorphous pharmaceuticals is the crystallization of the samples.

Crystallization can be triggered by the intermolecular dynamics involving the β -relaxation mode². Intermolecular secondary relaxations also play an important role in deciding their shelf-life. Molecular mobility of the amorphous state appears as a key factor responsible for the physical and chemical stability of the amorphous API. Hence it's crucial to understand the nature and molecular mechanism responsible for the secondary relaxations observed in the glassy state. One of the best tools to investigate the relaxation properties of the amorphous materials is broadband dielectric spectroscopy (BDS). Application of this technique enables us to monitor the molecular dynamics of examined systems over a very wide range of frequencies at different thermodynamic conditions (P, T). Thus critical study of broadband dielectric spectroscopy and other phase information will give insight to the basic physics and give way to device better technology for these issues. In this work broadband dielectric data have been obtained for 2 well-known drugs.

Materials and Methods

Atropine (synonym: (RS)-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)3-hydroxy-2-phenylpropanoate) with purity $\geq 99\%$ and tolnaftate (synonym: Methyl-(3-methylphenyl) carbamothioic acid O-2-naphthyl ester) were purchased from Sigma Aldrich and used without any further purification. Atropine occurs as white crystals or crystalline powder and is also known as Hyoscyamine. Tolnaftate is a white to creamy white crystalline odorless powder.

Methods: Glassy samples were prepared by cooling the melt. The samples were exposed to high cooling rate in order to avoid crystallization. Dielectric measurements were carried out using Novocontrol Alpha analyzer in the frequency range of 10^{-2} Hz – 10^7 Hz. The sample cell is made up of a parallel plate capacitor separated by silicon fiber spacers of 50 micron diameter to get an empty cell capacitance of 100 pF and the sample is filled between the plates. The temperature is controlled using dry nitrogen-flow in the Novocontrol Quatro Cryosystem. The sample was heated to few degrees above the melting point cooled rapidly to -170°C . Dielectric spectra were measured isothermally, after stabilizing the temperature.

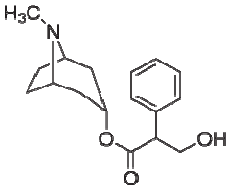
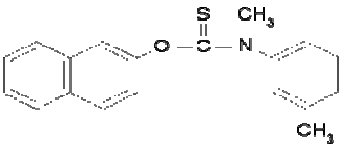
Results and Discussion

Atropine is a parasympatholytic agent and is usually used for the treatment of e.g. spasm, bradycardia, surgery or organophosphorus poisoning. It belongs to the group of tropane alkaloids and the skeleton of atropine consists of tropane acid and tropine. Even though a huge number of synthesis pathways have been described, atropine for pharmaceutical purposes is always of natural origin³. It has two enantiomers, have distinct pharmacological and biological properties⁴. It is used in emergency for activating patients. Bioavailability of atropine is only 25%, so amorphous phase is very important. Atropine has low solubility in water (approximately 1g atropine in 455ml water and 1 g atropine in 90ml water at 80°C). One gram is soluble in 2ml alcohol, 2.5ml alcohol at 60°C , 27 ml of glycerol, 25ml ether and 1 ml chloroform⁵. The sample was studied earlier by Fukuoka *et al.* using DSC experiment. They got the glass transition temperature $T_g = 281$ K, $T_m = 379$ K and $T_g/T_m = 0.74$ ⁶.

Tolnaftate is typically used as antifungal agent and have specific and significant fungicidal effect on Tricophytone, Microsporum and Epidermophytone. It is one of the most potent drug for treatment of Tinea Pedis (athlete's foot) and also used for the treatment of jock itch and ringworm. Tolnaftate is freely soluble in acetone and methylene chloride, very slightly soluble in alcohol, sparingly soluble in ether and practically insoluble in water (0.0702 mg/l)^{7,8}. The sample was earlier studied by Fukuoka *et al* and they got the glass transition temperature, $T_g = 287$ K, $T_m = 384$ K and $T_g/T_m = 0.75$ from the DSC experiments⁹. The chemical structure and properties of the samples are listed in Table-1.

Different relaxation phenomena can be observed in amorphous state due to the increase in viscosity when temperature decreases¹⁰. The variation of dielectric loss ϵ'' with temperature for different test frequencies is shown in Figure-1. From the Figure-1a it is clear that for tolinaftate there is only one dielectric relaxation process which can be identified as α -relaxation. For a typical glass former, the slowest among the relaxations is the α -relaxation process, which is observed near and above the glass transition and is directly related to the liquid glass transition. This process reflects the molecular rearrangements of a cooperative nature, whose strength increases as the temperature is decreased. The structural α - relaxation peak shifts towards lower frequencies as the temperature decreases and kinetically freezes at T_g . No secondary relaxation processes is observed in the loss spectra, but an excess contribution to the high-frequency tail of the α -peak, called excess wing is observed.

Table-1
Chemical structure and properties of the samples

Samples	Chemical structure	Chemical formula	Glass transition temperature, T_g (K)	Molecular weight (g/mol)	Melting point, T_m (K)
Atropine		$\text{C}_{17}\text{H}_{23}\text{NO}_3$	281 ⁶	289.37	388
Tolnaftate		$\text{C}_{19}\text{H}_{17}\text{NOS}$	287 ⁹	307.41	383-386

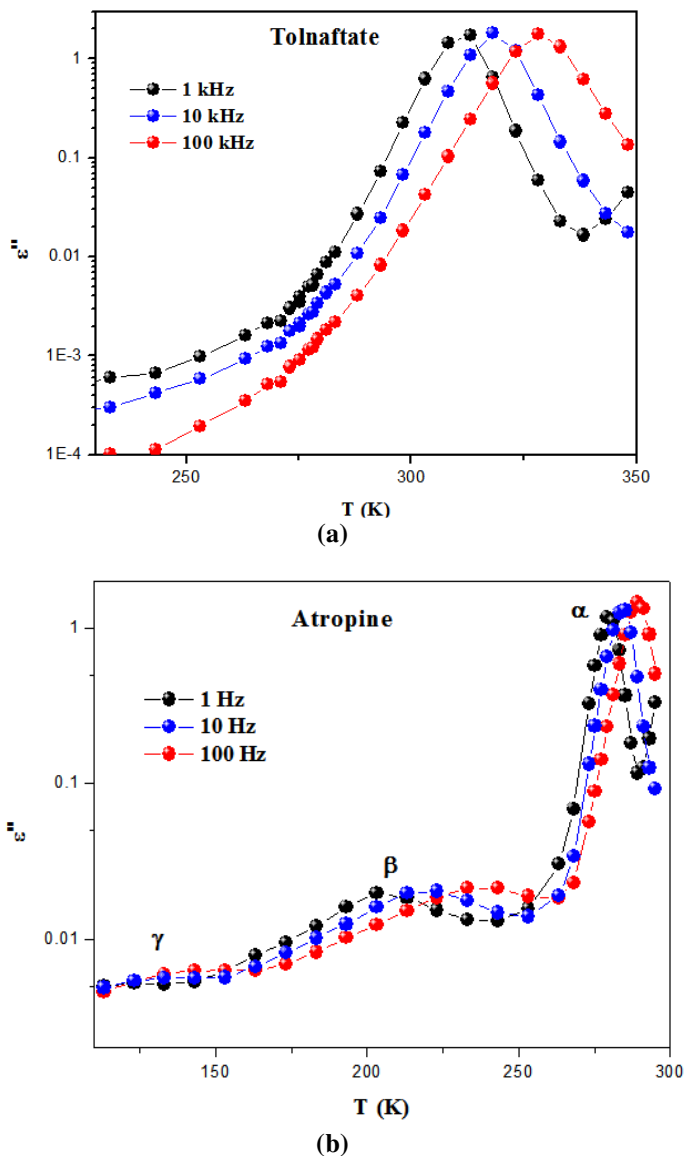


Figure-1
 Variation of ϵ'' with temperature (a) tolnaftate and (b) atropine

From the Figure-1b, three clear and distinct relaxation processes can be seen for atropine which are known as α -process, β -process and γ -process. The α -process freezes at T_g while β -process survives even below T_g . When the temperature decreases below the glass transition temperature, faster relaxations come into the experimental window which is generally called as secondary relaxations. Depending upon the intra-molecular degrees of freedom more and more relaxations can be observed. The strength of these relaxations are associated with the molecular mobility and dipolar fluctuations which in turn associated with the rotation of that group or subgroup. Even in the case of molecules without intra-molecular degrees of freedom, Johari and coworkers have discovered molecular motions of considerable magnitude in the glassy state and

identified this intermolecular relaxation to be the characteristic of the glass transition phenomena¹¹. To honor this discovery, the slowest and which involves the motion of the entire molecule is termed as Johari-Goldstein β -relaxation, and has intermolecular character. The faster ones (termed as γ , δ in order of decreasing time scale) involve the trivial rotational motion of small isolated parts of a molecule and have no connection with the α -relaxation process. The temperature variation of dielectric permittivity ϵ' is shown in Figure-2.

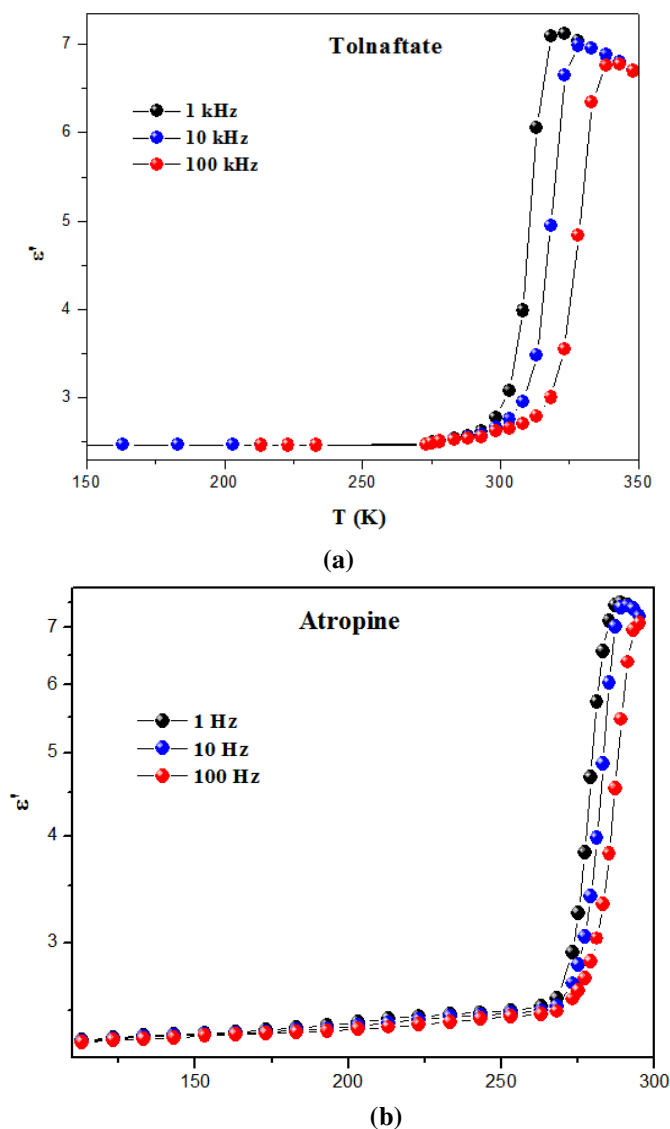


Figure-2
 Variation of ϵ' with temperature (a) tolnaftate and (b) atropine

The non-Arrhenius behavior of α - process can be described by the Vogel-Fulchers-Tammans equation,

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

Where T_0 is the limiting temperature below which the density fluctuations are frozen¹¹, $f_{0,\alpha}$ is a constant and $B=E/R$, where E corresponds to the activation energy. The parameters of equation (1) for tolnaftate are $\log f_0(\text{Hz}) = 20.2$ and $B = 5292$ and $T_0 = 176.3\text{K}$. From the VFT fit we also got the glass transition temperature $T_g = 276.4\text{K}$, the activation energy for α - process, $E_\alpha = 44\text{kJ/mol}$ and the fragility index $m = 63.37$. The parameters of the above equation for atropine are $\log f_0(\text{Hz}) = 15.6$ and $B = 2299$ and $T_0 = 214.8\text{K}$. From the VFT fit we got the glass transition temperature $T_g = 269.5\text{K}$, the activation energy for α - process, $E_\alpha = 19\text{ kJ/mol}$ and the fragility index $m = 90.07$ for atropine. The fragility index of atropine is greater than that of tolnaftate which means that atropine is more fragile than tolnaftate.

The secondary process shows Arrhenius behavior and is analyzed using the equation given by

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

The f_m value for this process is analyzed using the Arrhenius equation given above. The corresponding values are $\log f_0 = 15$, activation energy $E = 58\text{kJ/mol}$ for atropine.

One of the important parameter for the classification and characterization of amorphous pharmaceutical is the Kauzmann temperature T_K at which entropies of supercooled liquid and solid become equal¹². By definition T_K is below the melting temperature T_m and glass transition temperature T_g . At temperatures below T_K or its equivalent, the translational molecular motions responsible for the majority of unwanted physical and chemical changes in pharmaceutical products can be considered to be negligible over the normal product life time. Thus T_K represent the conservative maximum temperature for amorphous pharmaceutical formulations and it may be considered to be a critical molecular mobility region for such systems¹³. If determined properly the VFT Temperature T_0 is very close to T_K ¹⁴. Hence the maximum temperature at which amorphous tolnaftate remains stable is around 176K and Atropine will remain stable in its amorphous form below 214K.

Conclusion

The molecular dynamics in the supercooled liquid and glassy states of tolnaftate and atropine is investigated using broadband dielectric spectroscopy over wide frequency and temperature ranges. For tolnaftate there is only one relaxation process i.e. the α - process and no secondary relaxation processes is observed in the loss spectra, but an excess wing is observed. For atropine, dielectric studies revealed a number of relaxation processes of different molecular origin namely the α - process, β -relaxation process and γ -process. The fragility index of tolnaftate is 63.37 and that for atropine is 90.07. Hence atropine is more fragile than tolnaftate.

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