

# Fragility of Cimetidine Drug Probed by Broadband Dielectric Spectroscopy

Sailaja U<sup>1\*</sup> and Shahin Thayyil M<sup>2</sup><sup>1</sup>Department of Physics, M E S Keveeyam College, Valanchery, Malappuram, Kerala, India<sup>2</sup>Department of Physics, University of Calicut, Kerala, India

## Abstract

Cimetidine is a histamine H<sub>2</sub>-receptor antagonist that inhibits stomach acid production. It is largely used in the treatment of heartburn and peptic ulcers. One of the promising methods to improve the solubility and bioavailability of an active pharmaceutical ingredient is the amorphous phase which will have high free energy than that of the crystalline phase. The relaxation dynamics of cimetidine above the glass transition temperature has been studied by Broadband Dielectric Spectroscopy. Dielectric measurements of amorphous cimetidine were performed after its vitrification by fast cooling from few degrees above the melting point (412.50K). The relaxation processes observed above the glass transition temperature, were labeled as alpha and characterized. The temperature dependence of the structural relaxation time can be described over the entire measured range by single Vogel-Fulcher-Tamman (VFT) equation. From the VFT fits, the glass transition temperature was estimated as 316.27 K and a fragility or steepness index as 69, showing that cimetidine is an intermediate glass former.

## Keywords:

Amorphous cimetidine; Bioavailability; Broadband dielectric spectroscopy; Glass transition; Molecular mobility; Solubility

## Introduction

In the pharmaceutical industry, the most popular method of drug formulation is in the solid form or crystalline form and it has a definite arrangement of atoms having long range order and is highly stable. But, the solubility and bioavailability of this form is found to be low [1]. There are different methods to improve the solubility and bioavailability of an active pharmaceutical ingredient (API). Amorphous form which is one of the recognized forms of solid matter is one of the alternatives. The amorphous form is highly unstable and reverts into the crystalline form and loss in the therapeutic activity [2]. The amorphous form is having high free energy, enthalpy, specific volume and viscosity and it offers greater solubility, dissolution rate and bioavailability. But they have high molecular mobility which will reduce the shelf-life of the drugs during processing, handling and storage [3]. It is easier to make tablets from amorphous form and can avoid the use of excipients and chemicals during the formulation process of tablets [4].

Recent studies show that molecular mobility is the key factor responsible for the devitrification of the drug in the amorphous form and devitrification can also occur even below the glass transition temperature (T<sub>g</sub>). Therefore, it is not safe to store the drug below T<sub>g</sub>. Hence, the production of the drug in the amorphous form is very limited even though it is economical [5,6].

Different relaxation phenomena can be observed in the amorphous state due to the increase in viscosity, alpha (α)-relaxation which is found to be the slowest one and originating from the cooperative rearrangement of molecules is present above T<sub>g</sub>. Below the glass transition temperature, different relaxation processes can be seen due to inter or intra molecular motions called the secondary relaxations [7]. Knowledge about the molecular dynamics of amorphous pharmaceuticals will be very important in the pharmaceutical industry.

Cimetidine is chosen as model drug for the current study. Cimetidine, a histamine H<sub>2</sub>-receptor antagonist that inhibits stomach acid production, is largely used in the treatment of heartburn and peptic ulcers. Cimetidine is taken orally, absorbed adequately and its bioavailability is 60-80%. But penetration in brain is poor because of its hydrophilic nature [8]. Here we want to stress the understanding of molecular dynamics above the glass transition temperature T<sub>g</sub>. To study the molecular dynamics of supercooled cimetidine we decided

to carry out Broadband Dielectric Spectroscopic (BDS) measurements. BDS is an effective tool to probe the molecular dynamics in the amorphous state in a wide frequency ( $f=10^1$  to  $10^2$  Hz) and temperature range (264°C to -140°C).. Recently this technique has been used as an investigative tool to study the dielectric properties of various amorphous pharmaceuticals [9,10]. Our observation might be very useful for predicting the appropriate conditions during processing, handling and storage of this API in the amorphous form.

## Materials and Methods

### Material

Cimetidine, a white crystalline powder CAS NO 51481-61-9 was purchased from Sigma Aldrich (purity  $\geq 98\%$ ). Cimetidine is chemically described as 2-cyano-1-methyl-3-(2-[5-methyl-1H-imidazol-4-yl] methylthio) ethyl) guanidine. Its empirical formula is C<sub>10</sub>H<sub>16</sub>N<sub>6</sub>S and molecular weight is 252.34 gmol<sup>-1</sup>. The chemical structure is presented in Figure 1. The purchased material was used without further purification.

### Broadband dielectric spectroscopy

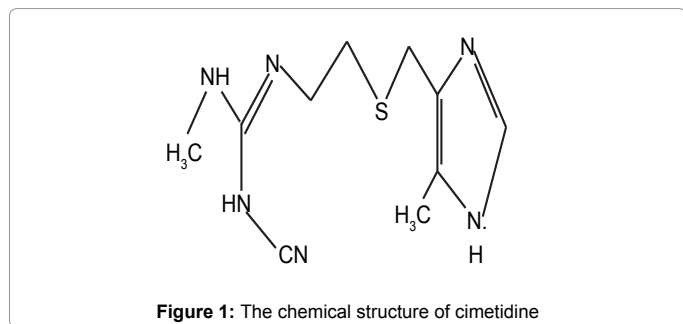
Dielectric measurements at ambient pressure were carried out using Novo-Control GMBH alpha analyzer covering a frequency range from  $10^{-2}$  to 10<sup>7</sup> Hz. Temperature was controlled using nitrogen gas cryostat with temperature stability better than 0.1 K. The tested sample was placed in a measurement capacitor made of stainless steel (diameter: 30 mm, gap: 0.20 mm). Teflon is used as the spacer. Dielectric measurements of cimetidine were performed after its vitrification by fast cooling (10 K/min) from a few degrees above the melting point (T<sub>m</sub> = 412.50K). The temperature measurements were carried out from 324.15K-368.15K in steps of 2K and from 368.15K to 373.15K in steps

\*Corresponding author: Sailaja U, Department of Physics, M E S Keveeyam College, Valanchery, 676 552, Malappuram, Kerala, India, Tel: 0466-2240364; E-mail: [sailajaurpayil@gmail.com](mailto:sailajaurpayil@gmail.com)

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of 5K. The sample does not crystallize during cooling from the melting temperature. It means that cimetidine is a very good glass former and can be easily supercooled.

## Results and Discussion

The dielectric loss spectra (i.e. imaginary part of dielectric permittivity plotted as a function of frequency) above the glass transition temperature  $T_g$  is shown in Figure 2a.  $T_g$  is defined as a temperature at which dielectric relaxation time  $\tau\alpha$  is equal to 100 s and its value for cimetidine is 316.27 K. Dielectric loss spectra collected above  $T_g$  exhibits  $\alpha$ -relaxation and dc-conductivity. dc-conductivity is due the translational motions of ions from the nitrile group. To get a clear picture of the  $\alpha$ -peak, conductivity is subtracted from the total dielectric loss and the spectra above the glass transition temperature is fitted using Havriliak-Negami (HN) function along with an ionic conductivity term and presented in Figure 2b.

$$\epsilon''(\omega) = \epsilon'' - i\epsilon'' = -i \left( \frac{\sigma_0}{\epsilon_0 \omega} \right)^N + \left[ \epsilon_\infty + \sum_k \left( \frac{\Delta\epsilon}{1 + (i\omega\tau_{HNk})^{\alpha_{HNk}}} \right)^{\beta_{HNk}} \right] \quad (1)$$

The first term denotes the conductivity effects ( $\sigma_0 / \epsilon_0 \omega$ ) and added to the imaginary part of the fit function  $\sigma_0$  is the conductivity due to the translational motion of the ions, and after a fit is complete the conductivity term can be subtracted from fit function of the measured data,  $\epsilon_0$  is the dielectric permittivity of vacuum.  $N$  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,  $\omega$  is the angular frequency,  $\tau_{HN}$  is the characteristic relaxation time which is related to the frequency of maximal loss  $f_{max}$ ,  $\Delta\epsilon$  is the dielectric strength,  $\epsilon_\infty$  the high frequency limit of the real part  $\epsilon'(\omega)$ ;  $\alpha_{HN}$ ,  $\beta_{HN}$  are the shape parameters. The relaxation time  $\tau$  can be calculated by using the equation given below

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

A well-pronounced  $\alpha$ -peak moving towards the lower frequency side characterizes the increase of structural relaxation with decreasing temperature. From 360.15 K onwards the dielectric strength of  $\alpha$ -process starts decreasing in a non-significant manner, which shows tendency for crystallization of cimetidine.

Dielectric spectra obtained after removing the conductivity contribution were used for further analysis of the main relaxation process ( $\alpha$ -relaxation). In the supercooled region close to the glass transition, the temperature evolution of the  $\alpha$ -relaxation time  $\tau\alpha$ , very often follows the time honoured Vogel-Fulcher-Tamman (VFT) equation [11],

$$\langle \tau \rangle = \tau_{VF} \exp \left[ \frac{B}{(T - T_0)} \right] \quad (5)$$

Where  $\tau_{VF}$ ,  $B$ ,  $T_0$  are constants. The temperature  $T_0$  is often

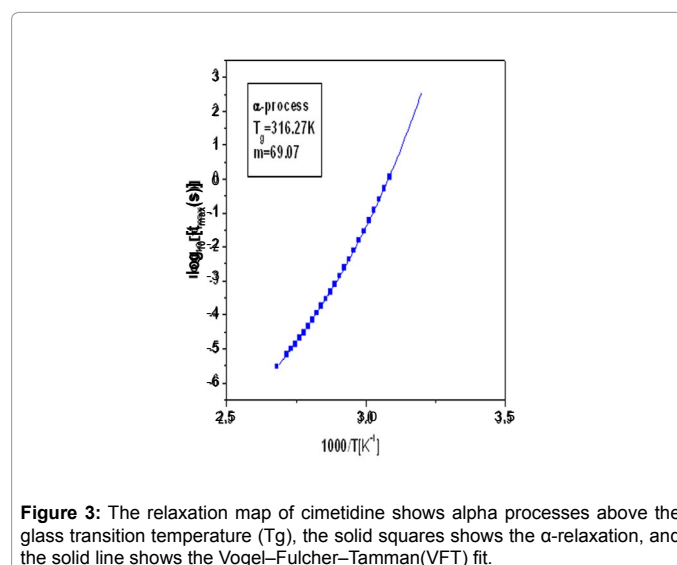
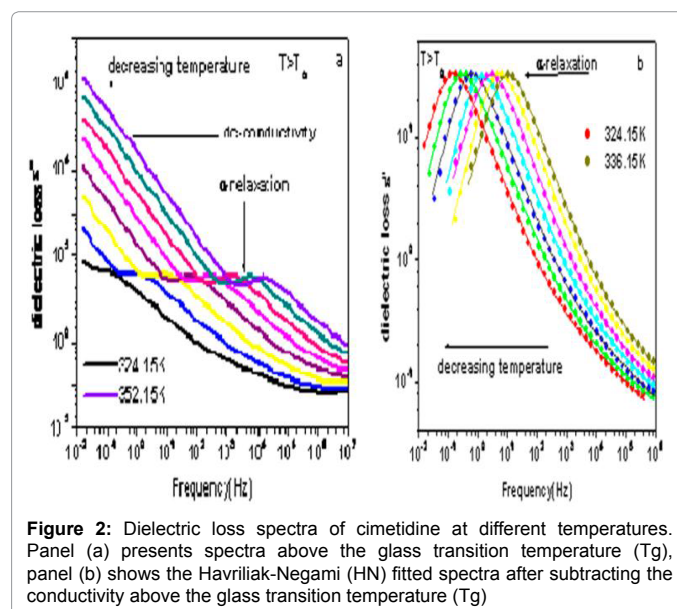
referred to the Kauzmann temperature  $T_K$ , a hypothetical temperature where configurational entropy of super cooled liquid would be equal to entropy of the crystal and molecular mobility would reduce to the same level as that of the crystal (not completely be zero). For most of the glassy systems, it lies between 50 and 70K, below  $T_g$  and it is sufficient to ensure safety storage.

From VFT fit we calculated the fragility or steepness index  $m$  of cimetidine by using the equation given below:

$$m = \frac{d \log_{10} \tau_\alpha}{d \left( \frac{T_g}{T} \right)} \quad T = T_g \quad (6)$$

Relaxation map of cimetidine is shown in Figure 3.

Fragility is the measure of deviation from Arrhenius behavior [12]. From VFT fit the glass transition temperature ( $T_g$ ) was estimated as 316.27K. This value is in close agreement with the result ( $T_g = 319.67K$ ) reported by Pajula et al., in their Differential Scanning Calorimetry (DSC) experiment [13]. This relatively high value of  $T_g$  indicates the possibility of preparing oral dosage form of cimetidine in the



amorphous form completely at room temperature and even at human body temperature. So, high T<sub>g</sub> amorphous pharmaceuticals with stable glassy phase can be a better substitute than its traditional counterpart. Fragility (m) is estimated as 69, proving the system as an intermediate glass former. T<sub>0</sub> as 238K, assuming that this corresponds to the temperature at which normally all important molecular motions stops. It is concluded that storage temperature in a freezer for cimetidine is (<238K) and should provide at least 3-5 years shelf-life stability [14]. Another method for giving stability to amorphous drugs is to raise its T<sub>g</sub> by mixing it with high-T<sub>g</sub> glass former such as PVP (K 29/32) [15, 16].

Finally we present the results of solubility measurements of crystalline and amorphous form of cimetidine at 37°C in methanol which is found to be the solvent of cimetidine according to Indian Pharmacopoeia [17]. During the determination of solubility the differences between both forms of examined drugs were found. The solubility of amorphous cimetidine was found to be double than that of crystalline form. This is one of the reasons for higher bioavailability of the drug.

## Conclusions

We studied the dielectric properties of supercooled cimetidine above the glass transition temperature. The tested sample is found to be an ionically conducting glass-former. In the whole temperature range above the glass transition a well pronounced peak indicates the  $\alpha$ -relaxation process.

The glass transition temperature calculated from VFT fit is equal to 316.27K. The high value of T<sub>g</sub> indicates the preparation of the drug in amorphous form at room temperature or at higher temperature for the formulation process of tablet manufacturing. A steepness or fragility index m of 69 was estimated which designates that the examined drug is an intermediate glassformer. The storage temperature for amorphous cimetidine is found to be (<238K) and this will provide at least 3-5 years shelf-life stability. Finally we present the results of solubility of crystalline and amorphous cimetidine, solubility of amorphous form is double than that of crystalline form at 37°C.

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