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Dielectric Spectroscopy in Ibuprofen-Dioxane Mixture

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Abstract

In recent years, the dielectric study of amorphous pharmaceuticals has made a considerable effort towards correlating the molecular mobility with their physical and chemical stability. The molecular mobility of amorphous materials is affected by temperature, additives (such as water) and specific interactions (such as Hydrogen bond). Therefore, to understand the physicochemical instability of amorphous materials, nature of their molecular mobility needs to comprehend.

In this order, the Dielectric and Calorimetric measurements were performed on a mixture of ibuprofen and 1,4-dioxane. The dielectric spectroscopy reveals two relaxation processes, (designated as α_D, and α) in the supercooled region. The spectral shape of α_D and α process can be explained satisfactorily throughout the frequency range using Havriliak-Negami (HN) shape function. The α_D process is found to be Debye-like (i.e., $\alpha_{HN} = 0$ and $\beta_{HN} = 1$) in nature and α process kinetically freezes at $T_{g\text{-onset}}$ (DSC) implies that α- process indeed corresponds to the glass transition event. Both processes are found to be non-Arrhenius in nature. In addition, two secondary relaxation processes (designated as β_{JG} and β) are observed and are comparable with the literature. The activation energy of β process indicates that it‟s originating from the fluctuations of the side group larger than -OH group. Also, the calculated fragility index demonstrates that ibuprofen is a fragile glass former.

Keywords: Debye relaxation; Dielectric spectroscopy; Ibuprofen; Dioxane

Introduction

The study of vitrification transition phenomena has always been interested in hydrogen-bonded supercooled liquids composed of small molecules [1-6]. It is known for decades that several monohydroxy alcohols [7-15] and amides [16] hydrogen bonded glass forming systems results in intramolecular and intermolecular hydrogen bonding and behave differently. A study of monohydroxy alcohols reveals that hydrogen-bonded networks aggregate their polar -OH group in the chain or ring-like structures [9-12]. The aggregation of the chain-like structure shows a Debye relaxation, where the strength of Debye process depends on temperature, pressure, dilution, and confinement volume. On the basis of the position of -OH group in molecular structure, monohydroxy alcohols can classify in three different groups;

(i) If -OH group is situated at end position (e.g., 2-ethyl-1-hexanol) then observed Debye peak dominates the dielectric loss spectra.

(ii) If -OH group is sterically hindered (e.g., 4-methyl-3-heptanol) then observed Debye peak is weaker. Moreover, if a large cyclic group (e.g., phenyl ring) is located in the molecular structure, it can limit the formation of H-bonding.

If two or more -OH groups are present in the proximity of the same molecule (e.g., glycerol) then Debye peak vanishes [12] or may be hidden under conductivity contribution in the imaginary part of permittivity [13-16]. It is reported that Debye process could not be detected in calorimetric [17], light scattering [18] and nuclear magnetic resonance [19,20]. Therefore, dielectric spectroscopy is the most useful technique to study the strength of relaxation processes, which can be discussed in terms of Kirkwood correlation factor [7,21].

Recent [1,2] dielectric studies of supercooled pharmaceuticals are revealing the existence of the Debye-like process in complex molecules, and its presence has been reported in ibuprofen. However, the dielectric strength of the Debye process is found to be very low. Moreover, this Debye-like process is reported to be absent in magnetic resonance or shear mechanical experiments [22].

In this work, the detailed dielectric and calorimetric study of supercooled ibuprofen and its liquid mixtures with 1,4-dioxane at test concentrations is reported. The 1,4-dioxane (also known as p-dioxane) is used as a non-polar [23,24] solute in a solution. The measurements can perform up to 3% (weight fraction of 1,4-dioxane) because heterogeneous crystallization intervened for higher concentration.

Experimental Section

Material characterization

The samples studied are:

(i) Ibuprofen (IBP) ($C_{13}H_{18}O_2$) (purity ≥ 98%) (Molecular weight (MW) = 206.29 g/mol), also known as α-Methyl-4-(isobutyl) phenylacetic acid, (±)-2-(4-Isobutylphenyl) propanoic acid

1,4-dioxane (DXN) ($C_4H_8O_2$) (purity ≥ 99.5%) (MW=88.11 g/mol). Short-term inhalation exposure to high levels of 1,4-dioxane may cause nausea, drowsiness, headache, and irritation of the eyes, nose, and throat. The U.S. Environmental Protection Agency (EPA) has classified 1,4-dioxane as likely to be carcinogenic to humans‟ by all routes of exposure [25]. The IBP sample is obtained from Sigma-Aldrich co., and DXN is obtained from Fisher Scientific (ExcelaR). Both the samples were dried to remove absorbed water and used without further purification.

Experimental techniques

Perkin-Elmer sapphire differential scanning calorimeter (DSC) with

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quench-cooling accessory was used for the calorimetric measurements. The DSC cell was calibrated for temperature using indium and mercury as standards. The sample in DSC pans was cooled rapidly at a rate of 10 - 40 K/min to 103 K in a nitrogen atmosphere, and then DSC scan was made for a heating rate of 10 K/min.

Frequency domain dielectric measurements were carried out with Agilent E4980A LCR Meter in the frequency range of 20Hz - 2MHz. The design of the dielectric cell is similar to the one used before, with the empty cell capacitance (C_0) of about 15 pF. The binary liquids were prepared by mixing well the components using a magnetic stirrer for apparent homogenization. The dielectric cell was then filled with the liquid mixture without entrapping air bubbles, and data was taken during cooling and heating cycles in the argon atmosphere. Before each dielectric scan, the dielectric cell was calibrated with benzene at room temperature. For details of the experimental setup, the reader may consult the earlier publications [4-6].

Data analysis

To analyzed the complex dielectric function $\varepsilon^*(f) = \varepsilon'(f) - \varepsilon''(f)$, (where f is frequency, ε'= real, and ε''= imaginary part of the complex permittivity) associated with reorientation of dipoles, imaginary part was fitted to Havriliak-Negami (HN) shape function [26],

$$\frac{\varepsilon^*(f)-\varepsilon_\infty}{\varepsilon_o-\varepsilon_\infty}=\left[1+i\left[\frac{f}{f_o}\right]^{1-\alpha_{HN}}\right]^{-\beta_{HN}} \qquad (1)$$

where f_0 is the average relaxation frequency, ε_0 and ε_∞ are the limiting dielectric constant and $\varepsilon_0 - \varepsilon_\infty = \Delta\varepsilon$ is the dielectric strength of the process under consideration, α_{HN} and β_{HN} are the spectral shape parameters. The parameter α_{HN} is a measure of the distribution of relaxation times in the sample, and the parameter $(1-\beta_{HN})$ is a measure of cooperation among the molecules. The exact identity of peak loss frequency (f_m) [27] is determined with the help of the estimated values of α_{HN}, β_{HN} and f_0 as,

$$f_m = f_o\left[\frac{k'}{\left[\cos\left(\alpha_{HN}\pi/2\right)-\sin\left(\alpha_{HN}\pi/2\right).k'\right]}\right]^{1/(1-\alpha_{HN})} \qquad (2)$$

$$k' = \tan\left[\frac{(1-\alpha_{HN})\pi}{2(1+\beta_{HN})}\right]$$

Where,

The Arrhenius plot of the primary relaxation process has been analysed using the Vogel-Fulcher-Tammann [28] equation given by,

$$f_{m,\alpha} = f_{o,e}\ e^{\left[\frac{-B}{T-T_o}\right]} \qquad (3)$$

where T_0 is the limiting glass transition temperature, $f_{0,\alpha}$ is a constant and B = E/R, where E corresponds to the activation energy. The secondary relaxation process has been analyzed using the Arrhenius equation [29].

$$f_m = f_o\ e^{[-E/RT]} \qquad (4)$$

Results and Discussion

Prior to the dielectric measurements, DSC measurements were performed on neat IBP and its liquid mixtures with DXN. The pure IBP sample was heated from room temperature to 363.15 K, and an endothermic peak is (T_m = 347.7 K) obtain with an enthalpy of fusion (ΔH_f=29 kJ/mol) (shown in the inset of Figure 1). The molten sample of IBP, is cooled rapidly at a rate of 10-40 K/min to 103 K. The vitrified sample is then heated at a rate of 10 K/min, and the resultant thermal scan (black line) is depicted in Figure 1. The thermal scan shows a glass transition ($T_{g\text{-onset}}$) event at 225.6 K for IBP. Also, the DSC scan of IBP-DXN (x_w = 3%) (Where x_w is the weight fraction of DXN) mixture is shown in Figure 1 and the observed $T_{g\text{-onset}}$ = 215.1 K is indicated. Moreover, it has been noticed that neat 1,4-dioxane exhibited a transition (at T_t = 272 K) just a few degrees below its melting temperature (i.e., T_m = 281.7 K), and the observed onset values are in agreement with literature data [1,7,30].

The dielectric measurements were performed in frequency range of 20Hz - 2MHz on IBP and its DXN mixture, and the obtained temperature variation of dielectric permittivity (ε') and dielectric loss (ε'') is shown in Figure 2 (at f = 1 kHz), which reveals two (designated as α_D, and α) processes in supercooled region. The spectral shape dependence of α_D, and α relaxation is shown in Figure 3a (at T = 261.2 K). The dielectric loss spectra of α_D and α process can be explained satisfactorily throughout the frequency range using HN Eqn. (1), and the peak loss frequency (f_m) is determined with the help Eqn. (2). In Figure 3b, the Cole-Cole diagram is shown for the purpose of clarity. Arrhenius plots resolved for both samples are shown in Figure 4. The inverse temperature dependence of peak loss frequency is described well by VFT Eqn. (3) for α_D, and α process and the details of fit parameters are tabulated in Table 1.

The presence of two relaxation processes in hydrogen-bonded systems in their supercooled regime is not new, similar behavior has been reported for monohydroxy alcohols [7-15] and also, recently observed in neat IBP [1,2]. As discussed above, in such systems, sterically hindered -OH group can limit the formation of hydrogen bond chain-like structures. Therefore, it's difficult to resolve the Debye process as the structural relaxation dominates. Therefore, in this study a small amount of DXN is added in IBP to disturbed the hydrogen bonds. This results as an enhancement of the dielectric strength of the α_D and α relaxation. However, the dielectric strength of α_D process is still small in comparison to α process, but it can be resolved more significantly, and this enhancement is strengthening its existence in IBP. The α processes observed are kinetically frozen at $T_{g\text{-onset}}$ (DSC) (Figure 4), indicates that α process indeed corresponds to the glass transition event. Moreover, both processes are found to be non-Arrhenius in nature.

In addition, the dynamic fragility index (m) defined as [5];

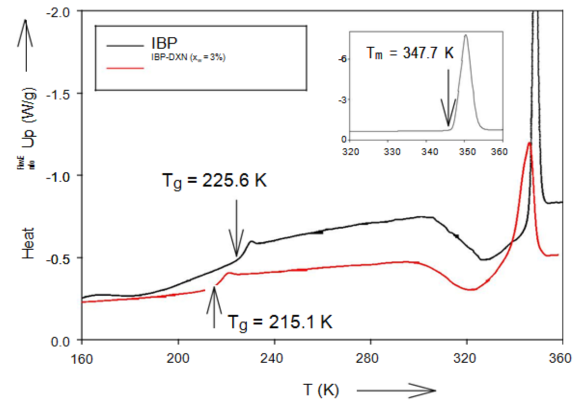

Figure 1: DSC scans taken while heating at a rate of 10 K/min. for quenched melts of IBP (black line) (sample size 4.3 mg) and for IBP-DXN (x_w=3%) (red line) (sample size 10.5 mg). Shown in inset is the melting endotherm of neat IBP.

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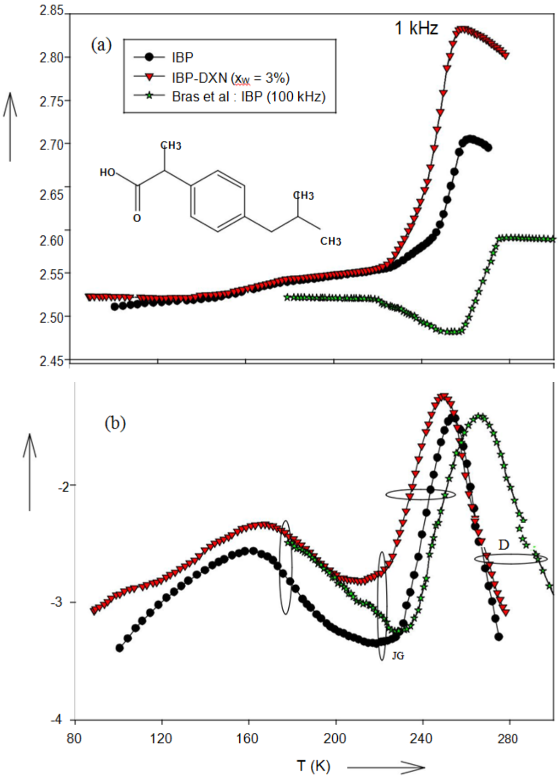

Figure 2: Variation with temperature of (a) the real (ε'), and (b) the imaginary (ε'') part of the complex permittivity at a particular frequency (1 kHz) for IBP and IBP-DXN (x_w = 3%) mixture. Data of pure IBP (100 kHz) are taken from reference [1] for the purpose of comparison. Molecular structure of IBP is shown in the inset.

$$m = \left.\frac{-d\left(\log f_m\right)}{d\left(T_{g-die}/T\right)}\right|_{T=T_{g-die}} \qquad (5)$$

or

$$m = \frac{0.4342\ BT_{g\text{-}die}}{\left(T_{g\text{-}die}-T_o\right)^2}$$

has been calculated using VFT-parameters. Fragility measures the rapidity of liquid‟s properties, such as viscosity, relaxation time, etc. change as the glassy state is approached. The m value is expected to be smaller for a kinetically strong material than that for a fragile material. The values of m thus determined for IBP and its mixture are entered in Table 1. The observed m-index is indicating that IBP is a fragile glass former. Also, the change in fragility values (the mixture is less fragile) is remarkable.

The secondary relaxation processes (designated as β_{JG} and β) observed in dielectric measurement are shown in Figure 4. Albeit, the secondary relaxation process of intermolecular origin (i.e., β_{JG}), reported in an earlier study [1] is not resolved apparently (due to experimental setup limits and short frequency range). Therefore, the f_m values corresponding to the β_{JG} process are not stringent and hence, considered with the error bars shown in the Arrhenius diagram is comparable with literature [1]. The β process observed is found to be non-Debye in nature, and can be described well by a symmetrical Cole-Cole function (i.e., Eqn. 1 with β_{HN} = 1) with α_{HN} ~ 0.5 (for IBP), and α_{HN} ~ 0.6 (for IBP-DXN (x_w = 3%) mixture). The inverse temperature dependence of peak loss frequency is described well by Arrhenius Eqn. (4), and the corresponding details are tabulated in Table 1. The

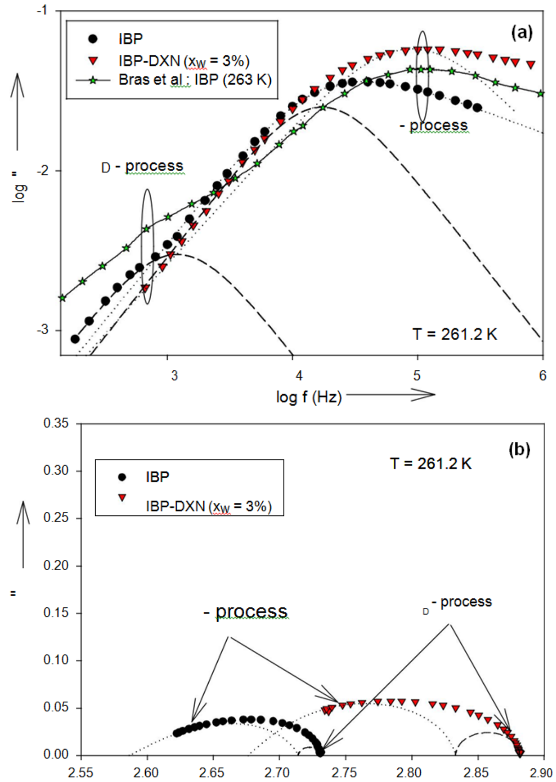

Figure 3: Shown in (a) is the variation of dielectric loss (ε'') vs. frequency (f) at T = 261.2 K in IBP and IBP-DXN (x_w=3%). The dashed and dotted lines represent the individual HN Eqn fit corresponds to α_D and α process respectively. Data of pure IBP (at 263 K) are taken from reference [1] for the purpose of comparison; and (b) is the Cole-Cole diagram for the purpose of clarity.

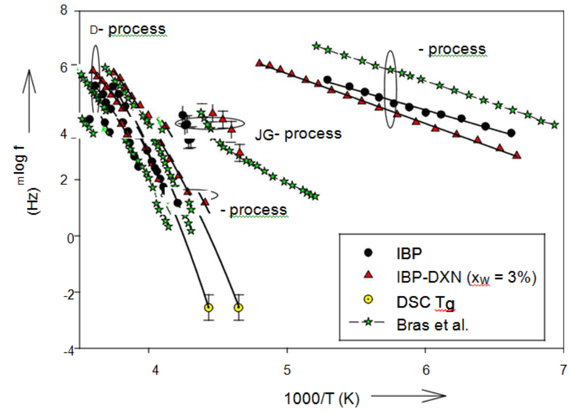

Figure 4: Depicting the Arrhenius plot of IBP and IBP-DXN (x_w = 3%). The thick line along the α_D and α process is corresponds to Eqn. (3), and that along the β process is corresponds to Eqn. (4). The f_m values corresponding to β_{JG} process are not stringent and hence, considered with the error bars shown in the Arrhenius diagram. Data of pure IBP are taken from ref [1] are also shown for the purpose of comparison. Additionally, shown in the diagram is the enthalpy relaxation frequency at $T_{g\text{-}onset}$ determined by the DSC which corresponds to an approximate log f_m (Hz) = -2.55 ± 0.45.

Sample	Process	VFT Eqn. (3)			$T_{g\text{-}die^*}$		Arrhenius Eqn. (4)	
		log f_0 (Hz)	B (K)	T_0 (K)	(K)	m	log f_0 (Hz)	E_β (kJ/mol)
IBP	αD-	9.1	439.8	225.8	-	-	-	-
	α-	19.1	3581.9	153.7	224.1	70	-	-
	β-	-	-	-	-	-	12.9	27
IBP-DXN	αD-	10.7	824	204.3	-	-	-	-
(x_w=3%)	α-	17.2	3173.5	145.3	213.5	63	-	-
	β-	-	-	-	-	-	14.6	30.9

[*] $T_{g\text{-}die}$ is the temperature at which the f_m value is ~ 10^{-3} Hz

Table 1: Details of the various fit parameters are tabulated.

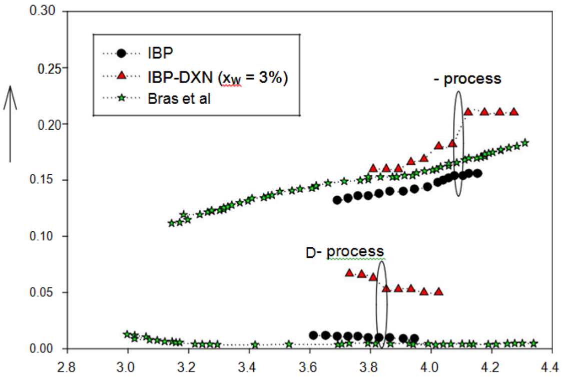

Figure 5: Depicting the variation of dielectric strength (Δε) with inverse of temperature for α_D and α processes in IBP and IBP-DXN (x_w = 3%). Data of pure IBP are taken from ref [1] for the purpose of comparison. The dotted lines are used to guide eyes.

estimated activation energies (E_β) are comparable with literature data [1]. This agreement of activation energies with literature is indicating that the observed β process is intramolecular in nature and originates from the fluctuations of the side group larger than -OH group.

From Figure 5, it is evident that the dielectric strength (i.e., Δε) of α_D and α process is enhanced after adding a small amount of DXN. The dielectric strength is found to follow a linear correlation with temperature for α_D process. In contrast, an inverse correlation is observed for α process, which is well known for conventional glass formers. Such behaviour of Δε with temperature can be understood in terms Fuoss-Kirkwood correlation factor (g_k), which can be estimated by Onsager- Kirkwood-Frohlich equation [29-31].

$$g_k = (\varepsilon_o - \varepsilon_\infty)\frac{9Mk_BT(2\varepsilon_o + \varepsilon_\infty)}{4\pi N_A\rho\mu_o^2\varepsilon_o(\varepsilon_\infty + 2)^2} \qquad (6)$$

In this formula ε_0 is the equilibrium dielectric constant, ε_∞ is limiting high frequency permittivity due to induced polarization, N_A is the Avogadro‟s number, M is the molecular weight, ρ is the density, μ_0 is the dipole moment of the isolated molecule, g_k is Fuoss-Kirkwood correlation factor, and k_B is the Boltzmann constant. Fuoss-Kirkwood correlation factor g_k is a measure of the correlation of the neighboring dipole vectors. When g_k >1, indicates the tendency of parallel alignment of neighboring dipoles and g_k < 1, indicates the tendency of anti-parallel alignment of neighboring dipoles. Here, the small values of Δε are in agreement that hydrogen bonding in these samples favors an anti-parallel correlation of the neighboring dipoles [1,7,32]. Some information of the dipole moment (μ_0) is necessary to understand the dielectric strength variation. Unfortunately, the experimental value of μ_0 is not available for neat IBP. Although, it is reported in the literature [33] that the dipole moment of IBP is mostly originated from O=C-O-H group. According to Bras et al. [1] the Molecular Dynamics (MD) simulation reveals a strong tendency of IBP to form noncovalent molecular aggregates such as dimer (μ_0 = 1.29D to 2.15D) and trimer (μ_0 = 1.68D to 2.50D) either cyclic or linear, where cyclic structures were found to have a smaller dipole moment and less g_k‟ value (~0.3 (for cyclic) and ~0.8 (for linear)) at T = 360K. Also, it is suggested that hydrogen bonded cyclic structures might be associated with Debye process in IBP. Later, Affouard et al. [2] attempts to reveal the origin of the Debye type process in IBP and performed the MD simulation on racemic IBP. This simulation suggests that the Debye type process is dominated by the internal „cis (μ_0 = 1.6D)‟ to „trans (μ_0 = 4.6D)‟ conversion of the O=C-O-H group coupled to the change of the intermolecular linear/cyclic hydrogen-bonded structures. Also, it is found that the linear structures (dimers/trimers) are favoring the conversion and stabilize to the trans isomer. However, for internal dipolar reorientations (i.e. cis-trans conversion in the effective potential of neighboring dipoles), the breaking and reforming of intermolecular hydrogen bonds is necessary.

Conclusions

The dielectric measurements of pure ibuprofen and its mixture with 1,4-dioxane exhibit two relaxations, designated as α_D, and α processes. The α_D process is found to be Debye type in nature, and α process kinetically freezes at $T_{g\text{-onset}}$ (DSC) implies that α process indeed corresponds to the glass transition event. The spectral shape of α_D, and α processes can be explained satisfactorily throughout the frequency range using HN shape function, and are found to be non-Arrhenius in nature. The enhancement of dielectric strength of both processes is remarkable. Although, the dielectric strength of α_D process is still small in comparison to α process, but it can be resolved more significantly, and this enhancement is strengthening its existence in IBP. The dielectric strength is found to follow a linear correlation with temperature for α_D process. In contrast, an inverse correlation is observed for process, which is well known for conventional glass formers. The secondary relaxation processes are comparable with the literature [1], and the activation energy of β process indicates that its originating from the fluctuations of the side group larger than -OH group. Also, the calculated fragility index demonstrates that ibuprofen is a fragile glass former. Moreover, the experimental evidence of the origin of α_D process in IBP, needs to be probe further.

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