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Study of glass transition phenomena in the supercooled liquid phase of methocarbamol, acetaminophen and mephenesin

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ABSTRACT

We studied the thermochemical behaviour of five commonly used drugs namely naproxen, atenolol, methocarbamol (ML), acetaminophen and mephenesin (MP) using dielectric spectroscopy (10^{-3} Hz–1 MHz) and differential scanning calorimeter (DSC) down to liquid nitrogen temperature. The first two samples quickly crystallize during cooling, and we are able to study the glass transition phenomena in the latter three drugs only. The dielectric spectroscopy of the supercooled liquids of the latter three sample reveals the glass transition process as a pronounced relaxation process identifiable with so called primary relaxation process, or α-process, which is non-Debye in nature, and can be described well using Hevriliak–Negami (HN) equation. One sub-T_g process much smaller in magnitude is found in temperature range of 150 K–250 K that is arrhenius in its temperature dependence, which does not appear to be inter-molecular in nature.

1. Introduction

When a liquid is cooled fast enough (to avoid crystallization) the viscosity keeps on increasing towards lower temperatures where it ultimately reaches a highly viscous region compatible with that of a solid. At this temperature called the glass transition temperature (T_g) the viscosity is 10^{12} poise or the structural relaxation is the order of 200 s [1]. This approach to the glass transition is manifests as a relaxation process called as the primary or α-relaxation which kinetically freezes at T_g. Studies have shown that the glassy state at temperatures below T_g is not a completely dead state [2,3]. Other relaxation processes which are smaller in magnitude than the α-relaxation continue to occur below T_g. Such processes are known as secondary processes and are usually designated as β-, γ-, and δ-processes as we move away from T_g towards lower temperatures [2–15]. Studies conducted on the stability of glass against crystallization have shown that crystallization is possible below T_g. This has been demonstrated by Oguni and coworkers in the case of o-terphenyl [16], triphenylethylene [17], 3,3′-dimethoxy-4,4′-bis(2,2′-diphenylvinyl)biphenyl [18], toluene [19], 2-salol [20], benzylphenol [21] and 2,2′-dihydroxybenzophenone [22]. These studies emphasize the importance of the effect of secondary process on crystallization below T_g, as has been studied by Johari et al. [23] in binary mixtures of certain commonly used drugs, and by Power and Vij [24] in sorbitol.

Lowering of temperature substantially reduces the decomposition rate of any chemical, and hence increases the shelf life. Glass formation of the pharmaceutical by supercooling the melt apart from increasing the shelf life also increases the probability of dissolution to be absorbed by the human body [25–39] as the amorphous supercooled liquid or glassy solid dissolves more briskly in comparison of crystalline solid. In the past decade some researchers have conducted studies on the glassy phase of aspirin (acetylsalicylic acid) [36,40–42], ibuprofen [42], progesterone [42,43], quinidine [42], acetaminophen [44–46], ternidazole [47], felodipine [48], ketoprofen [49] and benzodiazepines [50]. In addition a lot more information is now available about the T_g of a number of drugs as studied by differential scanning calorimetry (DSC) [29,51]. However some of the above studies are incomplete in the sense that secondary relaxation occurring below T_g so important for the study of stability against crystallization, were not reported in detail as in the case of acetaminophen [44], mephenesin [52,53] and in other drugs.

The samples chosen for the present study are: naproxen (a non-steroidal anti-inflammatory drug (NSAID)), atenolol (widely used for cardiovascular diseases and was once the first line treatment for hypertension), methocarbamol (muscular relaxant used to treat skeletal muscle spasms), acetaminophen or paracetamol (used as analgesic and antipyretic) and mephenesin (centrally acting muscle relaxant and can be used as an antidote for strychnine poisoning). Methacarbomol is important in the above set of drugs as it can also

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be administered in combination of acetaminophen (paracetamol), ibuprofen, nimesulide and diclofenac free acid, and is available under different commercial names. Similarly mephenesin is also administered in combination of ibuprofen and diclofenac diethylamine.

Here in this paper, we report detailed dielectric- and DSC-measurements on methocarbamol, acetaminophen and mephenesin in its supercooled liquid state which may be of interest to the researchers working in biomedical and pharmaceutical field. To the best of our knowledge no dielectric measurements were ever reported for methocarbamol and mephenesin although some information on solubility, X-ray, IR spectra and NMR spectra is available [53–58].

2. Experimental methods

The samples studied in this paper are: (i) naproxen ($C_{14}H_{14}O_3$) with meets USP testing specifications (molecular weight (MW) = 230.26 g/mol) known as (*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid; (ii) atenolol ($C_{14}H_{22}N_2O_3$) (MW = 266.34 g/mol and with purity ≥98%) also known as 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy] benzeneacetamide, 4-[2′-hydroxy-3′-(isopropylamino)propoxy] phenylacetamide, (iii) methocarbamol ($C_{11}H_{15}NO_5$) (MW = 241.24 g/mol and purity ≥98%) known as guaiacol glyceryl ether carbamate, 3-(2-methoxyphenoxy)-1, 2-propanediol 1-carbamate, (RS)-2-hydroxy-3-(2-methoxyphenoxy)propyl carbamate and (iv) acetaminophen ($C_8H_9NO_2$) with (MW = 151.16 g/mol and purity ≥99%) also known as 4′-hydroxyacetanilide, 4-acetamidophenol, n-(4-hydroxyphenyl) acetamide, n-acetyl-4-aminophenol or paracetamol, (v) mephenesin ($C_{10}H_{14}O_3$) with (MW = 182.22 g/mol and purity ≥98%) also known as 3-(2-methylphenoxy)propane-1,2-diol. The samples were obtained from Sigma–Aldrich co. (made in China), and were used after drying the samples for removal of absorbed water (which appears to be the main impurity in these samples) as detailed in Section 3. The details of the molecular structure of the drugs studied in this article are given in supplementary file SI attached to this article.

Two different experimental methods have been used to study the samples.

2.1. Differential scanning calorimeter (DSC) measurements

DSC measurements, using Perkin-Elmer sapphire DSC with quench-cooling accessory to study the various thermal events during heating or cooling. The DSC cell was calibrated for temperature using indium (melting transition = 429.75 K), and mercury (melting transition = 234.3 K) as standards.

2.2. Dielectric relaxation technique

The pharmaceutical molecules generally contain proton donor and acceptor groups like amine, amide, single or several hydroxyls, etc. which form hydrogen bond with a native protein, water or carbohydrates and are highly polar, and hence an in-depth study of these chemicals can done using dielectric spectroscopy. Using this technique, frequency domain dielectric measurements were made using HP 4284A precision LCR meter for the frequency range of 20 Hz–1 MHz. The frequency range from $10^{-0.5}$ Hz to 10^{-3} Hz is covered by using a d.c. step response technique [59,60], where Hamon's approximation [61,62] is used for the estimation of the loss data from the absorption current. For further details of the experimental setup the reader may consult the earlier publications from this laboratory [14,15].

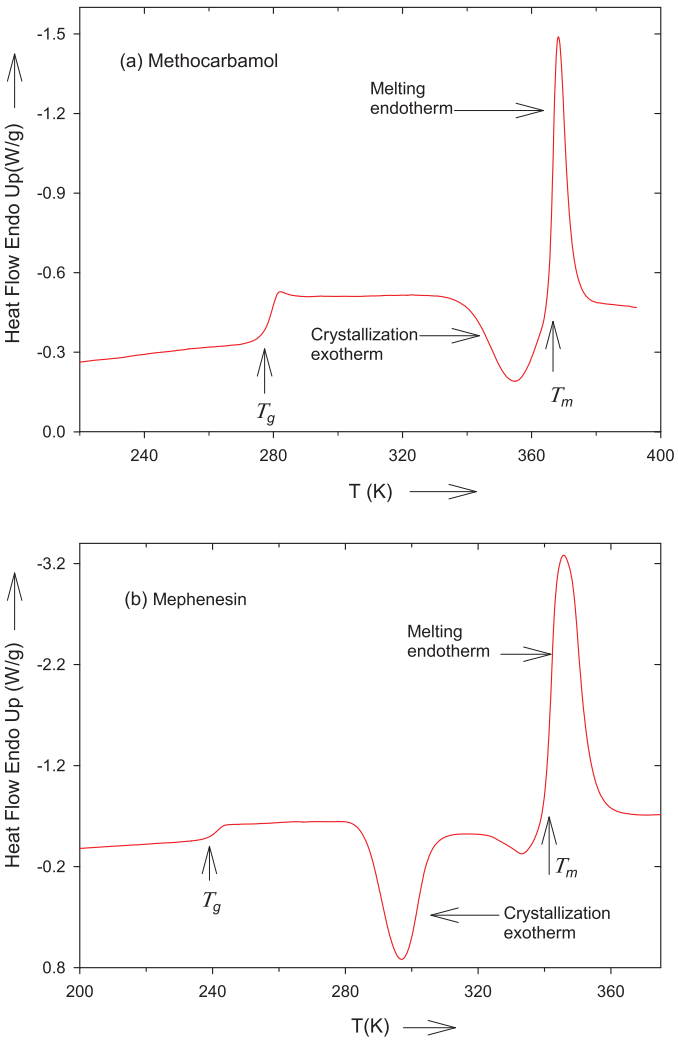

Fig. 1. DSC curves during heating at a rate of 10 K/min. for quenched melts of (a) supercooled liquid ML (sample size 3 mg) and (b) supercooled liquid MP (sample size 12.4 mg).

The dielectric measurements of the supercooled liquid phase of samples were made using a concentric cylindrical capacitor whose empty cell capacitance C_0 is about 43 pF, by melting the crystalline sample in argon atmosphere to fill the capacitor plates. The sample is then cooled at a desired rate for dielectric measurements, and the data was taken during cooling and heating cycles from which the desired information is obtained as detailed in Section 3.

3. Results

Prior to the dielectric measurements, all the samples were tested using the DSC technique for the ability of glass formation. The sample melted in DSC pans in nitrogen atmosphere is cooled rapidly at a rate of 10–50 K/min to 103 K, and then DSC scan was made for a heating rate of 10 K/min. The details of the DSC scans obtained thereby, are shown in Fig. 1(a and b). The enthalpy of fusion and melting temperature (T_m) for all the samples are given in Table 1. The values reported in Table 1 are an average of three scans. These values thus measured, are compared with the literature data to give the reader some confidence in the purity of the samples, and accuracy of the data reported in this study. Glass formation is not found in naproxen and atenolol even for very