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Ultrasonic studies on paracetamol in aqueous solutions of sodium salicylate and nicotinamide

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ABSTRACT

Solubility enhancement of poorly soluble drug, paracetamol using hydrotropic agents like sodium salicylate and nicotinamide has been studied. In the present investigation, 1, 2, 3 and 4M of both sodium salicylate and nicotinamide are employed to enhance the solubility of poorly soluble paracetamol to study its different physico-chemical properties at 298.15, 303.15, 308.15 and 313.15 K. The values of density (d) and sound velocity (U) have been measured in aqueous paracetamol and paracetamol + aqueous solutions of sodium salicylate and nicotinamide separately in five different concentrations. Densities of these solutions were measured at the above said four temperatures but the ultrasonic velocities (U) have been measured at 298.15 K only. Experimental density data have been used to estimate various important parameters, such as apparent molar volume (V_ϕ), limiting apparent molar volume (V_ϕ^0), apparent molar expansibility (E_ϕ) and limiting apparent molar expansibility (E_ϕ^0). Further, from the ultrasonic data, different thermo-acoustical parameters, such as isentropic compressibility (K_s), apparent molar isentropic compressibility ($K_{s,\phi}$), acoustic impedance (Z), molar compressibility (W), free volume (V_f), internal pressure (π_i), molar sound velocity (R) and relative association (R_A) have been evaluated and discussed in the light of solute-solute and solute-solvent interactions.

1. Introduction

The study on encapsulation, targeted delivery and solubilization of poorly water soluble drugs is a challenging task [1,2]. From this point of view, numerous approaches to enhance the solubility of poorly water-soluble drugs are available and reported in literature. A special kind of compounds called hydrotropes is of more interest in the study of physico-chemical properties of aqueous solutions [3–6]. In the extension of our previous work [7], the present study includes the solubility enhancement of poorly water soluble drug paracetamol, by using hydrotropic agents like sodium salicylate and nicotinamide. The study on paracetamol - hydrotropic agent interactions is very important for immunology, pharmacology and medicine. Although a lot of attention has been given to the behavior of paracetamol in different salt-water mixed solvents [8–10], very few studies have been carried out on the study of physico-chemical properties of paracetamol in aqueous sodium salicylate and nicotinamide solutions.

Paracetamol (*N*-acetyl-para-aminophenol (APAP), Fig. 1, is an acetanilide-derived analgesic drug widely used in current therapeutics [11,12]. APAP is slightly soluble in cold water, considerably more soluble in hot water [13] and alcohols. Due to its low solubility in water, some aqueous and non-aqueous co-solvent mixtures have been looked for to increase the solubility of this drug in order to develop homogeneous liquid pharmaceutical dosage forms [14–19].

Experimental drug behavior in solvent mixtures is frequently estimated for purification, pre-formulation studies, and pharmaceutical dosage design [3,20,21]. The present investigation aims at studying the molecular interactions of paracetamol in aqueous solutions of 1, 2, 3 and 4M hydrotropic agents (sodium salicylate and nicotinamide) at temperatures ranging from 298.15 K to 313.15 K at an interval of 5 K. Solubility can be enhanced by many hydrotropic agents but sodium salicylate and nicotinamide (aromatic hydrotropes, Fig. 2.) are of very much importance as they are the important raw materials for the chemical industry.

Sodium salicylate is used in medicine as analgesic and antipyretic, and induces apoptosis in cancer cells. It is also potential replacement for aspirin to the people sensitive to it [22,23].

Nicotinamide, known as 3-Pyridinecarboxamide and Niacinamide, the active form of vitamin B_3, is an important biologically active compound functioning as a component of the coenzyme NAD, used as a medication and found in food. Besides this, due to its anti-inflammatory properties, it is also used in dermatology. Nicotinamide, a hydrotropic agent can also be demonstrated to solubilize the poorly water soluble drug, APAP [24].

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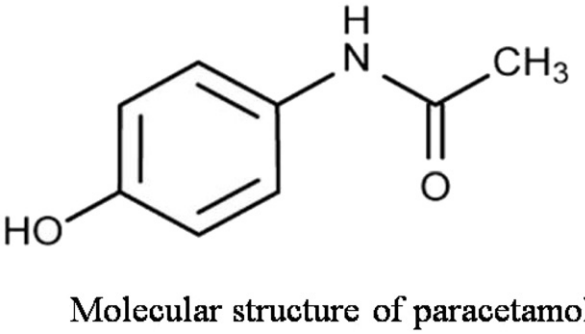

Fig. 1. Molecular structure of paracetamol.

In the present investigation, we have focused on studying various important parameters, like apparent molar volume (V_ϕ), limiting apparent molar volume (V_ϕ^0) apparent molar expansibility E_ϕ) and limiting apparent molar expansibility (E_ϕ^0) for paracetamol in aqueous sodium salicylate and nicotinamide solutions over the temperature range 298.15 K to 313.15 K at 5 K interval and the isentropic compressibility (K_s), acoustic impedance (Z), molar compressibility (W), free volume (V_f), isentropic compressibility (K_s), internal pressure (π_i), molar sound velocity (R) and relative association (R_A) have been evaluated from the sound velocity values at 298.15 K only. All these parameters have been discussed in the light of solute-solute and solute-solvent interactions and various structural effects [25,26].

2. Experimental

2.1. Chemicals

In this study all chemicals used are of analytical grade. Conductivity water (Sp.cond.~10^{-6} S·cm^{-1}) was used to prepare 1, 2, 3 and 4M solutions of hydrotropic agents.

2.2. Measurement of density

The densities of pure solvents, aqueous paracetamol and that of the solutions of paracetamol + hydrotropic agents (sodium salicylate and nicotinamide) at the corresponding solubilizing temperatures (T = 298.15, 303.15, 308.15 and 313.15 K) were determined by using a specific gravity bottle (25 mL capacity) as described elsewhere [27]. At least five observations were taken and differences in any two readings did not exceed ±0.02%. Density values of water at the required temperatures were obtained from literature [28].

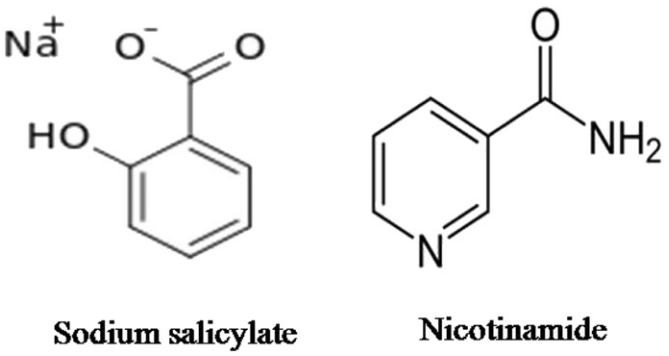

Fig. 2. Molecular structure of sodium salicylate and nicotinamide.

2.3. Measurement of ultrasonic velocity

For the measurement of sound velocity in the solutions of both aqueous systems and aqueous hydrotropic agent systems of paracetamol, Ultrasonic Interferometer (Model No. F-81, Mittal Enterprises, New Delhi, India) was used at a frequency of 2 MHz at 298.15 K only. The measurement was carried out three times in each case and the accuracy of the sound velocity measurement is found to be within ±0.5 m/s [29].

2.4. Theoretical aspects

From the density data of paracetamol solutions obtained in aqueous and aqueous hydrotropic agent solutions, the apparent molar volume V_ϕ was calculated by using Eq. (1) [30].

$$V_\phi = [1000/cd_0](d_0 - d) + (1/Md_0) \quad (1)$$

where d_0 is the density of solvent (water) or aqueous hydrotropic

Table 1
Values of density, d (kg·m^{-3}) of the solutions of paracetamol in aqueous and in aqueous sodium salicylate and nicotinamide solutions (in mol/m^3) at different temperatures, T (K).

Conc. of solvent (10^{-3} mol·m^{-3})	Conc. of paracetamol (mol·m^{-3}) (c)	d (kg·m^{-3})			
		298.15 K	303.15 K	308.15 K	313.15 K
0(water)	10.0	998.7	996.9	995.4	993.7
	30.0	998.9	997.4	996.1	993.8
	50.0	999.7	998.2	997.6	995.6
	70.0	1000.7	999.1	997.8	995.9
	90.0	1000.9	999.8	998.1	996.2
Paracetamol + sodium salicylate					
1	10.0	1097.0	1093.1	1092.0	1090.0
	30.0	1098.5	1095.5	1093.8	1091.5
	50.0	1100.0	1097.2	1095.5	1092.5
	70.0	1101.8	1099.0	1097.0	1094.0
	90.0	1103.3	1100.7	1098.5	1095.0
2	10.0	1125.4	1123.3	1118.5	1116.6
	30.0	1126.0	1123.6	1119.5	1117.1
	50.0	1126.7	1124.0	1120.4	1117.6
	70.0	1127.4	1124.3	1121.0	1118.2
	90.0	1127.9	1124.7	1122.0	1118.7
3	10.0	1186.2	1182.9	1177.5	1174.6
	30.0	1186.8	1183.7	1178.9	1175.7
	50.0	1187.6	1184.4	1180.0	1176.8
	70.0	1188.5	1185.1	1181.3	1178.0
	90.0	1189.3	1185.7	1182.8	1179.1
4	10.0	1241.6	1237.8	1234.4	1231.1
	30.0	1242.5	1238.8	1235.5	1232.1
	50.0	1243.2	1239.7	1236.7	1233.1
	70.0	1244.2	1240.5	1237.7	1233.9
	90.0	1244.8	1241.5	1239.0	1234.9
Paracetamol + nicotinamide					
1	10.0	1024.5	1023.7	1021.0	1019.3
	30.0	1025.6	1024.2	1021.6	1019.6
	50.0	1026.4	1024.6	1022.2	1020.1
	70.0	1027.2	1025.0	1022.7	1020.5
	90.0	1028.0	1025.4	1023.2	1021.0
2	10.0	1051.3	1049.3	1047.3	1044.9
	30.0	1051.8	1049.8	1047.6	1045.3
	50.0	1052.2	1050.2	1047.9	1045.7
	70.0	1052.6	1050.7	1048.1	1046.1
	90.0	1053.1	1051.1	1048.3	1046.7
3	10.0	1080.4	1078.0	1076.3	1072.1
	30.0	1080.7	1078.6	1076.7	1072.6
	50.0	1081.1	1079.0	1077.2	1073.2
	70.0	1081.5	1079.5	1077.8	1073.8
	90.0	1082.0	1080.1	1078.1	1074.2
4	10.0	1102.9	1101.8	1098.3	1095.3
	30.0	1104.4	1102.5	1099.1	1096.0
	50.0	1105.5	1103.2	1099.8	1096.5
	70.0	1106.5	1103.7	1100.5	1096.9
	90.0	1107.5	1104.4	1101.2	1097.4