Conductometric Study of Nimesulide in Aqueous Solutions of Hydrotropic Agents at Different Temperatures

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Abstract: Conductance values of nimesulide have been determined in water in 0.1, 0.2, 0.4, 0.6, 0.8, 1 and 2 mol dm⁻³ aqueous solutions of hydrotropic agents (sodium benzoate, sodium salicylate, sodium bromide and nicotinamide) at temperatures 298.15, 303.15, 308.15 and 313.15 K. The conductance values have been used to evaluate the limiting molar conductance and association constants by means of Shedlovsky extrapolation technique. Thermodynamic parameters for the association process of nimesulide in aqueous solutions of hydrotropic agents have also been calculated.

Keywords: Nimesulide, Hydrotropic agents, Limiting molar conductance, Association constants, Walden product

Introduction

Solubility and permeability are the two key biopharmaceutical parameters responsible for effective bioavailability and good *in vitro* and *in vivo* correlation¹. Enhancement of solubility and dissolution rate and oral bioavailability of poorly water soluble drugs are still the challenging aspects for the pharmaceutical technologists². Hydrotropic solubilisation is considered as one of the safest methods of solubilisation³. Aqueous solubilisation of insoluble

drugs can be achieved by addition of hydrotropic agents. Many work highlighted the effect of the solubility enhancers (hydrotropic agents)^{4,5} and hence improved solubility of the drug, but no detailed explanation is available relating to the improvement phenomenon. Recently, we have reported volumetric and viscometric studies on nimesulide in aqueous solutions of four different hydrotropic agents (sodium benzoate, sodium salicylate, sodium bromide and nicotinamide) at different temperatures, so as to highlight the solute-solvent interactions correlating the solubility findings⁶. Conductometric studies of solutes at definite and infinite dilution in a solvent system provide valuable information regarding the ion-ion and ion-solvent interactions. By examining the limiting molar conductivity (Λ_0), association constant (K_A), Walden products ($\Lambda_0\eta_0$) of ionic solutions as a function of size, nature, temperature and composition of the solvent, it is possible to examine the parameters on solute-solvent interaction with the hope of obtaining a better understanding of interactions in solutions⁷. The present study aimed to highlight the solute (drug nimesulide) - solvent (water) interactions and related modifications in case of the presence of hydrotropic agents at different temperatures.

Experimental

Sodium benzoate, sodium salicylate, sodium bromide and nicotinamide were of analytical reagents and kept in a vacuum desiccator over anhydrous CaCl_2 until required. Nimesulide was a gift sample (procured from M/S Alkem Laboratory, Mumbai, India) and used as such. The solutions were prepared freshly by mass using a metler balance with a precision of ± 0.01 mg in doubly distilled deionized and degassed water and conversion of molality to molarity was done by standard expression⁸.

A conductivity meter with accuracy of $\pm 0.5\%$ and a conductivity cell (Model –ELICO, India) were used for the measurement of conductivity of each sample. The conductance cell was equipped with a water circulating jacket and the temperature was controlled within ± 0.02 K with a water thermostat. The cell constant is 1.01 cm^{-1} which was calculated by repeated measurements of KCl solutions. All data were corrected with specific conductivity of pure water at the experimental temperatures.

Different concentrations (0.1 to 2.0 M) of each of the hydrotropic agents (sodium benzoate, sodium salicylate, sodium bromide and nicotinamide) were prepared separately in double distilled water using 100 mL conical flask and excess amount of drug, nimesulide was added to each flask containing the required molar solutions of the corresponding hydrotropic agents. All the conical flasks were put in a mechanical shaker maintained at the required temperature within an accuracy of ± 0.02 K and shaken for a maximum period of 6 h. The solutions were filtered and the specific conductivities were measured. The different molar solutions of hydrotropic agents without the drug were also measured for the specific conductivities. For each sample six data points were considered to calculate the average, which was further used to calculate the equivalent conductance for the samples.

Results and Discussion

The experimental data of the conductance measurements for the aqueous solutions of sodium benzoate, sodium salicylate, sodium bromide and nicotinamide with and without nimesulide after solvent correction were analyzed using Shedlovsky⁹ and Fuoss-Kraus^{10,11} extrapolation. As the limiting molar conductivity values, Λ_0 obtained by two methods using the values of ion-size parameter, $a_0 = 0$, q and $2q$ are very close to each other, as presented elsewhere⁷, the values of the Λ_0 for $a_0 = q$ (but for nicotinamide a_0 is taken as 0) are given

in Table 1 for the Shedlovsky method only and so also the values of K_A , the association constants of hydrotropic agents and also of nimesulide in aqueous solutions of hydrotropic agents at experimental temperatures. It is noted that the obtained Λ_0 values of the hydrotropic agents in water are in good agreement with the values that are available in the literature¹².

Table 1. The values of limiting molar conductance Λ_0 ($S\ cm^2\ mol^{-1}$), association constant, K_A , ($dm^3\ mol^{-1}$) and Walden product $\Lambda_0\eta_0$, (Wod = without drug; Wd = with drug)

Sodium Benzoate	T/K	Λ_0	K_A	$\Lambda_0\eta_0$
Wod	298.15	145.2	4.97	129.78
Wd	298.15	100.5	12.11	89.77
Wod	303.15	156.7	-1.91	125.43
Wd	303.15	117.5	-1.07	94.04
Wod	308.15	173.7	-2.44	125.48
Wd	308.15	128.7	-2.49	92.96
Wod	313.15	190.6	1.12	125.03
Wd	313.15	146.4	-1.09	96.02
Sodium Salicylate	T/K	Λ_0	K_A	$\Lambda_0\eta_0$
Wod	298.15	146.5	-3.76	130.90
Wd	298.15	99.9	-1.23	89.25
Wod	303.15	157.1	21.91	125.80
Wd	303.15	115.8	18.08	92.70
Wod	308.15	177.0	10.09	127.91
Wd	308.15	127.3	31.98	91.98
Wod	313.15	193.7	11.48	127.06
Wd	313.15	144.4	62.45	94.74
Sodium Bromide	T/K	Λ_0	K_A	$\Lambda_0\eta_0$
Wod	298.15	228.9	15.71	204.57
Wd	298.15	145.3	-17.09	129.86
Wod	303.15	239.7	16.24	191.90
Wd	303.15	168.5	-2.68	134.95
Wod	308.15	257.7	17.45	186.17
Wd	308.15	188.6	14.80	136.24
Wod	313.15	288.1	15.75	189.01
Wd	313.15	206.9	1.39	135.74
Nicotinamide	T/K	Λ_0	K_A	$\Lambda_0\eta_0$
Wod	298.15	180.5	-53.19	161.30
Wd	298.15	153.4	-20.77	137.10
Wod	303.15	194.9	-55.39	156.10
Wd	303.15	123.2	-25.05	98.64
Wod	308.15	212.9	-56.12	153.79
Wd	308.15	117.9	-25.60	85.17
Wod	313.15	232.3	-56.47	152.41
Wd	313.15	120.28	-26.06	78.90

As observed, the values of Λ_0 of nimesulide in aqueous solutions of hydrotropic agents are very low. This is due to the fact that the hydrodynamic radii of the ions (generated from the hydrotropic agents) increase in the presence of nimesulide in the solution which causes a decrease in their mobility¹³.

It is evident from Table 1 that the values of Λ_0 of nimesulide increase with increase in temperature in the aqueous solutions of sodium benzoate, sodium salicylate and sodium bromide but decrease in the aqueous solutions of nicotinamide. The increased Λ_0 values with increase in temperature indicate less solvation or higher mobility of ions, which can be attributed to the fact that the increased thermal energy results in greater bond breaking and variation in vibrational, rotational and translational energy of the molecules that lead to higher frequency and higher mobility of the ions⁷. But the reverse is the case in the solutions of nicotinamide where the Λ_0 value decreases with increase in temperature and that can be attributed to the increased solvation and hydrodynamic radii of the ions there by decreasing the mobility. As observed, the values of Λ_0 of sodium bromide and also of nimesulide in solutions of sodium bromide are higher as compared to others. This is reasonable in view of the difference in transport properties of the hydrated bromide which reflects factors affecting its effective size and the strength of the coulombic field in the range of the hydration shell. The higher Λ_0 values in the solutions of sodium bromide are consistent with the lower viscosity values and lower solubility of nimesulide in sodium bromide solutions.

The variation of the Walden product, $\Lambda_0\eta_0$ (Table 1) is somewhat complex. The variation in the values of $\Lambda_0\eta_0$ indicates variation in the ionic radii and mobility of the ions due to varying degree of the ion-solvation in solution. The smaller $\Lambda_0\eta_0$ of the systems in nicotinamide solutions may be due to its large effective radius (due to large molecular aggregates) as compared to other systems.

A perusal of Table 1 shows that the association constant values are negative in the nicotinamide solutions at all the experimental temperatures and at certain temperatures in the solutions of sodium benzoate, sodium salicylate and sodium bromide. The negative association constant values in nicotinamide solutions are consistent with the result obtained from the lower Λ_0 values due to the formation of molecular aggregates in solution. This is also the case in the solutions of sodium benzoate, sodium salicylate and sodium bromide at certain temperatures where the molecular aggregates predominate over the ion pair formation. These findings are well supported by the previous research reports, which stated molecular aggregation being the mechanism of solubility enhancement of poorly soluble drugs in presence of hydrotropic agents¹⁴⁻¹⁶.

Since the conductance measurements of an ion depend upon mobility, it is quite reasonable¹⁷ to treat the conductance data similar to the one employed for the rate process taking place with the change of temperature, *i.e.*,

$$\Lambda_0 = A e^{-E_s/RT} \text{ Or } \log \Lambda_0 = \log A - E_s/2.303RT \quad (1)$$

Where A is the frequency factor, R is the gas constant and E_s is the arrhenius activation energy of the transport process. From the plot of $\log \Lambda_0$ vs. $1/T$, the E_s values have been computed from the slope ($= -E_s/2.303 R$) and are recorded in Table 2. The free energy change, ΔG_0 for the association process is calculated from.

$$\Delta G_0 = - RT \ln K_A \quad (2)$$

The heat of association ΔH_0 is calculated from the slope of the plot of $\ln K_A$ vs $1/T$ and the entropy change, ΔS_0 from Gibbs - Helmholtz equation,

$$\Delta G_0 = \Delta H_0 - T\Delta S_0 \quad (3)$$

The values of ΔG_0 , ΔH_0 and ΔS_0 at 298.15 K are given in Table 2. It can be seen from Table 2 that the values of ES are positive. The negative ΔG_0 values for the systems of sodium benzoate with and without nimesulide and sodium bromide without nimesulide indicate that the association process predominates over the dissociation process. The negative ΔH_0 values for the systems containing sodium salicylate and sodium bromide with and without nimesulide show that the association processes are exothermic. The values of ΔS_0 are found to be positive in cases of sodium benzoate with and without, nimesulide and of sodium salicylate with nimesulide. The positive ΔS_0 values indicate the ions are hydrated in these systems.

Table 2. Thermodynamic parameters, ΔG^0 (kJ mol⁻¹), ΔH^0 (kJ mol⁻¹), ΔS^0 (kJ mol⁻¹K⁻¹) and ES(kJ mol⁻¹) at 298.15 K

Without drug				
System	ΔG^0	ΔH^0	ΔS^0	ES
Sodium Benzoate	-28.32	36.2	0.2	14.23
Sodium Salicylate	57.02	-137.1	-0.7	14.84
Sodium Bromide	-89.53	-154.8	-0.2	11.79
Nicotinamide	303.13	360.7	0.2	13.09
With drug				
Solution System	ΔG^0	ΔH^0	ΔS^0	ES
Sodium Benzoate	-69.02	99.0	0.6	18.96
Sodium Salicylate	57.00	-129.8	0.6	18.65
Sodium Bromide	97.45	-248.7	-1.0	18.22
Nicotinamide	118.37	132.2	-0.5	12.16

Conclusion

In this study conductivities for the (hydrotropic agents +water with or without nimesulide) systems were determined at the temperature range between 298.15 and 313.15 K. The limiting molar conductivities of nimesulide are low in aqueous solutions of hydrotropic agents. These suggest that the studied hydrotropes form molecular aggregates in aqueous solutions. The variation in the values of Walden product ($\Lambda_0\eta_0$) indicates variation in the ionic radii and mobility of ions due to varying degree of ion solvations in solutions. The non-constant Walden product in all the systems is expected due to highly viscous nature of the aqueous solutions of the hydrotropes with or without nimesulide and also due to the formation of the molecular aggregates.

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