Short Articles

Volumetric and Viscometric Studies of Salicyl Amide, Salicylic Acid, and Acetyl Salicylic Acid in Alcohols at Different Temperatures†

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Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit analgesic, anti-inflammatory, antipyretic and platelet inhibitory properties. Density and viscosity of salicyl amide, salicylic acid, and acetyl salicylic acid in water, methanol, and ethanol at T = (293.15 to 313.15) K have been measured in a molality range of ($9.7 \cdot 10^{-3}$ to $32.5 \cdot 10^{-3}$) mol·kg^{-1} with the help of a commercially available vibrating-tube densimeter and viscometer. From the density data, apparent molar volume ($V_{\phi,1}$), partial molar volume (V_m^{∞}), thermal expansion coefficient ($\alpha^{\infty}{}_2$), and ($\partial^2 V_m^{\infty}/\partial T^2$) are calculated. The viscosity data are analyzed by the Jones−Dole equation to determine the values of the viscosity B-coefficient.

Introduction

The partial molar volume is a characteristic parameter which is indicative of molecular interactions in the solution phase. The hydrophobic character of the aromatic ring of the nonsteroidal anti-inflammatory drugs (NSAIDs) is useful in probing the relationship between molecular architecture and thermodynamic properties. The characterization of the nonsteroidal anti-inflammatory drugs, i.e., salicyl amide, salicylic acid, and acetyl salicylic acid (aspirin), has been the subject of interest due to their antifungal, analgesic, and platelet inhibitory properties.[1] In this regard, it has been shown that because the NSAIDs inhibit platelet aggregation they are useful as inhibitors for clotting in the blood vessels and thus help in the prevention of heart attack and strokes. However, these drugs have serious side effects such as gastrointestinal toxicities and hemorrhage due to inhibition of prostaglandin production. The transport properties of drug molecules have important implications for the permeation of the drug molecules through biological membranes. Thus, the behavior of these drugs in solutions may be of importance from a pharmacological point of view. The effect of short and medium chain length alcoholic solvents on the volumetric properties of the drug molecules has also been investigated because alcohols are often present in drug delivery formulation.

There is a shortage of information about the physicochemical effects of alcohols on NSAIDs and elucidation of the factors that affect the binding of drug with its target site. This work is a continuation of a systematic investigation of the volumetric and transport properties of drugs in various solvents.[2−6] To the best of our knowledge, density and viscosity data on salicyl amide, salicylic acid, and acetyl salicylic acid (aspirin) in alcohols are reported for the first time, and the explanation of interactions that govern the solution behavior of these drugs is presented. The data at T = (293.15 to 313.15) K provide relevance to the drug macromolecule behavior near physiological temperatures.

Materials and Methods

Salicyl amide, salicylic acid, and acetyl salicylic acid of the best available purity (99 %) were purchased from Aldrich. The solvents used were methanol (99.8 %, Sigma-Aldrich) and ethanol (99.8 %, Merck). Solutions were prepared in a molality range of ($9.7 \cdot 10^{-3}$ to $32.5 \cdot 10^{-3}$) mol·kg^{-1}. The precision of balance was ± 0.001 g. The experiments were carried out at T = (293.15 to 313.15) K. To avoid concentration gradients, the solutions were stirred gently before each measurement.

Density and Viscosity Measurement. The densities of solutions were measured with an automated vibrating tube densimeter (Anton Paar DMA 5000) with an uncertainty of ± 10^{-5} g·cm^{-3} which was calibrated with deionized and doubly distilled water for the temperature range investigated. The density and viscosity measurements were performed at temperatures from T = (293.15 to 313.15) K with an uncertainty in temperature measurement of ± 0.01.

The solution viscosities were measured by means of an Anton Paar SVM 3000 viscometer at the desired temperatures. The viscometer was calibrated with deionized and doubly distilled water. The uncertainty of viscosity measurements was ± 0.003 mPa·s. All experiments were repeated thrice.

Results

The experimental values of solution densities are given in Table 1 which are used to calculate the apparent molar volumes $V_{\phi,1}$ of NSAIDs in alcohols using the following expression[4]

$$V_{\phi,1} = \frac{1000(\rho_o - \rho)}{c\rho\rho_o} + \frac{M_2}{\rho} \quad (1)$$

where ρ and ρ_0 are the densities of the drug solutions and the solvent, respectively. M_2 is the molar mass; and c is the concentration. The values of $V_{\phi,1}$ are listed in Table 1.

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Partial molar volume, V_m^∞, of NSAIDs is calculated graphically according to the following equation

$$V_{\phi,1} = V_m^\infty + S_v c \quad (2)$$

where S_v is the semiempirical solute−solute interaction parameter and c is the molality of the drug. The values of V_m^∞ have been estimated by the least-squares fitting of the plot of $V_{\phi,1}$ versus molality of the drug solution method. The calculated values are listed in Table 2. Since S_v values for large organic molecules are not of much significance, they have not been reported here.

The temperature dependence[7] of V_m^∞ for the studied compounds can be expressed by the equation

Table 1. Densities, η, and Apparent Molar Volume, $V_{\phi,1}$, and Viscosities, η, of Salicyl Amide Solutions in Methanol at T = (293.15 to 313.15) K

T	$c \cdot 10^{-3}$	η	$V_{\phi,1}$	η	T	$c \cdot 10^{-3}$	η	$V_{\phi,1}$	η
(K)	(mol·kg^{-1})	(g·cm^{-3})	(cm^3·mol^{-1})	(m·Pa·s)	(K)	(mol·kg^{-1})	(g·cm^{-3})	(cm^3·mol^{-1})	(m·Pa·s)
313.15	9.7	0.775744	62.15	0.4502	310.15	9.7	0.775881	60.37	0.4602
	13.0	0.775898	70.14	0.4503		12.9	0.776055	66.12	0.4603
	16.2	0.776045	75.68	0.4504		16.1	0.776195	73.21	0.4604
	19.4	0.776165	82.28	0.4506		19.3	0.776355	76.68	0.4607
	22.7	0.776285	86.55	0.4508		21.8	0.776449	83.72	0.4608
	25.9	0.776375	91.75	0.4509		25.8	0.776585	86.20	0.4609
	32.5	0.776558	98.87	0.4511		32.3	0.776765	94.58	0.4612
308.15	9.6	0.777775	58.55	0.4852	303.15	9.5	0.782541	56.79	0.5003
	12.8	0.777951	64.49	0.4853		12.7	0.782725	62.14	0.5005
	16.0	0.778085	72.54	0.4855		15.9	0.782859	70.61	0.5007
	19.2	0.778255	75.23	0.4857		19.1	0.783029	73.64	0.5009
	22.4	0.778368	81.01	0.4859		22.3	0.783149	79.07	0.5012
	25.6	0.778495	84.41	0.4862		25.5	0.783261	83.67	0.5015
	32.1	0.778659	93.97	0.4866		31.9	0.783449	92.00	0.5019
298.15	9.5	0.787285	55.60	0.5471	293.15	9.5	0.792015	53.05	0.5970
	12.6	0.787479	59.97	0.5475		12.6	0.792215	57.33	0.5976
	15.8	0.787615	68.63	0.5480		15.8	0.792352	66.37	0.5981
	19.0	0.787819	69.05	0.5485		19.0	0.792555	67.30	0.5987
	22.2	0.787921	76.43	0.5490		22.1	0.792688	72.59	0.5993
	25.3	0.788019	82.22	0.5495		25.3	0.792801	77.85	0.5997
	31.7	0.788218	90.18	0.5503		31.7	0.792965	88.39	0.6008

Table 2. Partial Molar Volumes at Infinite Dilution (V_m^∞), Isobaric Thermal Expansion Coefficient ($\alpha^\infty{}_2$) (B/V_m^∞), Viscosity B-Coefficients, and Hepler's Constant ($\partial^2 V_m^\infty/\partial T^2$) of Salicyl Amide, Salicylic Acid, and Acetyl Salicylic Acid Dissolved in Methanol and Ethanol at T = (293.15 to 313.15) K

	methanol					ethanol				
T	V_m^∞	$\alpha^\infty{}_2 \cdot 10^{-3}$		B	$\partial^2 V_m^\infty/\partial T^2$	V_m^∞	$\alpha^\infty{}_2 \cdot 10^{-3}$		B	$\partial^2 V_m^\infty/\partial T^2$
(K)	(cm^3·mol^{-1})	(K)	B/V_m^∞ 10^{-3}	(cm^3·mol^{-1})	(cm^6·mol^{-2}·K^{-2})	(cm^3·mol^{-1})	(K)	B/V_m^∞ 10^{-3}	(dm^3· mol^{-1})	(cm^6·mol^{-2}·K^{-2})
					Salicyl Amide					
293.15	39.00	12.68	8.30	0.324	0.018	46.25	8.72	6.50	0.301	0.016
298.15	41.06	12.04	7.37	0.303		47.96	8.47	5.98	0.287	
303.15	43.16	11.45	6.67	0.288		49.30	8.20	5.19	0.256	
308.15	45.39	10.89	5.88	0.267		51.19	8.05	4.68	0.240	
310.15	47.32	10.45	5.09	0.241		52.97	7.92	4.17	0.221	
313.15	49.00	10.09	4.38	0.215		54.00	7.59	3.70	0.200	
					Salicylic Acid					
293.15	40.06	12.66	8.88	0.356	0.022	47.19	8.28	6.99	0.330	0.020
298.15	42.38	11.98	7.85	0.333		49.00	8.01	6.30	0.309	
303.15	44.26	11.45	5.91	0.262		50.00	7.82	5.40	0.270	
308.15	46.62	10.87	5.79	0.270		52.02	7.51	5.09	0.265	
310.15	48.41	10.47	5.06	0.245		53.95	7.25	4.26	0.230	
313.15	50.52	10.03	4.25	0.215		55.14	7.09	2.54	0.140	
					Acetyl Salicylic Acid					
293.15	64.95	8.96	6.15	0.400	0.032	73.48	6.77	4.92	0.362	0.0244
298.15	66.02	8.82	5.81	0.384		75.70	6.57	4.44	0.334	
303.15	70.57	8.25	4.46	0.315		78.21	6.36	3.83	0.300	
308.15	71.98	8.09	3.82	0.275		79.60	6.25	3.61	0.288	
310.15	72.76	8.00	3.64	0.265		80.89	6.15	3.33	0.275	
313.15	77.43	7.52	2.84	0.220		84.49	5.89	2.78	0.235	

Table 3. Transfer Volumes (ΔV_m^∞) of Salicyl Amide, Salicylic Acid, and Acetyl Salicylic Acid in Methanol and Ethanol at T = (293.15 to 313.15) K

		ΔV_m^∞/cm^3·mol^{-1}					
drug compounds	solvents	T/K = 293.15	T/K = 298.15	T/K = 303.15	T/K = 308.15	T/K = 310.15	T/K = 313.15
salicyl amide	methanol	−31.55	−33.60	−35.69	−37.91	−39.84	−41.51
	ethanol	−38.80	−40.50	−41.83	−43.71	−45.48	−46.71
salicylic acid	methanol	80.99	81.90	81.18	79.45	79.78	78.53
	ethanol	43.15	43.00	42.41	42.0	42.00	41.00
acetyl salicylic acid	methanol	−15.96	−5.98	−5.75	−5.53	−2.84	−1.48
	ethanol	−28.00	−25.00	−19.0	−21.0	−20.0	−15

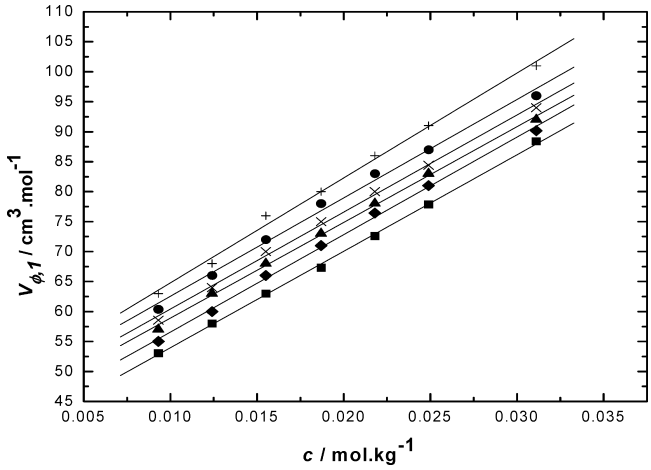

Figure 1. Apparent molar volumes, $V_{\phi,1}$, as a function of concentration, c, of salicyl amide in methanol at ■, 293.15 K; ♦, 298.15 K; ▲, 303.15 K; ×, 308.15 K; ●, 310.15 K; and +, 313.15 K. The value of Regression coefficient $R^2 = 0.99$ in the case of all temperatures.

$$V_m^{\infty} = \propto + \beta T + \gamma T^2 \tag{3}$$

where $\propto$, β, and γ have been estimated by the least-squares fitting of partial molar volume data in the equation. To obtain the qualitative information on hydration of drugs, the value of $(\partial^2 V_m^{\infty}/\partial T^2)$, i.e., Hepler's constant, has been calculated. The $(\partial^2 V_m^{\infty}/\partial T^2)$ values are included in Table 2.

The isobaric thermal expansion coefficient $\alpha^{\infty}{}_2$ is calculated by the following equation

$$\alpha^{\infty}{}_2 = \frac{1}{V_m^{\infty}}\left[\frac{\partial V_m^{\infty}}{\partial T}\right] \tag{4}$$

ΔV_m^{∞} is the transfer volume of solute from solvent I to solvent II and is defined by the following equation[8]

$$\Delta V_m^{\infty}(\mathrm{I}\cdot\mathrm{II}) = V_m^{\infty}(\mathrm{II}) - V_m^{\infty}(\mathrm{I}) \tag{5}$$

where V_m^{∞} (II) is the partial molar volume of a drug, for instance, salicyl amide in water, and V_m^{∞} (I) is its partial molar volume at infinite dilution in an alcohol. The values are given in Table 3.

The solute−solvent interaction can be discussed through the change of a dynamic property such as viscosity. The viscosity data given in Table 1 are analyzed by using the Jones−Dole equation.[9]

$$\frac{\eta_r - 1}{c^{1/2}} = \psi = A + Bc^{1/2} \tag{6}$$

where $\eta_r = \eta/\eta_o$ and η and η_o are viscosities of solution and the solvent, respectively, and c is the molality of drug. Linear plots for ψ versus $c^{1/2}$ were obtained from where the A- and B-coefficients have been evaluated by the least-squares method. The A-coefficient is independent of concentration, and B is related to the effect of drug on the structure of solvents.

Discussion

Inspection of Table 1 indicates that the density of salicyl amide solution increases with an increase in its concentration. Figure 1 shows plots of the apparent molar volume $V_{\phi,1}$ of salicyl amide solution in methanol over the temperature range $T =$ (293.15 to 313.15) K. Similar behavior is observed for salicylic acid and acetyl salicylic acid (aspirin) in alcoholic solvents.

The calculated values of V_m^{∞} are listed in Table 2. Positive values of V_m^{∞} in the alcoholic solvents reflect strong solute−solvent interactions and suggest a structure making effect. Values of viscosity B-coefficient as given in Table 2 also compliment the behavior of the partial molar volume of salicyl amide. Values of the partial molar volumes of the three drugs in ethanol are large as compared to those in methanol in the temperature range studied here. From Table 2, it is evident that the partial molar volume of the three drugs increases with increasing temperature due to a reduction of electrostriction and release of some solvent molecules from the loose hydration layers of the solute in the solution. Positive values of the Hepler's constant $(\partial^2 V_m^{\infty}/\partial T^2)$ suggest that salicyl amide, salicylic acid, and acetyl salicylic acid (aspirin) are structure makers in alcoholic solvents.

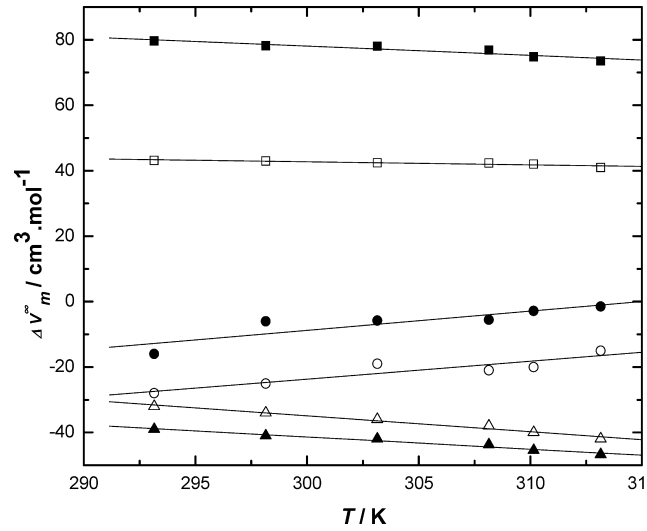

Figure 2. Plot of the transfer volume ΔV_m^{∞}, for salicyl amide in ▲, methanol and △, ethanol. The value of Regression coefficient $R^2 = 0.85$. For salicylic acid in ■, methanol and □, ethanol. The value of Regression coefficient $R^2 = 0.82$. For acetyl salicylic acid in ●, methanol and ○, ethanol at $T =$ (293.15 to 313.15) K. The value of Regression coefficient $R^2 = 0.98$.

The values of the transfer volumes ΔV_m^{∞} of salicyl amide, salicylic acid, and acetyl salicylic acid (aspirin) from water to alcohols are at $T =$ (293.15 to 313.15) K and are listed in Table 3. The value of ΔV_m^{∞} is negative for salicyl amide and acetyl salicylic acid at low temperatures but positive for salicylic acid at all the temperatures investigated here. The observed positive and negative values of the transfer volume result from the dominance of ion−ion, ion−solvophilic, and solvophobic−solvophilic interactions. Figure 2 shows the dependence of ΔV_m^{∞} on temperature.

The calculated values of isobaric thermal expansion coefficient $(\alpha^{\infty}{}_2)$ are listed in Table 2. The highest value of $\alpha^{\infty}{}_2$ is obtained for salicylic acid in methanol and the lowest for salicylic acid in ethanol.

The hydration of any solute can be judged from the magnitude of B/V_m^{∞}, i.e., ratio of viscosity B-coefficient and partial molar volume.[10] The value of B/V_m^{∞} is an important indicator of a drug molecule being hydrated or unhydrated: a value of B/V_m^{∞} between (0 and 2.5) indicates unhydrated molecules, but a value higher than 2.5 is an indication of solvated drug molecules. Salicylic acid has the highest value of B/V_m^{∞} in methanol, and the acetyl salicylic acid in ethanol has the lowest value showing that salicylic acid and acetyl salicylic acid are more solvated in methanol and ethanol, respectively.

Figure 3 shows a representative plot of ψ versus $c^{1/2}$ for salicyl amide in methanol over the temperature range analyzed in this study. Similar plots also have been obtained for salicylic acid and acetyl salicylic acid (aspirin) in alcoholic solutions. The calculated values of B-coefficients for the three drugs are

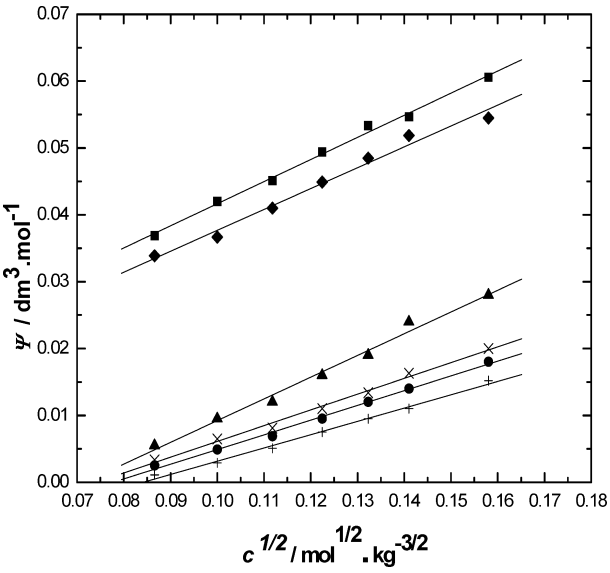

Figure 3. Plot of Ψ versus $c^{1/2}$ for salicyl amide in methanol at T = ■, 293.15 K; ♦;, 298.15 K; ▲, 303.15 K; ×, 308.15 K; ●, 310.15 K; and +, 313.15 K. The value of Regression coefficient $R^2 = 0.99$ in the case of all temperatures.

positive and large as shown in Table 2. *B*-Coefficients are known to provide information regarding the hydration of the solutes and their effects on the structure of the solvent in the near environment of the solute molecules. The values of *B*-coefficient for acetyl salicylic in methanol are the highest of the three drugs and the smallest for salicyl amide in ethanol. Positive values of the *B*-coefficient suggest hydrogen bonding of the solvent with the drug molecule and indicate an increase in viscosity of the solution due to the large size of the moving molecules. This phenomenon can be attributed to the break up of the hydration shell due to thermal motion. These observations are in excellent agreement with the conclusions drawn from the analysis of Hepler's constant ($\partial^2 V_m^\infty/\partial T^2$) discussed earlier. Thus, the volumetric and viscometric properties of these drugs in the present work provide useful information in medicinal and pharmaceutical chemistry for the prediction of absorption and permeability of drug through membranes.

Conclusions

In this work, the volumetric and viscometric properties of three structurally related drugs, namely, salicyl amide, salicylic acid, and acetyl salicylic acid (aspirin) dissolved in methanol and ethanol have been determined. The values of partial molar volume in dilute solutions are positive indicating strong solute−solvent interactions which may have implications for the permeation of drugs through the biological membranes. Change of solvent from methanol to ethanol lowers the value of dielectric constant that increases the electrostriction of the solvent, and hence the values of the partial molar volume decrease much more in methanol than in ethanol. The values of Jones−Dole viscosity *B*-coefficient indicate a structure promoting tendency of the three drugs.

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