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Research Article

Effect of 1-Octyl-3-Methylimidazolium Salicylate as an Active Pharmaceutical Ingredient (API-IL) on the Thermodynamic Behavior of Aqueous Glycine Solutions at T= 298.15 K

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ABSTRACT

Background: The thermophysical properties of 1-octyl-3-methylimidazolium salicylate as an active pharmaceutical ingredient based on ionic liquid have been investigated in the presence of aqueous solutions of glycine. Therefore, the scope of this article was to determine these properties by measuring the densities, speeds of sound, viscosities, electrical conductances and refractive indices for ternary (glycine + 1-octyl-3-methylimidazolium salicylate + water) soloutions at T = 298.15 K.
Methods: A commercial density and speed of sound measurement apparatus was used to measure the density and speed of sound data. Viscosities, electrical conductivities and refractive indices of the studied solutions were measured using digital viscometer, conductivity meter and refractometer, respectively.
Results: Variety of properties such as partial molar volume of transfer $\Delta_{tra}V_{\varphi}^{0}$, partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_{\varphi}^{0}$, viscosity B-coefficients of transfer $\Delta_{tra}B$, ion association constants (K_A) and molar refraction R_D were determined to investigate the solute-solute and solute-solvent interactions in these systems.
Conclusion: The positive values of transfer properties including partial molar volume of transfer ($\Delta_{tra}V_{\varphi}^{0}$), partial molar isentropic compressibility of transfer ($\Delta_{tra}\kappa_{\varphi}^{0}$), and viscosity B-coefficients of transfer ($\Delta_{tra}B$) indicated that in these systems, the ion-polar and polar-polar interactions are dominant. The calculated hydration number showed that dehydration of glycine occurs in presence of this ionic liquid.

Introduction

Salicylic acid is one of the active pharmaceutical ingredients (API) which is utilized in medical skin care, food preservative and an antiseptic in toothpaste. However, bioavailability and therapeutic applications of this API were hindered due to its low water solubility.[1] Recently, some strategies have been proposed to increase the its bioavailability. One of these approaches is the combination of this API with the third generation of ionic liquids (IL) namely API-IL.[2,3] Compared to the solid pharmaceutical form of API, this form presents the improved characteristics such as the higher solubility, stability, and permeability due to its hydrophophilicity and hydrophobicity natures.[4-7] In the literature, variety of API-ILs were synthesized for special applications. For example, 1-butyl-3-methylimidazolium ibuprofenate and salicylate are proposed as new gels for drug delivery.[8,9]
Thermophysical studies of the mixtures containing pharmaceutically active ionic liquid form and biomolecules such as proteins can provide useful information in regard with the interactions occurring in these systems and also able us to design and improve the biotechnological processes.[10-12] The scope of this work is to study the interactions of amino acids as units of proteins and API-ILs.[13,14] In this respect, the thermophysical properties including the volumetric and transport properties of amino acids in the presence of API-IL give us the useful information about the solute-solvent and solute-solute interactions in these systems.
In the literature, there are some reports in regard with the thermodynamic properties of the mixtures consisting of amino acids and the first generation of ionic liquids in the aqueous media at different temperatures.[15-20] In our previous papers, thermodynamic properties of the mixtures containing the active pharmaceutical ingredient in the ionic liquids form (API-ILs), 1-(butyl or hexyl or octyl)-3-methylimidazolium salicylate and ibuprofenate and amino acids such as glycine or L-alanine in aqueous media have been studied. According to these papers, the ion-polar and polar-polar interactions between these amino acid and API-IL are dominant.[20-25]

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Table 1. A sample description of the used chemicals.

Chemical name	**CAS No.**	**Supplier**	**Initial Mas Fraction Purity**	**Purificatio Method**	**Final Mass Fraction Purity**	**Analysis Method**
Glycine	56-41-7	Merck	> 0.99	None	-	-
[OMIm][Sal]	This work	Synthesized	-	Rotary/evaporator and vacuum	~0.98	Karl Fischer ,^{1}HNMR
N-methylimidazole	7-47-616	Merck	> 0.99	None	-	-
1-Chlorooctane	544-10-5	Merck	≥ 0.98	None	-	-
Sodium salicylate	54-21-7	Merck	≥ 0.995	None	-	-
Ethyl acetate	6-78-14	Merck	> 0.998	None	-	-
Dichloromethane	75-09-2	Fluka	≥ 0.999	None	-	-

In this work, in continuation to our previous thermodynamic studies of ternary systems (amino acid + API-IL + water),[20-22] the density, speed of sound, viscosity, electrical conductance and refractive index were measured for ternary (glycine + 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal] + water) systems at T = 298.15 K and atmospheric pressure. Variety of properties such as partial molar volume of transfer $\Delta_{tra}V_{\varphi}^{0}$, partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_{\varphi}^{0}$, viscosity *B*-coefficients of transfer $\Delta_{tra}B$, ion association constants (K_A) and molar refraction R_D were determined to investigate the solute-solute and solute-solvent interactions in these systems.

Materials and Methods

Reagents

The origin, purity and analysis method of the utilized chemicals are listed in Table 1. The mass fractions of water in glycine and ionic liquid 1-octyl-3-methylimidazolium salicylate analyzed by Karl–Fischer titrator (Metrohm 756 KF) were approximately 0.003, and 0.001 in mass fractions, respectively. The water contents of the synthesized ionic liquid and glycine were taken into account in the calculations. The bidistilled deionized water with a specific conductivity less than 1 µS cm^{-1} at 298.15 K was utilized. In the ternary solutions, (water + API-IL) solutions have been used as solvent.

Synthesis of ionic liquid

To synthesize the API-IL, 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal], the ionic liquid 1-octyl-3-methylimidazolium chloride [OMIm][Cl] and sodium salicylate are required. The ionic liquid, 1-octyl-3-methylimidazolium chloride was synthesized and purified as described in the literature.[26,27] The ^{1}HNMR spectrum of the synthesized ionic liquid was in good agreement with the literature[26] and confirmed the absence of any significant impurities. The purity of prepared ionic liquid was 0.98 in mass fraction. The ionic liquid 1-octyl-3-methylimidazolium salicylate [OMIm][Sal], was synthesized by dissolving (0.4 mol) sodium salicylate in dried acetonitrile and adding slowly to (0.4 mol) [OMIm][Cl] which is dissolved in a minimum amount of dried acetonitrile. The next step the resulting mixture was stirred overnight at room temperature. After that, to extract the water in the mixture, a rotary evaporator at 350 K and reduced pressure was used. The resulting mixture was subsequently dissolved in a large amount of dichloromethane to observe white precipitate containing sodium chloride. The white precipitate was then filtered and this process was continued until no white solid observed with the addition of dichloromethane.[23,25] The silver test confirmed the lack of sodium chloride. The obtained product (a yellowish solid) was further evaporated at 343.15 K by rotary evaporator.[26] The mass fraction of water in the [OMIm][Sal] analyzed using coulometric Karl Fischer titrator (Metrohm 756 KF) was approximately 0.001. The synthesized API-IL was characterized by the ^{1}H NMR (Brucker Av-400) spectroscopy. The ^{1}H NMR chemical shift of this ionic liquid were:; (400 MHz, $CDCl_3$): 10.401 (s, 1H); 7.928 (dd, 1H arom); 7.238 (td, 1H arom); 7.099 (s, 1H); 7.061 (s, 1H); 6.825-6.689 (m, 2H arom); 4.137 (t, 2H); 3.955 (s, 3H); 3.671 (OH); 1.763 (m, 2H); 1.277-1.207 (m, 10H); 0.85 (t, 3H). The structure of ionic liquid [OMIm][Sal] has been illustrated in Figure 1.

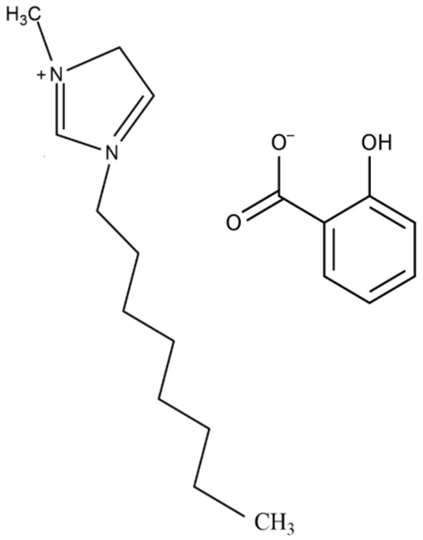

Figure 1. The structure of 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal].

Apparatus and procedure

To prepare the solutions in molality concentration, an analytical balance (Shimadzu, 321-34553, Japan) with a precision of ±1 × 10^{-7} kg was utilized. The density (d) and speed of sound (u) for the studied solutions were simultaneously measured under atmospheric pressure (≈ 85 kPa) using a commercial density and speed of sound measurement apparatus (Anton Paar DSA 5000) at the approximate frequency of 3 MHz. For calibrating the instrument, distilled deionized and degassed water as well as dry air were utilized.[28] Due to sensitivity of the density and speed of sound values to temperature, the Peltier thermostat embedded in densitometer was applied for controlling the temperature within $\pm 10^{-3}$ K.

Viscosities of the studied solutions were measured using an Anton Paar Rolling-ball, viscometer Lovis 2000 M/ME. Due to sensitivity of viscosity values to temperature, the temperature was kept constant within ± 0.005 K using the Peltier technique built in the thermostat. The uncertainty of the viscosity measurements was about 0.015 mPa·s.

Electrical conductivities κ were measured by a conductivity meter (Metrohm model 712, Switzerland) with the accuracy of ± 0.5%. The instrument was calibrated using the specific electrical conductivities of the KCl solution with 0.01 molality. The κ values were measured by adding the weighed drop of pure API-IL into the cell container of the conductivity meter with 60 mL capacity which was stirring using a magnetic stirrer. The temperature was fixed by circulation of water from thermostatically adjusted bath around the cell with an uncertainty ± 0.02 K. The molar conductivity (Λ) values of the solutions were computed using the relation, $\Lambda = \frac{1000\kappa}{c}$, where κ and c are the specific electrical conductance and the molarity of the solutions, respectively.

Refractive indices n_D of the solutions measurements were carried out by a digital refractometer (ATAGO-DRA1, Japan) with an uncertainty of ±0.002. To keep the temperature constant, a circulating bath thermostat (Cooling Bath 490, Iran) with the thermal stability of ± 0.01 K was utilized.

Results and Discussion

Volumetric properties

To investigate the interactions present in aqueous (glycine + ionic liquid, 1-octyl-3-methylimidazolium salicylate) solutions, density data for these mixtures have been measured at different molalities of [OMIm][Sal] (see Table 2). The apparent molar volumes (V_φ) for glycine in presence of studied AP-IL were computed according to the following equation:

$$V_\varphi = \frac{M}{d} - \left[\frac{1000(d - d_0)}{mdd_0}\right] \qquad \text{Eq. (1)}$$

Table 2. The values of density (d), apparent molar volume (V_φ), speed of sound (u), apparent molar isentropic compressibility (κ_φ) viscosity (η), refractive index (n_D) and molar refraction (R_D) of glycine in the aqueous solutions of [OMIm][Sal] at T = 298.15 K and P = 0.0868 MPa.[a]

[b] m/ mol·kg^{-1}	$10^{-3}d$/ kg·m^{-3}	$10^6\,V_\varphi$/ m^3·mol^{-1}	u/ m·s^{-1}	$10^{14}\,\kappa_\varphi$/ m^3·mol^{-1}·Pa^{-1}	η/ mPa·s	n_D	$10^6\,R_D$ / m^3·mol^{-1}
glycine in $m_{\text{API-IL}}$ ([OMIm][Sal] + water)							
$m_{\text{API-IL}}$ = 0.1054 mol·kg^{-1}							
0.0000	1.000224		1507.19		1.171	1.3389	3.871
0.1042	1.00348	43.67	1512.40	-2.36	1.192	1.3402	3.906
0.1438	1.004718	43.61	1514.39	-2.37	1.200	1.3407	3.915
0.1997	1.006478	43.48	1517.19	-2.37	1.212	1.3414	3.927
0.2657	1.008547	43.38	1520.51	-2.37	1.226	1.3422	3.942
0.2946	1.009450	43.35	1521.97	-2.37	1.232	1.3425	3.948
0.3459	1.011059	43.27	1524.56	-2.37	1.243	1.3431	3.959
0.3988	1.012714	43.21	1527.25	-2.38	1.255	1.3437	3.970
0.4454	1.014171	43.15	1529.62	-2.38	1.264	1.3443	3.981
$m_{\text{API-IL}}$ = 0.2007 mol·kg^{-1}							
0.0000	1.004246		1514.93		1.391	1.3440	4.031
0.0980	1.007275	43.97	1519.89	-2.30	1.422	1.3451	4.069
0.1495	1.008859	43.95	1522.49	-2.29	1.437	1.3458	4.082
0.2136	1.010822	43.94	1525.74	-2.29	1.456	1.3466	4.097
0.2479	1.011868	43.93	1527.49	-2.29	1.466	1.3471	4.106
0.2949	1.013300	43.91	1529.88	-2.28	1.480	1.3477	4.117
0.3440	1.014792	43.89	1532.38	-2.28	1.494	1.3484	4.129
0.3990	1.016455	43.88	1535.15	-2.27	1.512	1.3492	4.143
0.4575	1.018216	43.86	1538.13	-2.26	1.529	1.3500	4.158
$m_{\text{API-IL}}$ = 0.2961 mol·kg^{-1}							
0.0000	1.008029		1522.25		1.571	1.3488	4.228
0.1199	1.011695	44.21	1528.13	-2.12	1.623	1.3505	4.308
0.1500	1.012616	44.18	1529.65	-2.14	1.637	1.3509	4.316
0.2005	1.014163	44.09	1532.18	-2.15	1.657	1.3516	4.329
0.2532	1.015779	44.01	1534.82	-2.16	1.679	1.3523	4.342
0.2972	1.017130	43.94	1537.05	-2.16	1.698	1.3529	4.353
0.3503	1.018760	43.86	1539.79	-2.18	1.720	1.3536	4.366
0.3996	1.020268	43.80	1542.31	-2.18	1.741	1.3543	4.379
0.4402	1.021508	43.75	1544.31	-2.18	1.757	1.3548	4.388

[a] Standard uncertainties u are, u (T) = 0.01 K, u(d) = 0.3 kg·m^{-3}, speed of sound u (u) = 0.5 m·s^{-1}, u(η) = 0.015 mPa·s, u (n_D) = 0.002 and u(P) = 0.01 MPa. The estimated uncertainty are, u_c (V_φ) = 0.05·10^{-6} m^3·mol^{-1}, u_c (κ_φ) = 0.02·10^{-14} m^3·mol^{-1}·Pa^{-1} and u_c (R_D) = 0.003 m^3·mol^{-1}.

[b] Relative standard uncertainties u_r for molalities of API-IL and glycine are u_r ($m_{\text{API-IL}}$) = 0.02 and u_r (m) = 0.005, respectively, where $m_{\text{API-IL}}$ is the molal concentration of API-IL in water.

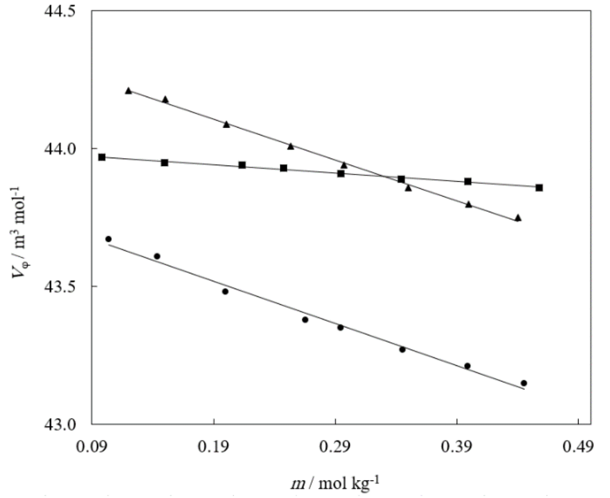

Figure 2. The apparent molar volume of glycine in the solutions of ([OMIm][Sal] + water) with several molalities of 0.1054 (●), 0.2007 (■) and 0.2961(▲) mol·kg^{-1} at T = 298.15 K.

where m and M indicate the molality and molar mass of glycine. d_0 and d are the densities of the solvent ([OMIm][Sal] + water) and (glycine + [OMIm][Sal] + water) solutions. Table 2 ad Figure 2 shows the values of V_φ for glycine in presence of ionic liquid [OMIm][Sal]. the values of obtained V_φ were fitted by least squares methos and the standard partial molar volume V_φ^0 was obtained:

$$V_\varphi = V_\varphi^0 + S_v m \qquad \text{Eq. (2)}$$

where S_v is an experimental parameter. The evaluated V_φ^0 and S_v values accompanied with their standard deviation $\sigma(V_\varphi)$ values are given in Table 3.

To evaluate the hydration behavior of glycine in the studied system originated from the solute-solvent interactions, the following equation was used:[29]

$$n_H = \frac{V_\varphi^0(\text{elect})}{V_E^0 - V_B^0} \qquad \text{Eq. (3)}$$

where $V_\varphi^0(\text{elect})$ and V_B^0 denote the molar volume of electrostrictive and bulk water , respectively. For electrolytes at 298.15 K, the value of almost 3.0 cm^3·mol^{-1} for $(V_E^0 - V_B^0)$ is used. To compute the $V_\varphi^0(\text{elect})$ values, the following equation is utilized:[30]

$$V_\varphi^0(\text{elect}) = V_\varphi^0 - V_\varphi^0(\text{int}) \qquad \text{Eq. (4)}$$

where $V_\varphi^0(\text{int})$ is the intrinsic partial molar volume. The $V_\varphi^o(\text{int})$ term can be determined by combining of the volume from Vander-Waals and packing effects:[31]

$$V_\varphi^0(\text{int}) = \frac{0.7}{0.634} V_\varphi^0(\text{cryst}) \qquad \text{Eq. (5)}$$

where $V_\varphi^0(\text{cryst}) = \dfrac{M}{d\,(\text{cryst})}$ is the molar volume of the crystal which was computed using the densities of the amino acid (crystal form) supposed by Berlin and Pallansch at 298.15 K.[32] The calculated n_{H} values for glycine in presence of studied ionic liquid are given in Table 3. In our previous article, the value of 2.56 was reported for n_{H} of glycine in water at T= 298.15 K (computed with the same method).[21] The results show that n_{H} values for glycine in the aqueous solutions of ionic liquids [OMIm][Sal] was less than the corresponding value in water which is 2.56. This indicated that the ionic liquid [OMIm][Sal] showed dehydration effect on aqueous glycine solutions. The values of n_{H} decrease by increasing ionic liquid molalities. This demonstrated that dehydration effect of investigated ionic liquids on the aqueous glycine solutions increased by ionic liquid concentrations

Another suitable parameter which was attributed only to glycine -ionic liquid interactions was the partial molar volume of transfer:[33]

$$\Delta_{tra} V_\varphi^0 = V_\varphi^0\ (\text{API-IL + water}) - V_\varphi^0\ (\text{in water}) \quad \text{Eq. (6)}$$

The data for V_φ^0 values of glycine in water were taken from our earlier published data.[21] The results showed that the calculated values of $\Delta_{tra} V_\varphi^0$ for the studied solutions (given in Table 3) were positive. According to the co-sphere overlap model, the types of the interactions between glycine and API-IL can be classified as: (i) ion–polar interactions (ii) polar-polar interactions (iii) ion–nonpolar interactions and (iv) nonpolar-nonpolar interactions. Based on this model, the positive values obtained for $\Delta_{tra} V_\varphi^0$ indicate that ion–polar and polar-polar interactions were stronger than other interactions. In addition, the results showed that increase in the API-IL concentration, lead to increment in the $\Delta_{tra} V_\varphi^0$ values. This phenomenon suggested that attractive interactions between the zwitterionic center of glycine and the ions of [OMIm][Sal] were stronger than the interactions between glycine and water, therefore water molecules were released from the hydration layer to the bulk.[34]

Compressibility properties

Compressibility properties are important thermodynamic parameters for evaluating the solute-solvent interaction in these systems in which the speed of sound measurement are required. The experimental speed of sound values for (glycine + [OMIm][Sal] + water) solutions are reported in Table 2. The isentropic compressibility $\kappa_s(\text{Pa}^{-1})$ was calculated using the Laplace–Newton's equation as follows:

$$\kappa_s = \frac{1}{du^2} \qquad \text{Eq. (7)}$$

Table 3. The values of standard apparent molar volume ($V_{\varphi}^{\llcorner}$), experimental slope (S_v), transfer volume ($\Delta_{tra}V_{\varphi}$, hydration number (n_H), viscosity *B*-coefficient (*B*), free energy of activation per mole of solvent ($\Delta\mu_1^{\circ\neq}$) and the solute ($\Delta\mu_2^{\circ\neq}$), viscosity *B*-coefficients of transfer ($\Delta_{tra}B$), Pair (V_{AB} and κ_{AB}) and triplet (V_{ABB} and κ_{ABB}) interaction coefficients of glycine in the aqueous solutions of [OMIm][Sal] at T= 298.15 K.

Glycine in m_{API-IL} ([OMIm][Sal] + water)			
^{a} m_{API-IL}/ mol·kg^{-1}	0.1054	0.2007	0.2961
$10^6 V_{\varphi}^{\llcorner}$/ m^3·mol^{-1}	43.81 ± 0.023	44.00 ± 0.003	44.39 ± 0.013
$10^6 S_v$ / m^3·mol^{-2}·kg	-1.54 ± 0.067	-0.32 ± 0.010	-1.47 ± 0.037
$10^6 \sigma(V_{\varphi})$	0.02	0.01	0.01
$10^6 \Delta_{tra}V_{\varphi}^{\llcorner}$/ m^3·mol^{-1}	0.58	0.78	1.16
n_H	2.32	2.27	2.15
$10^6 V_{AB}$/ m^3·mol^{-2}·kg	2.651		
$10^6 V_{ABB}$/ m^3·mol^{-3}·kg^2	-1.68		
$10^{14} \kappa_{\varphi}$/ m^3·mol^{-1}·Pa^{-1}	-2.36 ± 0.01	-2.31 ± 0.00	-2.11 ± 0.01
$10^{14} S_k$/ m^3·mol^{-2}·kg·Pa^{-1}	-0.04 ± 0.01	0.09 ± 0.01	-0.17 ± 0.03
$10^{14} \sigma(\kappa_{\varphi})$	0.01	0.00	0.01
$10^{14} \Delta\kappa_{\varphi}$/ m^3·mol^{-1}·Pa^{-1}	0.29	0.34	0.54
$10^{14} \kappa_{AB}$/ m^3·mol^{-2}·kg·Pa^{-1}	1.24		
$10^{14} \kappa_{ABB}$/ m^3·mol^{-3}·kg^2·Pa^{-1}	-0.82		
B/ dm^3·mol^{-1}	0.1054	0.2007	0.2961
$\Delta\mu_1^{\circ\#}$/ kJ·mol^{-1}	0.1054	0.2007	0.2961
$\Delta\mu_2^{\circ\#}$/ kJ·mol^{-1}	0.1054	0.2007	0.2961
$\Delta_{tra}B$/ dm^3·mol^{-1}	0.1054	0.2007	0.2961

Based on the speed of sound *u* and density *d* of solvent and solution, the apparent molar isentropic compressibility κ_{φ} values can be calculated:

$$\kappa_{\varphi} = \frac{(\kappa_s d_0 - \kappa_{s0} d)}{m d d_0} + \kappa_s \frac{M}{d} \qquad \text{Eq. (8)}$$

where κ_{s0} and κ_s denote the isentropic compressibility of the solvent ([OMIm][Sal] + water) and ternary solutions (glycine + [OMIm][Sal] + water), respectively. The obtained κ_{φ} values for glycine in presence of the studied ionic liquid are reported in Table 2. The apparent molar isentropic compressibility κ_{φ} of glycine in several molalities of ([OMIm][Sal] + water) was presented in Figure 3.

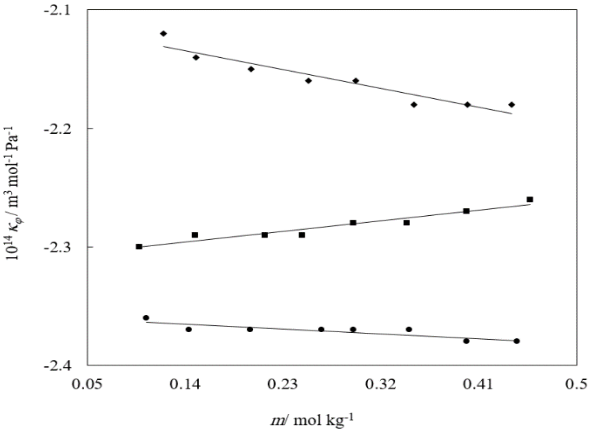

Figure 3. The apparent molar isentropic compressibility of glycine in the solutions of ([OMIm][Sal] + water) with several molalities of 0.1054 (●), 0.2007 (■) and 0.2961(♦) mol·kg^{-1} at T = 298.15 K.

As shown in Table 2 and Figure 3, the κ_{φ} values increased with an increase in the ionic liquid concentrations which may be related to release of the water molecules from the hydration layer to the bulk.

According to the following relation, the partial molar isentropic compressibility κ_{φ}^0 was obtained from the extrapolation of κ_{φ} values to zero concentration:

$$\kappa_{\varphi} = \kappa_{\varphi}^0 + S_k m \qquad \text{Eq. (9)}$$

where S_k, is the experimental slope. The values of κ_{φ}^0 and S_k for the studied systems are reported in Table 3. As can be in this table, increase in the API-IL concentrations lead to increase in the κ_{φ}^0 values. In fact the strong interactions between the ions of [OMIm][Sal] and glycine lead to the increase in the compressibility of the medium.[35,36]

The partial molar isentropic compressibility of transfer from water to the aqueous ionic liquid solutions has been computed as follows:

$$\Delta_{tra}\kappa_{\phi}^0 = \kappa_{\phi}^0(\text{aqueous API} - \text{IL}) - \kappa_{\phi}^0(\text{water}) \qquad \text{Eq. (10)}$$

The data for κ_{φ}^0 values of glycine in water required for calculation of $\Delta_{tra}\kappa_{\varphi}^0$ values were taken from our earlier published data.[21] Table 3 represents that the obtained $\Delta_{tra}\kappa_{\varphi}^0$ values for investigated solutions were positive. The positive values of the $\Delta_{tra}\kappa_{\varphi}^0$ values were indicative of the dominance of the ion-polar and polar-polar interactions between glycine and the ions of ionic liquid. Increasing $\Delta_{tra}\kappa_{\varphi}^0$ values by increasing in the API-IL concentration showed that ion-polar and polar-polar interactions increase by increase in concentration of API-IL.[36] In fact more water molecules are released from the hydration layer surrounding glycine to the bulk due to strong attractive interaction between glycine and ions of [OMIm][Sal], and this made the solution difficult to compress. These results were in agreement with the ones obtained from the volumetric properties discussed above.

Pair and triplet interaction coefficients

The McMillar Mayer theory[35,37] of solutions can be used to express partial molar volume of transfer and partial molar isentropic compressibility of transfer through the following equation:

$$\Delta_{tra} V_\varphi^0 = 2V_{\mathrm{AB}}\, m_B + 3V_{\mathrm{ABB}}\, m_B^2 \qquad \text{Eq. (11)}$$

$$\Delta_{tra} \kappa_\varphi^0 = 2\kappa_{\mathrm{AB}} m_B + 3\kappa_{\mathrm{ABB}} m_B^2 \qquad \text{Eq. (12)}$$

where A denotes amino acid, B represents ionic liquid and m_{B} is the molality of ionic liquid. In the above relation (V_{AB}, κ_{AB}) and (V_{ABB}, κ_{ABB}) are the paired and triplet volumetric and compressibility interaction parameters, respectively. The results presented in Table 3 show that the estimated V_{AB} and κ_{AB} are positive, while V_{ABB} and κ_{ABB} are negative for the studied systems. The positive values of V_{AB} and κ_{AB} indicate that the interactions between API-IL and glycine in aqueous media were mainly pairwise.[38]

Viscometric properties

Viscometric properties provide us valuable information in regard with the interactions occurring in these systems and can help to confirm volumetric and acoustic results. The measured viscosities η of (glycine + [OMIm][Sal] + water) with several molalities of ([OMIm][Sal] + water) were presented in Table 2. The variation of the relative viscosity $\eta_r = \frac{\eta}{\eta_0}$ of these ternary solutions is expressed by Jones-Dole equation:[39]

$$\eta_r = 1 + Ac^{1/2} + Bc \qquad \text{Eq. (13)}$$

The A-coefficient and B-coefficient are attributed to solute–solute and solute–cosolute interactions, respectively. The B-coefficient viscosity are affected by the variety of factors such as size, shape, structure and charge of solute molecules in addition of solute-solvent interactions.[40] The A-coefficient is negligible for nonelectrolytes. So equation 13 is simplified to the following equation:

$$\eta_r = 1 + Bc \qquad \text{Eq. (14)}$$

where η_0 is the viscosity of the solvent ([OMIm][Sal] + water) and c is the molarity of glycine in the studied solutions. Using the least square method, the slope of the linear plot of $(\eta_r - 1)$ vs. c gives the viscosity B-coefficient. The computed viscosity B-coefficients and $\sigma(\eta)$ of the studied solutions are listed in Table 3.

The following relation presents the variation of B-coefficients $\Delta_{tra}B$ from water to the aqueous [OMIm][Sal] solutions:

$\Delta_{tra}B$ = B-coefficients in (API-IL + water) – B-coefficients (in water) Eq. (15)

The value of 0.135 $\mathrm{dm^3 \cdot mol^{-1}}$ is reported for viscosity B-coefficients values of glycine in water at T = 298.15 K.[21] The results show that the viscosity B-coefficients in ternary solutions, have larger values compared to their corresponding values in binary solutions, so it was concluded that the attractive interactions between glycine and ionic liquid are stronger compared to attractive glycine–water interactions. In addition, $\Delta_{tra}B$ values increase with an increase in the API-IL concentration. The viscosity of ternary (glycine + [OMIm][Sal] + water) with different molalities of ([OMIm][Sal] + water) at T = 298.15 K is illustrated in Figure 4.

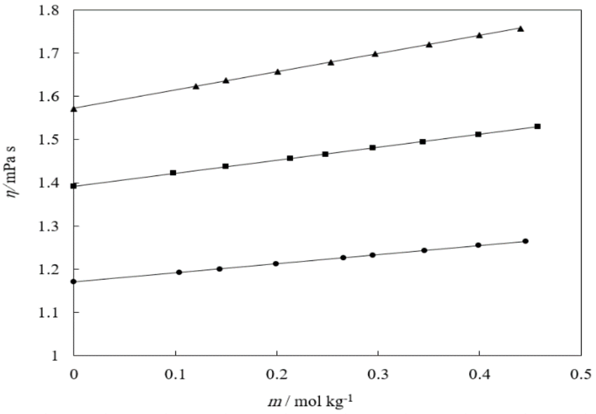

Figure 4. The viscosity of ternary (glycine + [OMIm][Sal] + water) solutions at different ionic liquid molalities 0.1054 (●), 0.2007 (■) and 0.2961(▲) mol·kg^{-1} at T = 298.15 K.

According to the theory proposed by Feakins and co-worker based on the transition state treatment of relative viscosity, viscosity B-coefficient is expressed as:

$$B = (\overline{V}_1^0 - \overline{V}_2^0) + \overline{V}_1^0\left(\frac{\Delta\mu_2^{\circ\neq} - \Delta\mu_1^{\circ\neq}}{RT}\right) \qquad \text{Eq. (16)}$$

where $(\overline{V}_1^0 = \sum \frac{x_i M_i}{\rho})$ is the mean volume of the solvent and $(\overline{V}_2^0 = V_\varphi^0)$ is the standard partial molar volume of the pure solute. The terms, x_i, M_i and ρ are mole fraction, molar masses and density of the solvent ([OMIm][Sal] + water). Based on Eyring's simple model, the free energy of activation per mole of the solvent $\Delta\mu_1^{\circ\neq}$ and $\Delta\mu_2^{\circ\neq}$ can be determined:

$$\Delta\mu_1^{\circ\neq} = \Delta G_1^{\circ\neq} = RT \ln \frac{\eta_1 V_1^0}{hN_A} \qquad \text{Eq. (17)}$$

$$\Delta\mu_2^{\circ\neq} = \Delta\mu_1^{\circ\neq} + \frac{RT}{V_1^0}[B - (\overline{V}_1^0 - \overline{V}_2^0)] \qquad \text{Eq. (18)}$$

where h is the Planck's constant, and N_A is the Avogadro number. The results listed in Table 3 showed that $\Delta\mu_2^{\circ\neq}$ values were positive and greater than $\Delta\mu_1^{\circ\neq}$ in all molalities of ionic liquid.

Table 4 The values of molar electrical conductivity (Λ) of the [OMIm][Sal] in water and aqueous solutions of glycine as a function of API-IL concentration at T = 298.15 K and P = 0.0868 MPa.

$^b c$ / mol·m^{-3}	$10^4\ \Lambda$/ S·m^2·mol^{-1}	c/ mol·m^{-3}	$10^4\ \Lambda$/ S·m^2·mol^{-1}	c / mol·m^{-3}	$10^4\ \Lambda$/ S·m^2·mol^{-1}	c / mol·m^{-3}	$10^4\ \Lambda$/ S·m^2·mol^{-1}
$^c m_{Gly}$ = 0.0 mol·kg^{-1}		m_{Gly} = 0.1 mol·kg^{-1}		m_{Gly} = 0.3 mol·kg^{-1}		m_{Gly} = 0.5 mol·kg^{-1}	
0.0599	67.46	0.0687	63.93	0.0979	57.12	0.1058	54.09
0.1239	66.56	0.1522	62.76	0.1796	56.48	0.1899	53.80
0.1829	65.61	0.2311	62.07	0.2984	55.92	0.2876	53.55
0.2435	64.85	0.3043	61.54	0.4079	55.28	0.3873	53.21
0.3078	64.05	0.3871	60.79	0.5106	54.79	0.4760	52.89
0.3746	63.50	0.4572	60.37	0.6041	54.29	0.5729	52.68
0.4537	62.96	0.5509	59.66	0.7062	53.74	0.6733	52.36
0.5388	62.40	0.6299	59.17	0.8120	53.20	0.7543	52.17
0.6319	61.85	0.7263	58.52	0.9083	52.82	0.8450	51.95
0.7107	61.22	0.8206	57.94	1.0357	52.23	0.9561	51.72
0.7727	60.89	0.9136	57.45	1.1318	51.86	1.0501	51.48
0.8601	60.33	0.9946	57.08	1.2238	51.48	1.1466	51.30
0.9267	59.95	1.0853	56.61				51.02
1.0003	59.55	1.1557	56.25				50.90
1.0722	59.15	1.1916	56.13				
1.1517	58.93						

^{a} Standard uncertainties u are: $u(\Lambda)$ = 3×10^{-6} S· m^2· mol^{-1} , $u(T)$= 0.01 K and $u(P)$ = 0.01 MPa
^{b} Relative standard uncertainties u_r for molarities of AP-IL is $u_r(c)$ = 0.004.
^{c} m_{Gly} is the molal concentration of glycine in water.

This indicated that there was stronger interactions between glycine and solvent ([OMIm][Sal]+ water) in the ground state rather than the transition state.

Conductometric properties

Conductometric study was another appropriate approach to investigate the possible interactions in these systems. In this respect, the molar conductivity data for [OMIm][Sal] in the aqueous solution of glycine were determined. The values of molar conductivity, Λ for [OMIm][Sal] in water and aqueous solutions of glycine are listed in Table 4 and shown in Figure 5.

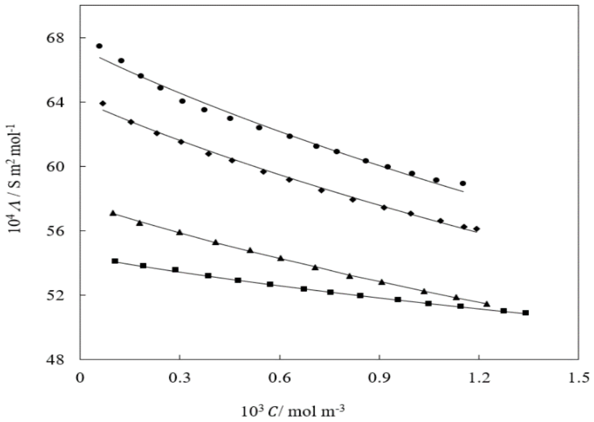

Figure 5. The molar conductivities of [OMIm][Sal] in water (●) and in the aqueous solutions of glycine with different molalities 0.1 (♦), 0.3 (▲) and 0.5 (■) mol·kg^{-1} at T = 298.15 K.

As can be seen in Table 4 and Figure 5, by increasing the API-IL concentrations, Λ values decreased due to ionic atmosphere effects. In fact, in more concentrated solutions, the ion pairing is the reason for decrease in molar conductivities. The experimental data were analyzed using the low concentration Chemical Model (lcCM) by the following set of equations:

$$\Lambda = \alpha[\Lambda_0 - S(c\alpha)^{1/2} + Ec\alpha\ln(c\alpha) + J_1 c\alpha + J_2(c\alpha)^{3/2}] \quad \text{Eq. (19)}$$

$$K_A = \frac{1-\alpha}{\alpha^2 c\gamma_\pm^2} \quad \text{Eq. (20)}$$

$$\ln\gamma_\pm = \frac{\kappa q}{1+\kappa R} \quad \text{Eq. (21)}$$

$$\kappa^2 = \frac{16000 N_A z^2 e^2 \alpha c}{\varepsilon_0 \varepsilon K_B T} \quad \text{Eq. (22)}$$

$$q = \frac{z_+ z_- e^2}{8\pi\varepsilon_0\varepsilon kT} \quad \text{Eq. (23)}$$

in which, Λ_0 is the molar conductivity at infinite dilution, (1-α) is the fraction of oppositely charged ions acting as ion pairs, $\gamma_\pm$ is the corresponding mean activity coefficient of the free ions, $\kappa$is the Debye parameter, e is the electronic charge, z is the ionic charge, ε_0 is the permittivity of vacuum, ε is the dielectric constant of the solvent, and the other symbols have their usual meanings. The coefficients E, J_1, and J_2 that are necessary for calculations were taken from the literature.[41,42] The estimated Λ_0, K_A and R for the studied API-IL in water and the aqueous glycine solutions were listed in Table 5. The results showed that the increase in the concentration of glycine lead to decrease in the Λ_0 values. This was indicative of the low mobility of the solvated ions by (COO$^-$ /NH$_3^+$) zwitterionic centers with large radii and increasing the viscosity of medium with the addition of glycine. Further, increase in the concentration of glycine, lead to decrease in the K_A values API-IL.

This was related to the strong interaction of ions with zwitterions and the reduced ion-pair formation in the concentrated solutions.

Table 5. The values of limiting molar conductivity (Λ_0), Walden product ($\Lambda_0\eta$), ion association constant (K_A), standard free Gibbs energy of ion-pairing formation (ΔG_A°), distance parameter (R), and standard deviation ($\sigma(\Lambda)$) of [OMIm][Sal] in water and aqueous solutions of glycine and the values of the ionic limiting molar conductivity (λ_0), Walden product ($\lambda_0\eta$), Stoke's radius (r_s), diffusion coefficient (D^0_{ion}), and transport number (t) of [OMIm]$^+$, [Sal]$^-$ in water at T = 298.15 K [a].

m_{gly}/ mol·kg^{-1}	[a]K_A/ dm^3·mol^{-1}	[a]$10^4\ \Lambda_0$/ S·m^2·mol^{-1}	$10^{10}\ R$/ m	σ (Λ)	$10^4\ \Lambda_0\ \eta$/ S·m^2·mPa·s·mol^{-1}	ΔG_A°/ kJ·mol^{-1}
			[OMIm][Sal] in m_{gly} (glycine + water)			
0.0	42.45	67.40 ± 0.22	50.40	0.34	60.32	-9.29
0.1	39.88	64.15 ± 0.11	49.45	0.18	59.27	-9.14
0.3	24.70	57.79 ± 0.03	48.04	0.05	54.89	-7.95
0.5	16.69	54.50 ± 0.02	40.30	0.03	53.63	-6.98
ions	**$10^4\ \lambda_0$/ S·m^2·mol^{-1}**	**$10^4\ \lambda_0\ \eta$/ S·m^2·mPa·s·mol^{-1}**	**$10^{10}\ r_s$/ m**	**$10^4\ D^0_{ion}$/ m^2·s^{-1}**	***t***	
			[OMIm][Sal] in water			
[HMIm]$^+$	32.2[b]	31.50	2.85	8.57	0.478	
[Sal]$^-$	35.2	28.82	2.60	9.37	0.522	

[a] The estimated uncertainties for u (K_A) = 0.2 dm^3 mol^{-1}, u ($10^4\Lambda_0$) = 0.04 S· m^2 ·mol^{-1} .
[b] The λ_0 values of the cations were taken directly from Ref. [46]

The distance parameter R that represents the maximum center-to-center distance between the ions or separated ion pairs in the solvent have no meaningful trend.[42- 44]

In order to eliminate the effect of viscosity on the ionic mobility, the Walden product is computed. Because of the dependency of the ions conductivity only to their mobility at infinite dilution, it is expected that the product of the viscosity of the solvent by the ion conductivity be independent of the solvent nature.[45] The large effective radius of the ions and high association of API-IL in glycine solutions maybe the because of lower $\Lambda_0\eta_0$ values. The Walden product ($\Lambda_0\eta_0$) of the [OMIm][Sal] in the glycine solution is represented in Table 5.

The following equation is used to express the standard deviations of the experimental molar conductivities (Λ) and the calculated ones (Λ_{cal}):

$$\sigma(\Lambda)=\left[\frac{\sum(\Lambda-\Lambda_{\mathbf{cal}})^2}{n-p}\right]^{\frac{1}{2}} \qquad \text{Eq.(24)}$$

in which n and p denote the number of experimental data and parameters, respectively. The calculated standard deviations of electrical conductivity using lcCM model is listed in Table 5.

Diffusion coefficients Walden products of ions

Ionic limiting molar conductivity values of the individual ions can be determined using the following relation:

$$\Lambda_0=z_+\lambda_0^+ + z_-\lambda_0^- \qquad \text{Eq. (25)}$$

The ionic limiting molar conductivity of the λ_0^+ in water for [OMIm]$^+$ is taken from literature.[47] The limiting molar conductivity of the λ_0^- (see in Table 5) was calculated using Eq. (25). The following equation expresses the diffusion coefficients of the individual ions:[45,48]

$$D^0_{ion}=\frac{RT\lambda_0}{|z_{ion}|F^2} \qquad \text{Eq. (26)}$$

The computed values of the diffusion coefficient D^0_{ion} and limiting molar conductivity λ_0 of the ions are listed in Table 5.

The Stoke's radius (r_s) or effective hydrodynamic radius of the ions can be computed by the help of D^0_{ion} and η values of the pure water. This property depend on the solute mobility and is affected by size as well as the solvent.

$$r_s=\frac{kT}{6\pi\eta D^0_{ion}} \qquad \text{Eq. (27)}$$

The calculated values of r_s for the ions are collected in Table 5. By replacing Eq. (26) in Eq. (27) and its rearrangement, the following relation is resulted:[43,47]

$$\lambda_0\eta=\frac{k|z_{ion}|F^2}{6\pi Rr_s} \qquad \text{Eq. (28)}$$

This equation is indicative of an inverse relationship between the effective hydrodynamic radius of an ion and its Walden product ($\lambda_0\eta$). As all parameters in the right hand of the equation (28) are constant except r_s, therefore, the Walden product must depend only to r_s value.

The contribution of an ion to the total molar conductivity of the solution is called the ion transport number or the transference number and can be determined as:

$$t_\pm=\frac{\lambda_0}{\Lambda_0} \qquad \text{Eq. (29)}$$

The transport numbers of cation and anion are usually expressed by the symbols t_+ and t_- , respectively. The calculated values of t_+ and t_- are given in Table 5.

The standard Gibbs free energy (ΔG_A°) of the ion-association process can be computed using the ion association constants. The estimated ΔG_A° values for the ion association process of API-IL in water and glycine solutions listed in Table 5 is negative. The negative values of the ΔG_A° for the [OMIm][Sal] in the studied solutions indicate the spontaneously and feasibility of the ion association process in this API-IL.

Refractometric properties

Refractometric properties are other physicochemical properties that can be used to investigate solute-solute and solute-solvent interactions in these systems. The measured refractive index data n_D for (glycine + [OMIm][Sal] + water) in this work with several molalities of ([OMIm][Sal] + water) are reported in Table 2. The molar refraction R_D is calculated using Lorentz-Lorenz equation:[47-49]

$$R_D = \left[\frac{n_D - 1}{n_D^2 + 2}\right]\left(\sum_{i=1}^{3} \frac{x_i M_i}{d}\right) \qquad \text{Eq. (30)}$$

where x_i, M_i and d are the mole fraction and molar mass of components and density of the solutions, respectively. The calculated molar refractions of the investigated solutions are listed in Table 2 and illustrated in Figure 6. As seen in Table 2 and Figure 6, the R_D values increased with an increase in the API-IL concentration. As the molecule structure is more complicated, the electron cloud become more distributed, and the polarizability of the molecule was intensified.

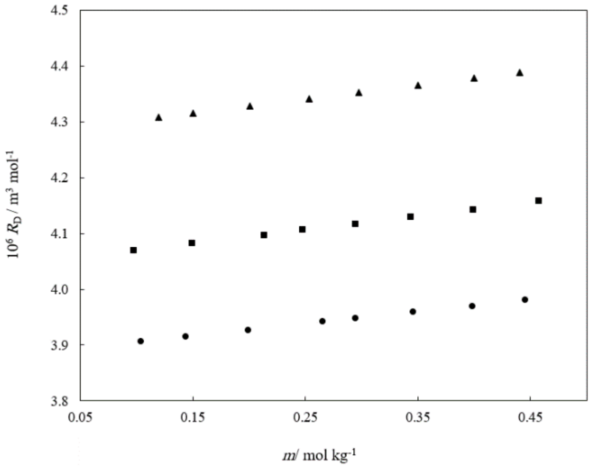

Figure 6. The molar refraction of ternary (glycine + [OMIm][Sal] + water) with several molalities of [OMIm][Sal] in water 0.1054 (●), 0.2007 (■) and 0.2961(▲) mol·kg^{-1}at T = 298.15 K.

Conclusion

In this work, to investigate the effect of active pharmaceutical ingredient based ionic liquids (API-IL), 1-octyl-3-methylimidazolium salicylate ([OMIm][Sal]) on the volumetric, compressibility, viscometric, electrical conductivity and refractometric properties of aqueous (glycine + water) solution have been determined at T = 298.15 K. The positive values of partial molar volumes of transfer $\Delta_{tra}V_{\varphi}^{0}$, partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_{\varphi}^{0}$ and viscosity B-coefficients of transfer indicate that the ion–polar and polar-polar interactions between glycine and API-IL were dominant. Also, the results showed that increase in ionic liquid concentration, the attractive interactions between glycine and API-IL was increased. The positive paired volumetric and compressibility interaction parameters V_{AB} and κ_{AB} indicate that pairwise interactions were more favored. Viscosity B-coefficient values in ternary solutions were higher than the corresponding values in binary solutions. This indicated the strong interactions between glycine and ionic liquid in comparison to the glycine and water. The lower values of Λ_0 with the addition of glycine to the aqueous [OMIm][Sal] solutions indicating the low mobility of the solvated ions by (COO^- /NH_3^+) zwitterionic centers with large radii and increase in the viscosity of the medium. From the thermodynamic data analysis, the negative values of ΔG_A° for [OMIm][Sal] in the aqueous solutions of glycine suggest the spontaneous process of ion association of this API-IL.

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Conflict of interests

The authors claim that there is no conflict of interest.

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