Volumetric properties of some pharmaceutical binary mixtures at low temperatures and correlation with the Jouyban-Acree model

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Summary

Excess molar volumes and partial molar volumes were investigated from density values for a) ethanol (1) + water (2), b) 1,2-propanediol (1) + water (2), and c) ethanol (1) + 1,2-propanediol (2) mixtures, at temperatures from (278.15 to 288.15) K. Excess molar volumes were fitted by Redlich-Kister equation. The systems exhibit negative excess volumes probably due to increased interactions like hydrogen bonding and/ or large differences in molar volumes of components. The Jouyban-Acree model was used for density and molar volume correlations of the studied mixtures at different temperatures. The mean relative deviations between experimental and calculated data in density data were 0.15, 0.08, and 0.01 %, for a), b), and c), respectively; whereas, in molar volume data the values were 1.9, 2.1, and 0.1 %, for a), b), and c), respectively.

Key words: ethanol, 1,2-propanediol, water, binary liquid mixtures, density, excess volume, Jouyban-Acree model.

Resumen

Propiedades volumétricas de algunas mezclas binarias de uso farmacéutico a bajas temperaturas y correlación con el modelo Jouyban-Acree

En este trabajo se calcularon los volúmenes molares de exceso a partir de valores de densidad para los sistemas: a) etanol + agua, b) 1,2-propanodiol + agua y c) etanol + 1,2-propanodiol, en todo el intervalo de composición, a temperaturas entre 278,15 y 288,15 K. Los volúmenes molares de exceso se modelaron de acuerdo a la ecuación de Redlich-Kister. Los sistemas estudiados presentan volúmenes de exceso altamente negativos probablemente debido a las fuertes interacciones por unión de hidrógeno entre las moléculas de los dos compuestos y a la gran diferencia en los volúmenes molares de los dos componentes puros. Finalmente se usó el modelo Jouyban-Acree para correlacionar la densidad y el volumen molar de las diferentes mezclas. Las desviaciones medias relativas en densidad fueron, 0,15, 0,08 y 0,01 %, para a), b) y c), respectivamente; mientras que el caso de volumen molar los valores fueron 1,9, 2,1 y 0,1 %, para a), b) y c), respectivamente.

Palabras clave: etanol, 1,2-propanodiol, agua, mezclas líquidas binarias, volúmenes de exceso, modelo de Jouyban-Acree.

Introduction

Water-cosolvent mixtures have been used widely in pharmacy in order to increase the solubility of drugs poorly soluble in water during the design of homogeneous pharmaceutical dosage forms, such as syrups and elixirs, among others (1, 2). Ethanol and 1,2-Propanediol are the cosolvents most used in design nowadays, especially those intended for elaboration of peroral and parenteral medications (3). Thus, several examples of pharmaceutical formulations using these cosolvents have been presented by Rubino (1) and Yalkowsky (2).

The mixtures obtained using these cosolvents and water show highly non-ideal behavior due to increased interactions between unlike molecules and large differences in molar volumes of pure components, which leads to non-additive volumes on mixing (4, 5). For this reason it is necessary to characterize the volumetric behavior of these binary mixtures as a function of temperature in order to extend the physicochemical information available for liquid mixtures used in pharmacy. This information is useful

to understand the intermolecular interactions present in liquid pharmaceutical systems (8). Also, data related to density of solute free mixture of solvents might be useful in prediction of the density of pharmaceutical substances in mixture of solvents (6).

In this report, the excess molar volumes and the molar and excess molar volumes of the respective binary systems conformed by ethanol, 1,2-propanediol, and water at various low temperatures (from 278.15 to 288.15 K) were calculated according to modified procedures widely exposed in the literature (7-9). This report is a continuation of those presented previously about some volumetric properties for the same binary systems at temperatures from 293.15 to 313.15 K (10-12). It is important to note that in the literature is scarce the volumetric information about these mixtures at low temperatures. Additionally, the Jouyban-Acree model is used to correlate densities and molar volumes with solvent compositions as has been for other binary systems at several temperatures (13-16).

Experimental

Materials

In this investigation dehydrated ethanol (from Merck, Germany) and dehydrated 1,2-propanediol (propylene glycol from Dow Chemical Company, U.S.A.) were used and they were in agreement with the quality requirements indicated for medicinal products indicated in the American Pharmacopeia USP (17); distilled water with conductivity lower than $2 \, \mu S \, cm^{-1}$ was also used. The dehydrated ethanol and 1,2-propanediol employed were maintained over molecular sieve to obtain dry solvents prior to prepare the solvent mixtures. Solvent dryness was verified based on densities obtained which were compared with the literature values (9-12).

Cosolvent mixtures preparation

All binary mixtures were prepared in quantities of 40.00 g by mass using a Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in concentrations from 0.10 to 0.90 varying in 0.10 in mass fraction of solvent 1, to study 9 mixtures and the two pure solvents. This procedure implies an uncertainty of $\pm \, 2 \times 10^{-5}$ in mole fraction. The mixtures were allowed to stand in Magni Whirl Blue M or Neslab RTE 10 Digital Plus (Thermo Electron Company) water baths at temperatures from 278.15 K to 288.15 K varying in 5.00 ± 0.05 K for at least 30 minutes prior to density determinations.

Density determination

This property was determined using a DMA 45 Anton Paar digital density meter connected to a Neslab RTE 10 Digital Plus (Thermo Electron Company) recirculating thermostatic water bath according to a procedure previously described (18). The equipment was calibrated according to Instruction Manual using air and water at the different temperatures studied (19). Density measurements were carried out at least three times and averaged. From density values, volumetric properties were calculated as will be indicate in the next section.

Results and discussion

In Table 1 the composition of the three binary mixtures, in mass percent and mole fraction, in addition to density values at several temperatures are presented. Density values follow the same tendency as those reported for the same systems at temperatures from 293.15 to 313.15 K (10-12). Our density values for ethanol (1) + water (2) at 283.15 and 288.15 K are similar to those reported in the literature (20). In similar way, our density values for 1,2-propanediol (1) + water (2) are similar to those reported by Geyer et al. at 278.15 and 288.15 K (21, 22). It is important to note that up to the best of our knowledge for ethanol (1) + 1,2-propanediol (2) no density values at these temperatures have been reported. In all cases the density decreases almost linearly as the temperature increases.

Table 1. Densities $(g\,cm^{-3})^a$ for all binary mixtures at various temperatures. μ and x represent mass and mole fraction of the first component, respectively.

Ethanol (1) + Water (2)				
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	1.0000	0.9998	0.9992
0.10	0.0416	0.9860	0.9850	0.9836
0.20	0.0891	0.9740	0.9726	0.9708
0.30	0.1435	0.9628	0.9600	0.9572
0.40	0.2068	0.9460	0.9428	0.9393
0.50	0.2811	0.9257	0.9222	0.9184
0.60	0.3697	0.9040	0.9000	0.8968
0.70	0.4771	0.8808	0.8768	0.8736
0.80	0.6100	0.8569	0.8525	0.8493

(*Continued*)

Table 1. Densities $(g\,cm^{-3})^a$ for all binary mixtures at various temperatures. μ and x represent mass and mole fraction of the first component, respectively (*continuation*).

Ethanol (1) + Water (2)				
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.90	0.7787	0.8315	0.8271	0.8238
1.00	1.0000	0.8024	0.7983	0.7952
1,2-Propanediol (1) + Water (2)				
μ_{PD}	x_{PD}	278.15 K	283.15 K	288.15K
0.00	0.0000	1.0000	0.9998	0.9992
0.10	0.0256	1.0086	1.0078	1.0069
0.20	0.0559	1.0180	1.0168	1.0154
0.30	0.0921	1.0283	1.0265	1.0245
0.40	0.1363	1.0379	1.0354	1.0328
0.50	0.1914	1.0453	1.0423	1.0391
0.60	0.2621	1.0500	1.0467	1.0432
0.70	0.3558	1.0519	1.0482	1.0448
0.80	0.4864	1.0513	1.0477	1.0441
0.90	0.6806	1.0485	1.0451	1.0414
1.00	1.0000	1.0445	1.0420	1.0389
Ethanol (1) + 1,2-Propanediol (2)				
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	1.0445	1.0420	1.0389
0.10	0.1551	1.0153	1.0123	1.0089
0.20	0.2923	0.9875	0.9842	0.9807
0.30	0.4145	0.9612	0.9575	0.9539
0.40	0.5241	0.9361	0.9322	0.9286
0.50	0.6229	0.9120	0.9080	0.9043
0.60	0.7124	0.8889	0.8848	0.8811
0.70	0.7940	0.8664	0.8622	0.8586
0.80	0.8685	0.8446	0.8403	0.8366
0.90	0.9370	0.8234	0.8191	0.8154
1.00	1.0000	0.8024	0.7983	0.7950

[a] The mean standard deviation was 0.0001 $g\,cm^{-3}$

Molar volumes and excess molar volumes

Table 2 summarizes the molar volumes (V^0) for the binary mixtures at all temperatures. V^0 values were calculated from Eq. 1.

$$V^0 = \frac{x_1 M_1 + x_2 M_2}{\rho}$$

(Eq. 1)

where, x_1 and x_2 are the mole fractions and M_1 and M_2 are the molar masses, for both components respectively, and ρ is the mixture density.

Table 2. Molar volumes $(cm^3 \ mol^{-1})^a$ for all binary mixtures at various temperatures.

Ethanol (1) + Water (2)				
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	18.02	18.02	18.03
0.10	0.0416	19.46	19.48	19.50
0.20	0.0891	21.06	21.09	21.13
0.30	0.1435	22.89	22.96	23.03
0.40	0.2068	25.18	25.26	25.36
0.50	0.2811	27.98	28.09	28.20
0.60	0.3697	31.40	31.54	31.65
0.70	0.4771	35.65	35.81	35.94
0.80	0.6100	40.99	41.21	41.36
0.90	0.7787	47.94	48.19	48.39
1.00	1.0000	57.41	57.71	57.93
1,2-Propanediol (1) + Water (2)				
μ_{PD}	x_{PD}	278.15 K	283.15 K	288.15K
0.00	0.0000	18.02	18.02	18.03
0.10	0.0256	19.34	19.35	19.37
0.20	0.0559	20.88	20.91	20.94
0.30	0.0921	22.72	22.76	22.81
0.40	0.1363	24.99	25.05	25.11
0.50	0.1914	27.87	27.95	28.04
0.60	0.2621	31.65	31.75	31.86
0.70	0.3558	36.77	36.90	37.02

(*Continued*)

Table 2. Molar volumes (cm^3 mol^{-1})^a for all binary mixtures at various temperatures (*continuation*).

	Ethanol (1) + Water (2)			
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.80	0.4864	44.01	44.16	44.31
0.90	0.6806	54.88	55.06	55.26
1.00	1.0000	72.85	73.03	73.25
	Ethanol (1) + 1,2-Propanediol (2)			
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	72.85	73.03	73.25
0.10	0.1551	70.36	70.57	70.81
0.20	0.2923	68.17	68.40	68.64
0.30	0.4145	66.22	66.47	66.73
0.40	0.5241	64.48	64.75	65.00
0.50	0.6229	62.93	63.21	63.47
0.60	0.7124	61.54	61.82	62.08
0.70	0.7940	60.31	60.61	60.86
0.80	0.8685	59.22	59.52	59.78
0.90	0.9370	58.25	58.55	58.82
1.00	1.0000	57.41	57.71	57.95

^{a} The mean standard deviation 0.01 cm^3 mol^{-1}

On the other hand, the excess volumes ($V^{0\text{-Exc}}$) calculated from Eq. 2 (where, ρ_1 and ρ_2 are the densities of pure components) at all temperatures studied are presented in Table 3. This behavior is shown graphically in Figure 1 for the three systems at all temperatures.

$$V^{0\text{-Exc}} = \frac{x_1 M_1 + x_2 M_2}{\rho} - \left(\frac{x_1 M_1}{\rho_1} + \frac{x_2 M_2}{\rho_2} \right)$$

(Eq. 2)

Table 3. Excess molar volumes (cm^3 mol^{-1})^a for all binary mixtures at various temperatures.

|	Ethanol (1) + Water (2)			
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	0.000	0.000	0.000
0.10	0.0416	−0.200	−0.196	−0.188

(*Continued*)

Table 3. Excess molar volumes ($cm^3 mol^{-1}$)[a] for all binary mixtures at various temperatures (*continuation*).

		Ethanol (1) + Water (2)		
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.30	0.1435	−0.777	−0.755	−0.730
0.40	0.2068	−0.987	−0.965	−0.926
0.50	0.2811	−1.110	−1.090	−1.044
0.60	0.3697	−1.180	−1.152	−1.129
0.70	0.4771	−1.163	−1.143	−1.125
0.80	0.6100	−1.054	−1.024	−1.010
0.90	0.7787	−0.757	−0.732	−0.717
1.00	1.0000	0.000	0.000	0.000
		1,2-Propanediol (1) + Water (2)		
μ_{PD}	x_{PD}	278.15 K	283.15 K	288.15K
0.00	0.0000	0.000	0.000	0.000
0.10	0.0256	−0.083	−0.076	−0.075
0.20	0.0559	−0.195	−0.183	−0.177
0.30	0.0921	−0.344	−0.324	−0.309
0.40	0.1363	−0.505	−0.472	−0.448
0.50	0.1914	−0.642	−0.598	−0.562
0.60	0.2621	−0.733	−0.682	−0.640
0.70	0.3558	−0.755	−0.690	−0.654
0.80	0.4864	−0.681	−0.616	−0.576
0.90	0.6806	−0.455	−0.397	−0.353
1.00	1.0000	0.000	0.000	0.000
		Ethanol (1) + 1,2-Propanediol (2)		
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.00	0.0000	0.000	0.000	0.000
0.10	0.1551	−0.097	−0.081	−0.065
0.20	0.2923	−0.169	−0.150	−0.130
0.30	0.4145	−0.235	−0.203	−0.180
0.40	0.5241	−0.282	−0.250	−0.229
0.50	0.6229	−0.306	−0.279	−0.251
0.60	0.7124	−0.313	−0.289	−0.262
0.70	0.7940	−0.282	−0.259	−0.240

Table 3. Excess molar volumes ($cm^3\ mol^{-1}$)[a] for all binary mixtures at various temperatures (*continuation*).

	Ethanol (1) + 1,2-Propanediol (2)			
μ_{EtOH}	x_{EtOH}	278.15 K	283.15 K	288.15K
0.80	0.8685	−0.225	−0.201	−0.174
0.90	0.9370	−0.139	−0.121	−0.093
1.00	1.0000	0.000	0.000	0.000

[a] The mean standard deviation 0.01 $cm^3\ mol^{-1}$

(a) Ethanol + Water

EtOH mole fraction

(b) 1,2-Propanediol + Water

1,2-PD mole fraction
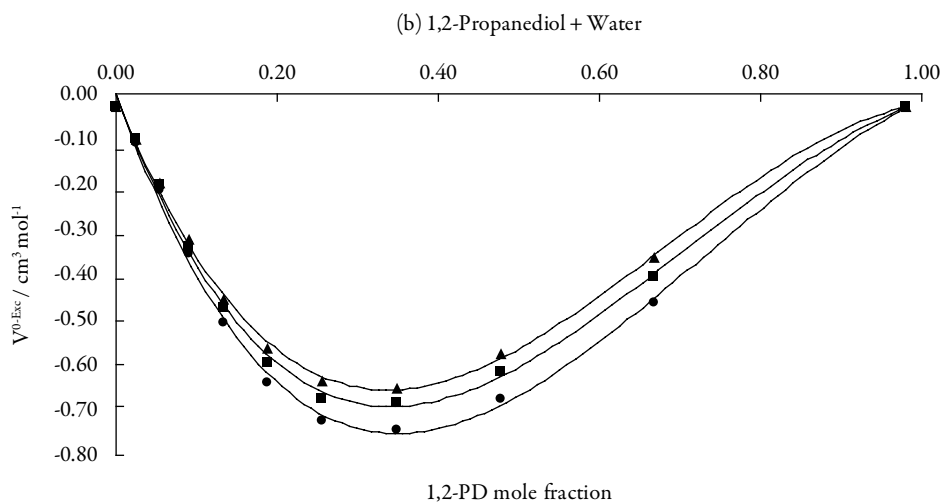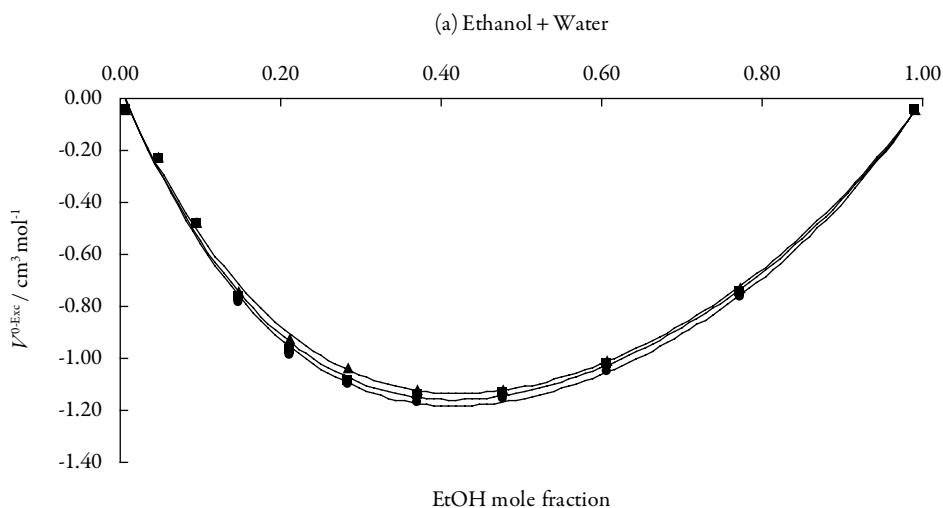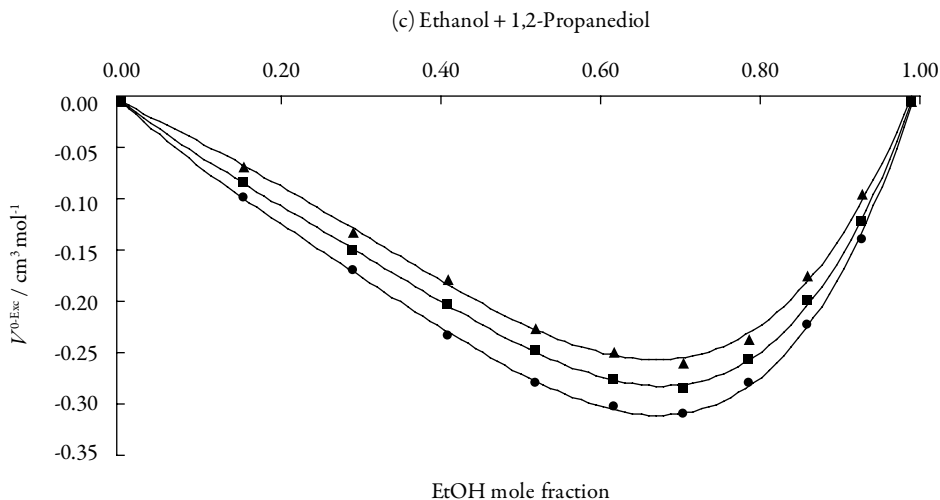
Figure 1. Excess molar volumes for all the binary mixtures at several temperatures. (●): 278.15 K; (■): 283.15 K; (▲): 288.15 K.

Analogous to the behavior obtained at upper temperatures (10-12), in all cases the excess volumes are negative indicating contraction in volume. As mentioned before (10-14), according to Fort and Moore (23), a negative excess volume is an indication of strong heteromolecular interactions in the liquid mixtures and is attributed to charge transfer, dipole-dipole, dipole-induced dipole interactions, and hydrogen bonding between the unlike components, while a positive sign indicates a weak interaction and is attributed to dispersion forces (London interactions) which are likely to be operative in all cases.

In the aqueous evaluated systems, where the hydrogen bonding predominates, the contraction in volume has been interpreted basically in qualitative terms considering the following events, first: expansion due to depolymerization of water by addition of cosolvent; second: contraction due to free volume difference of unlike molecules; and third: contraction due to hydrogen bond formation between cosolvent and water through –OH---OH bonding (23).

Thus, the large negative values of $V^{0\text{-Exc}}$ over the free volume contribution indicate the presence of strong specific interactions with predominance of formation of hydrogen bonds between cosolvent and water over the rupture of hydrogen bonding in water-water.

The excess molar volumes becomes less negative as the temperature is raised indicating volume expansion which points out the decrease in the interactions between cosolvent and water molecules with increase in temperature.

Correlation of excess molar volume by using the Redlich-Kister equation

Redlich and Kister (24) introduced in 1948 the general form of Eq. 3 to facilitate the representation of thermodynamic properties and the classification of solutions in multicomponent systems, especially those important in petroleum chemistry. The Redlich-Kister equation has been used in recent decades for manipulating several kinds of physicochemical values of mixtures such as: excess volumes, excess viscosities, solubilities in cosolvent mixtures, among others.

$$V^{0-\text{Exc}} = x_1 x_2 \sum a_i \left(x_1 - x_2 \right)^i \tag{Eq. 3}$$

In the analysis of excess volume data, Eq. 3 was used in the form of third degree polynomial equations using least square analyses, and therefore, obtaining four coefficients as presented in Eq. 4. Polynomials of second and third degrees are the most widely used in this case again, based on their relevant statistic parameters such as determination coefficients and standard deviations.

$$\frac{V^{0\text{-Exc}}}{x_1 x_2} = a_0 + a_1 \left(x_1 - x_2 \right) + a_2 \left(x_1 - x_2 \right)^2 + a_3 \left(x_1 - x_2 \right)^3 \tag{Eq. 4}$$

The Redlich-Kister parameters for the three mixtures at all temperatures studied are presented in Table 4 in addition to determination coefficients and standard deviations calculated according to Eq. 5 (where D is the number of compositions studied and N is the number of terms used in the regression, that is 9 and 4 respectively in this case). Eq. 5 has been widely used in the literature (7-16). Figure 2 shows the Redlich-Kister equation applied to excess molar volume data at all temperatures studied.

$$\sigma \left(V^{0\text{-Exc}} \right) = \sqrt{\frac{\sum \left(V_{\text{expt}}^{0\text{-Exc}} - V_{\text{calc}}^{0\text{-Exc}} \right)^2}{D - N}} \tag{Eq. 5}$$

Table 4. Redlich-Kister regression results for the excess molar volumes of all binary mixtures at various temperatures.

Ethanol (1) + Water (2)						
T / K	a_0	a_1	a_2	a_3	r^2	σ / cm^3 mol^{-1}
278.15	−4.5777	2.6201	−1.9795	−4.3671	0.8683	0.054
283.15	−4.4732	2.5887	−1.8839	−4.1846	0.8797	0.050
288.15	−4.4002	2.3606	−1.6425	−3.7622	0.8494	0.049
1,2-Propanediol (1) + Water (2)						
T / K	a_0	a_1	a_2	a_3	r^2	σ / cm^3 mol^{-1}
278.15	−2.4848	2.7835	−3.0877	−5.2267	0.9698	0.028
283.15	−2.2159	2.7705	−3.0834	−5.1935	0.9663	0.029
288.15	−2.0826	2.6760	−2.5346	−4.4295	0.9726	0.025
Ethanol (1) + 1,2-Propanediol (2)						
T / K	a_0	a_1	a_2	a_3	r^2	σ / cm^3 mol^{-1}
278.15	−1.0798	−0.7223	−0.5168	−0.3159	0.9973	0.005
283.15	−0.9695	−0.7667	−0.4320	−0.0739	0.9984	0.004
288.15	−0.8870	−0.8819	−0.2405	0.3658	0.9946	0.007

(a) Ethanol + Water

(b) 1,2-Propanediol + Water
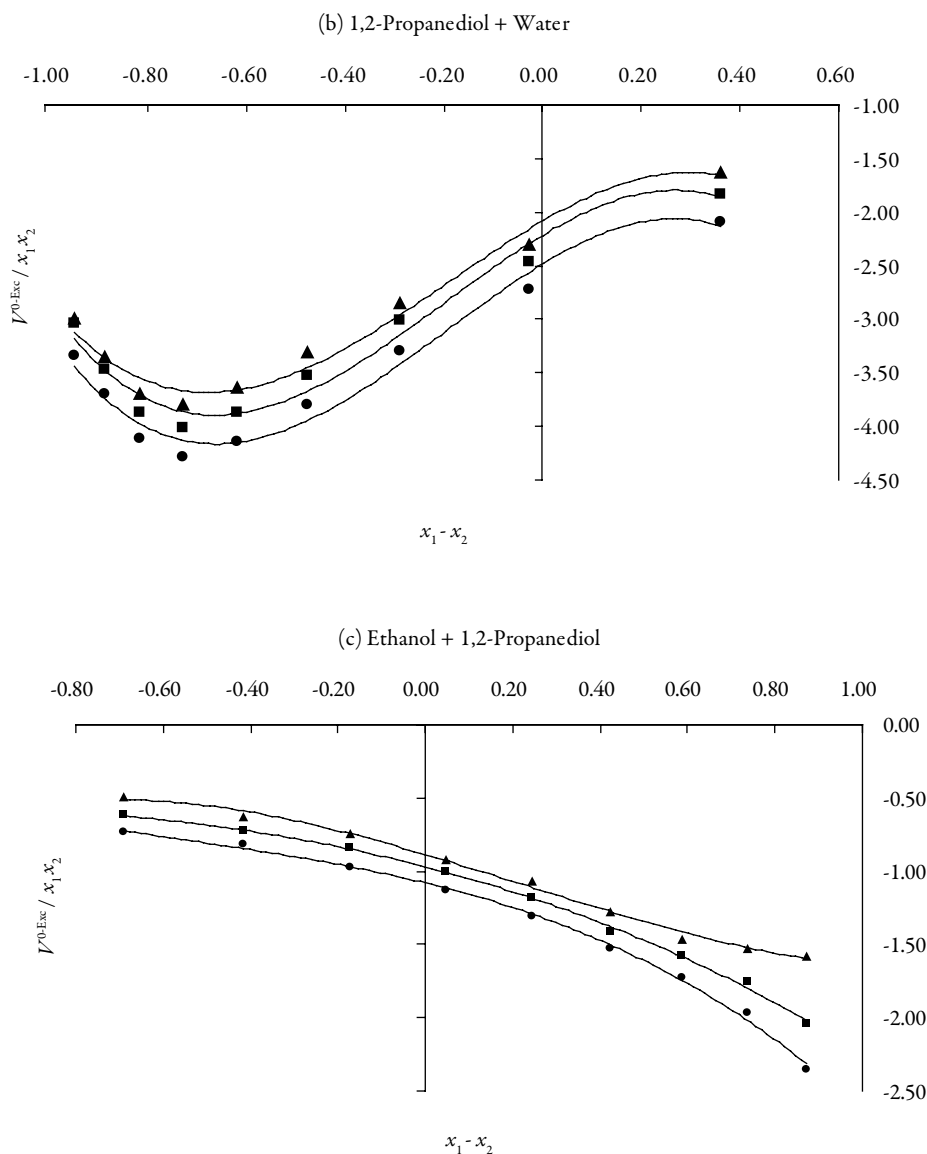

(c) Ethanol + 1,2-Propanediol
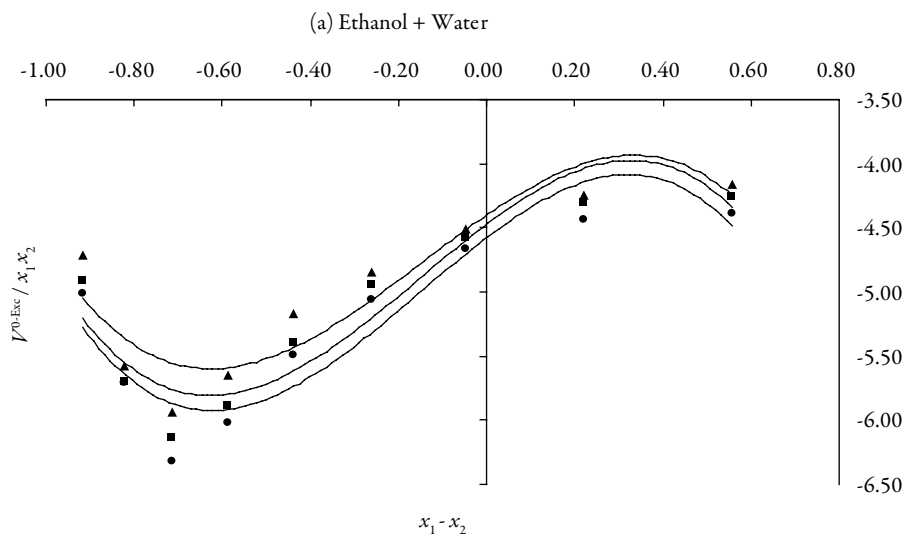
Figure 2. Regression adjusted to Redlich-Kister equation using four terms for all binary mixtures at several temperatures. (●): 278.15 K; (▪): 283.15 K; (▲): 288.15 K.

The coefficients of determinations are lower than 0.88 for ethanol (1) + water (2) mixtures, whereas they were greater than 0.96 and 0.99 for 1,2-propanediol (1) + water (2) and ethanol (1) + 1,2-propanediol (2) mixtures, respectively. These coefficients indicate that the obtained regular polynomials regressions describe adequately the excess

volumes for the last two kinds of mixtures because the standard deviations are similar to those presented in the literature for other mixtures (8, 10-15). For ethanol (1) + water (2) mixtures the behavior obtained was not satisfactory but it is similar to that obtained at upper temperatures (10). On the other hand, σ values obtained for all the binary mixtures are similar to those reported at temperatures from 293.15 to 313.15 K by using also third degree of regular polynomials (10, 12).

Data correlation using the Jouyban-Acree model

For binary data analyses, the Jouyban-Acree model was used to correlate the experimental density data of mixed solvents (15, 25):

$$\ln \rho_{m,T} = x_1 \ln \rho_{1,T} + x_2 \ln \rho_{2,T} + \frac{x_1 x_2}{T} \cdot \sum_{i=0}^{2} J_i \left(x_1 - x_2 \right)^i \qquad \text{(Eq. 6)}$$

where $\rho_{m,T}, \rho_{1,T}, \rho_{2,T}$ are densities of mixed solvents, solvents 1 and 2 at different temperatures (T), respectively. The x_1, x_2 are mole fractions of solvents 1 and 2, respectively. The methodology to find the J_i terms was described in previous works (15, 25). The main advantage of the Jouyban-Acree model over Redlich-Kister equation is that it includes the effects of temperature in the model constants and provides the possibility of density predictions at other temperatures using interpolation technique, whereas the constants of the Redlich-Kister equation is only valid for one temperature.

An adopted version of Eq. 6 could be used for representing the molar volume data of mixed solvents. The trained version of the model for glycerol + water mixtures (13) at various temperatures is:

$$\ln V_{m,T}^0 = x_1 \ln V_{1,T}^0 + x_2 \ln V_{2,T}^0 + \frac{x_1 x_2}{T} \cdot \sum_{i=0}^{2} M_i \left(x_1 - x_2 \right)^i \qquad \text{(Eq. 7)}$$

where $V_{m,T}^0$, $V_{1,T}^0$, $V_{2,T}^0$ are molar volumes of mixed solvents, solvents 1 and 2 at different temperatures and M_j are the model constants.

The mean relative deviation (MRD) between experimental and calculated data was calculated using:

$$MRD = \frac{100}{N} \left(\frac{\left| Calculated - Experimental \right|}{Experimental} \right) \qquad \text{(Eq. 8)}$$

where N in is the number of data points in the data set.

The computed model constants of the Jouyban-Acree model, the coefficients of determinations and MRD values for density and molar volume data of the investigated solvent systems are listed in Table 5. Careful examination of the results reveal that the model describes the density and molar volumes of the investigated solvent systems and could be recommended for practical applications where the simulation of such data is required in process design.

Table 5. The model constants of the Jouyban-Acree model, the coefficient of determinations and mean relative deviations for the density and molar volumes of the investigated binary mixtures.

Density					
Solvent system	J_0	J_1	J_2	r^2	MRD
Ethanol (1) + Water (2)	−25.066	-*	-	0.980	0.15
1,2-Propanediol (1) + Water (2)	29.141	−32.891	30.639	0.998	0.08
Ethanol (1) + 1,2-Propanediol (2)	31.614	9.204	3.194	>0.999	0.01
Molar volume					
	M_0	M_1	M_2	r^2	MRD
Ethanol (1) + Water (2)	129.807	-	-	0.905	1.9
1,2-Propanediol (1) + Water (2)	228.548	−65.117	-	0.960	2.1
Ethanol (1) + 1,2-Propanediol (2)	3.624	−3.406	−2.318	0.988	<0.1

* The constants were not statistically significant compared with that reported in the literature (25).

Conclusions

This report expands widely the experimental volumetric information about these three cosolvent binary systems available nowadays because it includes the behavior at other three temperatures commonly found in technological and storage conditions. As mentioned earlier, this information could be employed in several chemical engineering processes and for the theoretical understanding of the behavior of cosolvent mixtures used in the pharmaceutical industries. Based on the presented results and those reported in the literature, it can be concluded that these mixtures clearly show non ideal behavior. These observations demonstrate clearly that it is necessary to characterize systematically all possible pharmaceutical binary system in order to have complete experimental

information about the physical and chemical properties useful in the understanding of all kind of liquid pharmaceutical dosage systems.

Acknowledgments

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