STUDY OF SOME VOLUMETRIC PROPERTIES OF GLYCEROL FORMAL + ETHANOL MIXTURES AND CORRELATION WITH THE JOUYBAN-ACREE MODEL

Andrés R. Holguín[1], Daniel R. Delgado[1], Fleming Martínez[1]*, Mehri Khoubnasabjafari[2], Abolghasem Jouyban[3]

Abstract

Holguín, A. R., D. R. Delgado, F. Martínez, M. Khoubnasabjafari, A. Jouyban. Study of some volumetric properties of glycerol formal + ethanol mixtures and correlation with the Jouyban-acree model. Rev. Acad. Colomb. Cienc. **35** (136): 315-328, 2011. ISSN 0370-3908.

Molar volumes, excess molar volumes, and partial molar volumes were investigated for glycerol formal + ethanol mixtures by density measurements at several temperatures. Excess molar volumes are fitted by Redlich-Kister equation and compared with other systems. The system exhibits negative excess volumes probably due to increased H-bond interactions. Volume thermal expansion coefficients are also calculated. The Jouyban-Acree model was used for density and molar volume correlations at different temperatures. The mean relative deviations between experimental and calculated data were 0.03 ± 0.03% and 0.17 ± 0.13%, respectively for density and molar volume data. Also, using a minimum number of data points, the Jouyban-Acree model can predict density and molar volume with acceptable accuracies (0.03 ± 0.03% and 0.15 ± 0.12%, respectively).

Key words: glycerol formal; ethanol; binary liquid mixtures; excess volumes; partial volumes; Jouyban-Acree model.

Resumen

En este trabajo se calculan los volúmenes molares, molares de exceso y molares parciales a partir de valores de densidad para el sistema glicerol formal + etanol en todo el intervalo de composición a temperaturas entre 278,15 y 313,15 K. Los volúmenes molares de exceso se modelaron de acuerdo a la ecuación de Redlich-Kister y se compararon con los reportados para otros sistemas. El sistema estudiado presenta volúmenes de exceso negativos probablemente debido a

1 Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, A.A. 14490, Bogotá, D.C., Colombia.

* Correspondence: E-mail: fmartinezr@unal.edu.co

2 Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

3 Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

fuertes interacciones por unión de hidrógeno. También se analizó el efecto de la temperatura sobre las diferentes propiedades volumétricas estudiadas. Así mismo se calcularon los coeficientes térmicos de expansión volumétrica. Finalmente se usó el modelo Jouyban-Acree para correlacionar la densidad y el volumen molar de las diferentes mezclas encontrando desviaciones medias relativas de 0,03 ± 0,03% y 0,17 ± 0,13% para densidades y volúmenes molares respectivamente.

Palabras clave: glicerol formal; etanol; mezclas líquidas binarias; volúmenes de exceso; modelo de Jouyban-Acree.

Introduction

Non-aqueous solvent mixtures have sometimes been used in human and veterinarian pharmacy in order to increase the solubility of drugs poorly soluble in water during the design of injectable homogeneous dosage forms (**Rubino, J.T.**, 1988). Ethanol and propylene glycol are the cosolvents most used in design nowadays and sometimes have been employed blended (**Yalkowsky, S.H.**, 1999). Glycerol formal is a non-toxic and environmentally-friendly organic solvent (**Budavari, S.** ***et al.*** 2001), miscible with water, ethanol and propylene glycol in all possible compositions and has been widely used as cosolvent for veterinarian formulations such as those containing the antinematodal drug, ivermectin (**Lo, P.K.A.** ***et al.*** 1985; **DiPietro, J.A.** ***et al.*** 1986; **Reinemeyer, C.R. & Courtney, C.H.**, 2001). Glycerol formal is available as the mixture of 5-hydroxy-1,3-dioxane and 4-hydroxymethyl-1,3-dioxolane (60:40) and as the individual isomers (**Budavari, S.** ***et al.*** 2001; **Pivnichny, J.V.**, 1984).

The mixtures obtained using these cosolvents are non-ideal due to increased interactions between unlike molecules and differences in molar volumes of pure components, which leads to non-additive volumes on mixing (**Battino, R.**, 1971; **Kapadi, U.R.** ***et al.*** 2001). For this reason it is necessary to characterize the volumetric behavior of these binary mixtures as a function of composition and temperature in order to extend the physicochemical information available for liquid mixtures used in pharmacy. This information is useful to represent the intermolecular interactions present in liquid pharmaceutical systems and to facilitate the processes of medicines design at industrial level (**Jiménez, J.** ***et al.*** 2004).

In this report, the excess molar volumes and the partial molar volumes of the binary system of glycerol formal + ethanol at various temperatures as well as other volumetric properties are reported. The physicochemical properties reported here were calculated according to several mathematical procedures widely exposed in the literature (**Wahab, M.A.** ***et al.*** 2002; **Salas, J.A.** ***et al.*** 2002; **Peralta, R.D.** ***et al.*** 2003; **Resa, J.M.** ***et al.*** 2004). This work is a continuation of those presented previously about some volumetric properties of glycerol formal + water mixtures (**Delgado, D.R.** ***et al.*** 2011) and glycerol formal + propylene glycol mixtures (**Rodríguez, G.A.** ***et al.*** 2011).

Experimental

Materials

In this investigation glycerol formal (5-hydroxy-1,3-dioxane isomer) from Lambiotte & Cie S.A. was employed and is in agreement with the quality requirements indicated for veterinarian medicinal products. Density and refractive index of glycerol formal (ρ = 1.2214 g·cm^{-3} and n_D = 1.4535 at 298.15 K, respectively) were in good agreement with the values reported for the single 5-hydroxy-1,3dioxane isomer (ρ_4^{25}= 1.2200 g·cm^{-3} and n_D^{25}= 1.4527) (**Budavari, S.** ***et al.*** 2001). Figure 1 shows the molecular structure of 5-hydroxy-1,3-dioxane isomer . In the same way, dehydrated ethanol A.R. (Merck, Germany) was also used and is in agreement with the quality requirements indicated for medicinal products indicated in the American Pharmacopeia USP (**US Pharmacopeia**, 1994). The dehydrated glycerol formal and ethanol employed were maintained over molecular sieve to obtain dry solvents prior to prepare the solvent mixtures.

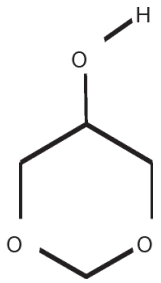

Figure 1. Molecular structure of glycerol formal (5-hydroxy-1,3-dioxane isomer).

Cosolvent mixtures preparation

All glycerol formal + ethanol 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 0.05 to 0.95 in mass fraction (varying in 0.05) of glycerol formal, to study 19 mixtures and the two pure solvents. This procedure implies an uncertainty of ± 2 x 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 313.15 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 (**Martínez, F.** ***et al.*** 2002). The equipment was calibrated according to Instruction Manual using air and water at the different temperatures studied (**Kratky, O.** ***et al.*** 1980). From density values, all thermodynamic properties were calculated as will be indicate in the next section.

Results and discussion

In order to define the solvents 1 and 2 in the binary mixtures according to polarity the Hildebrand solubility parameter (δ) of glycerol formal was calculated as 24.8 $MPa^{1/2}$ according to procedures described by **Barton, A.F.M.** (1991), which are presented in Table 1. Accordingly, glycerol formal is a solvent less polar compared with ethanol (δ value is 26.5 $MPa^{1/2}$, **Barton, A.F.M.,** 1991).

In Table 2 the composition of glycerol formal + ethanol, in mass (μ_{GF}) and mole (x_{GF}) fraction, in addition to studied density values at several temperatures, is presented. Figure 2 plotted experimental density data against fraction of glycerol formal and temperature.

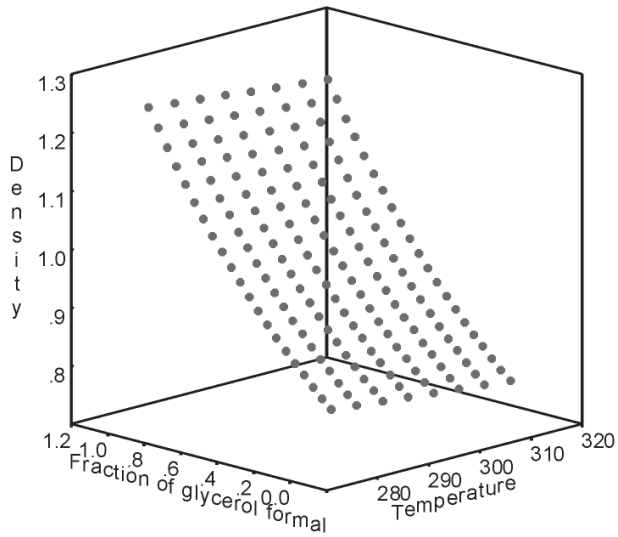

Figure 2. Experimental density values (g·cm^{-3}) in mixtures of glycerol formal + ethanol at different temperatures (K).

In the literature no values are available for this binary solvent system and therefore no direct comparison is possible. Nevertheless, it is important to remember that **Pineda, L.M.** ***et al.*** (2003) and **Arias, L.J.** ***et al.*** (2004) reported density values at 298.15 K for binary mixtures obtained employing material raw without any dehydration process, just as they are used in the pharmaceutical industries. Accordingly, the cosolvents studied by these authors had

Table 1. Hansen partial solubility parameters and total solubility parameter of glycerol formal (5-hydroxy-1,3-dioxane isomer).

Group or atom	Group Number	Van Krevelen		
		F_d / $J^{1/2}$ $cm^{3/2}$ mol^{-1} [a]	F_p^2 / J cm^3 mol^{-2} [a]	U_h / J mol^{-1} [a]
–OH	1	1 × 210	1 × $(500)^2$	1 × 20000
–O–	2	2 × 100	2 × $(400)^2$	2 × 3000
–CH_2–	3	3 × 270	3 × $(0)^2$	3 × 0
>CH–	1	1 × 80	1 × $(0)^2$	1 × 0
		1300	570000	26000
		δ_d = (1300/85.23) = 15.25 $MPa^{1/2}$ [b]	δ_p = $((570000)^{1/2}/85.23)$ = 8.86 $MPa^{1/2}$ [c]	δ_h = $(26000/85.23)^{1/2}$ = 14.47 $MPa^{1/2}$ [d]
		δ_T [e] = $(15.25^2 + 8.86^2 + 17.47^2)^{1/2}$ = 24.82 $MPa^{1/2}$		

[a] Calculated from values and procedures described by **Barton, A.F.M.** (1991).

[b] Dispersion parameter.

[c] Dipolar parameter.

[d] Hydrogen-bonding parameter.

[e] Total solubility parameter.

some low quantities of water, i.e. 0.31 % m/m and 6.52% m/m for glycerol formal and ethanol, respectively. Table 2 shows that in all cases the density increases as the glycerol formal proportion increases in the mixtures and it decreases linearly as the temperature increases. In the other hand, density values decrease as the ethanol proportion increases in the mixtures following concave parabolic trends

Molar volumes and excess molar volumes

In Table 3 the molar volumes (V^0) for binary mixtures at all studied temperatures are presented which were calculated from Equation (1).

$$V^0 = \frac{x_1 M_1 + x_2 M_2}{\rho} \quad (1)$$

Table 2. Densities [a, b] for glycerol formal + ethanol mixtures at various temperatures

Glycerol formal		Temperature / K							
μ_{GF}	x_{GF}	278.15		283.15		288.15		293.15	
		Exp.	Cal.	Exp.	Cal.	Exp.	Cal.	Exp.	Cal.
0.0000	0.0000	0.8035	0.8035	0.7990	0.7990	0.7946	0.7946	0.7895	0.7895
0.0500	0.0228	0.8174	0.8182	0.8132	0.8138	0.8089	0.8095	0.8047	0.8044
0.1000	0.0469	0.8331	0.8336	0.8286	0.8292	0.8246	0.8249	0.8202	0.8199
0.1500	0.0724	0.8494	0.8495	0.8449	0.8451	0.8408	0.8409	0.8364	0.8360
0.2000	0.0996	0.8661	0.8660	0.8616	0.8617	0.8574	0.8575	0.8531	0.8526
0.2500	0.1285	0.8832	0.8832	0.8789	0.8789	0.8747	0.8748	0.8704	0.8700
0.3000	0.1594	0.9011	0.9011	0.8968	0.8968	0.8925	0.8927	0.8882	0.8879
0.3500	0.1924	0.9197	0.9196	0.9156	0.9154	0.9112	0.9113	0.9069	0.9066
0.4000	0.2278	0.9395	0.9389	0.9352	0.9347	0.9308	0.9307	0.9264	0.9260
0.4500	0.2658	0.9596	0.9589	0.9552	0.9548	0.9509	0.9508	0.9464	0.9461
0.5000	0.3068	0.9803	0.9798	0.9760	0.9756	0.9716	0.9716	0.9672	0.9670
0.5500	0.3510	1.0019	1.0014	0.9976	0.9972	0.9932	0.9933	0.9889	0.9887
0.6000	0.3990	1.0243	1.0239	1.0199	1.0197	1.0156	1.0158	1.0114	1.0112
0.6500	0.4511	1.0476	1.0473	1.0433	1.0431	1.0389	1.0392	1.0346	1.0346
0.7000	0.5080	1.0722	1.0716	1.0680	1.0674	1.0636	1.0635	1.0592	1.0590
0.7500	0.5704	1.0973	1.0969	1.0930	1.0927	1.0887	1.0888	1.0841	1.0842
0.8000	0.6390	1.1236	1.1232	1.1192	1.1189	1.1147	1.1150	1.1104	1.1105
0.8500	0.7149	1.1511	1.1505	1.1472	1.1463	1.1428	1.1423	1.1382	1.1378
0.9000	0.7993	1.1796	1.1789	1.1751	1.1746	1.1710	1.1707	1.1664	1.1661
0.9500	0.8937	1.2092	1.2085	1.2049	1.2042	1.2002	1.2002	1.1957	1.1956
1.0000	1.0000	1.2393	1.2393	1.2349	1.2349	1.2309	1.2309	1.2263	1.2263
μ_{GF}	x_{GF}	298.15		303.15		308.15		313.15	
		Exp.	Cal.	Exp.	Cal.	Exp.	Cal.	Exp.	Cal.
0.0000	0.0000	0.7853	0.7853	0.7811	0.7811	0.7767	0.7767	0.7720	0.7720
0.0500	0.0228	0.8004	0.8002	0.7961	0.7961	0.7918	0.7917	0.7875	0.7870
0.1000	0.0469	0.8158	0.8157	0.8117	0.8116	0.8071	0.8073	0.8027	0.8026
0.1500	0.0724	0.8321	0.8318	0.8278	0.8277	0.8233	0.8234	0.8190	0.8188
0.2000	0.0996	0.8487	0.8485	0.8444	0.8444	0.8401	0.8402	0.8354	0.8356
0.2500	0.1285	0.8660	0.8658	0.8617	0.8617	0.8573	0.8576	0.8528	0.8530
0.3000	0.1594	0.8839	0.8838	0.8798	0.8797	0.8753	0.8756	0.8709	0.8710
0.3500	0.1924	0.9025	0.9024	0.8982	0.8983	0.8944	0.8943	0.8896	0.8897
0.4000	0.2278	0.9219	0.9218	0.9176	0.9177	0.9131	0.9137	0.9089	0.9091
0.4500	0.2658	0.9419	0.9419	0.9376	0.9378	0.9331	0.9339	0.9288	0.9293
0.5000	0.3068	0.9628	0.9628	0.9583	0.9586	0.9539	0.9547	0.9496	0.9501
0.5500	0.3510	0.9843	0.9844	0.9799	0.9803	0.9755	0.9764	0.9714	0.9718
0.6000	0.3990	1.0069	1.0069	1.0023	1.0027	0.9980	0.9989	0.9941	0.9943
0.6500	0.4511	1.0300	1.0303	1.0255	1.0261	1.0213	1.0223	1.0167	1.0176
0.7000	0.5080	1.0546	1.0546	1.0501	1.0503	1.0458	1.0466	1.0420	1.0419
0.7500	0.5704	1.0796	1.0798	1.0751	1.0754	1.0706	1.0718	1.0665	1.0670
0.8000	0.6390	1.1060	1.1060	1.1014	1.1016	1.0972	1.0979	1.0932	1.0932
0.8500	0.7149	1.1338	1.1332	1.1295	1.1287	1.1250	1.1251	1.1214	1.1203
0.9000	0.7993	1.1616	1.1615	1.1575	1.1569	1.1539	1.1533	1.1490	1.1484
0.9500	0.8937	1.1913	1.1908	1.1868	1.1862	1.1822	1.1826	1.1778	1.1777
1.0000	1.0000	1.2214	1.2214	1.2167	1.2167	1.2131	1.2131	1.2081	1.2081

[a] Unit: $g.cm^{-3}$. [b] The mean standard deviation was 0.0001 $g.cm^{-3}$

where M_1 and M_2 are the molar masses, for both components respectively (104.10 g·mol^{-1} for glycerol formal and 46.07 g·mol^{-1} for ethanol, **Budavari, S. *et al.*** 2001), x_1 and x_2 are the respective mole fraction of components, and ρ is the mixture density. Figure 3 shows the molar volume as a function of mixtures composition and temperature.

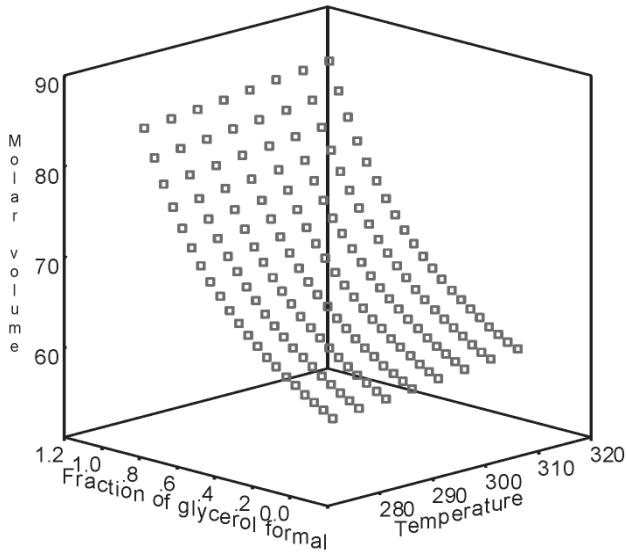

Figure 3. Experimental molar volumes (cm^3·mol^{-1}) in mixtures of glycerol formal + ethanol at different temperatures (K).

On the other hand, the excess molar volumes ($V^{0\text{-E}}$) calculated from Equation (2) (where, ρ_1 and ρ_2 are the densities of pure components) at all studied temperatures, are also presented in Table 3. This behavior is shown graphically in Figure 4 at all studied temperatures.

$$V^{0-\mathrm{E}} = \frac{x_1 M_1 + x_2 M_2}{\rho} - \left(\frac{x_1 M_1}{\rho_1} + \frac{x_2 M_2}{\rho_2} \right) \quad (2)$$

In similar way to the behavior obtained in other similar investigations developed in our reseach group with other solvent systems (**Jiménez, J. *et al.*** 2004; **Jiménez, J. & Martínez, F.** 2005, 2006; **Ruidiaz, M.A. & Martínez, F.**, 2009; **Rodríguez, S.J. *et al.*** 2010), in almost all cases the excess volumes are negative (especially around 0.60-0.70 in mole fraction of glycerol formal, where it is approximately equal to –0.60 cm^3·mol^{-1} at 313.15 K) indicating contraction in volume, except at 278.15 and 283.15 K in the mixture with composition 0.05 in mass fraction of glycerol formal where positive values near to 0.03 cm^3·mol^{-1} were obtained. It is interesting to note that glycerol formal + water mixtures

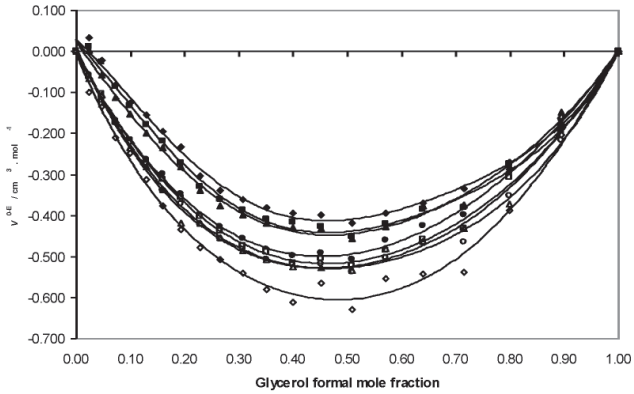

Figure 4. Excess molar volumes of glycerol formal + ethanol mixtures at several temperatures. (♦): 278.15 K; (■): 283.15 K; (▲): 288.15 K; (•): 293.15 K; (□): 298.15 K;(○): 303.15 K; (Δ): 308.15 K; (◇): 313.15 K.

exhibited negative excess volumes (**Delgado, D.R. *et al.*** 2011) whereas glycerol formal + propylene glycol exhibited positive excess volumes (**Rodríguez, G.A. *et al.*** 2011).

As was already said (**Jiménez, J & Martínez, F.**, 2005, 2006; **Delgado, D.R. *et al.*** 2011), according to **Fort, R.T. & Moore, W.R.** (1966), 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 every cases.

In the evaluated system, 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 glycerol formal and ethanol by one another, second: contraction due to free volume difference of unlike molecules, and third: contraction due to hydrogen bond formation between glycerol formal and ethanol through –OH---O< or –OH---OH bonding.

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

The excess molar volumes become more positive as the temperature although this result is not clear at molecular level.

Table 3. Experimental and calculated molar volumes, excess molar volumes, and partial molar volumes of components for glycerol formal + ethanol mixtures at various temperatures.

T / K	Glycerol formal		$V^{0\ a,b}$		$V^{0\text{-E}\ a,b}$	$\left(\frac{\partial V}{\partial \mu_{GF}}\right)^{a}$	$\overline{V}^{0}_{GF}{}^{a\,b}$	$\overline{V}^{0}_{EtOH}{}^{a,b}$
	μ_{GF}	x_{GF}	Exp.	Cal.				
	0.0000	0.0000	57.34	57.34	0.000	–0.4633	81.33	57.34
	0.0500	0.0228	57.98	57.86	0.034	–0.4610	81.77	57.42
	0.1000	0.0469	58.56	58.43	–0.022	–0.4587	81.99	57.41
	0.1500	0.0724	59.19	59.05	–0.081	–0.4564	82.18	57.39
	0.2000	0.0996	59.87	59.71	–0.126	–0.4540	82.39	57.38
	0.2500	0.1285	60.61	60.42	–0.155	–0.4517	82.60	57.37
	0.3000	0.1594	61.39	61.18	–0.194	–0.4494	82.78	57.34
	0.3500	0.1924	62.24	62.00	–0.233	–0.4471	82.94	57.30
	0.4000	0.2278	63.11	62.89	–0.302	–0.4447	83.03	57.23
	0.4500	0.2658	64.09	63.84	–0.339	–0.4424	83.16	57.18
278.15	0.5000	0.3068	65.16	64.89	–0.360	–0.4401	83.29	57.13
	0.5500	0.3510	66.32	66.02	–0.382	–0.4378	83.40	57.08
	0.6000	0.3990	67.58	67.27	–0.394	–0.4355	83.50	57.01
	0.6500	0.4511	68.97	68.65	–0.399	–0.4331	83.59	56.95
	0.7000	0.5080	70.46	70.17	–0.419	–0.4308	83.64	56.86
	0.7500	0.5704	72.15	71.86	–0.395	–0.4285	83.72	56.79
	0.8000	0.6390	74.01	73.75	–0.369	–0.4262	83.78	56.71
	0.8500	0.7149	76.07	75.87	–0.334	–0.4238	83.82	56.62
	0.9000	0.7993	78.38	78.26	–0.271	–0.4215	83.87	56.53
	0.9500	0.8937	80.99	80.95	–0.176	–0.4192	83.91	56.45
	1.0000	1.0000	84.00	84.00	0.000	–0.4169	84.00	56.38
	0.0000	0.0000	57.66	57.66	0.000	–0.4690	81.47	57.66
	0.0500	0.0228	58.28	58.19	0.011	–0.4665	81.88	57.73
	0.1000	0.0469	58.88	58.77	–0.026	–0.4640	82.16	57.74
	0.1500	0.0724	59.50	59.39	–0.087	–0.4615	82.37	57.72
	0.2000	0.0996	60.18	60.06	–0.134	–0.4591	82.59	57.70
	0.2500	0.1285	60.91	60.77	–0.178	–0.4566	82.80	57.68
	0.3000	0.1594	61.69	61.54	–0.219	–0.4541	82.99	57.65
	0.3500	0.1924	62.51	62.36	–0.272	–0.4516	83.14	57.60
	0.4000	0.2278	63.40	63.25	–0.330	–0.4491	83.26	57.54
	0.4500	0.2658	64.38	64.22	–0.360	–0.4467	83.41	57.49
283.15	0.5000	0.3068	65.44	65.26	–0.389	–0.4442	83.54	57.43
	0.5500	0.3510	66.60	66.40	–0.411	–0.4417	83.66	57.37
	0.6000	0.3990	67.87	67.65	–0.416	–0.4392	83.78	57.31
	0.6500	0.4511	69.25	69.03	–0.427	–0.4367	83.87	57.24
	0.7000	0.5080	70.74	70.55	–0.452	–0.4343	83.91	57.14
	0.7500	0.5704	72.43	72.23	–0.421	–0.4318	84.01	57.07
	0.8000	0.6390	74.30	74.12	–0.386	–0.4293	84.08	56.99
	0.8500	0.7149	76.32	76.23	–0.382	–0.4268	84.08	56.87
	0.9000	0.7993	78.68	78.60	–0.275	–0.4243	84.17	56.80
	0.9500	0.8937	81.28	81.27	–0.189	–0.4219	84.21	56.70
	1.0000	1.0000	84.30	84.30	0.000	–0.4194	84.30	56.63
	0.0000	0.0000	57.98	57.98	0.000	–0.4734	81.73	57.98
	0.0500	0.0228	58.59	58.52	0.003	–0.4708	82.13	58.04
	0.1000	0.0469	59.17	59.10	–0.057	–0.4683	82.37	58.03
	0.1500	0.0724	59.79	59.73	–0.113	–0.4658	82.60	58.01
	0.2000	0.0996	60.47	60.40	–0.154	–0.4632	82.84	58.00
	0.2500	0.1285	61.20	61.12	–0.199	–0.4607	83.05	57.98
	0.3000	0.1594	61.99	61.89	–0.234	–0.4581	83.26	57.95
	0.3500	0.1924	62.82	62.72	–0.281	–0.4556	83.42	57.91
288.15	0.4000	0.2278	63.70	63.61	–0.339	–0.4531	83.54	57.84
	0.4500	0.2658	64.67	64.58	–0.377	–0.4505	83.68	57.79
	0.5000	0.3068	65.74	65.63	–0.398	–0.4480	83.83	57.74
	0.5500	0.3510	66.90	66.77	–0.419	–0.4454	83.95	57.67
	0.6000	0.3990	68.16	68.02	–0.430	–0.4429	84.06	57.60
	0.6500	0.4511	69.54	69.39	–0.432	–0.4404	84.16	57.53
	0.7000	0.5080	71.03	70.91	–0.456	–0.4378	84.21	57.43
	0.7500	0.5704	72.72	72.59	–0.428	–0.4353	84.29	57.36
	0.8000	0.6390	74.60	74.46	–0.376	–0.4327	84.38	57.28

Continuation Table 3.

T / K	Glycerol formal		$V^{0\ a,b}$		$V^{0\text{-E}\ a,b}$	$\left(\frac{\partial V}{\partial \mu_{GF}}\right)^{a}$	$\overline{V}^{0}_{GF}{}^{a\,b}$	$\overline{V}^{0}_{EtOH}{}^{a,b}$
	μ_{GF}	x_{GF}	Exp.	Cal.				
	0.8500	0.7149	76.62	76.56	–0.375	–0.4302	84.38	57.16
	0.9000	0.7993	78.96	78.92	–0.282	–0.4276	84.45	57.07
	0.9500	0.8937	81.60	81.57	–0.149	–0.4251	84.53	56.99
	1.0000	1.0000	84.58	84.58	0.000	–0.4226	84.58	56.90
	0.0000	0.0000	58.35	58.35	0.000	–0.4803	81.86	58.35
	0.0500	0.0228	58.89	58.89	–0.065	–0.4774	82.15	58.35
	0.1000	0.0469	59.49	59.48	–0.112	–0.4746	82.46	58.36
	0.1500	0.0724	60.11	60.11	–0.168	–0.4718	82.72	58.34
	0.2000	0.0996	60.78	60.79	–0.218	–0.4690	82.97	58.32
	0.2500	0.1285	61.50	61.51	–0.264	–0.4662	83.21	58.30
	0.3000	0.1594	62.29	62.29	–0.299	–0.4634	83.44	58.27
	0.3500	0.1924	63.11	63.12	–0.347	–0.4606	83.63	58.23
	0.4000	0.2278	64.00	64.01	–0.398	–0.4578	83.78	58.17
	0.4500	0.2658	64.98	64.98	–0.428	–0.4550	83.95	58.11
293.15	0.5000	0.3068	66.04	66.03	–0.455	–0.4521	84.10	58.05
	0.5500	0.3510	67.19	67.17	–0.482	–0.4493	84.22	57.97
	0.6000	0.3990	68.44	68.42	–0.498	–0.4465	84.34	57.89
	0.6500	0.4511	69.83	69.79	–0.492	–0.4437	84.46	57.82
	0.7000	0.5080	71.33	71.30	–0.506	–0.4409	84.52	57.71
	0.7500	0.5704	73.03	72.98	–0.461	–0.4381	84.63	57.63
	0.8000	0.6390	74.89	74.84	–0.426	–0.4353	84.69	57.53
	0.8500	0.7149	76.93	76.93	–0.399	–0.4325	84.71	57.41
	0.9000	0.7993	79.27	79.27	–0.299	–0.4296	84.78	57.31
	0.9500	0.8937	81.91	81.91	–0.165	–0.4268	84.84	57.21
	1.0000	1.0000	84.89	84.89	0.000	–0.4240	84.89	57.10
	0.0000	0.0000	58.67	58.67	0.000	–0.4848	82.10	58.67
	0.0500	0.0228	59.21	59.22	–0.061	–0.4819	82.41	58.67
	0.1000	0.0469	59.81	59.82	–0.104	–0.4790	82.73	58.68
	0.1500	0.0724	60.42	60.46	–0.172	–0.4761	82.98	58.66
	0.2000	0.0996	61.09	61.14	–0.217	–0.4732	83.25	58.64
	0.2500	0.1285	61.81	61.87	–0.268	–0.4704	83.49	58.62
	0.3000	0.1594	62.59	62.65	–0.313	–0.4675	83.71	58.58
	0.3500	0.1924	63.42	63.49	–0.357	–0.4646	83.91	58.54
	0.4000	0.2278	64.31	64.39	–0.404	–0.4617	84.08	58.48
	0.4500	0.2658	65.29	65.36	–0.438	–0.4588	84.25	58.42
298.15	0.5000	0.3068	66.34	66.41	–0.474	–0.4559	84.39	58.35
	0.5500	0.3510	67.50	67.56	–0.490	–0.4531	84.54	58.28
	0.6000	0.3990	68.75	68.81	–0.516	–0.4502	84.64	58.20
	0.6500	0.4511	70.15	70.18	–0.505	–0.4473	84.77	58.12
	0.7000	0.5080	71.64	71.69	–0.522	–0.4444	84.84	58.02
	0.7500	0.5704	73.33	73.37	–0.485	–0.4415	84.94	57.93
	0.8000	0.6390	75.18	75.23	–0.458	–0.4386	84.99	57.82
	0.8500	0.7149	77.23	77.31	–0.433	–0.4358	85.01	57.70
	0.9000	0.7993	79.60	79.64	–0.307	–0.4329	85.12	57.61
	0.9500	0.8937	82.21	82.27	–0.200	–0.4300	85.15	57.49
	1.0000	1.0000	85.23	85.23	0.000	–0.4271	85.23	57.40
	0.0000	0.0000	58.98	58.98	0.000	–0.4893	82.34	58.98
	0.0500	0.0228	59.53	59.54	–0.057	–0.4863	82.67	58.99
	0.1000	0.0469	60.11	60.14	–0.118	–0.4834	82.97	58.98
	0.1500	0.0724	60.73	60.79	–0.175	–0.4804	83.25	58.97
	0.2000	0.0996	61.41	61.48	–0.223	–0.4775	83.52	58.96
303.15	0.2500	0.1285	62.12	62.21	–0.276	–0.4745	83.76	58.93
	0.3000	0.1594	62.88	63.00	–0.338	–0.4716	83.96	58.88
	0.3500	0.1924	63.73	63.85	–0.371	–0.4686	84.19	58.85
	0.4000	0.2278	64.62	64.75	–0.421	–0.4657	84.37	58.79
	0.4500	0.2658	65.59	65.73	–0.457	–0.4627	84.54	58.73
	0.5000	0.3068	66.65	66.79	–0.483	–0.4597	84.70	58.66

Continuation Table 3.

T / K	Glycerol formal		$V^{0\ a,b}$		$V^{0\text{-E}\ a,b}$	$\left(\frac{\partial V}{\partial \mu_{GF}}\right)^{a}$	$\bar{V}^{0}_{GF}{}^{a\,b}$	$\bar{V}^{0}_{EtOH}{}^{a,b}$
	μ_{GF}	x_{GF}	Exp.	Cal.				
	0.5500	0.3510	67.80	67.93	–0.508	–0.4568	84.84	58.59
	0.6000	0.3990	69.07	69.19	–0.521	–0.4538	84.97	58.51
	0.6500	0.4511	70.45	70.56	–0.519	–0.4509	85.09	58.43
	0.7000	0.5080	71.95	72.07	–0.537	–0.4479	85.15	58.32
	0.7500	0.5704	73.64	73.75	–0.502	–0.4450	85.25	58.23
	0.8000	0.6390	75.50	75.61	–0.468	–0.4420	85.32	58.12
	0.8500	0.7149	77.52	77.68	–0.464	–0.4391	85.31	57.98
	0.9000	0.7993	79.88	80.00	–0.351	–0.4361	85.40	57.88
	0.9500	0.8937	82.52	82.61	–0.217	–0.4332	85.46	57.78
	1.0000	1.0000	85.56	85.56	0.000	–0.4302	85.56	57.69
	0.0000	0.0000	59.32	59.32	0.000	–0.4946	82.54	59.32
	0.0500	0.0228	59.85	59.88	–0.066	–0.4916	82.86	59.32
	0.1000	0.0469	60.45	60.49	–0.106	–0.4886	83.21	59.33
	0.1500	0.0724	61.06	61.14	–0.171	–0.4855	83.48	59.31
	0.2000	0.0996	61.72	61.83	–0.235	–0.4825	83.74	59.28
	0.2500	0.1285	62.44	62.57	–0.281	–0.4795	84.00	59.26
	0.3000	0.1594	63.20	63.36	–0.337	–0.4764	84.22	59.22
	0.3500	0.1924	64.00	64.21	–0.419	–0.4734	84.36	59.14
	0.4000	0.2278	64.93	65.11	–0.419	–0.4703	84.63	59.12
	0.4500	0.2658	65.91	66.09	–0.454	–0.4673	84.81	59.06
308.15	0.5000	0.3068	66.96	67.15	–0.485	–0.4643	84.97	58.99
	0.5500	0.3510	68.11	68.29	–0.508	–0.4612	85.11	58.91
	0.6000	0.3990	69.36	69.54	–0.526	–0.4582	85.23	58.83
	0.6500	0.4511	70.74	70.91	–0.527	–0.4552	85.35	58.74
	0.7000	0.5080	72.24	72.42	–0.535	–0.4521	85.42	58.63
	0.7500	0.5704	73.95	74.09	–0.481	–0.4491	85.55	58.55
	0.8000	0.6390	75.79	75.94	–0.462	–0.4461	85.59	58.43
	0.8500	0.7149	77.83	78.00	–0.431	–0.4430	85.62	58.30
	0.9000	0.7993	80.13	80.31	–0.372	–0.4400	85.64	58.17
	0.9500	0.8937	82.84	82.90	–0.158	–0.4370	85.79	58.09
	1.0000	1.0000	85.82	85.82	0.000	–0.4339	85.82	57.97
	0.0000	0.0000	59.68	59.68	0.000	–0.5021	82.58	59.68
	0.0500	0.0228	60.18	60.25	–0.100	–0.4987	82.87	59.65
	0.1000	0.0469	60.78	60.86	–0.136	–0.4954	83.27	59.68
	0.1500	0.0724	61.38	61.52	–0.211	–0.4921	83.57	59.65
	0.2000	0.0996	62.07	62.21	–0.248	–0.4888	83.91	59.65
	0.2500	0.1285	62.77	62.96	–0.312	–0.4855	84.17	59.61
	0.3000	0.1594	63.52	63.75	–0.377	–0.4822	84.40	59.56
	0.3500	0.1924	64.34	64.60	–0.434	–0.4788	84.62	59.51
	0.4000	0.2278	65.23	65.51	–0.478	–0.4755	84.84	59.45
	0.4500	0.2658	66.21	66.49	–0.508	–0.4722	85.05	59.39
313.15	0.5000	0.3068	67.26	67.55	–0.541	–0.4689	85.22	59.32
	0.5500	0.3510	68.40	68.70	–0.579	–0.4656	85.36	59.22
	0.6000	0.3990	69.63	69.95	–0.612	–0.4622	85.47	59.12
	0.6500	0.4511	71.06	71.32	–0.566	–0.4589	85.67	59.06
	0.7000	0.5080	72.51	72.83	–0.629	–0.4556	85.68	58.91
	0.7500	0.5704	74.23	74.49	–0.554	–0.4523	85.84	58.82
	0.8000	0.6390	76.07	76.34	–0.542	–0.4490	85.88	58.69
	0.8500	0.7149	78.08	78.39	–0.538	–0.4456	85.88	58.53
	0.9000	0.7993	80.47	80.69	–0.387	–0.4423	86.00	58.44
	0.9500	0.8937	83.15	83.27	–0.204	–0.4390	86.10	58.33
	1.0000	1.0000	86.17	86.17	0.000	–0.4357	86.17	58.21

[a] Units: $cm^3 \cdot mol^{-1}$. [b] The mean standard deviation for V^0 and $V^{0\text{-E}}$ was 0.01 $cm^3 \cdot mol^{-1}$ while for and $\bar{V}^0_{EtOH}$ and was close to 0.03 $cm^3 \cdot mol^{-1}$

Partial molar volumes

The partial specific volumes of glycerol formal ($\bar{V}_{GF}$) and ethanol ($\bar{V}_{EtOH}$) were calculated using the classical Bakhuis-Roozeboom method by means of equations (3) and (4) applied to the variation of the respective specific volumes as a function of glycerol formal mass fraction (Reciprocal of densities reported in Table 3 and presented in Figure 5 at four temperatures) and adjusting them to second degree polynomials by least squares regression analyses (**Kestin, J.**, 1979; **Perrot, P.**, 1998). The first derivatives were taken out on the polynomials obtained and solved at each composition point.

$$\bar{V}_{GF} = V + \mu_{EtOH}\frac{dV}{d\mu_{GF}} \quad (3)$$

$$\bar{V}_{EtOH} = V - \mu_{GF}\frac{dV}{d\mu_{GF}} \quad (4)$$

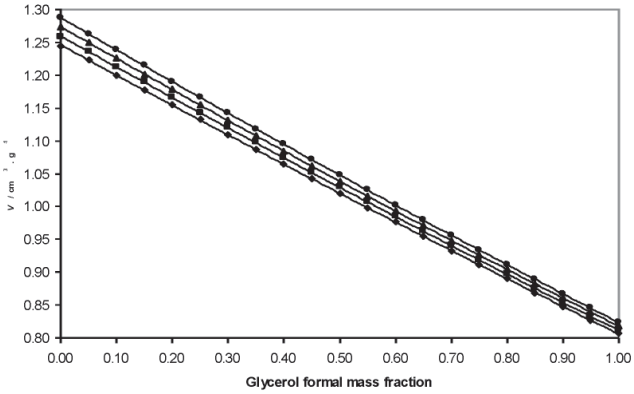

Figure 5. Specific volume of glycerol formal + ethanol mixtures as a function of the mixtures composition at several temperatures. 278.15 K (♦), 288.15 (■), 298.15 K (▲), 308.15 (•).

The partial molar volumes were calculated from the respective partial specific volumes multiplied by the molar masses. The $\bar{V}^0_{GF}$ and $\bar{V}^0_{EtOH}$ values are also presented in Table 3 in addition to the slopes obtained ($dV/d\mu_{GF}$) at each composition and temperature. In all cases the partial molar volumes of glycerol formal are lower than those obtained for the pure solvent at all temperatures. In the other hand, the partial molar volumes of ethanol are greater than those for the pure solvent in the mixtures where this cosolvent is in great proportion ($0.00 < \mu_{GF} < 0.30$) but they are lower in the other mixtures ($0.30 < \mu_{GF} < 1.00$). In cosolvent mixtures, the partial volumes for glycerol formal varied from 81.77 $cm^3 \cdot mol^{-1}$ (for $\mu_{GF} = 0.05$ at 278.15 K) to 86.10 $cm^3 \cdot mol^{-1}$ (for $\mu_{GF} = 0.95$ at 313.15 K), and for ethanol varied from 56.45 $cm^3 \cdot mol^{-1}$ (for $\mu_{GF} = 0.95$ at 278.15 K) to 59.68 $cm^3 \cdot mol^{-1}$ (for $\mu_{GF} = 0.10$ at 313.15 K). The results obtained for $\bar{V}^0_{GF}$ and $\bar{V}^0_{EtOH}$ are in agreement with the negative excess volumes obtained. The variation of this property is presented in Figure 6 as a function of glycerol formal mole fraction at 298.15 K for glycerol formal and ethanol, respectively. These values were calculated as the difference between partial molar volumes and molar volumes presented in Table 3. For both solvents the partial molar volume diminishes as their respective proportion in the mixtures diminishes, except for ethanol in those mixtures where it is in great proportion.

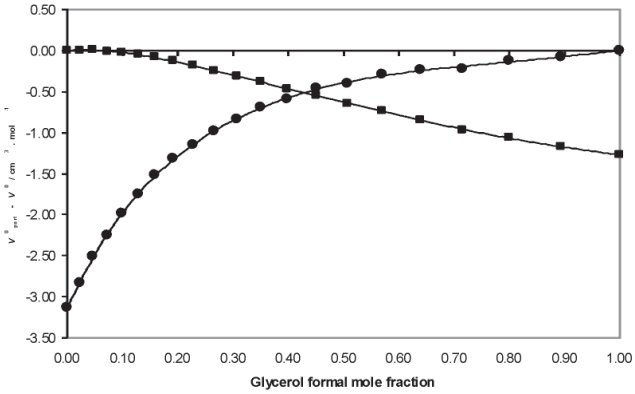

Figure 6. Partial molar volumes of glycerol formal (•) and ethanol (■) calculated as differences respect to pure solvent volumes in glycerol formal + ethanol mixtures at 298.15 K.

Redlich-Kister equation

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 (**Redlich, O. & Kister, A.T.**, 1948). When applied to excess molar volumes is presented as Equation (5),

$$V^{0-E} = x_1 x_2 \sum a_i (x_1 - x_2)^i \quad (5)$$

where x_1 and x_2 are the respective mole fractions.

In the analysis of our data about excess volumes, the Equation (5) was used in the form of third degree polynomial equations using least square analyses, obtaining four coefficients as presented in Equation (6).

$$\frac{V^{0-E}}{x_1 x_2} = a_0 + a_1(x_1 - x_2) + a_2(x_1 - x_2)^2 + a_3(x_1 - x_2)^3 \quad (6)$$

The Redlich-Kister parameters for glycerol formal + ethanol mixtures at all temperatures studied are presented in Table 4 beside related determination coefficients and standard deviations calculated according to Equation (7) (where D is the number of compositions studied and N is the number of terms used in the regression, that is 19 and 4 respectively). Figure 7 shows the Redlich-Kister equation applied to glycerol formal + ethanol data at several temperatures.

$$\sigma\left(V^{0-E}\right)=\sqrt{\frac{\sum\left(V^{0-E}_{expt}-V^{0-E}_{calc}\right)^2}{D-N}} \quad (7)$$

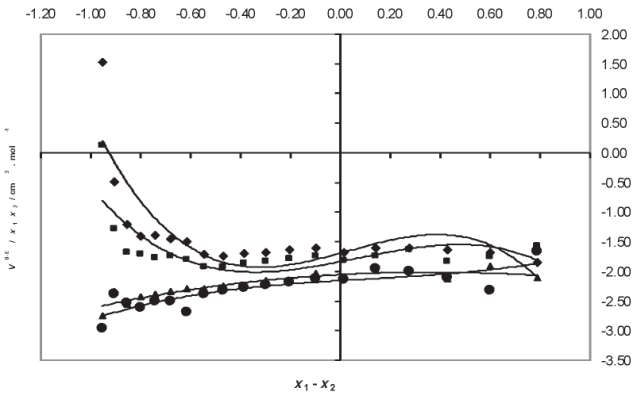

Figure 7. Regression adjusted to Redlich-Kister equation using four terms for glycerol formal + ethanol mixtures in mole fraction at several temperatures. 278.15 K (♦), 288.15 (■), 298.15 K (▲), 308.15 (•).

The variation coefficients greater than 0.94 (except at 288.15 and 293.15 K) indicate that the obtained regular polynomials regressions describe adequately the excess volumes. In similar way, standard deviations are similar to those presented in the literature for other kind of mixtures (**Kapadi, U.R.** ***et al.*** 2001; **Salas, J.A.** ***et al.*** 2002; **Wahab, M.A.** ***et al.*** 2002; **Peralta, R.D.** ***et al.*** 2003; **Resa, J.M.** ***et al.*** 2004; **Ruidiaz, M.A. & Martínez, F.** 2009; **Cristancho, D.M.** ***et al.*** 2011). On the other hand, σ values obtained for glycerol formal + ethanol mixtures were in general similarity to those obtained for glycerol formal + propylene glycol (near to 0.030 $cm^3 \cdot mol^{-1}$, **Rodríguez, G.A.** ***et al.*** 2011), ethanol + propylene glycol (varying from 0.003 to 0.021 $cm^3 \cdot mol^{-1}$, **Jiménez, J. & Martínez, F.**, 2006), and glycerol formal + water (near to 0.008 $cm^3 \cdot mol^{-1}$, **Delgado, D.R.** ***et al.*** 2011).

Volume thermal expansion

In pharmaceutical pre-formulation studies, it is too important to know the variation of physicochemical properties related to pharmaceutical dosage forms, with respect to temperature changes; especially the properties that affect the concentration of active ingredients. Thus, the volume thermal expansion coefficients (α) were calculated by means of Equation (8) (**Ott, J.B. & Boerio-Goates, J.**, 2000) by using the variation of molar volumes with temperature (Table 2).

$$\alpha=\frac{1}{V^0}\left(\frac{\partial V^0}{\partial T}\right)_{p,x} \quad (8)$$

Table 5 summarizes the ($\partial V^0/\partial T$) and α values for all mixtures and pure solvents. In all cases linear models were obtained with determination coefficients greater than 0.999. The α values varied from 7.28 x 10^{-4} K^{-1} in pure glycerol formal to 1.135 x 10^{-3} K^{-1} in pure ethanol at 298.15 K although the α variation is not linear with the mixtures composition.

Data correlation using the Jouyban-Acree model

The Jouyban-Acree model was introduced to correlate the physicochemical properties of the solution in mixed solvents including the dielectric constants (**Jouyban, A.** ***et al.*** 2004), viscosity (**Jouyban, A.** ***et al.*** 2005a), solvatochromic parameter (**Jouyban, A.** ***et al.*** 2006), density (**Jouyban, A.** ***et al.*** 2005b), speed of sound (**Hasan, M.** ***et***

Table 4. Redlich-Kister regression results for the excess volumes of glycerol formal + ethanol mixtures at various temperatures in mole fraction

T / K	a_0	a_1	a_2	a_3	r^2	σ / $cm^3 \cdot mol^{-1}$
278.15	–1.6945	1.1589	0.3270	–3.1113	0.6916	0.0409
283.15	–1.8038	0.9608	0.2374	–2.5712	0.7825	0.0339
288.15	–1.8381	0.8314	0.3572	–1.7244	0.5682	0.0306
293.15	–1.9841	0.1711	–0.1807	0.4539	0.9285	0.0114
298.15	–2.0536	0.2233	–0.3222	0.0254	0.8578	0.0102
303.15	–2.1235	0.2344	–0.4761	–0.1687	0.9150	0.0111
308.15	–2.1557	0.2543	–0.0994	0.3091	0.7230	0.0230
313.15	–2.4351	0.3196	–0.2935	1.5102	0.7235	0.0293

Table 5. Volume thermal expansion coefficients of glycerol formal + ethanol mixtures at 298.15 K.

Glycerol formal		$100\,(\partial V^0/\partial T)$ /	$10^4\ \alpha$/ K^{-1}
μ_{GF}	x_{GF}	cm^3·mol^{-1}·K^{-1}	
0.0000	0.0000	6.660	11.35
0.0500	0.0228	6.292	10.63
0.1000	0.0469	6.312	10.55
0.1500	0.0724	6.265	10.37
0.2000	0.0996	6.240	10.21
0.2500	0.1285	6.162	9.97
0.3000	0.1594	6.063	9.69
0.3500	0.1924	5.996	9.45
0.4000	0.2278	6.097	9.48
0.4500	0.2658	6.086	9.32
0.5000	0.3068	6.039	9.10
0.5500	0.3510	6.086	9.02
0.6000	0.3990	5.914	8.60
0.6500	0.4511	5.993	8.54
0.7000	0.5080	5.918	8.26
0.7500	0.5704	6.007	8.19
0.8000	0.6390	5.918	7.87
0.8500	0.7149	5.866	7.60
0.9000	0.7993	5.936	7.46
0.9500	0.8937	6.187	7.53
1.0000	1.0000	6.205	7.28

al. 2006; **Kadam, U.B. *et al.*** 2006) and more recently molar volumes (**Cristancho, D.M. *et al.*** 2011; **Delgado, D.R. *et al.*** 2011; **Rodríguez, G.A. *et al.*** 2011). The model uses the physicochemical properties of the mono-solvents as input data and a number of curve-fitting parameters representing the effects of solvent-solvent interactions in the solution. It is basically derived for representing the solvent effects on the solubility of non-polar solutes in nearly ideal binary solvent mixtures at isothermal conditions by **Acree Jr., W.E.** (1992); and then its applications were extended to the solubility of polar solutes in water + cosolvent mixtures at isothermal conditions (**Jouyban-Gharamaleki, A. *et al.*** 1998). Further extensions were made to represent the solvent composition and temperature effects on the solubility of drugs (**Jouyban, A. *et al.*** 1998); and also some other parameters such as acid dissociation constants (**Jouyban, A. *et al.*** 2005c), electrophoretic mobility in capillary electrophoresis (**Jouyban-Gharamaleki, A. *et al.*** 2000) and retention factors in high performance liquid chromatography (**Jouyban, A. *et al.*** 2005d) have been calculated perfectly.

The model for representing the solvent composition and temperature effects on the density of solvent mixtures is:

$$\ln \rho_{m,T} = x_1 \ln \rho_{1,T} + x_2 \ln \rho_{2,T} + \frac{x_1 x_2}{T} \cdot \sum_{i=0}^{2} J_i \left(x_1 - x_2\right)^i \quad (9)$$

where $\rho_{m,T}$, $\rho_{1,T}$, $\rho_{2,T}$ are densities of mixed solvent, solvents 1 (glycerol formal) and 2 (ethanol) at different temperatures (T), respectively. The x_1, x_2 are mole fractions of glycerol formal and ethanol, respectively. The J_i terms are coefficients of the model computed by using a no intercept regression analysis of:

$$\ln \rho_{m,T} - \left(x_1 \ln \rho_{1,T} + x_2 \ln \rho_{2,T}\right) = J_0 \frac{x_1 x_2}{T} + J_1 \frac{x_1 x_2 \left(x_1 - x_2\right)}{T} + J_2 \frac{x_1 x_2 \left(x_1 - x_2\right)^2}{T} \quad (10)$$

The following equation was obtained for density correlation of mixtures of glycerol formal and ethanol at different temperatures after excluding non-significant model constants:

$$\ln \rho_{m,T} = x_1 \ln \rho_{1,T} + x_2 \ln \rho_{2,T} - 20.397 \frac{x_1 x_2}{T} \quad (11)$$

The calculated density values using Equation (11) are presented in Table 1. The mean relative deviation (MRD) between experimental and calculated data was calculated as an accuracy criterion using:

$$MRD = \frac{100}{N} \left(\frac{|Calculated - Experimental|}{Experimental} \right) \quad (12)$$

and was 0.03 ± 0.03 % for Equation (11). The *N* in Equation (12) is the number of data points in the data set.

An adapted version of Equation (11) was used to represent the effects of solvent composition and temperature on the molar volume of mixed solvents in recent works (**Cristancho, D.M.** ***et al.*** 2011; **Delgado, D.R.** ***et al.*** 2011; **Rodríguez, G.A.** ***et al.*** 2011). A similar model could be trained to represent the molar volume data of glycerol formal + ethanol data at various temperatures as:

$$\ln V_{m,T} = x_1 \ln V_{1,T} + x_2 \ln V_{2,T} - 74.849\frac{x_1 x_2}{T} - 25.836\frac{x_1 x_2 (x_1 - x_2)}{T} - 8.430\frac{x_1 x_2 (x_1 - x_2)^2}{T} \quad (13)$$

The calculated molar volume values are presented in Table 2. The model fits very well to the experimental data and the MRD was 0.17 ± 0.13 %. In addition to the fitness capability of the model, it could be used to predict the molar volume data using the trained version of the model employing the minimum number of experimental data points. For this purpose, a minimum number of experimental data (11 odd data points of set 278.15 K and 11 odd data points of set 313.15 K) have been used for density and molar volume data and the following equations obtained:

$$\ln \rho_{m,T} = x_1 \ln \rho_{1,T} + x_2 \ln \rho_{2,T} - 20.217\frac{x_1 x_2}{T} \quad (14)$$

$$\ln V_{m,T} = x_1 \ln V_{1,T} + x_2 \ln V_{2,T} - 74.733\frac{x_1 x_2}{T} - 26.203\frac{x_1 x_2 (x_1 - x_2)}{T} - 7.988\frac{x_1 x_2 (x_1 - x_2)^2}{T} \quad (15)$$

The MRD values of Equations (14) and (15) for predicted densities and molar volumes were 0.03 ± 0.03 % and 0.15 ± 0.12 % (*N* = 150). Figures 8 and 9 show the predicted values versus experimental values of density and molar volume, respectively. High regression coefficients (R^2 = 1.0000 (i.e. > 0.9999) for density and R^2 = 0.9997 for molar volume) suggest the predictability and applicability of the Jouyban-Acree model to predict the density and molar volume data using a minimum number of experimental data.

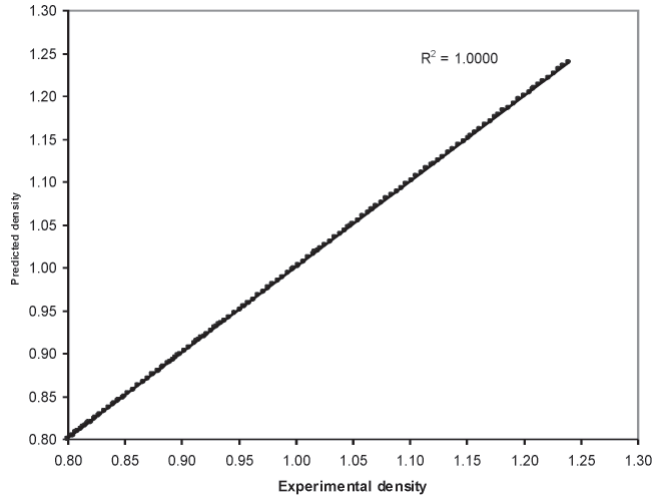

Figure 8. The predicted density values (g·cm^{-3}) using Equation (14) against the corresponding experimental values.

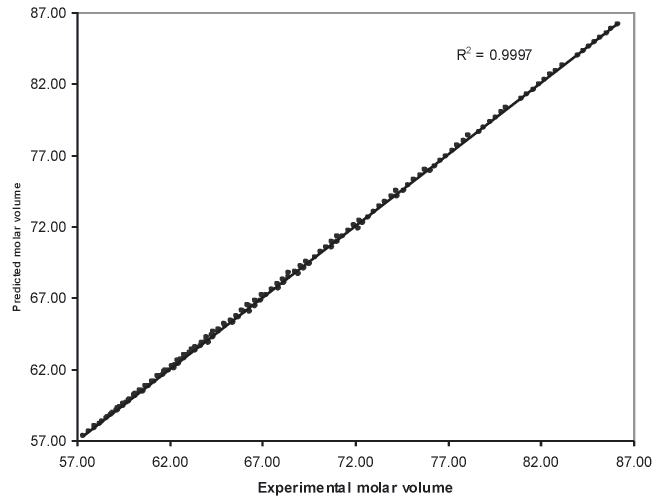

Figure 9. The predicted molar volume values (cm^3·mol^{-1}) using Equation (15) against the corresponding experimental values.

Conclusions

This work reports experimental information about the volumetric behavior of the glycerol formal + ethanol at eight temperatures commonly found in technological conditions. Thus, this work complements the information reported in the literature about volumetric properties of the possible binary mixtures conformed by glycerol formal, ethanol, propylene glycol, and water (**Jiménez, J.** ***et al.*** 2004; **Jiménez, J. & Martínez, F.**, 2005, 2006; **Delgado, D.R.** ***et al.*** 2011; **Rodríguez, G.A.** ***et al.*** 2011). It can be concluded that this binary system shows non ideal behavior exhibiting negative deviations. These observations demonstrate that it is necessary to characterize systematically representative binary systems in order to have complete experimental information about the physical and chemical properties useful in the understanding of liquid pharmaceutical systems. Also, the Jouyban-Acree model can predict density and molar volume of solution in

mixtures of solvents at different temperatures using minimum number of experimental data points with acceptable accuracy in comparison with experimental data. Furthermore, the reported experimental values could be used to challenge other theoretical methods developed for estimation of thermophysical properties in mixtures (**Prausnitz, J.M.** ***et al.*** 1986).

Acknowledgments

We thank the DIB of the Universidad Nacional de Colombia (UNC) by the financial support in addition to the Department of Pharmacy of UNC for facilitating the equipment and laboratories used in this investigation.

References

Acree Jr., W.E. 1992. Mathematical representation of thermodynamic properties: Part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model. *Thermochim Acta* **198:**71-79.

Arias, L.J., Díaz, A.J., Martínez, F. 2004. Viscosidad cinemática de mezclas ternarias formadas por agua, alcohol, propilenoglicol y glicerin formal a 25.0°C. *Rev Colomb Cienc Quím Farm* **33**:20-37.

Barton, A.F.M. 1991. "Handbook of Solubility Parameters and Other Cohesion Parameters". 2nd edition, New York, CRC Press, p.157-193.

Battino, R. 1971. Volume changes on mixing for binary mixtures of liquids. *Chem Rev* **7**:5-45.

Budavari, S., O'Neil, M.J., Smith, A., Heckelman, P.E., Obenchain Jr., J.R., Gallipeau, J.A.R., D'Arecea, M.A. 2001. "The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals", 13th edition, Merck & Co., Inc., Whitehouse Station, NJ, pp. 799-800.

Cristancho, D.M., Delgado, D.R., Martínez, F., Fakhree, M.A.A., Jouyban, A. 2011. Volumetric properties of glycerol + water mixtures at several temperatures and correlation with the Jouyban-Acree model. *Rev Colomb Cienc Quím Farm* **40**:92-115.

Delgado, D.R., Martínez, F., Fakhree, M.A.A., Jouyban, A. 2011. Volumetric properties of the glycerol formal + water cosolvent system and correlation with the Jouyban-Acree model. *Phys Chem Liq*. DOI: 10.1080/00319104.2011.584311.

DiPietro J.A., Todd Jr., K.S., Reuter, V. 1986. Anti-strongyle activity of a propylene glycol-glycerol formal formulation of ivermectin in horses (mares). *Am J Vet Res* **47**:874-875.

Fort, R.T., Moore, W.R. 1966. Viscosities of binary liquid mixtures. *Trans Faraday Soc* **62**:1112-1119.

Hasan, M., Kadam, U.B. Hiray. A.P., Sawant, A.B. 2006. Densities, viscosities, and ultrasonic velocity studies of binary mixtures of chloroform with pentan-1-ol, hexan-1-ol, and heptan-1-ol at (303.15 and 313.15) K. *J Chem Eng Data* **51:**671-675.

Jiménez, J., Manrique, J., Martínez F. 2004. Effect of temperature on some volumetric properties for ethanol + water mixtures. *Rev Colomb Cienc Quím Farm* **33**:145-155.

_____., Martínez, F. 2005. Study of some volumetric properties of 1,2-propanediol + water mixtures at several temperatures. *Rev Colomb Cienc Quím Farm* **34**:46-57.

_____.,2006. Volumetric properties of ethanol + 1,2-propanediol mixtures at different temperatures. *Phys Chem Liq* **44**:521-530.

Jouyban, A., Soltanpour, Sh., Chan, H.K. 2004. A simple relationship between dielectric constant of mixed solvents with solvent composition and temperature. *Int J Pharm* **269:**353-360.

_____., Khoubnasabjafari, M., Vaez-Gharamaleki, Z., Fekari, Z., Acree Jr., W.E. 2005a. Calculation of the viscosity of binary liquids at various temperatures using Jouyban-Acree model. *Chem Pharm Bull* (Tokyo), **53:**519-523.

_____., Fathi-Azarbayjani, A., Khoubnasabjafari, M., Acree Jr., W.E. 2005b. Mathematical representation of the density of liquid mixtures at various temperatures using Jouyban-Acree model. *Indian J Chem A* **44:**1553-1560.

_____., Soltani, S., Chan, H.K., Acree Jr., W.E. 2005c. Modeling acid dissociation constant of analytes in binary solvents at various temperatures using Jouyban–Acree model. *Thermochim Acta* **428:**119-123.

_____., Rashidi, M.R., Vaez-Gharamaleki, Z., Matin, A.A., Djozan, Dj. 2005d. Mathematical representation of solute solubility in binary mixture of Supercrititical fluids by using Jouyban-Acree Model. *Pharmazie* **60:**527-529.

_____., Khoubnasabjafari, M., Acree Jr., W.E. 2006. Modeling the solvatochromic parameter () of mixed solvents with respect to solvent composition and temperature using the Jouyban-Acree model. DARU, **14:**22-25.

Jouyban-Gharamaleki, A., Barzegar-Jalali, M., Acree Jr., W.E. 1998. Solubility correlation of structurally related drugs in binary solvent mixtures. *Int J Pharm* **166:**205-209.

_____., Valaee, L., Barzegar-Jalali, M., Clark, B.J., Acree Jr., W.E. 1999. Comparison of various cosolvency models for calculating solute solubility in water–cosolvent mixtures. *Int J Pharm* **177:**93-101.

_____., Khaledi, M.G., Clark, B.J. 2000. Calculation of electrophoretic mobilities in water-organic modifier mixtures. *J Chromatogr A* **868:**277-284.

Kadam, U.B., Hiray, A.P., Sawant, A.B., Hasan, M. 2006. Densities, viscosities, and ultrasonic velocity studies of binary mixtures of trichloromethane with methanol, ethanol, propan-1-ol, and butan-1-ol at T = (298.15 and 308.15) K. *J Chem Thermodyn* **38:**1675-1683.

Kapadi, U.R., Hundiwale, D.G., Patil, N.B., Lande, M.K., Patil, P.R. 2001. Studies of viscosity and excess molar volume of binary mixtures of propane-1,2 diol with water at various temperatures. *Fluid Phase Equilibr* **192**:63-70.

Kestin, J. 1979. "A Course in Thermodynamics", McGraw-Hill, New York, pp. 331-332.

Kratky, O., Leopold, H., Stabinger, H. 1980. "DMA45 Calculating Digital Density Meter, Instruction Manual", Anton Paar, K.G., Graz, Austria, pp. 1-12.

Lo, P.K.A., Fink, D.W., Williams, J.B., Blodinger, J. 1985. Pharmacokinetic studies of ivermectin: Effects of formulation. *Veter Res Comm* **9**:251-268.

Martínez, F., Gómez, A. Ávila, C.M. 2002. Volúmenes molales parciales de transferencia de algunas sulfonamidas desde el agua hasta la mezcla agua-etanol (X = 0.5). *Acta Farm Bonaerense* **21**:107-118.

Ott, J.B., Boerio-Goates, J. 2000. "Chemical Thermodynamics: Advanced Applications", Academic Press, London, pp. 271-291.

Peralta, R.D., Infante, R., Cortez, G. Ramírez, R.R., Wisniak, J. 2003. Densities and excess volumes of binary mixtures of 1,4-dioxane with either ethyl acrylate, or butyl acrylate, or methyl methacrylate, or styrene at T = 298.15 K. *J Chem Thermodyn* **35**:239-250.

Perrot, P. 1998. "A to Z of Thermodynamics", Oxford University Press, Inc., New York, pp. 221-225.

Pineda, L.M., Teatino, R.E., Martínez, F. 2003. Propiedades fisicoquímicas de mezclas ternarias formadas por agua, alcohol, propilenoglicol y glicerin formal a 25°C. *Rev Colomb Cienc Quím Farm* **32**:13-22.

Pivnichny, J.V. 1984. Separation and determination of the two components of glycerol formal by high-performance liquid chromatography. *J Pharm Biomed Anal* **2**:491-500.

Prausnitz, J.M., Lichtenthaler, R.N., Gomes de Acevedo, E. 1986. "Molecular Thermodynamics of Fluid-Phase Equilibria", 2nd edition, Prentice-Hall, Inc., Englewood Cliffs, NJ, pp. 181-186.

Redlich, O., Kister, A.T. 1948. Algebraic representation of thermodynamic properties and the classification of solutions. *Ind Eng Chem* **40**:345-348.

Reinemeyer, C.R., Courtney, C.H. 2001. Antinematodal drugs, in: "Veterinary Pharmacology and Therapeutics", 8th edition, edited by Adams, H.R., Iowa State University Press & Blackwell Publishing Professional, Ames, Iowa, p. 965.

Resa, J.M., González, C., Goenaga, J.M., Iglesias, M. 2004. Temperature dependence of excess molar volumes of ethanol + water + ethyl acetate. *J Solution Chem* **33**:169-198.

Rodríguez, S.J., Cristancho, D.M., Neita, P.C., Vargas, E.F., Martínez, F. 2010. Volumetric properties of the octyl methoxycinnamate + ethyl acetate solvent system at several temperatures. *Phys Chem Liq* **48**:638-647.

Rodríguez, G.A., Delgado, D.R., Martínez, F., Fakhree, M.A.A., Jouyban, A. 2011. Volumetric properties of glycerol formal + propylene glycol mixtures at several temperatures and correlation with the Jouyban-Acree model. *J Solution Chem* In press.

Rubino, J.T. 1988. Cosolvents and cosolvency, in: "Encyclopedia of Pharmaceutical Technology", Vol. 3, edited by Swarbrick, J., Boylan, J.C., Marcel Dekker, Inc., New York, pp. 375-398.

Ruidiaz, M.A., Martínez, F. 2009. Volumetric properties of the pharmaceutical model cosolvent system 1,4-dioxane + water at several temperatures. *Vitae Rev Fac Quím Farm* **16**:327-337.

Salas, J.A., Zurita, J.L., Katz, M. 2002. Excess molar volumes and excess viscosities of the 1-chlorobutane + pentane + dimethoxyethane ternary system at 298.15 K. *J Argent Chem Soc* **90**:61-73.

US Pharmacopeia. 1994. 23rd edition, The United States Pharmacopeial Convention, Rockville, MD, p. 43.

Wahab, M.A., Azhar, M., Mottaleb, M.A. 2002. Volumetric behaviour of binary liquid mixtures at a temperature of 303.15K. *Bull Kor Chem Soc* **23**:953-956.

Yalkowsky, S.H. 1999. "Solubility and Solubilization in Aqueous Media", American Chemical Society and Oxford University Press, New York, pp. 180-235.

Recibido: junio 22 de 2011.

Aceptado para su publicación: agosto 30 de 2011.