

VOLUMETRIC PROPERTIES OF THE PHARMACEUTICAL MODEL COSOLVENT SYSTEM 1,4-DIOXANE + WATER AT SEVERAL TEMPERATURES

ESTUDIO DE ALGUNAS PROPIEDADES VOLUMÉTRICAS DEL SISTEMA MODELO COSOLVENTE FARMACÉUTICO 1,4-DIOXANO + AGUA A VARIAS TEMPERATURAS

Miller A. RUIDIAZ M.¹, Fleming MARTÍNEZ R.^{1*}

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ABSTRACT

Although the cosolvent system 1,4-dioxane + water is poisonous, it is widely used in the pharmaceutical sciences as a versatile model for studying drug solubility and some other relevant physicochemical properties in the design of homogeneous dosage forms. For this reason, the excess molar volumes and partial molar volumes of components are investigated from density measurements of the entire range of mass fractions for the 1,4-dioxane + water system at 293.15 K; 298.15 K; 303.15 K; 308.15 K and 313.15 K. The results of excess molar volumes are fitted by Redlich-Kister equation using third degree polynomials and compared with those of literature for other systems. The system exhibits large negative excess volumes (up to $-0.71 \text{ cm}^3 \text{ mol}^{-1}$) probably due to increased interactions like hydrogen bonding between unlike molecules or very large differences in the molar volumes of pure components. The effect of temperature on the different volumetric properties studied is also analyzed. Besides, the volume thermal expansion coefficients are also calculated founding values varying from $2.50 \times 10^{-4} \text{ K}^{-1}$ for pure water up to $1.06 \times 10^{-3} \text{ K}^{-1}$ for pure 1,4-dioxane at 298.15 K.

Keywords: 1,4-dioxane, water, binary liquid mixtures, excess volumes, partial volumes.

RESUMEN

Aunque el sistema cosolvente 1,4-dioxano + agua es tóxico, este ha sido ampliamente utilizado en las ciencias farmacéuticas como un modelo versátil en el estudio de la solubilidad de fármacos y de otras propiedades fisicoquímicas de interés en el diseño de formulaciones líquidas homogéneas puesto que cubre un amplio espectro de polaridades. Por esta razón, en este trabajo se calculan los volúmenes molares de exceso y molares parciales a partir de medidas de densidad en el sistema 1,4-dioxano + agua en todo el intervalo de composición a 293,15 K; 298,15 K; 303,15 K; 308,15 K y 313,15 K. Los resultados de volumen molar de exceso son modelados de acuerdo a la ecuación de Redlich-Kister usando polinomios regulares de tercer grado y comparados con otros presentados en la literatura para otros sistemas. El sistema estudiado presenta volúmenes de exceso altamente negativos (hasta $-0,71 \text{ cm}^3 \text{ mol}^{-1}$) 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. También se analiza el efecto de la temperatura sobre las diferentes propiedades volumétricas estudiadas. Así mismo se calculan los coeficientes térmicos de expansión volumétrica encontrado valores desde $2,50 \times 10^{-4} \text{ K}^{-1}$ para el agua pura hasta $1,06 \times 10^{-3} \text{ K}^{-1}$ para el 1,4-dioxano puro a 298,15 K.

Palabras clave: 1,4-dioxano, agua, mezclas líquidas binarias, volúmenes de exceso, volúmenes parciales.

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

* Autor a quien se debe dirigir la correspondencia: fmartinezr@unal.edu.co

INTRODUCTION

Water-cosolvent mixtures have been used widely in pharmacy in order to increase the solubility of drugs that are poorly soluble in water during the design of homogeneous pharmaceutical dosage forms, such as syrups and elixirs, among others (1, 2). 1,2-propanediol and ethanol are the cosolvents most used in design nowadays, especially those that are intended for elaboration of peroral and parenteral medications (3). Several examples of pharmaceutical formulations using these cosolvents have been presented by Rubino (1). Nevertheless, 1,2-propanediol and ethanol are hydrogen-donor and hydrogen-acceptor solvents, and they have relatively large dielectric constants (24 and 32 at 293.15 K (4)) and thus, mixtures with low polarities could not be studied by using these two solvents and water. Otherwise, 1,4-dioxane is a toxic organic solvent, miscible with water in all possible compositions, although it has a low dielectric constant (2.2 at 293.15 K (4)). For this reason, this solvent allows to study polarities from 2 to 80 at room temperature when is blended with water. On the other hand, 1,4-dioxane acts only as a Lewis base in aqueous media, opposite to 1,2-propanediol and ethanol, which act as donor and acceptor as well. Although this is a toxic solvent, it has been widely used as model cosolvent for drugs' solubility studies developed by several authors (5-8).

The cosolvent mixtures obtained using these cosolvents and water are highly non-ideal due to increased interactions between unlike molecules and large differences in molar volumes of pure components, which leads to non-additive volumes on mixing (9, 10). 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, including those with poisonous behavior. This information is useful for predicting the intermolecular interactions present in liquid pharmaceutical systems (11).

In this report, the excess molar volumes and the partial molar volumes of the binary system of 1,4-dioxane + water at various temperatures in addition to other volumetric properties were calculated according to modified procedures widely exposed in literature (12-15). This report is a continuation of those presented previously about some volumetric properties of ethanol + water (16)

and 1,2-propanediol + water mixtures (17). As was already said, 1,4-dioxane has only proton-acceptor groups, which imply a significant degree of H-bonding with water, leading to mutual association in their binary mixtures (10).

EXPERIMENTAL

Materials

In this investigation, dehydrated 1,4-dioxane from Scharlau, Spain, and distilled water (conductivity $< 2 \mu\text{S cm}^{-1}$) were used. The dehydrated 1,4-dioxane employed was maintained over molecular sieve to obtain a dry solvent previously to prepare the cosolvent mixtures. The dryness obtained for 1,4-dioxane was demonstrated by the density value obtained which was coincident with those presented in literature (18, 19). Prior to mixtures preparation, distilled water was treated in an Elmasonic E 60 H ultrasonic bath at room temperature for 10 min. to remove dissolved air.

Cosolvent mixtures preparation

All 1,4-dioxane + water cosolvent 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 10% m/m to 90% m/m varying in 10% m/m, to study nine mixtures and the two pure solvents. This procedure imply an uncertainty of $\pm 2 \times 10^{-5}$ in mole fraction. The mixtures were allowed to stand in Magni Whirl Blue M water baths at temperatures from 293.15 K to 313.15 K varying in 5.00 ± 0.05 K for at least 30 minutes previous 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 (20). The equipment was calibrated according to Instruction Manual using air and water at the different temperatures studied (21). All mixture preparations and density measurements were repeated at least five times and the results were averaged. From density values all thermodynamic properties were calculated as will be indicated in the next section.

RESULTS AND DISCUSSION

Table 1 presents the composition of 1,4-dioxane + water mixtures, in mass percent and mole fraction, in addition to density values at several temperatures studied. Our density values are in agreement with those presented by Morcom and Smith (22) at 298.15 K and also with those pre-

sented by Matsuo *et al* (23). The differences found among all literature data were in general lower than 0.0003 g cm^{-3} . Nevertheless, some differences have been found with respect those presented by Nayak *et al* (24) at 303.15 K and 313.15 K, in particular, in 1,4-dioxane-rich mixtures. In all cases, the density decreases almost linearly as the temperature increases except for water.

Table 1. Densities ^(a, b) for 1,4-dioxane + water mixtures at various temperatures.

1,4-dioxane		Temperature / K				
% m/m	Mole fraction	293.15	298.15	303.15	308.15	313.15
0.00	0.0000	0.9982	0.9970	0.9957	0.9940	0.9920
10.00	0.0222	1.0070	1.0052	1.0034	1.0012	0.9987
20.00	0.0486	1.0161	1.0138	1.0115	1.0088	1.0059
30.00	0.0806	1.0244	1.0216	1.0189	1.0158	1.0124
40.00	0.1200	1.0312	1.0280	1.0250	1.0214	1.0175
50.00	0.1698	1.0366	1.0328	1.0294	1.0255	1.0212
60.00	0.2348	1.0398	1.0356	1.0318	1.0275	1.0228
70.00	0.3231	1.0408	1.0361	1.0320	1.0273	1.0223
80.00	0.4500	1.0399	1.0348	1.0304	1.0253	1.0200
90.00	0.6480	1.0370	1.0315	1.0268	1.0214	1.0157
100.00	1.0000	1.0363	1.0328	1.0289	1.0251	1.0214

(a) Unit: g cm^{-3}

(b) The mean standard deviation was 0.0001 g cm^{-3}

Molar volumes and excess molar volumes

In table 2 the molar volumes for binary mixtures at all temperatures are presented which were calculated from equation 1.

$$V = \frac{x_1 M_1 + x_2 M_2}{\rho} \quad \text{Equation 1.}$$

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.

On the other hand, the excess volumes calculated from equation 2 (where, ρ_1 and ρ_2 are the densities of pure components) at all temperatures studied are also presented in table 2. This behavior is shown graphically in figure 1 at 298.15 K.

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

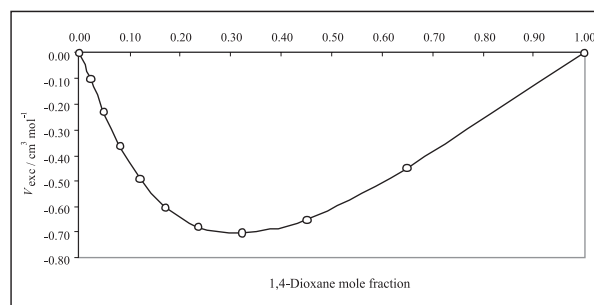


Figure 1. Excess molar volumes of 1,4-dioxane + water mixtures at 298.15 K.

Analogous to the behavior obtained in other investigations (10, 16, 17), in all cases the excess volumes are largely negative (especially around 0.32 in mole fraction of 1,4-dioxane, where it is near to $0.71 \text{ cm}^3 \text{ mol}^{-1}$) indicating contraction in volume. As was already said (16, 17), according to Fort and Moore (25), a negative excess volume is

Table 2. Molar volumes, excess molar volumes, and partial molar volumes of components for 1,4-dioxane + water mixtures at various temperatures.

T / K	1,4-dioxane		Molar volume ^(a, b)	Excess volume ^(a, b)	$10^2 \left(\frac{\partial V}{\partial \mu_D} \right)^{(a)}$	$\bar{V}_D^{(a, b)}$	$\bar{V}_W^{(a, b)}$
	% m/m	Mole fraction					
293.15	0.00	0.0000	18.05	0.000	-8.631	80.65	18.05
	10.00	0.0222	19.44	-0.105	-8.935	80.39	18.06
	20.00	0.0486	21.09	-0.234	-8.462	80.74	18.04
	30.00	0.0806	23.10	-0.367	-7.370	81.46	17.99
	40.00	0.1200	25.63	-0.491	-5.818	82.35	17.89
	50.00	0.1698	28.86	-0.605	-3.966	83.24	17.74
	60.00	0.2348	33.15	-0.684	-1.972	84.03	17.54
	70.00	0.3231	39.07	-0.707	0.005	84.64	17.31
	80.00	0.4500	47.65	-0.653	1.805	85.04	17.07
	90.00	0.6480	61.17	-0.451	3.270	85.24	16.85
	100.00	1.0000	85.29	0.000	4.240	85.28	16.68
298.15	0.00	0.0000	18.07	0.000	-8.051	81.27	18.07
	10.00	0.0222	19.48	-0.103	-8.433	80.95	18.08
	20.00	0.0486	21.14	-0.230	-8.009	81.26	18.06
	30.00	0.0806	23.17	-0.363	-6.945	81.96	18.01
	40.00	0.1200	25.71	-0.489	-5.405	82.84	17.92
	50.00	0.1698	28.97	-0.601	-3.553	83.73	17.77
	60.00	0.2348	33.29	-0.681	-1.555	84.52	17.57
	70.00	0.3231	39.24	-0.702	0.425	85.13	17.34
	80.00	0.4500	47.89	-0.650	2.223	85.53	17.09
	90.00	0.6480	61.49	-0.450	3.673	85.73	16.87
	100.00	1.0000	85.78	0.000	4.610	85.77	16.71
303.15	0.00	0.0000	18.10	0.000	-7.505	81.88	18.10
	10.00	0.0222	19.51	-0.100	-7.984	81.47	18.10
	20.00	0.0486	21.19	-0.225	-7.628	81.73	18.09
	30.00	0.0806	23.23	-0.357	-6.606	82.40	18.04
	40.00	0.1200	25.78	-0.485	-5.089	83.27	17.95
	50.00	0.1698	29.07	-0.596	-3.247	84.16	17.80
	60.00	0.2348	33.41	-0.675	-1.248	84.95	17.60
	70.00	0.3231	39.40	-0.698	0.736	85.56	17.37
	80.00	0.4500	48.09	-0.648	2.535	85.96	17.12
	90.00	0.6480	61.78	-0.449	3.981	86.15	16.90
	100.00	1.0000	86.20	0.000	4.903	86.20	16.75
308.15	0.00	0.0000	18.13	0.000	-6.954	82.51	18.13
	10.00	0.0222	19.55	-0.098	-7.526	82.03	18.13
	20.00	0.0486	21.24	-0.221	-7.229	82.24	18.12
	30.00	0.0806	23.30	-0.354	-6.241	82.89	18.08
	40.00	0.1200	25.88	-0.479	-4.737	83.75	17.98
	50.00	0.1698	29.18	-0.593	-2.895	84.64	17.83
	60.00	0.2348	33.55	-0.672	-0.891	85.43	17.63
	70.00	0.3231	39.58	-0.695	1.099	86.05	17.40
	80.00	0.4500	48.33	-0.643	2.898	86.45	17.16
	90.00	0.6480	62.10	-0.446	4.330	86.64	16.94
	100.00	1.0000	86.68	0.000	5.219	86.68	16.79

Table 2. *Continue.*

T / K	1,4-dioxane		Molar volume ^(a, b)	Excess volume ^(a, b)	$10^2 \left(\frac{\partial V}{\partial \mu_D} \right)^{(a)}$	$\bar{V}_D^{(a, b)}$	$\bar{V}_W^{(a, b)}$
	% m/m	Mole fraction					
313.15	0.00	0.0000	18.17	0.000	-6.554	83.04	18.17
	10.00	0.0222	19.60	-0.096	-7.094	82.58	18.17
	20.00	0.0486	21.30	-0.220	-6.794	82.80	18.16
	30.00	0.0806	23.38	-0.350	-5.822	83.44	18.11
	40.00	0.1200	25.97	-0.474	-4.346	84.28	18.02
	50.00	0.1698	29.30	-0.588	-2.535	85.16	17.87
	60.00	0.2348	33.70	-0.667	-0.556	85.94	17.68
	70.00	0.3231	39.77	-0.692	1.421	86.55	17.45
	80.00	0.4500	48.58	-0.644	3.229	86.95	17.20
	90.00	0.6480	62.45	-0.444	4.700	87.15	16.98
100.00	1.0000	87.19	0.000	5.665	87.19	16.81	

(a) Units: cm³ mol⁻¹(b) The mean standard deviation for V and V^E was 0.01 cm³ mol⁻¹ while for \bar{V}_D and \bar{V}_W was close to 0.03 cm³ mol⁻¹

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 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 water by addition of 1,4-dioxane; second: contraction due to free volume difference of unlike molecules; and third: contraction due to hydrogen bond formation between 1,4-dioxane and water through -OH...O< bonding (10).

Thus, the large negative values of V^E over the free volume contribution indicate the presence of strong specific interactions with predominance of formation of hydrogen bonds between 1,4-dioxane 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 indicates the decrease in the interactions between 1,4-dioxane and water molecules with increase in temperature.

Partial molar volumes

The partial molar volumes for 1,4-dioxane (\bar{V}_D) and water (\bar{V}_W) were calculated using the classical Bakhuis-Roozeboom method by means equations 3 and 4 applied to the variation of the respective specific volumes as a function of 1,4-dioxane mass fraction (table 2) and adjusting them to third degree polynomials by least squares regression analyses (11, 26, 27). Polynomials of third degree order are the most widely used in these cases, based upon their good statistical parameters, specially their determination coefficients (figure 2). The first derivatives were taken out on the polynomials obtained and solved at each composition point.

$$\bar{V}_D = V + \mu_W \frac{dV}{d\mu_D} \quad \text{Equation 3.}$$

$$\bar{V}_W = V - \mu_D \frac{dV}{d\mu_D} \quad \text{Equation 4.}$$

The \bar{V}_D and \bar{V}_W values are also presented in table 2, in addition to the slopes obtained ($dV/d\mu_D$) at each composition and temperature. Almost in all cases the partial molar volumes for 1,4-dioxane and water in the mixtures are lower than those for the pure solvents (except for water in mixtures with 10% m/m of 1,4-dioxane at 293.15 K and 298.15 K). The partial volumes for 1,4-dioxane

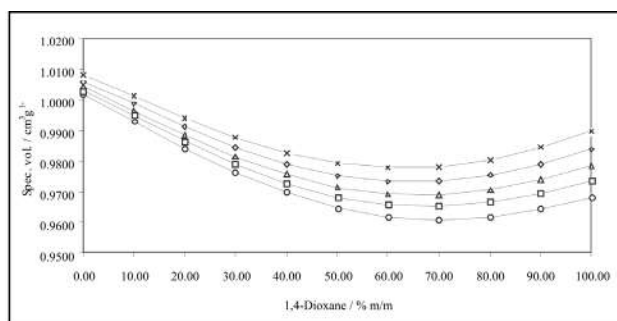


Figure 2. Specific volume as a function of the mixtures composition. 293.15 K (○), 298.15 (□), 303.15 K (△), 308.15 (◇), 313.15 (×).

varied from $80.39 \text{ cm}^3 \text{ mol}^{-1}$ (for 10% m/m of 1,4-dioxane at 293.15 K) to $87.15 \text{ cm}^3 \text{ mol}^{-1}$ (for 90% m/m of 1,4-dioxane at 313.15 K), and for water varied from $18.17 \text{ cm}^3 \text{ mol}^{-1}$ (for 10% m/m of 1,4-dioxane at 313.15 K) to $16.85 \text{ cm}^3 \text{ mol}^{-1}$ (for 90% m/m of 1,4-dioxane at 293.15 K). Our results for \bar{V}_D are almost coincident with those presented at 298.15 K by Matsuo *et al* (23). The results obtained for \bar{V}_D and \bar{V}_W are in agreement with the negative excess volumes obtained. The variation of this property is presented in Figure 3 as a function of 1,4-dioxane mole fraction at 298.15 K for 1,4-dioxane and water respectively. These values were calculated as the difference between partial molar volumes and molar volumes presented in table 2. For both solvents the partial molar volume diminishes as their respective proportion in the mixtures diminishes.

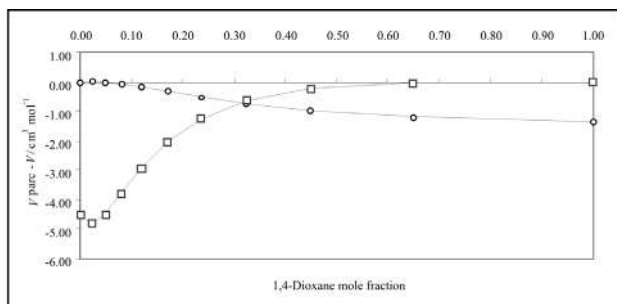


Figure 3. Partial molar volumes of water (circles) and 1,4-dioxane (squares) calculated as differences respect to pure solvent volumes in 1,4-dioxane + water mixtures at 298.15 K.

At this point it is important to consider that partial volumes were obtained by using specific volumes and mass fractions, in opposite way to that done previously with ethanol + water mixtures (16) and 1,2-propanediol + water mixtures (17). For 1,4-dioxane + water system straight lines were obtained for molar volume vs. mole fraction, which apparently indicates no variation of partial molar volumes with respect to molar volumes as pure compounds. Figure 4 shows the lineal behavior obtained at 298.15 K. For this reason, the classical method based on molar volumes and mole fractions was not used in this case.

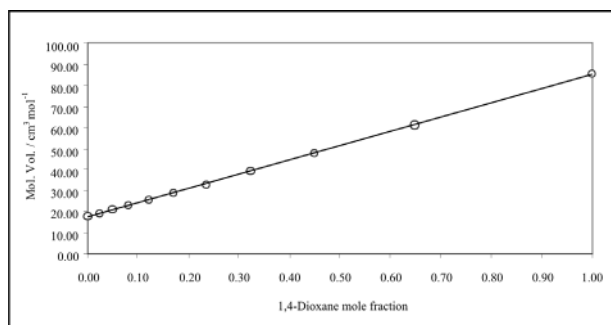


Figure 4. Molar volume as a function of the mixtures composition expressed as mole fraction at 298.15 K.

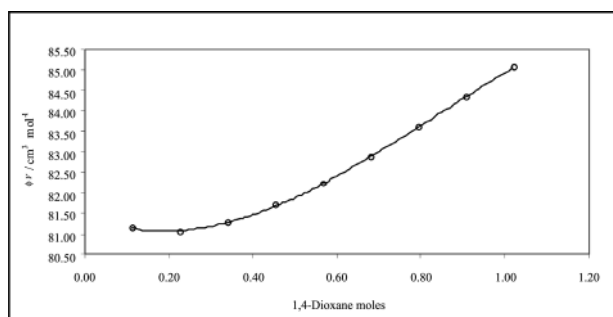
On the other hand, a method based on the variation of apparent molar volume (ϕ_V) of 1,4-dioxane with respect to cosolvent composition was also developed to obtain the partial molar volumes. Accordingly to equation 5, ϕ_V is defined as:

$$\phi_V = \frac{V - x_W V_W^0}{x_D} \quad \text{Equation 5.}$$

where V is the mixture molar volume, V_W^0 is the molar volume of water as pure compound ($18.07 \text{ cm}^3 \text{ mol}^{-1}$ at 298.15 K), and x_D and x_W are the mole fractions of 1,4-dioxane and water, respectively. Table 3 and figure 5 shows the behavior of ϕ_V with respect to cosolvent composition at 298.15 K. It is clear that ϕ_V increases as the 1,4-dioxane proportion increases in the mixtures. This behavior has been associated to water-structure breaking effects due to dissolved solutes (28).

Table 3. Apparent molar volumes and partial molar volumes of components for 1,4-dioxane + water obtained from the variation of apparent molar volumes with respect to 1,4-dioxane moles.

1,4-Dioxane		$\phi_V^{(a)}$	$\left(\frac{\partial \phi_V}{\partial n_2}\right)_{T,P,n1}$	$\bar{V}_D^{(a)}$	$\bar{V}_W^{(a)}$
% m/m	Mole fraction				
10.00	0.0222	81.16	-1.642	81.29	18.07
20.00	0.0486	81.04	0.708	81.63	18.04
30.00	0.0806	81.27	2.663	82.38	17.98
40.00	0.1200	81.70	4.223	83.39	17.84
50.00	0.1698	82.24	5.387	84.53	17.61
60.00	0.2348	82.88	6.155	85.66	17.22
70.00	0.3231	83.60	6.528	86.66	16.61
80.00	0.4500	84.33	6.505	87.38	15.58
90.00	0.6480	85.08	6.086	87.69	13.27

(a) Units: $\text{cm}^3 \text{mol}^{-1}$ **Figure 5.** Apparent molar volume of 1,4-dioxane in water at 298.15 K.

The variation of ϕ_V with respect to x_D was adjusted to a regular polynomial of third degree. \bar{V}_D was calculated according to:

$$\bar{V}_D = \phi_V^0 + n_2 \left(\frac{\partial \phi_V}{\partial n_2} \right)_{T,P,n1} \quad \text{Equation 6.}$$

where ϕ_V^0 is the apparent molar volume of 1,4-dioxane in water at infinite dilution (it is coincident with \bar{V}_D at concentration 0 of 1,4-dioxane) and n_2 is the number of 1,2-dioxane moles. The \bar{V}_D values obtained at 298.15 K are also presented in Table 3. \bar{V}_D increases as the 1,4-dioxane proportion increases in the mixtures. On similar way, \bar{V}_W was calculated according to equation 7:

$$\bar{V}_W = \frac{V - x_D \bar{V}_D}{x_W} \quad \text{Equation 7.}$$

The \bar{V}_W values as a function of cosolvent composition are also presented in table 3. \bar{V}_W diminishes as the water proportion is reduced in the mixtures.

By comparing the partial molar volumes obtained by both methods it could be stated that the trends obtained are similar, but the quantitative results are slightly different, in particular at large proportion of each component in the mixture.

Redlich-Kister equation

As was already said (16, 17), Redlich and Kister (29) introduced in 1948 the general form of equation 8 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 for various decades for manipulating several kinds of physicochemical values of mixtures such as: excess volumes, excess viscosities, solubilities in cosolvent mixtures, among others.

$$V^E = x_1 x_2 \sum a_i (x_1 - x_2)^i \quad \text{Equation 8.}$$

In the analysis of our data about excess volumes the equation 8 was used in the form of third degree polynomial equations using least square analyses, and therefore, obtaining four coefficients as presented in equation 9. Polynomials of third degree are the most widely used in this case again, because of their relevant statistic parameters such as determination coefficients and standard deviations.

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

Equation 9.

The Redlich-Kister parameters for 1,4-dioxane + water mixtures at all temperatures studied are presented in table 4 in addition to determination coefficients and standard deviations calculated according to equation 10 (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 our case). Equation 10 has been widely used in literature (16, 17). Figure 6 shows the Redlich-Kister equation applied to 1,4-dioxane + water data at 298.15 K.

$$\sigma(V^E) = \sqrt{\frac{\sum (V_{\text{expt}}^E - V_{\text{calc}}^E)^2}{D - N}}$$

Equation 10.

Table 4. Redlich-Kister regression results for the excess volumes of 1,4-dioxane + water mixtures at various temperatures in mole fraction.

T / K	a_0	a_1	a_2	a_3	r^2	$\sigma / \text{cm}^3 \text{mol}^{-1}$
293.15	-2.2993	2.0863	-2.9420	-2.2318	0.9902	0.0169
298.15	-2.2750	2.0970	-3.1381	-2.5414	0.9876	0.0188
303.15	-2.2565	2.0992	-3.2410	-2.7683	0.9864	0.0200
308.15	-2.2358	2.1114	-3.3362	-2.9602	0.9861	0.0199
313.15	-2.2360	2.1075	-3.2360	-2.9205	0.9833	0.0205

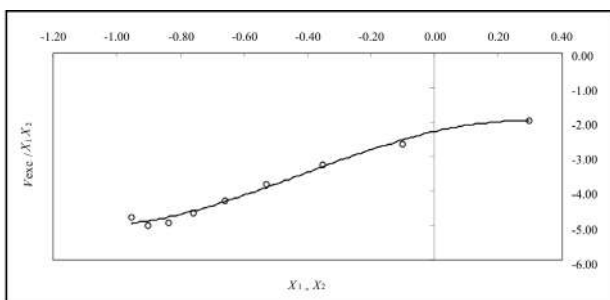


Figure 6. Regression adjusted to Redlich-Kister equation using four terms for 1,4-dioxane + water mixtures in mole fraction at 298.15 K.

The variation coefficients are greater than 0.983 indicating that the obtained regular polynomial regressions describe adequately the excess volumes, because the standard deviations are similar to those presented in literature for other mixtures (12-15). On the other hand, σ values obtained for 1,4-dioxane + water mixtures were in general lower than those obtained for ethanol + water (16) and 1,2-propanediol + water (17) mixtures when third degree regular polynomials were used as well.

Volume thermal expansion

On the other hand, in pharmaceutical and chemical preformulation studies is very important to predict the variation of physicochemical proper-

ties related to pharmaceutical dosage forms, with respect to temperature changes; specially those properties which affect the concentration of active ingredients in the developed formulations. For this reason the volume thermal expansion coefficients (α) were calculated by means of equation 11 (30) by using the variation of molar volumes with temperature (table 2).

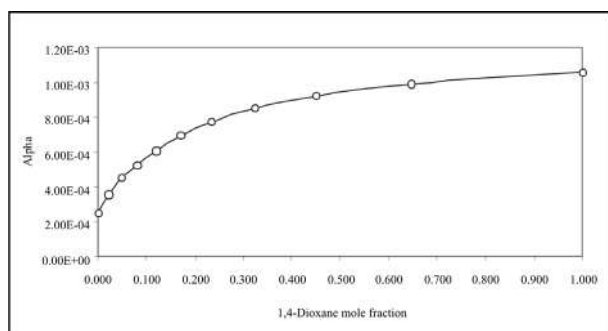
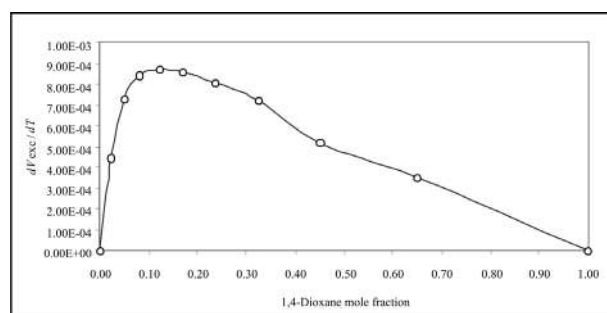
$$\alpha = \frac{1}{V} \left(\frac{\partial V}{\partial T} \right)_{P,x}$$

Equation 11.

Table 5 summarizes the $(\partial V/\partial T)$ and α values for all mixtures and pure solvents whereas Figure 7 shows the volume thermal expansion coefficients at 298.15 K. For all mixtures and pure solvents, quadratic polynomial models were used, obtaining determination coefficients greater than 0.999. The α values varied from $2.50 \times 10^{-4} \text{ K}^{-1}$ in water up to $1.06 \times 10^{-3} \text{ K}^{-1}$ in pure 1,4-dioxane. From 0 to 0.3 in mole fraction of 1,4-dioxane the α values increase readily. In a first approach this fact would be explained in terms of water-structure loosing by addition of 1,4-dioxane. It should be kept in mind that over 0.3 in mole fraction of 1,4-dioxane the most contributing component to all mixture volume is 1,4-dioxane, which is also the less polar solvent in these mixtures (1, 2).

Table 5. Volume thermal expansion coefficients of 1,4-dioxane + water mixtures at 298.15 K.

1,4-dioxane		$10^2 (\partial V/\partial T) / \text{cm}^3 \text{mol}^{-1} \text{K}^{-1}$	$10^4 \alpha / \text{K}^{-1}$
% m/m	Mole fraction		
0.00	0.0000	0.454	2.51
10.00	0.0222	0.696	3.57
20.00	0.0486	0.963	4.55
30.00	0.0806	1.22	5.26
40.00	0.1200	1.56	6.05
50.00	0.1698	2.02	6.96
60.00	0.2348	2.57	7.72
70.00	0.3231	3.34	8.50
80.00	0.4500	4.41	9.21
90.00	0.6480	6.09	9.91
100.00	1.0000	9.11	10.62

**Figure 7.** Volume thermal expansion coefficients (K^{-1}) for 1,4-dioxane + water mixtures at 298.15 K.**Figure 8.** Change of the excess molar volumes with temperature ($\text{cm}^3 \text{mol}^{-1} \text{K}^{-1}$) for 1,4-dioxane + water mixtures at 298.15 K (From 293.15 to 313.15 K).

Variation of excess molar volume with temperature

An additional and important treatment is the evaluation of change of the excess molar volumes with temperature ($\partial V^E/\partial T$). Figure 8 shows this property at 298.15 K (this value is constant over the entire temperature interval considered, that is, from 293.15 K to 313.15 K), which was obtained considering linear behavior of ($\partial V^E/\partial T$) in all mixtures studied (30). In almost all cases the determination coefficient values obtained were greater than 0,97. From figure 8 it follows that there is only a tendency according to composition, that is, this property is always positive, which reflects the fact that excess volume decreases with increasing temperature. This result could be due to weakening of hydrogen-bonding as the temperature increases which could lead to solvent structure loosing, and thus, leading to more ideal mixing behavior.

Variation of excess molar enthalpy with pressure

Finally, from the excess molar volumes presented in table 2 the change of the excess molar enthalpies with pressure according to equation 12 (30), was calculated:

$$\left(\frac{\partial H^E}{\partial p} \right)_T = V^E - T \left(\frac{\partial V^E}{\partial T} \right)_p \quad \text{Equation 12.}$$

Figure 9 shows ($\partial H^E/\partial p$) values at 298.15 K where it follows that this property is negative in all compositions, indicating an increase in the excess molar enthalpy as the pressure is increased. Unfortunately, there is not available experimental data in literature about this property for our system. Although, Suzuki *et al* (31) made a calorimetric study on heat of mixing of 1,4-dioxane and water

founding excess molar enthalpies negative from 0 to 0.4 in mole fraction of 1,4-dioxane and positive for the other mixtures at all the temperatures studied (from 298.15 K to 338.15 K).

Accordingly to Suzuki *et al* (31), the exothermic behavior shows that new strong hydrogen bonds might be formed in the water-rich region probably due to hydrophobic hydration around ethyl moieties of 1,4-dioxane. On the other hand, the same authors propose three composition regions based on the variation of partial molar enthalpies of water and 1,4-dioxane. These regions are characterized according to the aggregate species present as clusters in each of them. On the other hand, according to Takamuku *et al* (32), large hydrogen bonded clusters corresponding to water are dominant at $x_D < 0.1$, whereas for $0.1 < x_D < 0.3$ a structural transition is presented, where hydrogen bonded clusters of 1,4-dioxane and several free water molecules are formed.

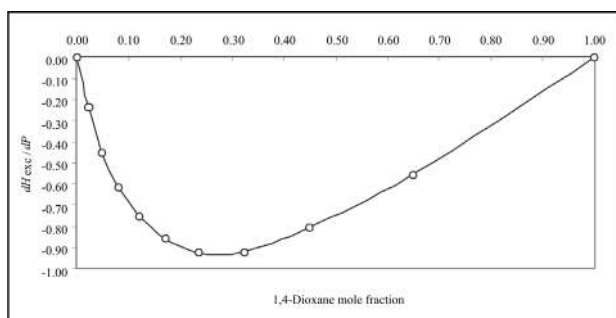


Figure 9. Change of the excess molar enthalpies with pressure ($\text{J mol}^{-1} \text{MPa}^{-1}$) obtained from the excess molar volumes for 1,4-dioxane + water mixtures at 298.15 K.

On the other hand, some other experimental techniques have been used to evaluate the nanoscopic structure of these mixtures (32, 33). Among these techniques, X-ray diffraction (32) and mass spectrometry (32) have been used to evaluate static structural properties and NMR relaxation (32) and thermal effusivity (33) to evaluate dynamic properties. In general, these techniques corroborate that described by means of thermodynamic methods.

CONCLUSIONS

This report expands widely the experimental volumetric information about the 1,4-dioxane + water cosolvent system available nowadays (22-24) because it includes the behavior at five temperatu-

res commonly found in technological conditions. As it was said earlier, this information could be employed in several engineering processes and for the theoretical understanding of the behavior of cosolvent mixtures used in the chemical and pharmaceutical industries. In general terms, based in our results and those presented in the literature for other experimental and theoretical procedures, it can be concluded that 1,4-dioxane + water mixtures clearly show non ideal behavior. Nevertheless, the observed deviations are lower than those observed earlier for aqueous mixtures containing ethanol and propylene glycol as cosolvents. These observations demonstrate clearly that it is necessary to characterize systematically this important binary system in order to have complete experimental information about the physical and chemical properties useful in the understanding of liquid pharmaceutical systems. It is important to keep in mind that the experimental information obtained for binary solvent mixtures could be employed to estimate the physicochemical behavior of ternary and quaternary mixtures by means of theoretical methods such as the one described by Mehlman *et al* (34) based on artificial neural networks, among others. Besides, several methods have been described in the literature to estimate activity coefficients from excess functions in binary mixtures (35). Ultimately, based on thermophysical properties of liquids Marcus (36) described some methods intended to the understanding the preferential solvation of drugs and other solutes in binary solvent mixtures.

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