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The effect of the composition of binary systems on the solubility and solubility parameter estimation of nalidixic and salicylic acids

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Summary

The solubility and solubility parameter of nalidixic and salicylic acids were determined in binary mixtures consisting of acetonitrile–water, dioxane–water, and propylene glycol–water. Non-linear relationships were obtained between drug solubility and cosolvent volume fraction. For nalidixic acid, the non-ideality resides mainly to cosolvent–water interactions. The deviation from the expected semi-logarithmic solubility profile in the case of salicylic acid resulted from two types of non-ideality: a non-ideality in the cosolvent–water systems; and a non-ideality involving the solute. Solubility parameters obtained from the peak solubility of nalidixic acid in acetonitrile–water and dioxane–waster binary mixtures were identical, and in good agreement with the theoretical δ_2-value calculated using the group contribution approach of Fedors, viz., 13.0 $cal^{1/2}\ cm^{-3/2}$. The "chameleonic" effect resulted in different solubility parameters for salicylic acid, ranging from 14.04 to 15.67 $cal^{1/2}\ cm^{-3/2}$, depending on the specific cosolvent–water system used. For instance, an increase in the δ_2 value of salicylic acid was observed for propylene glycol–water mixtures, a system with a high polarity, whereas a decrease in δ_2 was noticed in dioxane–water mixtures. The effects of temperature upon the solutes' solubilities and solubility parameters were also investigated. The utility of this report is to optimize drug solubility in an aqueous cosolvent combination.

Introduction

Solubility in water–miscible polar solvents is of great potential applicability in the designation of parenteral, topical, and liquid vehicles for drugs (Yalkowsky et al., 1975). An effective way of increasing aqueous solubility is by the cosolvency concept. It is nevertheless true that cosolvents are classified among the most powerful solubilizing agents. However, their mechanisms of action have not been thoroughly investigated (Yalkowsky and Rubino, 1985). Previous studies showed that the solubility of many drugs in binary mixtures is increased exponentially by the addition of cosolvents (Yalkowsky et al., 1972; Yalkowsky et al., 1976; Gould et al., 1984). Williams and Amidon (1984) have approached solubility prediction in mixed cosolvent systems by applying the excess Gibb's energy approach of Wohl. The parameters obtained have an approximate physical significance and can be used to compare different mixtures.

The solubility parameters of drugs have been determined from solubility measurements in single

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or binary solvents (Chertkoff and Martin, 1960; Restaino and Martin, 1964; James et al., 1976). Martin et al. (1981) reported that the solubility parameters of drugs as determined from peak solubility in mixed polar solvents may vary, depending on the specific solvent system used. The dependence of solute solubility parameters on solvent polarity was investigated, and suggestions for handling the "chameleonic" effect associated with solute–solvent interaction were presented (Martin et al., 1985). The concept of "chameleonic" materials which adopt the character of the surrounding environment, for instance, by dimerization as in the case of carboxylic acids, was first introduced by Hoy (1970). In polar or hydrogen bonding solvents, these materials act appropriately, whereas in other solvents the polar or hydrogen bonding interactions are intramolecular (Hoy, 1970).

A method involving a quadratic equation, based on the original Scatchard-Hildebrand solubility expression, was used to estimate the solubility parameters for solids (Martin and Carstensen, 1981). However, this method gave satisfactory results for drugs in hydrocarbons and less acceptable values in binary mixtures of polar solvents. A multiple regression mode for determining the solubility parameter of a solute in solvents was also reported (Cavé et al., 1980). In addition, a quantitative approach for predicting solubilities of crystalline compounds in binary solvent systems was offered (Martin et al., 1980). This approach modifies the Hildebrand equation to make it applicable to polar systems.

In a previous work (Amidon and Samaha, 1978), it has been demonstrated, using a free energy partitioning scheme, that the cyclic compounds are much more intrinsically hydrophilic than the acyclic ones. Accordingly, application of any group additivity method even though ring closure contribution is considered, showed a non-additive behavior. The solubility parameters of cyclic molecules are even more uncertain, since these compounds exhibit enhanced interaction affinity compared to flexible aliphatic molecules (Koenhen and Smolders, 1975).

The present work sets out to study the mechanisms of solubilization in binary cosolvent mixtures having different hydrogen bonding capacity, for nalidixic acid, a non-polar cyclic drug and for salicylic acid, a cyclic compound with a possible "chameleon-like" character. In addition, an evaluation of the solubility parameters values obtained from the relationships between solubilities and binary solvents composition is presented.

Materials and Methods

Materials

Nalidixic acid was obtained from Memphis Chemical Co. (Cairo, Egypt); salicylic acid was obtained from VEB Laborchemie (Apolda, G.D.R.); acetonitrile from Aldrich Chemical Co., dioxane from El-Nasr Pharmaceuticals Chemicals Co. (Cairo, Egypt); propylene glycol from Alexandria Co. for Pharmaceuticals (Alexandria, Egypt); and sodium hydroxide from Riedel-De Haënag (Seelze-Hannover, F.R.G.).

Mixed binary solvents preparation

Different concentrations ranging from 0 to 100% (v/v) of the cosolvent, viz., acetonitrile, dioxane, or propylene glycol, in water were prepared. The volume fraction, c, of a cosolvent is defined as the volume of the cosolvent divided by the sum of the volumes of cosolvent and water.

Solubility determinations

The solubilities of nalidixic and salicylic acids were determined in the prepared mixed cosolvents consisting of: acetonitrile ($\delta_{lc} = 11.9$), dioxane ($\delta_{lc} = 10.01$), and propylene glycol ($\delta_{lc} = 14.8$) individually with water ($\delta_{lw} = 23.45$) using a thermostatically controlled water bath. Excess solute was introduced into screw-capped bottles containing 10 ml of the cosolvent–water mixtures. The bottles were rotated at a speed of 60 ± 5 rpm for 24 h, and allowed to equilibrate for an additional 24 h at either $25 \pm 0.1°C$ or $37 \pm 0.1°C$.

After equilibrium was attained, the samples were filtered and aliquots were placed in volumetric flasks and brought to volume with the appropriate solvent. Nalidixic acid solutions were suitably diluted with 0.1 N NaOH, and assayed

spectrophotometrically at 259n nm, whereas salicylic acid solutions were diluted with 0.5 N NaOH and assayed at 300 nm. All experiments were run in triplicate, and average values were calculated.

Solubility parameter and mean molar volume of mixed solvents

The solubility parameter, δ_1, for each mixture of cosolvent, c, and water, w, is calculated according to Martin et al. (1980):

$$\delta_1 = \frac{\Phi_c\delta_w + \Phi_w\delta_c}{\Phi_c + \Phi_w} \quad (1)$$

And

$$\Phi_1 = \Phi_c + \Phi_w \quad (2)$$

where δ_1 is the solubility parameter of the binary mixtures between each of the 3 cosolvents and water, and Φ_1 is the total volume fraction of a cosolvent and water.

The mean molar volumes, V_1, of the binary solvent mixtures were calculated as the sum of the two molar volume fractions at different compositions assuming ideality. For each mixed solvent composed of cosolvent, c, and water, w, in various proportions, the mean molar volume is given by:

$$V_1 = X_cV_c + (1 - X_c)V_w \quad (3)$$

where X_i and V_i are the mole fraction and molar volume of the particular solvent in the mixture, respectively.

Solubility parameter and molar volume of solutes

The solubility parameters, δ_2, for nalidixic and salicylic acids were calculated by the Fedors method (1974), since the energy of vaporization and the molar volume are additive on functional group bases. For nalidixic acid, a δ_2 value of 13.0 $cal^{1/2}cm^{-3/2}$, and a molar volume of 147.6 cm^3/mole were obtained. A δ_2 value of 15.33 $cal^{1/2}cm^{-3/2}$ with a molar volume of 90.9 cm^3/mole were calculated for salicylic acid.

The solubility parameters for the two solutes were obtained at the peak solubilities where the δ_1 values of the binary solvents used should equal δ_2 as required by the Hildebrand–Scatchard equation (Martin et al., 1980).

Results and Discussion

In drug formulation, a suitable mixture of solvents is usually used to solubilize a drug. Based on their hydrogen bonding capacity, solvents were then classified into 3 classes: poor (P), including hydrocarbons, chlorinated hydrocarbons, and nitrohydrocarbons; moderate (M), including ketones, esters, and ethers; strong (S), such as alcohols (Barton, 1975). The effect of solvent molar volume, appearing in the solubility parameter term, has been reviewed by Barton (1975). When all other factors are equal, the solvent with lower molar volume is superior thermodynamically. Martin et al. (1981) back-calculated the drug's solubility in a binary solvent at a particular temperature by

TABLE 1

Solubility parameter and molar volume values, at 25°C, for some solvents which are poorly (P), moderately (M), or strongly (S) hydrogen-bonded

Solvent	H-bonding group [a]	μ [b] (D)	V_1 [a] (cm^3/mol)	$\frac{1}{\sqrt{V_1}}$	log V_1	δ_1 [a] ($cal^{1/2}\,cm^{-3/2}$)	log δ_1
Acetonitrile	P	3.44	52.6	0.138	1.721	11.9	1.076
Cyclohexane	P	0.00	108.7	0.096	2.036	8.2	0.914
Dimethylformamide	M	3.86	77.0	0.114	1.886	12.1	1.083
Dioxane	M	0.45	85.7	0.108	1.933	10.0	1.000
Isoamyl acetate	M	1.82	148.8	0.082	2.173	8.4	0.924
Propylene glycol	S	2.25	73.6	0.117	1.867	14.8	1.170
Water	S	1.85	18.1	0.235	1.257	23.5	1.370

[a] Data taken from Barton (1975).

[b] The dipole moments, μ, in Debye unit (D), are taken from Koenhen and Smolders (1975).

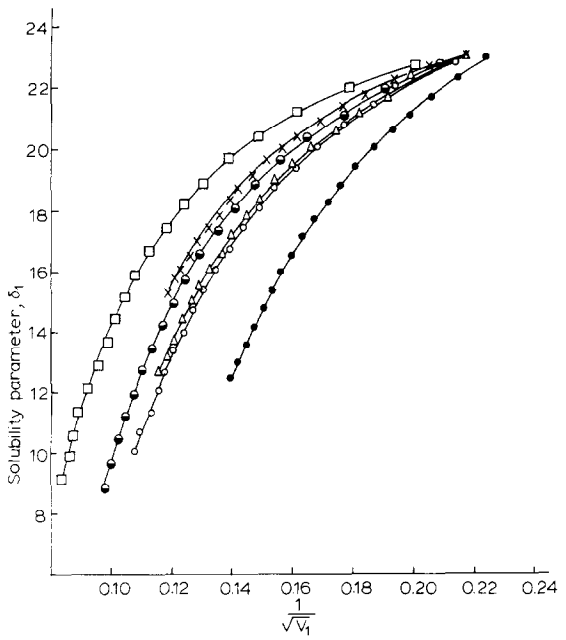

Fig. 1. Relationships between solubility parameters calculated for binary mixtures, δ_1, and the reciprocal of the square root of mean molar volumes, $1/\sqrt{V}_1$, at 25°C; ●, acetonitrile–water; ◒, cyclohexane–water; △, dimethylformamide–water; ○, dioxane–water; □, isoamyl acetate–water; ×, propylene glycol–water.

regressing the molar volume of the solvent mixture against log activity coefficient. The original definition (Hildebrand et al., 1970) of the solubility parameter, δ, was in terms of the energy of vaporization, ΔE^v, per unit volume. It is given by:

$$\delta = \left(\frac{\Delta E^v}{V}\right)^{1/2} \tag{4}$$

where V is the molar volume. The solubility parameters and molar volumes of some commonly used solvents, together with their hydrogen bonding capacity and dipole moments were presented in Table 1. The δ_1 values for binary mixtures between each of the solvents shown in Table 1, and water were calculated according to Eqn. 1, and plotted against the reciprocal of the square root of their mean molar volume, $1/\sqrt{V}_1$ (Fig. 1). A decrease in solvent-water mean molar volume increased the solubility parameter of the mixture. Since straight lines were not obtained, the energy of vaporization, ΔE_1^v, could not be estimated for these binary mixtures.

Considering a log–log relationship between the solubility parameter, δ_1, and the molar volume, V_1, of the binary mixtures, Eqn. 4 becomes:

$$\log \delta_1 = 1/2(\log \Delta E_1^v - \log V_1) \tag{5}$$

Plots of log δ_1 versus log V_1, for the different binary mixtures are illustrated in Fig. 2. A non-linear relation also resulted, and the curves obtained were all concave downward. The plots presented in Figs. 1 and 2 allow one to estimate the solubility parameter of the particular mixed solvent at any desired mean molar volume, and help in the selection of a suitable solvent binary system to optimize the drug's solubility.

In this investigation, 3 cosolvent–water systems representing different classes: acetonitrile (P), di-

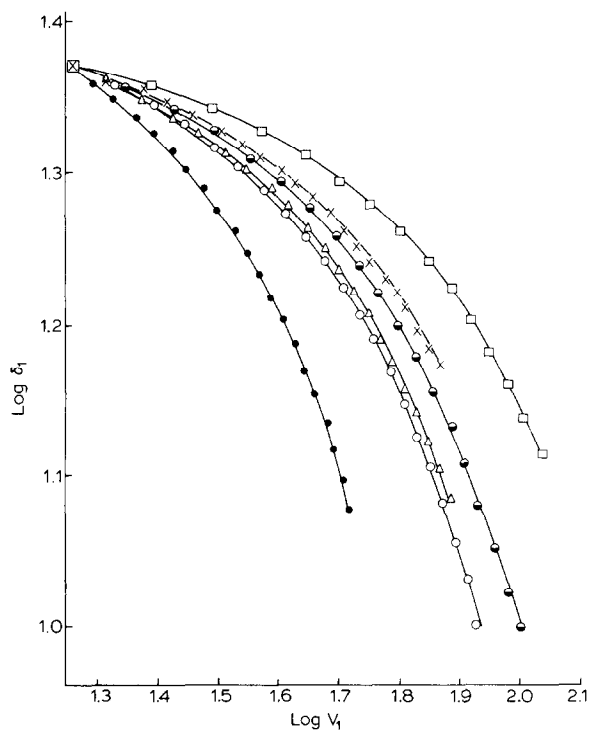

Fig. 2. A log-log relationship between molar volumes of solvent–water mixtures, at different composition, and their solubility parameters at 25°C; ●, acetonitrile-water; ◒, cyclohexane–water; △, dimethylformamide–water; ○, dioxane–water; □, isoamyl acetate–water; ×, propylene glycol–water.

TABLE 2

Calculated mean molar volume and solubility parameters at 25 °C, for cosolvent–water mixtures used in the experimental solubilization study

Solvent %	Acetonitrile		Dioxane		Propylene glycol	
	V_1	δ_1	V_1	δ_1	V_1	δ_1
5	19.790	22.87	21.443	22.78	20.840	23.02
10	21.514	22.29	24.820	22.11	23.614	22.59
15	23.241	21.72	28.200	21.43	26.390	22.15
20	24.970	21.14	31.581	20.76	29.168	21.72
25	26.700	20.57	34.961	20.09	31.950	21.29
30	28.420	19.99	38.342	19.42	34.720	20.89
35	30.150	19.41	41.721	18.75	37.500	20.42
40	31.876	18.83	45.101	18.07	40.276	19.99
45	33.603	18.25	48.481	17.40	43.053	19.56
50	35.330	17.68	51.862	16.74	45.830	19.13
55	37.060	17.10	55.242	16.06	48.610	18.69
60	38.780	16.52	58.622	15.39	51.380	18.26
65	40.510	15.94	62.002	14.72	54.160	17.83
70	42.240	15.37	65.382	14.04	56.940	17.40
75	43.970	14.79	68.762	13.37	59.720	16.96
80	45.690	14.21	72.142	12.70	62.490	16.53
85	47.420	13.63	75.523	12.03	65.270	16.10
90	49.146	13.06	78.903	11.35	68.046	15.67
95	50.870	12.48	82.280	10.68	70.820	15.23

V_1 is calculated according to Eqn. 3; δ_1 is calculated according to Eqn. 1.

oxane (M), and propylene glycol (S) hydrogen bonded, were used to solubilize two different drugs, viz., nalidixic acid, a non-polar water-insoluble drug; and salicylic acid, a possible "chameleonic" slightly soluble drug. The solubilization curves for nalidixic acid in binary cosolvent systems (acetonitrile, dioxane, and propylene glycol individually with water) at 25 and 37 °C are given in Figs. 3 and 4, respectively. The curves have been normalized by dividing the cosolvent-water solubility by the aqueous solubility. This normalization does not alter the shape of the curves and its advantages have been reported elsewhere (Yalkowsky and Rubino, 1985). Non-linear relationships between log (S_c/S_w) and C, where S_c is the solubility of solute in a binary solvent of volume fraction, C, of cosolvent, and S_w is the solubility of solute in water, were obtained. The curves were either concave downward at the high end or were sigmoidal in shape.

The greater solubility of nalidixic acid was found with the acetonitrile–water mixture, followed by dioxane with medium hydrogen bonding ability, then with propylene glycol, a strongly hydrogen bonded cosolvent. A common feature for the cosolvent–water systems used to solubilize nalidixic acid is that the data obtained followed the expected semi-logarithmic relationship between solubility and fraction cosolvent up to a volume fraction of 0.3, implying the absence of specific interactions between the drug and either itself or water. A maximum deviation from ideality was observed between 0.3 and 0.8 where cosolvent–water contacts are maximized and solvent–solvent interactions resulted in non-linear combinations of the mixed solvent components. At a volume fraction of 0.9, a maximum solubility of nalidixic acid in the acetonitrile–water mixture is spotted. This volume fraction corresponds to a cosolvent solubility parameter value of 13.06 (Table 2), which is in good agreement with the solubility parameter of nalidixic acid ($\delta_2 = 13.0$), calculated theoretically using Fedors method (1974). The original Hildebrand equation (Hildebrand and Scott, 1964) predicts that the solubility of a drug whose solubility parameter lies between the δ_1 values of the two solvents of a binary system, will exhibit a peak where the δ_1 of

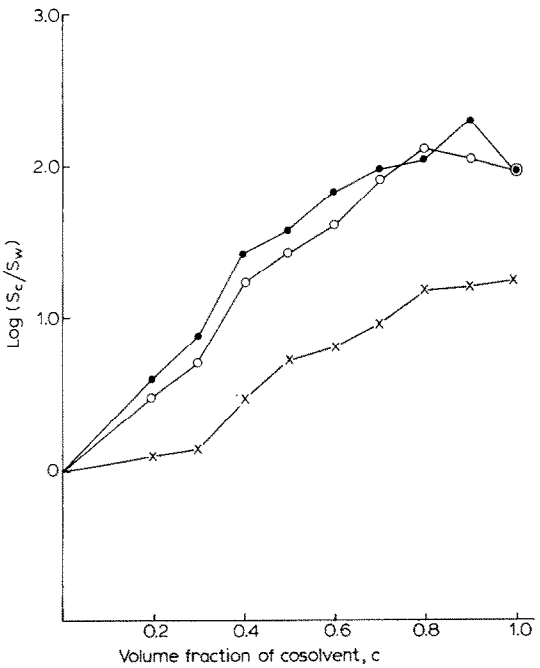

Fig. 3. Solubility of nalidixic acid in cosolvent–water mixtures at 25 °C; ●, acetonitrile–water; ○, dioxane–water; ×, propylene glycol–water.

the mixed solvents equals that of the solute, δ_2.

Considering the solubility of drug in dioxane–water system, the maximum solubility is obtained at 0.8, corresponding to a cosolvent–water solubility parameter of 12.70 (Table 2), which nearly matches the predicted solubility parameter for nalidixic acid. This small difference of 0.3, found between the experimental and theoretical δ_2 values may be overlooked because the solubility measurements were not spaced closely enough in the binary solvent composition. Maximum solubility of nalidixic acid was not found in the mixture of propylene glycol ($\delta_1 = 14.8$) and water ($\delta_1 = 23.5$), since the solubility parameter of this drug ($\delta_2 = 13.0$) does not fall between the solubility parameter values of these two solvents. A sigmoidal curve resulted in this cosolvent–water system, with a straight line at both ends of the curve indicating the absence of solute–solvent interactions between the drug and either water or propylene glycol. As can be seen in Figs. 3 and 4, the solubility of nalidixic acid in propylene glycol–water binary mixture is rather low. This poor solvency may be attributed to a

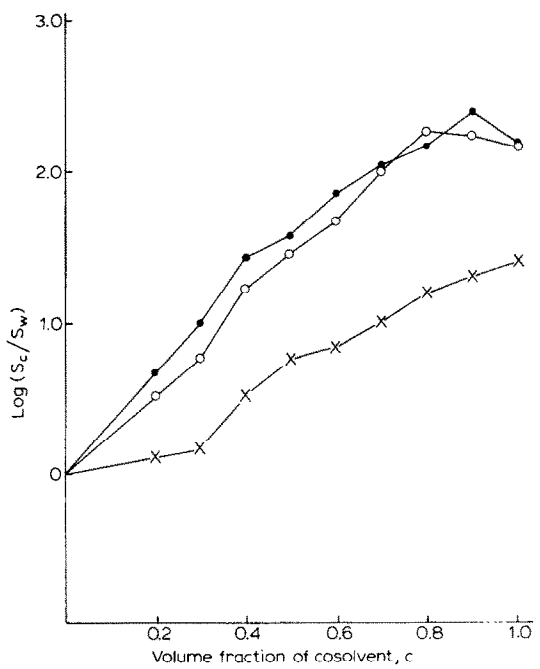

Fig. 4. Solubility of nalidixic acid in cosolvent-water mixtures at 37 °C; ●, acetonitrile–water; ○, dioxane–water; ×, propylene glycol–water.

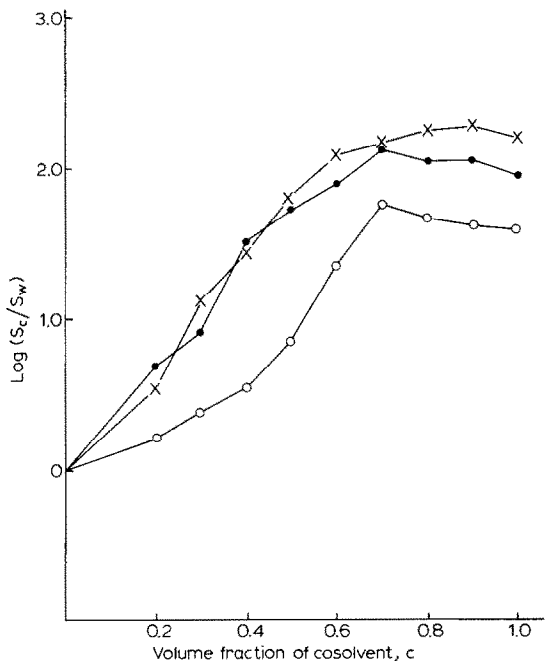

Fig. 5. Solubility of salicylic acid in cosolvent-water mixtures at 25 °C; ●, acetonitrile–water; ○, dioxane–water; ×, propylene glycol–water.

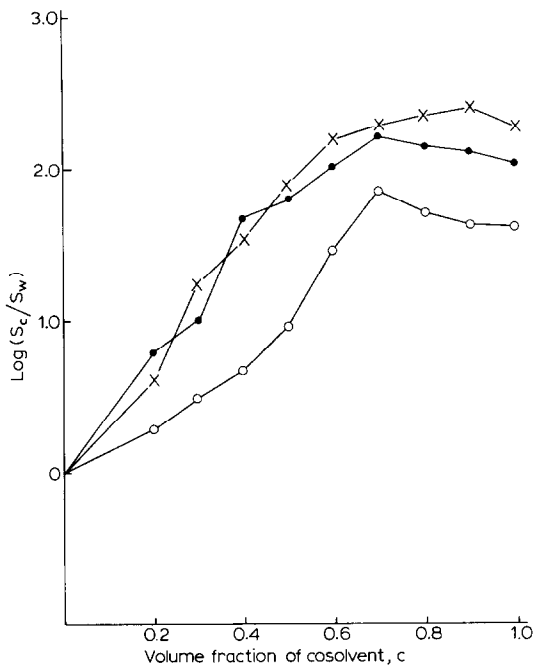

Fig. 6. Solubility of salicylic acid in cosolvent-water mixtures at 37°C; ●, acetonitrile–water; ○, dioxane–water; ×, propylene glycol–water.

combination of propylene glycol–solvophobic and water–hydrophobic interactions since this cosolvent exhibits self-association.

In Figs. 5 and 6, the solubilization curves for salicylic acid in binary cosolvent–water mixtures at 25 and 37°C, respectively, are illustrated. Non-linear relationships were obtained between log (S_c/S_w) and fraction of cosolvent at all volume fractions. This deviation from the semi-logarithmic relation, expected between solubility and cosolvent fraction resulted from two types of non-ideality: a non-ideality in the solvent systems due to cosolvent–water interactions that may lead the binary solvent to deviate from the linear combination of its components; and a non-ideality involving the solute, where specific interactions occur between salicylic acid and either itself or one of the mixed solvent components, or among the drug and both solvents that constitute the binary mixture.

In salicylic acid, intermolecular as well as intramolecular hydrogen bonding may occur. Using a quantum-mechanic computer program, an O–O distance of 0.2 nm with an O–H · · · O angle of 60°, was previously calculated (Samaha, 1979), indicating that salicylic acid is capable of strong intramolecular hydrogen bond formation.

The dioxane–water system exhibited the lowest solubilizing ability of the three cosolvent–water mixtures investigated (Figs. 5 and 6). The low solubility of salicyclic acid in dioxane-water mixtures may be attributed to solvent clustering (Martin et al., 1981). At a molecular level, the "lone pair" of electrons present in dioxane may undergo conjugation with the π molecular orbitals of the aromatic ring, and the resulting mesomeric effects would change the dipole moment of the groups (Grant and Abougela, 1983).

The solubility in propylene glycol–water hardly differs from that in acetonitrile–water. This is accounted for by the strong intramolecular hydrogen bonds in salicylic acid which inhibit very strong solvations by propylene glycol. Besides, acetonitrile is a polar aprotic solvent. In aprotic media, hydrogen bonding and ion–dipole interactions of anions with localized charge are much smaller than in protic solvent, such as water (Chantooni and Kolthofi, 1974).

The peak solubility of salicylic acid in dioxane–water was found at 70% cosolvent (μ_c = 0.45 D), which corresponds to a solubility parameter of 14.04 (Table 2), whereas a δ_2 value of 15.37 was determined in acetonitrile–water at a cosolvent volume fraction of 0.7. A peak solubility of the drug in propylene glycol–water mixtures was spotted at 90% cosolvent (μ_c = 2.25 D), equivalent to a solubility parameter of 15.67 (Table 2). The appropriate δ_2 value for salicylic acid was computed using the group contribution approach developed by Fedors, and was equal to 15.33. The theoretical δ_2 value was in accordance with the one obtained in the acetonitrile–water system, viz., in the aqueous cosolvent mixture with a poor hydrogen bonding capacity.

The variation of the salicylic acid solubility parameter with the cosolvent–waster system used, suggested that this drug behaves in a "chameleon-like" manner by adjusting its solubility characteristics to solvent environment. Similar results were reported for other solutes in binary mixtures (Martin et al., 1981; Martin et al., 1985). The variability in solute solubility parameters of small

rigid molecules, such as the xanthines, cholesterol, benzyl alcohol, and benzoic acid was attributed to a deviation from the geometric mean assumption of regular solution theory, rather than to a change in molecular size and shape (Martin et al., 1985).

The effects of temperature on the solubilization ability of the 3 cosolvent–water systems used, as well as on the solubility parameters determined in these solubilizing mixtures are demonstrated in Fig. 3–6. Increasing the temperature from 25 to 37 °C increased the solubilizing capacity of all cosolvents investigated, and similar patterns were followed at the two temperatures studied. Concerning the effect of temperature on the solubility parameters determination, increasing the temperature to 37 °C had no effect on the δ_2-values determined for nalidixic and salicylic acids in different mixtures. This result is in accordance with the previously reported studies (Barton, 1975; Hansen and Beerbower, 1971), where they related the success in handling solubility problems at various temperatures from the parameters at 25 °C to a feature of the regular solution model (Prausnitz, 1969). This feature is that the value of the complex functions $V_2\Phi_1^2(\delta_1 - \delta_2)^2$ and $V_1\Phi_2^2(\delta_1 - \delta_2)^2$ are independent of temperature due to the similar effect of temperature on δ_1 and δ_2, and since Φ_1 and Φ_2, the volume fraction of solvent and solute respectively, vary only very slightly with temperature (Hansen and Beerbower, 1971).

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