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Irregular solution behaviour of paracetamol in binary solvents

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Summary

The irregular solution behaviour of paracetamol was observed in two solvent systems: ethyl acetate-methanol; water and normal alcohols. The extended Hildebrand solubility approach was used to process the solubility data on paracetamol. The solubility parameter of paracetamol was determined from different methods of data analysis and found to be approx. 13.40 H. The parameters W and $(\log \gamma_2)/A$ were regressed against a polynomial of δ_1 of the binary mixture. The expressions allowed calculation of the mole fraction solubility of paracetamol in polar solvents. The expression for W regression was satisfactory for the determination of the solubility of paracetamol in methanol, ethanol and their mixtures, but deviated in the case of butanol and propanol.

Introduction

An irregular solution is one in which self-association of solute or solvent, solvation of the solute by the solvent molecules, or complexation of two or more solute species are involved. Polar systems exhibit irregular solution behaviour and are commonly encountered in pharmacy. The extended Hildebrand solubility approach (EHS) (Hildebrand et al., 1970; Martin et al., 1983), a modification of the Hildebrand-Scatchard equation, permits calculation of the solubility of polar and nonpolar solutes in solvents ranging from nonpolar hydrocarbons to highly polar solvents such as water, methanol and glycols. The solubility of caffeine (Adjei et al., 1980), theophylline (Martin et al., 1980), testosterone and testosterone propionate (Martin et al., 1982) and *p*-hydroxybenzoic acid (Wu and Martin, 1983) in different solvent blends was studied by the extended method. The solubility parameters of solute and solvent were introduced to explain the behaviour of regular and irregular solutions. The solubility parameter, δ, is an intrinsic physicochemical property of a substance, which has been used to explain drug action (Mullins, 1954), structure-activity relationships (Khalil et al., 1976a,b), drug transport kinetics (Khalil et al., 1967) and in situ release of theophylline (Adjei et al., 1984).

Paracetamol, an antipyretic, is commercially available in liquid dosage form. The solubility and related properties are of considerable importance to pharmacists in the design of dosage forms and in order to understand the absorption

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of paracetamol. The effect of vehicle dielectric properties on the rectal absorption of paracetamol from suppositories has been studied (Shangraw and Walking, 1971; Pagay et al., 1974) in humans. The solubility of paracetamol has been investigated (Walters, 1968) in sorbitol-water mixtures. The thermodynamics of paracetamol solubility in sugar-water cosolvents have recently been investigated (Etman and Naggar, 1990). The solution behaviour of paracetamol in different solvents is not clearly understood.

The present communication reports the behaviour of paracetamol solubility in the context of existing theories of solutions such as ideal, regular and irregular solutions. Furthermore, solubility studies permit determination of the solubility parameter of paracetamol (Chertkoff and Martin, 1960). Solubility of paracetamol in ethyl acetate-methanol, methanol-water systems and normal alcohols was investigated to highlight the irregular solution behaviour.

Materials and Methods

Paracetamol I.P (Fytochem Formulations, Vijayawada), purified solvents (ethyl acetate, butanol, ethanol, propanol, hexane, methanol) and double-distilled water were used. The absorbance of samples was taken on a Shimadzu Model UV-240 UV-Vis recording Spectrophotometer with matched 1 cm silica cells. For calculations, the necessary software was developed using BASIC and multiple regression analysis was performed on Lotus 1-2-3. A Neptune Minicomp PC/XT was used.

The solubilities of the paracetamol were determined by adding excess drug to different mixtures of ethyl acetate-methanol (δ 8.3–13.9 H) and methanol-water (δ 14.5–23.4 H) in stoppered glass container. The sealed flasks were equilibrated at $25 \pm 1^\circ$C in a constant-temperature shaker water bath for 24 h. The equilibrated solutions were filtered by means of glass wool tipped volumetric pipets. The saturated solutions were suitably diluted with 0.02 M hydrochloric acid and analysed at 244 nm. The reported solubility is an average of three samples. The densities of saturated solutions were determined at 25 °C. The molar volume of paracetamol was obtained from the molecular weight and density. The density of solid paracetamol was determined using the flotation technique (Beckett and Stenlake, 1986) by immersion of the solid in an insoluble solvent, *n*-hexane (δ = 7.3 H).

Results and Discussion

The mole fraction solubility (X_2) of a solute in non-ideal solutions may be expressed in terms of ideal mole fraction solubility (X_2^i) and rational activity coefficient (γ_2) at temperature, T:

$$-\log X_2 = -\log X_2^i + \log \gamma_2 \quad (1)$$

The ideal solubility expression (Hildebrand et al., 1970) for crystalline solids is

$$-\log X_2^i = \frac{\Delta S_f}{R} \log \frac{T_0}{T} \quad (2)$$

where ΔS_f denotes the entropy of fusion at melting point T_0; ΔS_f is calculated from the molar heat of fusion, ΔH_f ($\Delta S_f = \Delta H_f / T_0$); ΔH_f, 6800 cal/mol (Beckett and Stenlake, 1986); T_0, 443 K; ΔS_f, 15.35 cal/mol per K. The ideal solubility of paracetamol has a value of $X_2^i = 0.04676$ ($-\log X_2^i = 1.3302$).

In Eqn 1, $\log \gamma_2$ for a regular solution (Martin et al., 1983) may be expressed as

$$\log \gamma_2 = A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) \quad (3)$$

where

$$A = \frac{V_2 \phi_1^2}{2.303RT} \quad (4)$$

in which δ_1 and δ_2 are the solubility parameters of the solvent and solute, respectively, V_2 represents the molar volume of solute and ϕ_1 is the volume fraction of the solvent. ϕ_1 is expressed as

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + X_2 V_2} \quad (5)$$

where V_1 is the molar volume of the solvent. The rational activity coefficient, γ_2, for polar crystalline drug molecules in polar and non-polar solvents as given in EHS (Adjei et al., 1980) is given by:

$$\log \gamma_2 = A(\delta_1^2 + \delta_2^2 - 2W) \quad (6)$$

where W is the interaction energy term which in regular solution theory is taken to be equivalent to the geometric mean $(\delta_1^2\delta_2^2)^{1/2}$. $W = K\delta_1\delta_2$ where K is the proportionality constant between W and the geometric mean. Substituting the W term and rearranging, Eqn 6 yields

$$\frac{\log \gamma_2}{A} = \delta_1^2 + \delta_2^2 - 2K\delta_1\delta_2 \quad (7)$$

The solubility of paracetamol in polar solvents is mainly controlled by the presence of polar groups (-OH, -NH-) on the aromatic ring. The experimental mole fraction solubility of paracetamol in different solvent systems is listed in Table 1. The solvent systems used were ethyl acetate-methanol and methanol-water in order to highlight hydrogen-bonding interaction. The solubility of paracetamol in normal alcohols, viz., methanol, ethanol, propanol and butanol, was studied in order to corroborate further the results. The mole fraction solubility and other associated parameters are given in Tables 1 and 2.

Solubility predictions using regression of (log γ_2) / A

In the absence of the δ value of paracetamol and K, the right-hand side of Eqn 7, (log γ_2)/A, cannot be calculated and consequently the solubility cannot be evaluated (Eqn 1). However, Eqn 1 allows the calculation of (log γ_2)/A from a knowledge of X_2, X_2^i and A (Eqn 4). The experimental solubility data are given in Table 1. A values are calculated using Eqns 4 and 5. Molar volume (V_2) was determined from the molecular weight (151.16) and density. The density of the solid was established by the flotation technique (Beckett and Stenlake, 1986) using hexane (δ = 7.3 H). The molar volume as determined from both the experiments and from fragmental constants (Fedors, 1974) is 118.66 and 111.2 cm^3/mol, respectively.

The expression (log γ_2)/A was regressed against the δ_1 values of the solvent mixture at 25 °C for the analysis of data for caffeine (Adjei et al., 1980) and *p*-hydroxybenzoic acid (Wu and Martin, 1983) according to the EHS approach. The same technique was employed for paracetamol. The three polynomial equations and associated parameters * were calculated. The quartic expression was chosen as it provides precise results.

$$\frac{\log \gamma_2}{A} = 238.018614 - 56.6935650\delta_1 + 4.898113\delta_1^2 - 0.18369\delta_1^3 + 0.002602\delta_1^4 \quad (8)$$

$n = 20$; $s = 0.87$; $r^2 = 0.9818$;

$F(4,15,0.01) = 4.89$

Random scattering of points in the residual plots (scattergrams) for Eqn 8 was satisfactory. The (log γ_2)/A(calc) values were back calculated using Eqn 8 and are reported in Table 1. The mole fraction solubility of paracetamol (X_2(calc) values) are obtained from (log γ_2)/A(calc) (Eqn 1) and are listed in Table 1. The percent error at most of the points is approx. 20. The large error was expected because of small peaks and valleys in the solubility profile (Adjei et al., 1980). In fact, one of the limitations of the approach is that the regression expression (Eqn 8) is empirical and does not reflect acute changes in the solubility profile.

Determination of solubility parameter

The δ value of benzoic acid (Chertkoff and Martin, 1960) was determined by measuring the

* The statistical quantities associated with Eqn 8 are: r^2, squared correlation coefficient (index of determination); s, standard deviation; n, number of cases; $F(k,n-k-1,0.01)$, table value of F with k independent variables, and $(n-k-1)$ degrees of freedom at the 99% confidence level.

TABLE 1

Solubility of paracetamol in different solvent systems, at 25 °C

V_1	δ_1	ϕ_1 [a]	A [a]	X_2 (exp)	X_2 [b] (calc)	W [c] (exp)	W [d] (calc)	A [e]	Eqns 1 and 8			
									$(\log \gamma_2)/A$ (exp)	$(\log \gamma_2)/A$ (calc)	X_2 (calc)	Percent error
Ethyl acetate-methanol mixtures												
98.60	8.90	0.9990	0.08682	0.0066	0.00082	124.489	125.315	0.08563	9.9276	8.2568	0.00918	−39.05
92.81	9.46	0.9973	0.08652	0.0206	0.00212	132.469	131.915	0.08250	4.3139	5.3678	0.01686	18.14
87.02	10.02	0.9934	0.08584	0.0338	0.00489	139.160	138.479	0.07926	1.7777	3.1580	0.02627	22.27
75.44	11.14	0.9723	0.08225	0.0487	0.01777	151.937	151.678	0.07873	−0.2248	0.4355	0.04321	11.27
69.65	11.70	0.9539	0.07915	0.0506	0.02761	158.442	158.395	0.07312	−0.4691	−0.2324	0.04863	3.91
66.76	11.98	0.9434	0.07743	0.0519	0.03263	161.833	161.798	0.07928	−0.0571	−0.4239	0.05052	2.65
63.86	12.26	0.9329	0.07571	0.0519	0.03727	165.233	165.237	0.07167	−0.6321	−0.5312	0.05105	1.65
60.97	12.54	0.9228	0.07408	0.0471	0.04121	168.427	168.716	0.07936	−0.0403	−0.5617	0.05182	−10.01
58.07	12.82	0.9137	0.07262	0.0466	0.04196	171.946	172.238	0.07191	−0.0195	−0.5229	0.05099	−9.42
55.18	13.10	0.9059	0.07140	0.0458	0.04606	175.522	175.808	0.07147	0.1259	−0.4214	0.05012	−9.43
52.28	13.38	0.8998	0.07044	0.0471	0.04675	179.315	179.428	0.07032	−0.0455	−0.2638	0.04880	−3.61
49.39	13.66	0.8957	0.06979	0.0457	0.04625	183.007	183.101	0.07802	0.1269	−0.0559	0.04723	−3.35
46.49	13.94	0.8935	0.06945	0.0420	0.04462	186.607	186.831	0.07037	0.6622	0.1965	0.04530	−7.85
40.70	14.50	0.8955	0.06976	0.0421	0.03850	194.579	194.471	0.06835	0.6657	0.8140	0.04114	2.29
Methanol-water mixtures												
38.43	15.39	0.9308	0.07537	0.0317	0.02351	207.087	207.147	0.07176	2.3509	2.0288	0.03344	−5.49
36.16	16.28	0.9684	0.08159	0.0307	0.00984	221.180	220.531	0.07139	2.5592	3.4288	0.02661	13.32
31.62	18.06	0.9975	0.08656	0.0180	0.00066	249.746	249.565	0.07615	5.4432	6.5047	0.01494	16.98
27.08	19.84	0.9999	0.08698	0.0068	1.15×10^{-5}	281.781	281.656	0.08446	9.9124	9.8726	0.00685	−0.78
22.54	21.62	0.9999	0.08700	0.0024	6.17×10^{-8}	316.082	316.555	0.08483	15.1998	13.9910	0.00304	−26.64
18.00	23.40	0.9999	0.08700	0.0010	9.30×10^{-11}	353.964	353.682	0.08585	19.4467	19.9453	0.00090	9.37

$H_f = 6800$ cal/mol; m.p. = 170 °C; $V_2 = 118.66$ cm^3/mol; $\delta_2 = 13.4$ H.

[a] Φ was obtained by an iteration procedure and A was calculated accordingly (Eqn 4).

[b] Values are for regular solutions.

[c] From Eqn 12.

[d] From Eqn 13.

[e] From Eqn 4.

TABLE 2

Solubility of paracetamol in normal alcohol systems

Solvent(s)	V_1	δ_1	ϕ_1 [a]	A [a]	X_2 (exp)	X_2 [b] (calc)	W (exp)	Eqns 13, 6 and 1		
								W (calc)	X_2 (calc)	Percent error
Butanol	91.5	11.3	0.9747	0.06968	0.0292	0.02303	152.158	153.568	0.04618	−58.16
Propanol	75.2	12.0	0.9492	0.07838	0.0320	0.03282	160.730	162.042	0.05140	−60.64
Ethanol	58.5	13.0	0.9118	0.07230	0.0483	0.04550	174.378	174.527	0.05077	−5.12
Ethanol : methanol (1 : 1)	49.6	13.75	0.8969	0.06998	0.0451	0.04584	184.200	184.293	0.04649	−3.09
Methanol	40.7	14.5	0.8955	0.06976	0.0441	0.03849	194.723	194.471	0.04067	7.78

[a] ϕ was obtained by an iteration procedure and A was calculated accordingly (Eqn 4).
[b] X_2(calc) values are for regular solutions.

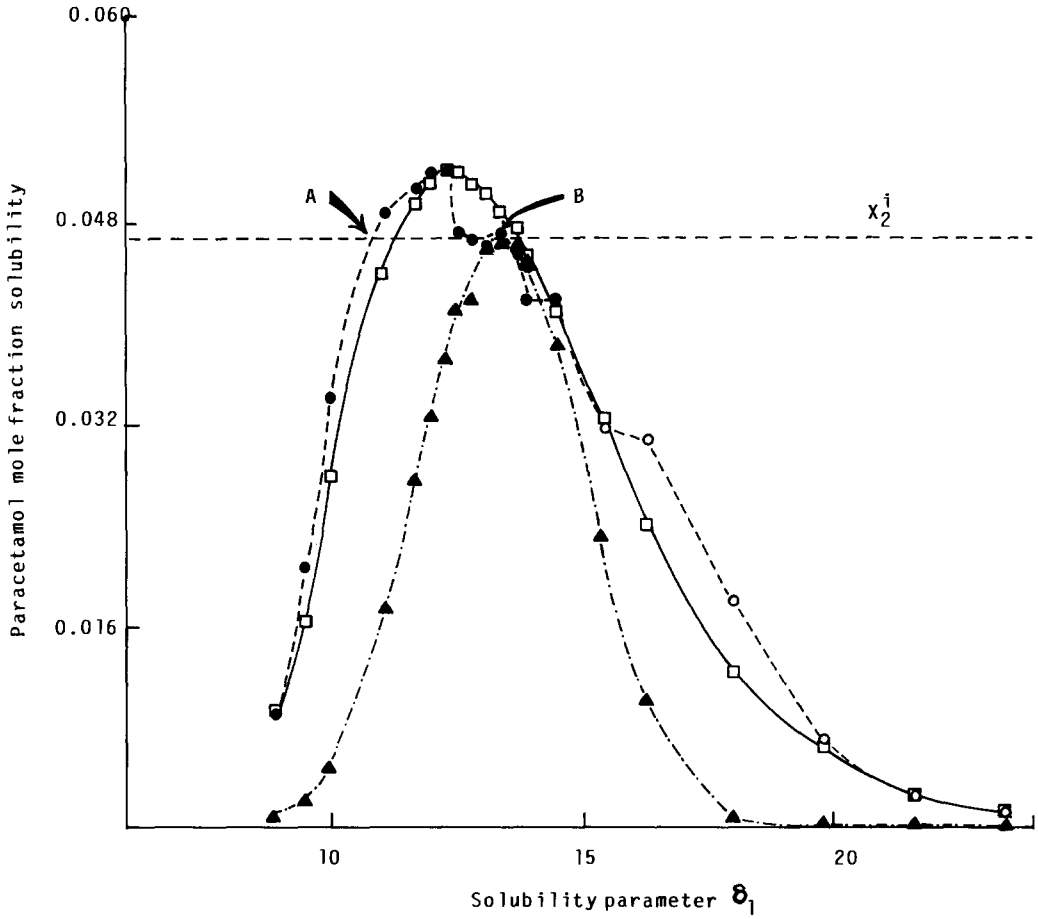

Fig. 1. Mole fraction solubility of paracetamol in different solvent systems at 25 °C. (- - - - -) Experimental; (———) based on regression of W (Eqn 13); (– · – · –) for regular solutions.

solubility in different solvent blends. It assumes the solution to be a regular solution in which the experimental mole fraction solubility of benzoic acid shows peak solubility and the δ value of solvent blend at peak solubility is taken as the solubility parameter of benzoic acid. In irregular solutions, these relations do not apply exactly as in regular solutions. In the case of the solubility of *p*-hydroxybenzoic acid in a dioxane-water system (Wu and Martin, 1983), the solute and solvent (Lewis acid-base) interaction might have unduly lowered the δ_2 value. Therefore, the peak solubility does not provide the δ value of solute in irregular solutions. According to regular solution theory, when $\delta_1 = \delta_2$, log γ_2 in Eqn 3 will become zero, i.e., the experimental mole fraction solubility is equal to the ideal mole fraction solubility (Eqn 1). It appears that the condition $X_2 = X_2^i$ is still valid, although the peak solubility technique was disregarded. The solubility parameter values (Fig. 1; points A and B) of paracetamol are 10.9 and 13.4 H. The value of 13.4 H may be a reasonable estimate of the solubility parameter for a polar compound like paracetamol. The mole fraction solubility was plotted vs the δ values of normal alcohols (Fig. 2). The δ_2 value for paracetamol was taken as 13.4 H (point B).

The solubility parameter of paracetamol, based on the group contribution method, was computed from molar attraction constants (Hoy, 1970) and substituent free energy constants (Fedors, 1974). The use of the experimental value of the molar volume (118.66 cm^3/mol) yields δ_2 values of 13.62 and 13.9 H, respectively.

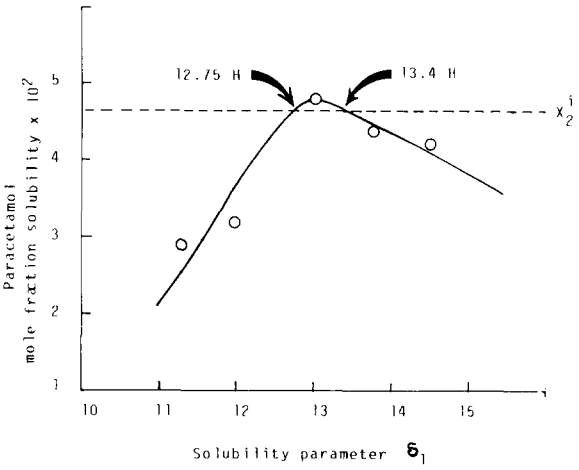

Fig. 2. Mole fraction solubility of paracetamol in normal alcohols at 25 °C.

The solubility parameters of parabens were determined (Martin and Carstensen, 1981) from solubility studies in a series of normal alcohols. The method involves the regression of (log γ_2)/A vs δ_1 in a second degree power series. The quadratic expression for paracetamol in solvent blends is

$$\frac{\log \gamma_2}{A} = 40.892 - 6.3014\delta_1 + 0.2422\delta_1^2 \qquad (9)$$

$n = 16$; $s = 0.6786$; $r^2 = 0.8752$;

$F(2,13,0.01) = 6.70$

or

$$\frac{\log \gamma_2}{A} = 0.2422\left(168.836 - 26.0173\delta_1 + \delta_1^2\right) \qquad (10)$$

To increase the accuracy and to decrease the s value, only 16 points were selected. Extreme points were omitted. The complete solubility equation equivalent to Eqn 10 is in the form

$$\log \gamma_2 = DA\left(\delta_1^2 + \delta_2^2 - 2K\delta_1\delta_2\right) \qquad (11)$$

where D is the coefficient of δ_1^2. Multiplication of A by D may be considered to yield an empirical coefficient; A is associated with the solubility parameter term. Comparison of Eqns 10 and 11 provides

$\delta_2^2 = 168.836$; $\delta_2 = 12.99$ H

$2K\delta_2 = 26.0173$; $K = 1.0014$

Processing the entire data for a second degree power series provided a δ value of 13.73 H. Therefore, the solubility parameter obtained for paracetamol is nearly in agreement with the value determined using other methods of analysis.

Eqn 11 can also be used to determine the mole fraction solubility of paracetamol by calculating the appropriate parameters.

Solubility predictions using regression of W against δ_1

There is no direct method to estimate the W term based on the fundamental physicochemical properties of the solute and solvent (Adjei et al., 1980). The W term can be calculated from the experimental solubility data using Eqns 6 and 1. Rearranging Eqn 6 for W

$$W = \frac{1}{2}\left(\delta_1^2 + \delta_2^2 - \frac{\log \gamma_2}{A}\right) \qquad (12)$$

W may be regressed vs a polynomial in δ_1 of the solvent mixture (Adjei et al., 1980). The quartic expression is

$$W = -32.9119 + 29.41338\delta_1 - 2.05647\delta_1^2 + 0.09635\delta_1^3 - 0.00137\delta_1^4 \qquad (13)$$

$n = 20$; $s = 0.418$; $r^2 = 1.0000$;

$F(4,15,0.01) = 4.89$

W(calc) values were obtained from Eqn 13 and the mole fraction solubility, X_2(calc), of paracetamol was calculated. The W(exp) and W(calc) values are presented in Table 1 and the X_2(calc) values are depicted in Fig. 1. The error at most of the points is below 20% and is quite high at extreme points where the solubility of paracetamol is quite low. The error of the order of 20% may be due to the peaks and valleys observed in the solubility profile of paracetamol. Eqn 13 was used to calculate the solubility of paracetamol in butanol, propanol, ethanol and methanol. Perusal of Table 2 indicates that the experimental W values agree with those calculated. The calculated X_2 values for ethanol, methanol and mixtures thereof have an error of 7%. The solubility in butanol and propanol showed an error of 60% as the latter are relatively less polar solvents.

The solubility of paracetamol in polar solvents gives irregular solutions. The EHS approach satisfactorily explains the solubility pattern with the help of polynomial regression expressions in terms of parameters W and $(\log \gamma_2)/A$. The solubility parameter of paracetamol as determined by different methods is as follows: present study, 13.4 H; Hoy's method, 13.6 H; Fedor's fragmental constants, 13.9 H; second degree polynomial of $(\log \gamma_2)/A$, 12.99 H. When the peak solubility is nearer to the ideal solubility, it may be appropriate to consider the solubility parameter of a polar drug molecule at a point that satisfies the condition $X_2 = X_2^i$ in irregular solutions.

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