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Prediction of solubility of sulfonamides in water and organic solvents based on the extended regular solution theory

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Summary

A method for prediction of the solubility of sulfonamides in water and in some organic solvents based on the modified Hildebrand-Scatchard equation for regular solutions is described Introduction into the equation of the dielectric constant or solvatochromic polarity parameter of the solvent allows the applicability of regular solution theory to be extended to polar systems which are widely employed in pharmaceutical practice The predicted solubilities of 14 sulfonamides in water at various temperatures and of eight sulfonamides in organic solvents of different polarity were compared with those determined experimentally

Several approaches have been employed to extend the Hildebrand solution theory (Hildebrand et al., 1970) to pharmaceutical solutions. Theoretical aspects concerning modification of the Hildebrand equation for ideal and non-ideal solutions have been described by various investigators (Adjei et al., 1980; Yalkowsky and Valvani, 1980; Martin et al., 1981, 1989; Grant and Abougela, 1983; Pinal and Yalkowsky, 1987, 1988; Bustamante et al., 1989).

This report is aimed at demonstrating how the introduction of the dielectric constant or solvatochromic polarity parameter of the solvent into the Hildebrand-Scatchard equation for regular solutions may be applied to the prediction of the solubility of sulfonamides in water and in various polar, semi-polar and non-polar organic solvents.

The proposed extended equations comprising the dielectric constant or solvatochromic polarity parameter $E_{T(30)}$ are expressed as:

$$-\log x_2 = \frac{\Delta H_f}{2.303RT} \cdot \frac{T_m - T}{T_m} + \frac{V_2 \cdot \phi_1^2}{2.303RT} \cdot \frac{(\delta_1 - \delta_2)^2}{\log\left[\epsilon\delta_1(\delta_1 - \delta_2)^2\right]} \quad (1)$$

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where x_2 is the mole fraction solubility of the solute, ΔH_f denotes the enthalpy of fusion (heat of fusion), R is the molar gas constant (1.9872 cal mol^{-1} deg^{-1}), T_m represents the melting point of the solute (in K), T is the absolute temperature at which the solubility is measured, V_2 corresponds to the molar volume of the solute, ϕ_1 is the volume fraction of the solvent, δ_1 and δ_2 denote the solubility parameters of the solvent and solute, respectively, and ϵ the dielectric constant.

The sulfonamides – sulfanilamide, sulfaproxyline, sulfadiazine, sulfamerazine, sulfadimidine, sulfamethoxypyridazine and sulfafurazole – were supplied by POLFA Pharmaceutical Works, Starogard, Poland. The compounds were recrystallized from benzene to constant melting point and their purity checked by TLC. Double-distilled water was used throughout this study.

The solubilities of the sulfonamides in water were determined in a shaker bath at 20, 25, 30, 37, 42 and 50 ± 0.5°C employing 50 ml screw-capped vials containing solvent at a given temperature and excess drug. Equilibrium was attained after 3 h. Subsequently, the samples were withdrawn from the bath and passed through a G_T-4 sintered glass filter. Concentrations of dissolved solutes were assayed spectrophotometrically at 255, 265, 255, 255, 258, 258 and 254 nm for sulfanilamide, sulfaproxyline, sulfadiazine, sulfamerazine, sulfadimidine, sulfamethoxypyridazine and sulfafurazole, respectively.

The experimental solubilities of sulfanilamide, sulfapyridine, sulfatiazole, sulfamethyltiazole, sulfametizole, sulfafenazole and acetylsulfanilamide in water at temperatures ranging from 20 to 75°C and for sulfanilamide, sulfapyridine, sulfatiazole, sulfamerazine, sulfadiazine, sulfamethoxazole, sulfisoxazole and sulfaguanidine in a number of organic solvents were compiled from literature data (Paruta and Piękoś, 1988, 1989). Some of the solubility data for individual temperatures were obtained from linear plots of $\log x_2$ vs T by interpolation or extrapolation.

Apparent heats of fusion (ΔH_f^{app}) were calculated based on the simplified formula given by Yalkowsky and Valvani (1980):

$$\Delta H_f^{app} = \frac{0.01(T_m - T) \cdot R}{\log \frac{T_m}{T}} \cdot T_m$$

TABLE 1

Some physicochemical properties of the solutes and solvents analyzed

Solute	Enthalpy of fusion (ΔH_f^{app})	Molar volume (V_2) (cm^3/mol)	Solubility parameter ($cal^{1/2}$ $cm^{-3/2}$)		
			δ_2	Solvent	δ_1
Orthanilamide	7035	110 4	12.98	water	24.52
Sulfanilamide	7304	110 4	12 98	methanol	13 77
Acetylsulfanilamide	7702	134 2	13.58	ethanol	12.58
Sulfaguanidine	7912	113 9	14.41	propanol-1	11.84
Sulfapyridine	7978	158.6	13 05	propanol-2	10 24
Sulfadiazine	9723	150 1	13.85	butanol-1	11 33
Sulfamethoxazole	7393	152.1	13.19	pentanol-1	10.96
Sulfatiazole	8231	145.8	13 84	octanol-1	10 28
Sulfamerazine	9185	164 6	13 48	decanol-1	10.01
Sulfisoxazole	8035	166 6	12 87	acetone	9.07
Sulfafurazole	8111	166.6	12.87	benzene	9 19
Sulfamethyltiazole	9579	160 3	13 46	chloroform	8 77
Sulfametizole	8461	151 8	14.25		
Sulfadimidine	8152	179 1	13 16		
Sulfamethoxypyridazine	7720	168 4	13 50		
Sulfafenazole	7702	196 2	12 95		
Sulfaproxyline	7859	222 9	12 55		

TABLE 2

Aqueous solubility of sulfonamides at various temperatures

Sulfonamide	Temperature (°C)	Solubility					
		Predicted				Determined experimentally	
		Eqn 1		Eqn 2		mol/l	log x_2
		mol/l	log x_2	mol/l	log x_2		
(1) Orthanilamide	37	2.68×10^{-2}	−3.316			6.97×10^{-2}	−2.896 [a]
	42	$3\,37 \times 10^{-2}$	−3.217			$8\,48 \times 10^{-2}$	−2.810 [a]
	50	4.75×10^{-2}	−3.068			1.16×10^{-1}	−2 671 [a]
(2) Sulfanilamide	20	8.55×10^{-3}	−3 812	7.77×10^{-3}	−3 854	$3\,10 \times 10^{-2}$	−3.254 [a]
	25	1.09×10^{-2}	−3 706	1.00×10^{-2}	−3 742	4.26×10^{-2}	−3.112 [b]
	30	$1\,40 \times 10^{-2}$	−3.599	$1\,30 \times 10^{-2}$	−3 631	5.46×10^{-2}	−3 003 [b]
	37	1.94×10^{-2}	−3.457			8.34×10^{-2}	−2 822 [a]
	42	$2\,44 \times 10^{-2}$	−3.358			$8\,40 \times 10^{-2}$	−2 817 [b]
	50	3.47×10^{-2}	−3.204			1.57×10^{-1}	−2 550 [b]
	75	$9\,95 \times 10^{-2}$	−2 747			$4\,76 \times 10^{-1}$	−2.070 [a]
(3) Acetylsulfanil-amide	20	$3\,14 \times 10^{-3}$	−4.247	2.84×10^{-3}	−4 292	$6\,21 \times 10^{-3}$	−3 951 [a]
	25	$4\,07 \times 10^{-3}$	−4.135	$3\,71 \times 10^{-3}$	−4.175	7.80×10^{-3}	−3 852 [c]
	30	5.26×10^{-3}	−4.023	$4\,85 \times 10^{-3}$	−4.058	$9\,96 \times 10^{-3}$	−3.746 [c]
	37	6.99×10^{-3}	−3.900			1.35×10^{-2}	−3.613 [a]
	42	$9\,49 \times 10^{-3}$	−3 767			$1\,77 \times 10^{-2}$	−3.497 [c]
	50	1.38×10^{-2}	−3 604			2.48×10^{-2}	−3 350 [a]
	75	4.13×10^{-2}	−3.128			$7\,17 \times 10^{-2}$	−2.893 [a]
(4) Sulfapyridine	20	4.94×10^{-4}	−5.051	4.33×10^{-4}	−5.108	7.70×10^{-4}	−4.853 [a]
	25	6.60×10^{-4}	−4.924	5.88×10^{-4}	−4.975	1.08×10^{-3}	−4 713 [a]
	30	$8\,77 \times 10^{-4}$	−4.801	7.88×10^{-4}	−4.848	2.00×10^{-3}	−4.441 [a]
	37	$1\,29 \times 10^{-3}$	−4 635			2.17×10^{-3}	−4.408 [a]
	42	1.67×10^{-3}	−4 521			2.65×10^{-3}	−4 321 [a]
	50	$2\,54 \times 10^{-3}$	−4 340			3.77×10^{-3}	−4 167 [a]
	75	8.44×10^{-3}	−3.818			9.63×10^{-3}	−3 760 [a]
(5) Sulfadiazine	20	1.46×10^{-4}	−5.580	1.31×10^{-4}	−5.627	1.81×10^{-4}	−5 486 [a]
	25	$1\,98 \times 10^{-4}$	−5 449	1.79×10^{-4}	−5.492	$2\,74 \times 10^{-4}$	−5.307 [b]
	30	2.66×10^{-4}	−5.320	$2\,44 \times 10^{-4}$	−5.358	3.04×10^{-4}	−5 262 [a]
	37	3.99×10^{-4}	−5 143			$5\,11 \times 10^{-4}$	−5.035 [a]
	42	5.26×10^{-4}	−5.023			$5\,54 \times 10^{-4}$	−5.001 [b]
	50	8.21×10^{-4}	−4.830			7.51×10^{-4}	−4 869 [b]
	75	2.92×10^{-3}	−4.279			2.16×10^{-3}	−4.409 [c]
(6) Sulfathiazole	20	$1\,28 \times 10^{-3}$	−4 636	1.15×10^{-3}	−4.682	$1\,39 \times 10^{-3}$	−4.600 [a]
	25	1.67×10^{-3}	−4.522	1.52×10^{-3}	−4.563	1.84×10^{-3}	−4 480 [a]
	30	$2\,12 \times 10^{-3}$	−4 418	1.95×10^{-3}	−4 454	2.40×10^{-3}	−4.364 [a]
	37	3.15×10^{-3}	−4.246			3.44×10^{-3}	−4 207 [a]
	42	4.06×10^{-3}	−4.136			$4\,52 \times 10^{-3}$	−4.089 [c]
	50	5.99×10^{-3}	−3.966			6.58×10^{-3}	−3 925 [a]
	75	$1\,89 \times 10^{-3}$	−3.467			2.09×10^{-2}	−3.425 [a]
(7) Sulfamerazine	20	1.20×10^{-4}	−5 664	1.06×10^{-4}	−5.719	4.82×10^{-4}	−5.061 [b]
	25	1.65×10^{-4}	−5 527	1.48×10^{-4}	−5 575	$6\,26 \times 10^{-4}$	−4 947 [b]
	30	2.23×10^{-4}	−5.396	2.01×10^{-4}	−5.440	7.15×10^{-4}	−4.890 [b]
	37	$3\,35 \times 10^{-4}$	−5.220			$9\,65 \times 10^{-4}$	−4.760 [a]
	42	$4\,45 \times 10^{-4}$	−5.096			1.12×10^{-3}	−4.694 [b]
	50	6.88×10^{-4}	−4 907			1.89×10^{-3}	−4.467 [a]
	75	$2\,50 \times 10^{-3}$	−4 347			6.52×10^{-3}	−3 930 [a]

(continued overleaf)

TABLE 2 (continued)

Sulfonamide	Temperature (°C)	Solubility					
		Predicted				Determined experimentally	
		Eqn 1		Eqn 2		mol/l	log x_2
		mol/l	log x_2	mol/l	log x_2		
(8) Sulfafurazole	20	2.43×10^{-4}	−5.359	2.10×10^{-4}	−5.421	3.84×10^{-4}	−5.160 [b]
	25	3.27×10^{-4}	−5.230	2.88×10^{-4}	−5.285	4.64×10^{-4}	−5.077 [b]
	30	4.38×10^{-4}	−5.103	3.92×10^{-4}	−5.151	6.45×10^{-4}	−4.935 [b]
	37	6.49×10^{-4}	−4.931			8.37×10^{-4}	−4.822 [b]
	42	8.60×10^{-4}	−4.810			1.02×10^{-3}	−4.734 [b]
	50	1.32×10^{-3}	−4.626			1.26×10^{-3}	−4.645 [b]
	75	4.56×10^{-3}	−4.085			3.20×10^{-3}	−4.239 [c]
(9) Sulfamethyl-thiazole	20	8.21×10^{-5}	−5.831	7.23×10^{-5}	−5.885	3.27×10^{-4}	−5.230 [a]
	25	1.12×10^{-4}	−5.695	1.00×10^{-4}	−5.743	4.32×10^{-4}	−5.109 [c]
	30	1.47×10^{-4}	−5.579	1.33×10^{-4}	−5.621	5.65×10^{-4}	−4.992 [c]
	37	2.32×10^{-4}	−5.379			8.17×10^{-4}	−4.832 [a]
	42	3.09×10^{-4}	−5.254			1.06×10^{-3}	−4.717 [c]
	50	4.82×10^{-4}	−5.061			1.57×10^{-3}	−4.548 [a]
	75	4.78×10^{-3}	−4.493			4.83×10^{-3}	−4.060 [a]
(10) Sulfametizole	37	2.77×10^{-3}	−4.302			3.27×10^{-3}	−4.229 [a]
(11) Sulfadimidine	20	1.91×10^{-4}	−5.463	1.65×10^{-4}	−5.526	1.19×10^{-3}	−4.670 [a]
	25	2.58×10^{-4}	−5.333	2.26×10^{-4}	−5.389	1.52×10^{-3}	−4.563 [b]
	30	3.48×10^{-4}	−5.203	3.11×10^{-4}	−5.252	1.74×10^{-3}	−4.504 [b]
	37	5.19×10^{-4}	−5.029			2.09×10^{-3}	−4.423 [b]
	42	6.88×10^{-4}	−4.907			2.39×10^{-3}	−4.365 [b]
	50	1.06×10^{-3}	−4.719			3.15×10^{-3}	−4.243 [b]
	75	3.72×10^{-3}	−4.173			5.44×10^{-3}	−4.008 [c]
(12) Sulfamethoxy-pyridazine	20	7.66×10^{-4}	−4.860	6.77×10^{-4}	−4.914	1.85×10^{-3}	−4.476 [b]
	25	1.02×10^{-3}	−4.738	9.05×10^{-4}	−4.788	2.07×10^{-3}	−4.427 [b]
	30	1.34×10^{-3}	−4.618	1.21×10^{-3}	−4.662	2.82×10^{-3}	−4.287 [b]
	37	1.95×10^{-3}	−4.453			3.78×10^{-3}	−4.166 [b]
	42	2.52×10^{-3}	−4.342			4.47×10^{-3}	−4.093 [b]
	50	3.80×10^{-3}	−4.164			6.39×10^{-3}	−3.938 [b]
	75	1.23×10^{-2}	−3.656			1.54×10^{-2}	−3.554 [c]
(13) Sulfafenazole	30	2.39×10^{-4}	−5.366	2.10×10^{-4}	−5.422	4.77×10^{-4}	−5.066 [a]
(14) Sulfaproxyline	20	1.85×10^{-5}	−6.476	1.52×10^{-5}	−6.562	5.01×10^{-5}	−6.044 [b]
	25	2.59×10^{-5}	−6.331	2.17×10^{-5}	−6.408	5.64×10^{-5}	−5.993 [b]
	30	3.60×10^{-5}	−6.188	3.08×10^{-5}	−6.256	7.04×10^{-5}	−5.897 [b]
	37	5.65×10^{-5}	−5.992			8.84×10^{-5}	−5.799 [b]
	42	7.73×10^{-5}	−5.856			9.82×10^{-5}	−5.752 [b]
	50	1.25×10^{-4}	−5.649			1.33×10^{-4}	−5.619 [b]
	75	5.01×10^{-4}	−5.044			2.61×10^{-4}	−5.327 [c]

[a] Taken from literature data (Paruta and Piękoś, 1988, 1989)
[b] Obtained in this work.
[c] Obtained by inter- or extrapolation.

The volume fraction of the solvent, ϕ_1, was generally assumed to equal unity.

Evaluation of V_1, δ_1 and δ_2 was based on the atomic and group additive constants of the energy of vaporization and molar volume proposed by Fedors (1974). The values obtained for the solutes and solvents considered are collected in Table 1. After introducing into Eqns 1 and 2 all

the parameters calculated, i.e., ΔH_f^{app}, ϕ_1, V_2 and δ_2 as well as those taken from the literature, e.g. ϵ (Reichardt, 1979) and $E_{T(30)}$ (Dimroth et al., 1963), the predicted solubilities for the sulfonamides were calculated. These values, along with those determined experimentally, are presented in Tables 2 and 3.

Regression analysis of the data led to the following results:

$$\log x_{2calc} = 0.9332(\log x_{2exp}) - 0.5904$$

log x_2 calculated according to Eqn 1

$$n = 82, \quad r = 0.9616, \quad s = 0.1321$$

$$\log x_{2calc} = 0.9494(\log x_{2exp}) - 0.605$$

log x_2 calculated according to Eqn 2

$$n = 34, \quad r = 0.9540, \quad s = 0.205$$

TABLE 3

Solubility of sulfonamides in some organic solvents at 25°C

Sulfonamide	Solvent	Solubility					
		Predicted				Determined experimentally [a]	
		Eqn 1		Eqn 2		mol/l	log x_2
		mol/l	log x_2	mol/l	log x_2		
(1) Sulfanilamide	2-propanol	2.12×10^{-1}	−1.900	2.24×10^{-1}	−1.876	4.63×10^{-2}	−2.557
	1-butanol	2.24×10^{-1}	−1.788	2.29×10^{-1}	−1.777	1.89×10^{-2}	−2.854
	acetone	1.62×10^{-1}	−2.031	1.74×10^{-1}	−2.001	1.42	−1.118
(2) Sulfapyridine	2-propanol	6.82×10^{-2}	−2.389	7.34×10^{-2}	−2.358	7.02×10^{-3}	−3.375
	acetone	4.02×10^{-2}	−2.633	4.45×10^{-2}	−2.589	5.99×10^{-2}	−2.460
(3) Sulfadiazine	methanol	2.45×10^{-2}	−3.105	2.46×10^{-2}	−3.104	4.71×10^{-3}	−3.821
	ethanol	1.47×10^{-2}	−3.169	1.50×10^{-2}	−3.162	1.32×10^{-3}	−4.216
	1-propanol	9.32×10^{-3}	−3.252	9.71×10^{-3}	−3.234	5.59×10^{-4}	−4.474
	2-propanol	5.02×10^{-3}	−3.522	5.53×10^{-3}	−3.479	1.72×10^{-3}	−3.986
	1-butanol	6.34×10^{-3}	−3.328	6.76×10^{-3}	−3.300	3.48×10^{-4}	−4.588
	1-pentanol	4.53×10^{-3}	−3.399			2.44×10^{-4}	−4.667
	1-decanol	1.48×10^{-3}	−3.630			3.88×10^{-4}	−4.212
(4) Sulfathiazole	2-propanol	5.81×10^{-2}	−2.458	6.10×10^{-2}	−2.438	2.25×10^{-2}	−2.870
	acetone	1.93×10^{-2}	−2.951	2.19×10^{-2}	−2.896	7.24×10^{-2}	−2.378
(5) Sulfamerazine	2-propanol	1.13×10^{-2}	−3.170	1.23×10^{-2}	−3.130	6.58×10^{-3}	−3.403
(6) Sulfamethoxazole	methanol	5.27×10^{-1}	−1.781	5.27×10^{-1}	−1.780	3.56×10^{-1}	−1.948
	2-propanol	2.29×10^{-1}	−1.866	2.36×10^{-1}	−1.854	3.50×10^{-2}	−2.678
	benzene	4.39×10^{-2}	−2.466	7.39×10^{-2}	−2.241	2.00×10^{-3}	−3.806
	chloroform	2.61×10^{-2}	−2.507	3.95×10^{-2}	−2.328	9.10×10^{-3}	−2.964
(7) Sulfaguanidine	2-propanol	9.20×10^{-2}	−2.260	9.66×10^{-2}	−2.239	8.26×10^{-3}	−3.304
	acetone	3.50×10^{-2}	−2.693	3.90×10^{-2}	−2.646	7.38×10^{-2}	−2.370
(8) Sulfisoxazole	methanol	2.02×10^{-1}	−2.192	2.03×10^{-1}	−2.189	1.84×10^{-1}	−2.232
	ethanol	1.51×10^{-1}	−2.161	1.51×10^{-1}	−2.160	7.14×10^{-2}	−2.484
	1-propanol	1.04×10^{-1}	−2.207	1.06×10^{-1}	−2.200	2.97×10^{-2}	−2.749
	1-butanol	7.43×10^{-2}	−2.261	7.71×10^{-2}	−2.246	1.61×10^{-2}	−2.924
	1-pentanol	5.52×10^{-2}	−2.315			9.80×10^{-3}	−3.064
	1-octanol	2.81×10^{-2}	−2.439			3.52×10^{-3}	−3.339
	1-decanol	1.98×10^{-2}	−2.506			2.13×10^{-3}	−3.472

[a] Taken from literature data (Paruta and Piękoś, 1988, 1989).

Regarding the effect of the temperature at which solubility occurs on the dielectric constant, the following correction was taken into account:

$$\epsilon = 78.54\left[1 - 4.579 \times 10^{-3}(t - 25) + 1.19 \times 10^{-5}(t - 25)^2 - 2.8 \times 10^{-8}(t - 25)^3\right]$$

where t is the temperature (in °C) at which the solubility is measured.

The extended formulae, Eqns 1 and 2, can be also used in predicting the solubility of sulfonamides in organic solvents. In Table 3 experimental data are listed for eight sulfonamides in solvents of different polarity at 25°C. The data may be compared with those predicted on the basis of Eqns 1 and 2. Satisfactory agreement is obtained as in the case of the aqueous solubility.

The results obtained in the present study indicate that the proposed extended Eqns 1 and 2 can be employed to determine reasonable estimates of the aqueous solubility of weak electrolytes such as sulfonamides within the temperature range from 20 to 75°C. The extended equations are not only reliable for estimating the aqueous solubility but can also be used in solubility prediction for sulfonamides in organic solvents of various polarity.

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