RESULTS AND DISCUSSION

Standard Curves Determination

Typical standard curves and data for phenobarbital and sulfadiazine concentrations in individual pure solvents as determined using simple linear regression are presented in Figures 1, 2 and Tables I, II, III and IV, respectively. The coefficient of determination of the fit to the straight lines were highly significant ($R^2 = 0.999$)

Molar Heat of Fusion, ΔHf, Determination

Some parameters used in the ΔHf determination by differential scanning colorimeter are listed in Table V. The molar heat of fusion of phenobarbital was calculated employing Eq. 23 and found to be 11,582.38 cal/mole. Meanwhile, the ΔHf value of sulfadiazine (9,740 cal/mole) was taken from the literature (1). These values were used for calculating the ideal solubilities of both drugs in this study.

Data Analysis

The molar volume and solubility parameters of phenobarbital, sulfadiazine, and individual pure solvents are reported in Table VI. The observed densities, the mole fraction solubilites ($X_{2\ obs}$), the volume fraction of the solvent ($\phi_{1\ obs}$), and the A_{obs} of phenobarbital and sulfadiazine are demonstrated in Tables VII and VIII, respectively. The ideal mole fraction solubilities of phenobarbital and sulfadiazine, X_2^i, were established as 193.32×10^5 and 103.95×10^5, respectively.

Tabel I Typical Standard Curve Data for Phenobarbital Concentration
in N-Butyl Alcohol Estimated Using Simple Linear Regression[1]

Std. No.	Conc. (μg/ml)	Absorbance	Inversely estimated concentration[2]	% Theory[3]
1	100	0.149	99.0105	99.01
2	150	0.223	152.6184	101.75
3	200	0.289	200.4309	100.22
4	250	0.355	248.2434	99.30
5	300	0.427	300.4025	100.13
6	350	0.492	347.4905	99.28
7	400	0.562	398.2007	99.55
8	450	0.643	456.8797	101.53
9	500	0.698	496.7234	99.34
			Mean	100.01
			S.D.	1.00
			C.V.[4]	1.00

[1] R^2 = 0.9995

[2] Inversely estimated concentration = (Absorbance – 0.0125)/0.0014

[3] % Theory = $\dfrac{\text{Inversely estimated concentration}}{\text{known concentration}}$ × 100

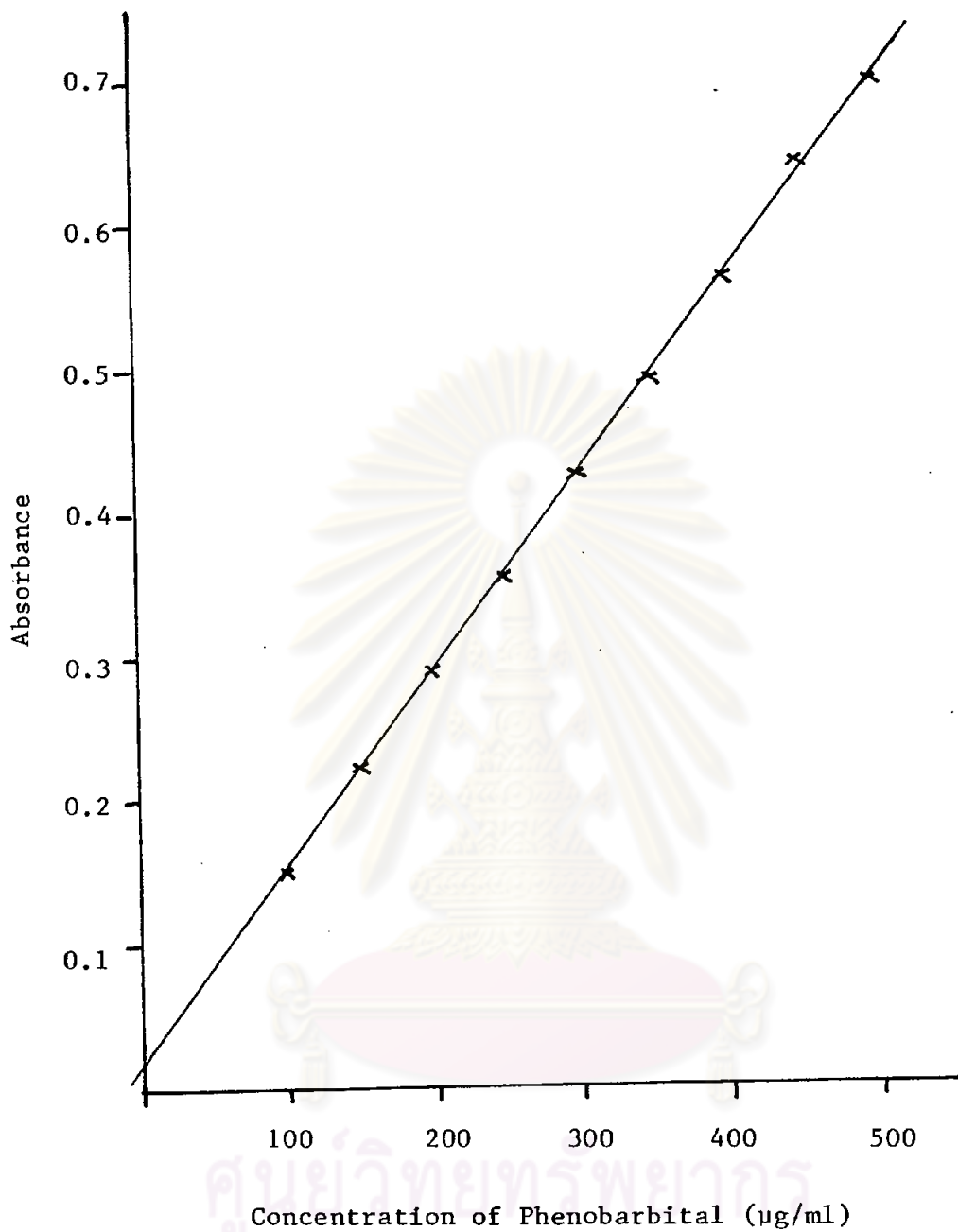[4] Coefficient of variation = $\dfrac{\text{S.D.}}{\text{Mean}}$ × 100

Fig 1 : Typical standard curve for phenobarbital concentration in n–butyl alcohol at 30°C

Table II Standard Curve Data for Phenobarbital Concentration in

Individual Pure Solvents at 30° C Estimated Using Simple

Linear Regression

No.	Solvents	Standard equations $y^{(1)} = a^{(2)} + b^{(3)} x^{(4)}$	$R^{2(5)}$	C.V.$^{(6)}$
1	Diethyl ether	y = -0.0752 + 0.0011 x	0.9992	0.87
2	Ethyl acetate	y = 0.1821 + 0.00002 x	0.9998	1.03
3	Chloroform	y = 0.2203 + 0.0002 x	0.9985	1.94
4	1, 4-Dioxane	y = -0.0816 + 0.0013 x	0.9991	1.16
5	Tert-Butyl alcohol	y = 0.0621 + 0.0013 x	0.9991	1.42
6	Amyl alcohol	y = 0.0376 + 0.0013 x	0.9995	1.64
7	Isobutyl alcohol	y = 0.0088 + 0.0013 x	0.9997	0.63
8	N-Butyl alcohol	y = 0.0125 + 0.0014 x	0.9995	1.00
9	Isopropyl alcohol	y = 0.0443 + 0.0400 x	0.9993	1.94
10	N-Propyl alcohol	y = 0.0130 + 0.0041 x	0.9997	0.91
11	Acetonitrile	y = 0.0146 + 0.0011 x	0.9996	0.69
12	Ethylene glycol monomethyl ether	y = 0.0123 + 0.0012 x	0.9996	0.88
13	Ethyl alcohol	y = 0.0046 + 0.0013 x	0.9996	0.83
14	Methyl alcohol	y = 0.0222 + 0.0014 x	0.9988	1.36
15	Propylene glycol	y = 0.0299 + 0.0013 x	0.9992	1.44
16	Ethylene glycol	y = 0.0450 + 0.0014 x	0.9996	1.33
17	Glycerin	y = 0.0218 + 0.0013 x	0.9992	1.54
18	Water	y = 0.0399 + 0.0014 x	0.9988	1.51

[1] y = Absorbance

[2] a = y-intercept

[3] b = Slope of the straight line

[4] x = Concentrations (μg/ml)

[5] R^2 = Coefficient of determination

[6] C.V. = Coefficient of variation

$= \dfrac{S.D.}{Mean} \times 100$

Table III Typical Standard Curve Data for Sulfadiazine Concentration in N-Butyl Alcohol Estimated Using Simple Linear Regression[1]

Std. No.	Conc. (μg/ml)	Absorbance	Inversely estimated concentration[2]	% Theory[3]
1	4	0.185	3.9953	99.88
2	6	0.275	5.9738	99.56
3	8	0.368	8.0183	100.23
4	10	0.459	10.0188	100.19
5	12	0.552	12.0633	100.53
6	14	0.636	13.9100	99.36
7	16	0.732	16.0205	100.13
			Mean	99.98
			S.D.	0.41
			C.V.[4]	0.41

[1] R^2 = 0.9999

[2] Inversely estimated concentration = (Absorbance − 0.0033)/0.0455

[3] % Theory = $\dfrac{\text{Inversely estimated concentration}}{\text{known concentration}}$ × 100

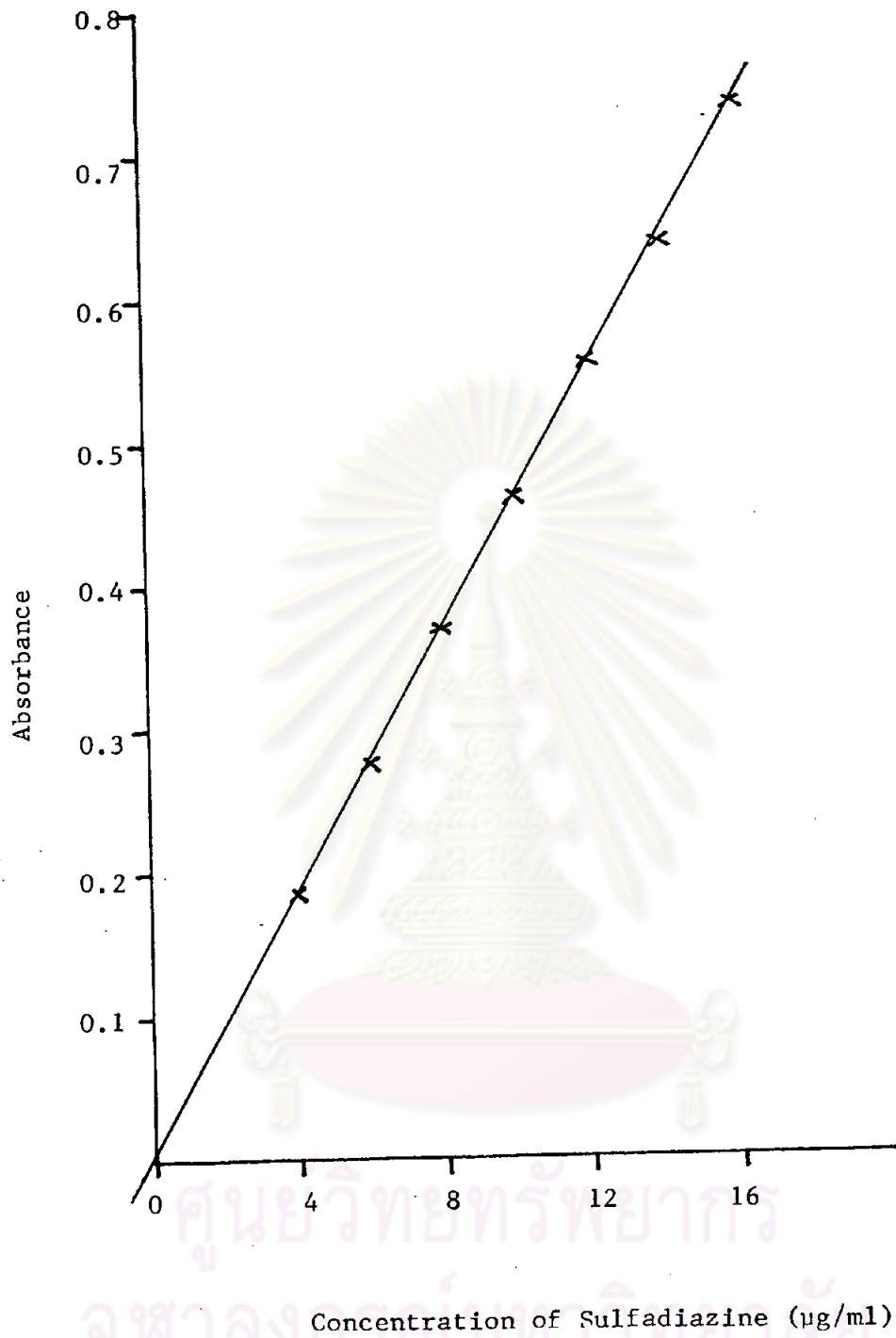[4] Coefficient of variation = $\dfrac{\text{S.D.}}{\text{Mean}}$ × 100

Fig 2 : Typical standard curve for sulfadiazine concentration
in n-butyl alcohol at 30°C

Table IV   Standard Curve Data for Sulfadiazine Concentration in

Individual Pure Solvents at 30° C Estimated Using Simple

Linear Regression

No.	Solvents	Standard equations $y^{(1)} = a^{(2)} + b^{(3)} x^{(4)}$	$R^{2(5)}$	$C.V^{(6)}$
1	Diethyl ether	y = 0.0184 + 0.0371 x	0.9999	0.36
2	Ethyl acetate	y = -0.0131 + 0.0476 x	0.9997	1.04
3	Chloroform	y = 0.0008 + 0.0527 x	0.9999	0.46
4	1, 4-Dioxane	y = 0.0124 + 0.0469 x	0.9999	0.76
5	Tert-Butyl alcohol	y = 0.0117 + 0.0396 x	0.9998	0.72
6	Amyl alcohol	y = 0.0102 + 0.0396 x	0.9988	1.65
7	Sec-Butyl alcohol	y = 0.0701 + 0.0421 x	0.9977	2.51
8	Isobutyl alcohol	y = 0.0034 + 0.0438 x	0.9996	0.84
9	N-Butyl alcohol	y = 0.0033 + 0.0455 x	0.9999	0.41
10	Isopropyl alcohol	y = 0.0200 + 0.0374 x	0.9993	2.23
11	N-Propyl alcohol	y = 0.0160 + 0.0389 x	0.9986	2.11
12	Acetonitrile	y = -0.0017 + 0.0431 x	0.9999	0.30
13	Ethylene glycol monomethyl ether	y = -0.0011 + 0.0365 x	0.9998	0.56
14	Ethyl alcohol	y = 0.0467 + 0.0281 x	0.9996	0.71
15	Methyl alcohol	y = 0.0035 + 0.0527 x	0.9999	0.61
16	Propylene glycol	y = 0.0052 + 0.0374 x	0.9999	0.95
17	Ethylene glycol	y = 0.0202 + 0.0437 x	0.9987	1.84
18	Glycerin	y = -0.0672 + 0.0216 x	0.9957	1.66
19	Water	y = 0.0319 + 0.0560 x	0.9999	0.33

[1] y = Absorbance

[2] a = y-intercept

[3] b = Slope of the straight line

[4] x = Concentrations (μg/ml)

[5] R^2 = Coefficient of determination

[6] C.V = Coefficient of variation

$= \dfrac{S.D.}{Mean} \times 100$

Table V Some Physical Properties of Phenobarbital and Indium

Parameters	Phenobarbital (Sample)	Indium (Standard)
Atomic or Molecular weight	232.24	114.82
Experimental weight (mg)	2.80	17.00
Peak area* (cm^2)	5.06	4.19
ΔHf (cal/mole)	11,582.38	781.00
Sensitivity (mcal/sec)	1.00	1.00

*Calculated by Peak height at max. X Peak width at half height method

  (Ref 36)
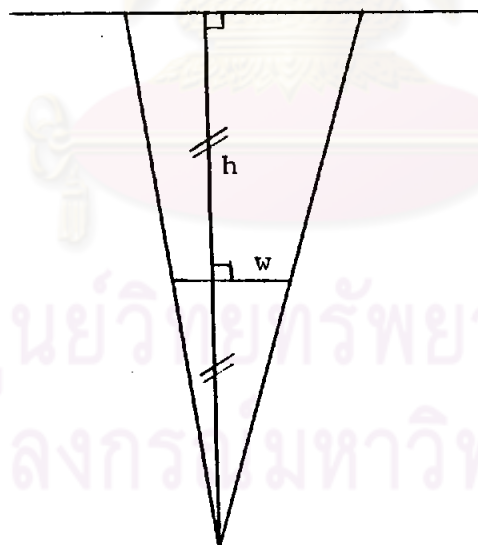
Peak area (cm^2)   =   h × w

Table VI Molar Volume and Solubility Parameters of Phenobarbital, Sulfadiazine, and Individual Pure Solvents (1, 11, 18-21)

No.	Chemicals	$V(cm^3/mole)$	Solubility Parameter $(cal/cm^3)^{\frac{1}{2}}$			
			δ_D	δ_P	δ_H	δ_{total}
1	Phenobarbital	137.0	10.3	4.8	5.3	12.60
2	Sulfadiazine	182.0	9.5	4.8	6.6	12.50
3	Diethyl ether	104.8	7.1	1.4	2.5	7.66
4	Ethyl acetate	98.5	7.4	2.6	4.5	9.04
5	Chloroform	80.8	8.7	1.5	2.8	9.26
6	1, 4-Dioxane	85.7	9.3	0.9	3.6	10.01
7	Tert-Butyl alcohol	94.3	7.3	2.5	6.8	10.28
8	Amyl alcohol	109.0	7.8	2.2	6.8	10.58[*]
9	Sec-Butyl alcohol	92.5	7.7	2.8	7.1	10.83
10	Isobutyl alcohol	92.4	7.4	2.8	7.8	11.13
11	N-Butyl alcohol	92.0	7.8	2.8	7.7	11.29
12	Isopropyl alcohol	76.9	7.7	3.0	8.0	11.50
13	N-Propyl alcohol	75.1	7.8	3.3	8.5	11.99
14	Acetonitrile	52.6	7.5	8.8	3.0	12.00
15	Ethylene glycol monomethyl ether	79.1	7.9	4.5	8.0	12.10
16	Ethyl alcohol	58.7	7.7	4.3	9.5	12.96
17	Methyl alcohol	40.7	7.4	6.0	10.9	14.49
18	Propylene glycol	73.6	8.2	4.6	11.4	14.80
19	Ethylene glycol	55.9	8.3	5.4	12.6	15.99
20	Glycerin	73.2	8.5	5.9	14.3	17.64
21	Water	18.1	7.6	7.8	20.7	23.40

[*] Calculated by Eq.21

Table VII Observed Solubilities of Phenobarbital in Individual Pure

Solvents at 30°C

No.	Solvents	Solution density	$X_{2\ obs}^{(1)} \times 10^5$	$\phi_{1\ obs}^{(2)} \times 10^4$	$A_{obs}^{(3)} \times 10^4$
1	Diethyl ether	0.7397	3095.00	9599.22	909.91
2	Ethyl acetate	0.9157	4416.98	9396.09	871.81
3	Chloroform	1.3885	2585.99	9569.28	904.24
4	1, 4-Dioxane	1.1216	7190.98	8897.89	781.81
5	Tert-Butyl alcohol	0.8146	4059.98	9420.81	876.40
6	Amyl alcohol	0.8342	4981.01	9381.86	869.17
7	Isobutyl alcohol	0.8148	3883.99	9434.72	878.99
8	N-Butyl alcohol	0.8425	4684.03	9318.11	857.40
9	Isopropyl alcohol	0.8450	4422.01	9238.52	842.82
10	N-Propyl alcohol	0.8416	4313.99	9240.05	843.09
11	Acetonitrile	0.8237	2593.01	9351.61	863.58
12	Ethylene glycol monomethyl ether	1.0040	4814.12	9194.58	834.82
13	Ethyl alcohol	0.8476	3595.00	9199.35	835.68
14	Methyl alcohol	0.8360	2347.99	9251.24	845.14
15	Propylene glycol	1.0090	2585.00	9529.31	896.71
16	Ethylene glycol	1.0731	1825.00	9564.26	903.30
17	Glycerin	1.1590	904.99	9831.95	954.57
18	Water	1.0316	11.65	9991.19	985.74

[1] Mole fraction solubilities obtained experimentally

[2] Observed volume fraction of the solvent calculated by Eq. 12

[3] Calculated by Eq. 11

Table VIII   Observed Solubilities of Sulfadiazine in Individual Pure

Solvents at 30°C

No.	Solvents	Solution density	$X_{2\ obs}^{(1)} \times 10^7$	$\phi_{1\ obs}^{(2)} \times 10^4$	$A_{obs}^{(3)} \times 10^4$
1	Diethyl ether	0.7149	20.48	9999.96	1311.82
2	Ethyl acetate	0.9004	221.01	9999.59	1311.73
3	Chloroform	1.3028	260.00	9999.41	1311.68
4	1, 4-Dioxane	1.0134	239.67	9999.49	1311.70
5	Tert-Butyl alcohol	0.7888	155.77	9999.70	1311.75
6	Amyl alcohol	0.8142	350.44	9999.41	1311.68
7	Sec-Butyl alcohol	0.8059	557.77	9998.90	1311.54
8	Isobutyl alcohol	0.8057	274.95	9999.46	1311.69
9	N-Butyl alcohol	0.8114	685.34	9998.64	1311.48
10	Isopropyl alcohol	0.7867	667.27	9998.42	1311.42
11	N-Propyl alcohol	0.8080	832.86	9997.98	1311.30
12	Acetonitrile	0.8003	67.97	9999.76	1311.77
13	Ethylene glycol monomethyl ether	0.9669	2832.11	9993.49	1310.12
14	Ethyl alcohol	0.7898	1349.82	9995.82	1310.73
15	Methyl alcohol	0.7906	478.35	9997.86	1311.27
16	Propylene glycol	1.0008	3380.03	9991.65	1309.64
17	Ethylene glycol	1.0608	3437.17	9988.82	1308.90
18	Glycerin	1.1090	3026.17	9992.48	1309.86
19	Water	1.0086	55.48	9999.44	1311.69

[1] Mole fraction solubilities obtained experimentally

[2] Observed volume fraction of the solvent calculated by Eq. 12

[3] Calculated by Eq. 11

The predicted mole fraction solubilities of both drugs were also

calculated using the three methods as described in Chapter II. Results

obtained may be individually presented and discussed as follows :

1. Regular Solution Theory (Scatchard-Hildebrand Equation)

The observed and predicted mole fraction solubilities of

phenobarbital and sulfadiazine in individual pure solvents are listed

in Tables IX and XI, respectively, together with the example steps of

the iteration procedure which are shown in Tables X and XII. When

observed and predicted mole fraction solubilities of each drugs were

compared, the residuals expressed in percentages, are unsatisfactory.

These indicated that the two drug solutions do not follow regular

solution theory. Results may be due to the fact that the two drug

molecules having side chains and functional groups attached to the

aromatic ring, the regular behavior of their solubilities is not

expected to be found with single or binary solvents (21, 37).

2. The Extended Hildebrand Solubility Approach (EHS)

The observed and predicted mole fraction solubilities of these

two drugs in individual pure solvents are listed in Tables XIII and XV,

respectively. The observed and predicted interaction energy between the

solute and the solvent, (W_{obs}, W_{calc}) of phenobarbital and sulfadiazine

were also included. The example steps of the iteration procedure are

shown in Tables XIV and XVI, respectively.

The observed values of W of these two drugs were regressed

versus the total solubility parameters of each solvent, δ_1, in a

second (quadratic) degree expression using polynomial regression. The

computer output yields Eqs. 23 and 24 for phenobarbital and sulfadiazine,

respectively.

Table IX Comparison of Observed and Predicted Mole Fraction Solubilities of Phenobarbital

$(\delta_2 = 12.60)$ in Individual Pure Solvents at 30°C Using Regular Solution Theory

(Scatchard-Hildebrand Equation)

No.	Solvents	$\delta_1^{(1)}$	$(\delta_1-\delta_2)^2$	$X_{2\ obs}^{(2)}\times10^5$	$X_{2\ calc}^{(3)}\times10^5$	Residual $\times 10^5$	Percent Error
1	Diethyl ether	7.66	24.40	3095.00	0.75	3094.25	99.98
2	Ethyl acetate	9.04	12.67	4416.98	10.84	4406.14	99.75
3	Chloroform	9.26	11.16	2585.99	15.32	2570.67	99.41
4	1, 4-Dioxane	10.01	6.71	7190.98	42.15	7148.83	99.41
5	Tert-Butyl alcohol	10.28	5.38	4059.98	56.97	4003.01	98.59
6	Amyl alcohol	10.58	4.08	4981.01	76.58	4904.43	98.46
7	Isobutyl alcohol	11.13	2.16	3883.99	118.48	3765.51	96.95
8	N-Butyl alcohol	11.29	1.72	4684.03	131.06	4552.97	97.20
9	Isopropyl alcohol	11.50	1.21	4422.01	147.03	4274.98	96.68
10	N-Propyl alcohol	11.99	0.37	4313.99	177.73	4136.26	95.88
11	Acetonitrile	12.00	0.36	2593.01	178.26	2414.75	93.13
12.	Ethylene glycol monomethyl ether	12.10	0.25	4814.12	182.70	4631.42	96.20
13	Ethyl alcohol	12.96	0.13	3595.00	187.75	3407.25	94.78
14	Methyl alcohol	14.49	3.57	2347.99	86.21	2261.78	96.33
15	Propylene glycol	14.80	4.84	2585.00	64.49	2520.51	97.51
16	Ethylene glycol	15.99	11.49	1825.00	14.20	1810.81	99.22
17	Glycerin	17.64	25.40	904.99	0.60	904.39	99.93
18	Water	23.40	116.64	11.65	5.87×10^{15}	11.65	100.00

[1] Obtained from literature

[2] Mole fraction solubilities obtained experimentally

[3] Predicted mole fraction solubilities

Table X Iteration Procedure for Calculating the Predicted Mole Fraction
Solubility of Phenobarbital in N—Butyl Alcohol at 30° C Using
Regular Solution Theory (Scatchard—Hildebrand Equation)

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$X_{2\ calc}^{(3)} \times 10^5$
1	10,000.00	987.48	130.86
2	9,980.53	983.64	131.06

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 14

Table XI Comparison of Observed and Predicted Mole Fraction Solubilities of Sulfadiazine (δ_2 = 12.50) in Individual Pure Solvents at 30°C Using Regular Solution theory (Scatchard-Hildebrand Equation)

No.	Solvents	$\delta_1^{(1)}$	$(\delta_1-\delta_2)^2$	$X_{2\,obs}^{(2)} \times 10^7$	$X_{2\,calc}^{(3)} \times 10^7$	Residual $\times 10^7$	Percent Error
1	Diethyl ether	7.66	23.43	20.48	8.79	11.69	57.10
2	Ethyl acetate	9.04	11.97	221.01	279.58	−58.57	−26.50
3	Chloroform	9.26	10.50	260.00	436.50	−176.50	−67.88
4	1, 4-Dioxane	10.01	6.20	239.67	1599.64	−1359.97	−567.43
5	Tert-Butyl alcohol	10.28	4.93	155.77	2348.99	−2193.22	−1407.96
6	Amyl alcohol	10.58	3.67	350.44	3418.03	−3067.59	−875.35
7	Sec-Butyl alcohol	10.83	2.79	557.77	4483.38	−3925.61	−703.81
8	Isobutyl alcohol	11.13	1.88	274.95	5904.35	−5629.40	−2047.42
9	N-Butyl alcohol	11.29	1.46	685.34	6687.44	−6002.10	−875.78
10	Isopropyl alcohol	11.50	1.00	667.27	7693.28	−7026.01	−1052.95
11	N-Propyl alcohol	11.99	0.26	832.86	9612.94	−8780.08	−1054.21
12	Acetonitrile	12.00	0.25	67.97	9643.63	−9575.66	−14087.26
13	Ethylene glycol monomethyl ether	12.10	0.16	2832.11	9906.60	−7074.49	−249.80
14	Ethyl alcohol	12.96	0.21	1349.82	9755.00	−8405.18	−622.69
15	Methyl alcohol	14.49	3.96	478.35	3153.39	−2675.04	−559.22
16	Propylene glycol	14.80	5.29	3380.03	2106.59	1273.44	37.68
17	Ethylene glycol	15.99	12.18	3437.17	262.58	3174.59	92.36
18	Glycerin	17.64	26.42	3026.17	3.56	3022.61	99.88
19	Water	23.40	118.81	55.48	2.70×10^{19}	55.48	100.00

[1] Obtained from literature

[2] Mole fraction solubilities obtained experimentally

[3] Predicted mole fraction solubilities

Table XII   Iteration Procedure for Calculating the Predicted Mole

Fraction Solubility of Sulfadiazine in N-Butyl Alcohol at

30° C Using Regular Solution Theory (Scatchard-Hildebrand

Equation)

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$x_{2\ calc}^{(3)} \times 10^7$
1	10,000.00	1311.83	6,679.64
2	9,986.79	1308.37	6,687.44

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 14

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$$W = 76.8058 + 1.9319 \, \delta_1 + 0.4106 \, \delta_1^2 \qquad \text{(Eq.23)}$$

$$n = 18 \quad R^2 = 0.9998$$

$$W = 49.6208 + 3.2293 \, \delta_1 + 0.3989 \, \delta_1^2 \qquad \text{(Eq.24)}$$

$$n = 19 \quad R^2 = 0.9994$$

The W_{calc} for each drug was back-calculated to obtain the corresponding predicted solubilities following the method described earlier.

Comparisons were made between observed solubilities of both drugs and those obtained using this technique. Results demonstrated the residual expressed in percentages of phenobarbital and sulfadiazine as seen in Tables XIII and XV, are clearly reasonable for the solubilities of these two drugs in most solvents at 30°C. Thirty percent error is taken to account in this study as a criterion acceptability (18). However, some large errors resulted from this method : chloroform (55.23 %), 1, 4-dioxane (40.70 %), acetonitrile (38.60 %), for phenobarbital; diethyl ether (44.58 %), ethyl acetate (51.61 %), chloroform (50.59 %), tert-butyl alcohol (78.51 %), isobutyl alcohol (74.69 %), acetonitrile (1029.10 %), ethylene glycol monomethyl ether (71.59 %), methyl alcohol (267.62 %), propylene glycol (45.37 %), ethylene glycol (41.60 %), glycerin (44.14 %) for sulfadiazine. These large errors may be resulted from the particular regression program and iteration procedure used.

3. The Extended Hansen Solubility Approach

The observed values of $\log \left[x_2^i / x_2 \right]$ of phenobarbital and sulfadiazine were regressed against the square of differences of the

Table XIII Comparison of Observed and Predicted Mole Fraction Solubilities of Phenobarbital ($\delta_2 = 12.60$) in Individual Pure

                Solvents at 30°C Using the Extended Hildebrand Solubility Approach

No.	Solvents	$\delta_1^{(1)}$	$(\delta_1^2+\delta_2^2)$	δ_1^2	$W_{obs}^{(2)}$	$X_{2\,obs}^{(3)} \times 10^5$	$W_{calc}^{(4)}$	$X_{2\,calc}^{(5)} \times 10^5$	Residual $\times 10^5$	Percent Error
1	Diethyl ether	7.66	217.44	58.68	115.3360	3095.00	115.6984	3490.59	−395.59	−12.78
2	Ethyl acetate	9.04	240.48	81.72	128.0341	4416.98	127.8248	4155.67	261.31	5.92
3	Chloroform	9.26	244.51	85.75	128.4819	2585.99	129.9046	4014.27	−1428.28	−55.23
4	1, 4-Dioxane	10.01	258.96	100.20	139.5241	7190.98	137.2868	4264.61	2926.37	40.70
5	Tert-Butyl alcohol	10.28	264.44	105.68	139.7628	4059.98	140.0586	4421.15	−361.17	−8.90
6	Amyl alcohol	10.58	270.70	111.94	143.4654	4981.01	143.2086	4625.50	355.51	7.14
7	Isobutyl alcohol	11.13	282.64	123.88	148.7304	3883.99	149.1738	4414.94	−530.95	−13.67
8	N-Butyl alcohol	11.29	286.22	127.46	151.1850	4684.03	150.9528	4395.25	288.78	6.17
9	Isopropyl alcohol	11.50	291.01	132.25	153.5693	4422.01	153.3254	4146.44	275.57	6.23
10	N-Propyl alcohol	11.99	302.52	143.76	159.2580	4313.99	158.9981	4026.73	287.26	6.66
11	Acetonitrile	12.00	302.76	144.00	157.9083	2593.01	159.1160	3594.02	−1001.01	−38.60
12	Ethylene glycol monomethyl ether	12.10	305.17	146.41	160.9476	4814.12	160.2987	4061.15	752.97	15.64
13	Ethyl alcohol	12.96	326.72	167.96	170.9559	3595.00	170.8088	3459.79	135.21	3.76
14	Methyl alcohol	14.49	368.72	209.96	190.7757	2347.99	191.0102	2505.48	−157.49	−6.71
15	Propylene glycol	14.80	377.80	219.04	195.1796	2585.00	195.3374	2721.77	−136.77	−5.29
16	Ethylene glycol	15.99	414.44	255.68	212.6169	1825.00	212.6810	1865.78	−40.78	−2.23
17	Glycerin	17.64	469.93	311.17	238.4762	904.99	238.6534	974.13	−69.14	−7.64
18	Water	23.40	706.32	547.56	346.9720	11.65	346.8451	10.99	0.66	5.67

[1] Obtained from literature

[2] Observed interaction energy between solute and solvent calculated by Eq.15

[3] Mole fraction solubilities obtained experimentally

[4] Predicted interaction energy between solute and solvent calculated by Eq.17

[5] Predicted mole fraction solubilities

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Table XIV   Iteration Procedure for Calculating the Mole Fraction

Solubility of Phenobarbital in N-Butyl Alcohol at 30° C

Using the Extended Hildebrand Solubility Approach (EHS)

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$x_{2\ calc}^{(3)} \times 10^5$
1	10,000.00	987.48	6,841.13
2	9,014.25	802.39	3,506.08
3	9,486.70	888.70	4,788.55
4	9,303.24	854.67	4,234.59
5	9,382.21	869.24	4,463.40
6	9,349.54	863.19	4,367.05
7	9,363.29	865.73	4,407.30
8	9,357.55	864.67	4,390.43
9	9,359.95	865.12	4,397.49
10	9,358.95	864.93	4,394.53
11	9,359.37	865.01	4,395.77
12	9,359.19	864.98	4,395.25

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 16

Table XV   Comparison of Observed and Predicted Mole Fraction Solubilities of Sulfadiazine (δ_2 = 12.50) in Individual Pure Solvents

at 30°C Using the Extended Hildebrand Solubility Approach

No.	Solvents	$\delta_1^{(1)}$	$(\delta_1^2+\delta_2^2)$	δ_1^2	$W_{obs}^{(2)}$	$X_{2\ obs}^{(3)}\times10^7$	$W_{calc}^{(4)}$	$X_{2\ calc}^{(5)}\times10^7$	Residual × 10^7	Percent Error
1	Diethyl ether	7.66	214.93	58.68	97.1506	20.48	97.7626	29.61	−9.13	−44.58
2	Ethyl acetate	9.04	237.97	81.72	112.6110	221.01	111.4089	106.94	114.07	51.61
3	Chloroform	9.26	242.00	85.75	114.8927	260.00	113.7268	128.45	131.55	50.59
4	1,4-Dioxane	10.01	256.45	100.20	121.9843	239.67	121.9124	229.49	10.18	4.24
5	Tert-Butyl alcohol	10.28	261.93	105.68	124.0104	155.77	124.9701	278.07	−122.30	−78.51
6	Amyl alcohol	10.58	268.19	111.94	128.4813	350.44	128.4358	340.63	9.81	2.80
7	Sec-Butyl alcohol	10.83	273.54	117.29	131.9264	557.77	131.3770	400.07	157.70	28.27
8.	Isobutyl alcohol	11.13	280.13	123.88	134.0500	274.95	134.9743	480.32	−205.37	−74.69
9	N-Butyl alcohol	11.29	283.71	127.46	137.3548	685.34	136.9190	527.14	158.20	23.08
10	Isopropyl alcohol	11.50	288.50	132.25	139.7033	667.27	139.5077	592.85	74.42	11.15
11	N-Propyl alcohol	11.99	300.01	143.76	145.8251	832.86	145.6810	763.42	69.44	8.34
12	Acetonitrile	12.00	300.25	144.00	141.7986	67.97	145.8090	767.45	−699.48	−1029.10
13	Ethylene glycol monomethyl ether	12.10	302.66	146.41	149.1748	2832.11	147.0932	804.71	2027.40	71.59
14	Ethyl alcohol	12.96	324.21	167.96	158.7240	1349.82	158.4660	1155.32	194.50	14.41
15	Methyl alcohol	14.49	366.21	209.96	178.0067	478.35	180.1592	1758.52	−1280.17	−267.62
16	Propylene glycol	14.80	375.29	219.04	185.7823	3380.03	184.7820	1846.48	1533.55	45.37
17	Ethylene glycol	15.99	411.93	255.68	204.1291	3437.17	203.2393	2007.34	1429.83	41.60
18	Glycerin	17.64	467.42	311.17	231.6641	3026.17	230.7008	1690.33	1335.84	44.14
19	Water	23.40	703.81	547.56	343.2417	55.48	343.5896	68.46	−12.98	−23.40

[1] Obtained from literature

[2] Observed interaction energy between solute and solvent calculated by Eq.15

[3] Mole fraction solubilities obtained experimentally

[4] Predicted interaction energy between solute and solvent calculated by Eq.17

[5] Predicted mole fraction solubilities

Table XVI   Iteration Procedure for Calculating the Predicted Mole

Fraction Solubility of Sulfadiazine in N-Butyl Alcohol at

30° C Using the Extended Hildebrand Solubility Approach

(EHS)

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$X_{2 \ calc}^{(3)} \times 10^7$
1	10,000.00	1311.83	526.82
2	9,998.96	1311.56	527.14

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 16

partial solubility parameters of these two drugs and the individual solvents multiplied by the observed values of A of each solvent. The computer output of multiple regression produces Eqs. 25 and 26 for phenobarbital and sulfadiazine, respectively.

$$\log\left[x_2^i/x_2\right] = \log \alpha_2 = -1.5902 + 0.2489\,(\delta_{1D}-\delta_{2D})^2$$
$$+ 0.1256\,(\delta_{1P}-\delta_{2P})^2$$
$$+ 0.1080\,(\delta_{1H}-\delta_{2H})^2 \qquad (Eq.25)$$

n = 18 R^2 = 0.9856

$$\log\left[x_2^i/x_2\right] = \log \alpha_2 = 0.1286 + 1.7493\,(\delta_{1D}-\delta_{2D})^2$$
$$+ 0.7242\,(\delta_{1P}-\delta_{2P})^2$$
$$+ 0.0163\,(\delta_{1H}-\delta_{2H})^2 \qquad (Eq.26)$$

n = 19 R^2 = 0.9543

The back-calculated solubilities of phenobarbital and sulfadiazine were established using the iteration procedure as shown for the examples in Tables XVIII and XX, respectively. The predicted mole fraction solubilities of these two drugs were compared favorably with the observed ones (Tables XVII and XIX). As expected, they were within 30 % errors from the observed values; except for those in chloroform (72.42 %) and dioxane (35.50 %) for phenobarbital; diethyl ether (32.18 %), chloroform (82.55 %), acetonitrile (61.06 %), and ethylene glycol monomethyl ether (31.37 %) for sulfadiazine.

Table XVII Comparison of Observed and Predicted Mole Fraction Solubilities of Phenobarbital in Individual Solvents at 30°C Using the
Extended Hansen Solubility Approach

No.	Solvents	$\Lambda^{(1)}_{obs} \times 10^4$	$(\delta_{1D}-\delta_{2D})^2$	$(\delta_{1P}-\delta_{2P})^2$	$(\delta_{1H}-\delta_{2H})^2$	$\log\left[X_2^i/X_2\right] \times 10^3$	$X_{2\ obs}^{(2)} \times 10^5$	$X_{2\ calc}^{(3)} \times 10^5$	Residual $\times 10^5$	Percent Error
1	Diethyl ether	909.91	10.24	11.56	7.84	-1204.3880	3095.00	2695.47	399.53	12.91
2	Ethyl acetate	871.81	8.41	4.84	0.64	-1358.8521	4416.98	4307.10	109.88	2.49
3	Chloroform	904.24	2.56	10.89	6.25	-1126.3541	2585.99	4458.72	-1872.73	-72.42
4	1, 4-Dioxane	781.81	1.00	15.21	2.89	-1570.5151	7190.98	4638.32	2552.66	35.50
5	Tert-Butyl alcohol	876.40	9.00	5.29	2.25	-1322.2515	4059.98	3980.67	79.31	1.95
6	Amyl alcohol	869.17	6.25	6.76	2.25	-1411.0443	4981.01	4393.14	587.87	11.80
7	Isobutyl alcohol	878.99	8.41	4.00	6.25	-1303.0050	3883.99	3881.02	2.97	0.08
8	N-Butyl alcohol	857.40	6.25	4.00	5.76	-1384.3467	4684.03	4413.34	270.69	5.78
9	Isopropyl alcohol	842.82	6.76	3.24	7.29	-1359.3464	4422.01	4294.20	127.81	2.89
10	N-Propyl alcohol	843.09	6.25	2.25	10.24	-1348.6064	4313.99	4242.19	71.80	1.66
11	Acetonitrile	863.58	7.84	16.00	5.29	-1127.5319	2593.01	3131.10	-538.09	-20.75
12	Ethylene glycol monomethyl ether	834.82	5.76	0.09	7.29	-1396.2437	4814.12	4905.88	-91.76	-1.91
13	Ethyl alcohol	835.68	6.76	0.25	17.64	-1269.4262	3595.00	3771.11	-176.11	-4.90
14	Methyl alcohol	845.14	8.41	1.44	31.36	-1084.4235	2347.99	2533.88	-185.89	-7.92
15	Propylene glycol	896.71	4.41	0.04	37.21	-1126.1876	2585.00	2616.86	-31.86	-1.23
16	Ethylene glycol	903.30	4.00	0.36	53.29	-974.9907	1825.00	1831.13	-6.13	-0.34
17	Glycerin	954.57	3.24	1.21	81.00	-670.3723	904.99	890.01	14.98	1.66
18	Water	985.74	7.29	9.00	237.16	+1219.9470	11.65	11.51	0.14	1.20

[1] Calculated by Eq. 11

[2] Mole fraction solubilities obtained experimentally

[3] Predicted mole fraction solubilities

Table XVIII   Iteration Procedure for Calculating the Predicted Mole

Fraction Solubility of Phenobarbital in N-Butyl Alcohol

at 30° C Using the Extended Hansen Solubility Approach

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$X_{2\ calc}^{(3)} \times 10^5$
1	10,000.00	987.48	4,090.81
2	9,402.78	873.05	4,390.15
3	9,359.99	865.12	4,411.68
4	9,356.92	864.56	4,413.22
5	9,356.70	864.52	4,413.34

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 22

Table XIX Comparison of Observed and Predicted Mole Fraction Solubilities of Sulfadiazine in Individual Solvents at 30°C Using the Extended Hansen Solubility Approach

No.	Solvents.	$A_{obs}^{(1)} \times 10^4$	$(\delta_{1D}-\delta_{2D})^2$	$(\delta_{1P}-\delta_{2P})^2$	$(\delta_{1H}-\delta_{2H})^2$	$\log\left[x_2^{\frac{1}{2}}/x_2\right] \times 10^3$	$X_{2\ obs}^{(2)} \times 10^7$	$X_{2\ calc}^{(3)} \times 10^7$	Residual $\times 10^7$	Percent Error
1	Diethyl ether	1311.82	5.76	11.56	16.81	2705.5508	20.48	27.07	−6.59	−32.18
2	Ethyl acetate	3111.73	4.41	4.84	4.41	1672.3991	221.01	255.40	−34.39	−15.56
3	Chloroform	1311.68	0.64	10.89	14.44	1601.8489	260.00	474.62	−214.62	−82.55
4	1, 4-Dioxane	1311.70	0.04	15.21	9.00	1637.2034	239.67	260.10	−20.43	−8.52
5	Tert-Butyl alcohol	1311.75	4.84	5.29	0.04	1824.3287	155.77	188.41	−32.64	−20.95
6	Amyl alcohol	1311.68	2.89	6.76	0.04	1472.2023	350.44	382.81	−32.37	−9.24
7	Sec-Butyl alcohol	1311.54	3.24	4.00	0.25	1270.3659	557.77	581.43	−23.66	−4.24
8	Isobutyl alcohol	1311.69	4.41	4.00	1.44	1577.5629	274.95	311.45	−36.50	−13.28
9	N-Butyl alcohol	1311.48	2.89	4.00	1.21	1180.9106	685.34	696.30	−10.96	−1.60
10	Isopropyl alcohol	1311.42	3.24	3.24	1.96	1192.5161	667.27	680.98	−13.71	−2.05
11	N-Propyl alcohol	1311.30	2.89	2.25	3.61	1096.2463	832.86	1009.42	−176.56	−21.20
12	Acetonitrile	1311.77	4.00	16.00	12.96	2184.4765	67.97	26.47	41.50	61.06
13	Ethylene glycol monomethyl ether	1310.12	2.56	0.09	1.96	564.7085	2832.11	1943.62	888.49	31.37
14	Ethyl alcohol	1310.73	3.24	0.25	8.41	886.5416	1349.82	1269.70	80.12	5.94
15	Methyl alcohol	1311.27	4.41	1.44	18.49	1337.0713	478.35	501.87	−23.52	−4.92
16	Propylene glycol	1309.64	1.69	0.04	23.04	487.8982	3380.03	2806.32	573.71	16.97
17	Ethylene glycol	1308.90	1.44	0.36	36.00	480.6176	3437.17	2803.31	633.86	18.44
18	Glycerin	1309.86	1.00	1.21	59.29	535.9253	3026.17	2618.47	407.70	13.47
19	Water	1311.69	3.61	9.00	198.81	2272.7150	55.48	60.43	−4.95	−8.92

[1] Calculated by Eq. 11

[2] Mole fraction solubilities obtained experimentally

[3] Predicted mole fraction solubilities

Table XX Iteration Procedure for Calculating the Predicted Mole Fraction Solubility of Sulfadiazine in N-Butyl Alcohol at 30° C Using the Extended Hansen Solubility Approach

Step	$\phi_1^{(1)} \times 10^4$	$A^{(2)} \times 10^4$	$x_{2\ calc}^{(3)} \times 10^7$
1	10,000.00	1,311.83	695.84
2	9,998.62	1,311.47	696.30

[1] Volume fraction of the solvent calculated by Eq. 12

[2] Calculated by Eq. 11

[3] Predicted mole fraction solubilities calculated by Eq. 22

Comparison of Three Methods of Solubility Analysis

As can be seen after comparing all of the residuals for each drug, expressed in percentage error of the three methods used in this study (Tables XXI and XXII). The Extended Hansen Solubility Approach must be accepted as the best method studies since its percentage errors are :

< 5 % for 11 solvents (61.11 %)

> 5 to < 10 % for 2 solvents (11.11 %)

> 10 to < 20 % for 2 solvents (11.11 %)

> 20 to < 30 % for 1 solvent (5.56 %)

> 30 % for 2 solvents (11.11 %)

for phenobarbital, and

< 5 % for 4 solvents (21.05 %)

> 5 to < 10 % for 4 solvents (21.05 %)

> 10 to < 20 % for 5 solvents (26.32 %)

> 20 to < 30 % for 2 solvents (10.53 %)

> 30 % for 4 solvents (21.05 %)

for sulfadiazine,

whereas the percentage errors produced employing the Extended Hildebrand Solubility Approach are :

< 5 % for 2 solvents (11.11 %)

> 5 to < 10 % for 10 solvents (55.56 %)

> 10 to < 20 % for 3 solvents (16.67 %)

> 30 % for 3 solvents (16.67 %)

for phenobarbital, and

< 5 % for 2 solvents (10.53 %)

> 5 to < 10 % for 1 solvent (5.26 %)

> 10 to < 20 % for 2 solvents (10.53 %)

> 20 to < 30 % for 3 solvents (15.79 %)

> 30 % for 11 solvents (57.89 %)

for sulfadiazine.

Finally, the percentage errors obtained utilizing the Regular Solution Theory (Scatchard-Hildebrand Equation) are much higher for acceptable consideration.

In earlier studies (4-6, 14), the Extended Hildebrand Solubility Approach was successful in reproducing the solubility of solid drugs in binary solvents, both polar and nonpolar. Although it is satisfactory in the current work for most solvents studied, this method cannot be expected to apply where strong interactions exist. The predictive power of the Extended Hildebrand Solubility Approach is, therefore, less than that of the Extended Hansen Solubility Approach, this may be due to the three partial solubility parameters of Hansen and/or statistical technique used are more potential than those of Hildebrand in prediction both drugs solubilities in selected individual pure solvents. However, the Extended Hildebrand solubility Approach can be the second best method in this study.

The Regular Solution Theory (Scatchard-Hildebrand Equation), however, is the last method of choice since it produces obviously unsatisfactory estimation for both drugs in individual pure solvents.

In conclusion, one can quickly predict the solubilities of solute in various individual solvents using these techniques. Also, in drug formulation, these approaches may be used to assist in selecting

the suitable solvents for preparing the most effective and economic drug solutions.

Knowledge gained from these relatively simple and well-behaved systems must be applied to other drug solutions in individual solvents before conclusions can be reached regarding the more applicability of the Regular Solution Theory, the Extended Hildebrand Solubility Approach, and the Extended Hansen Solubility Approach.

Table XXI Comparison of Three Methods of Solubility Analysis for Phenobarbital in Individual Pure Solvents at 30°C

No.	Solvents	$x_{2\ obs}^{(1)} \times 10^5$	Regular		Extended Hildebrand		Extended Hansen	
			$x_{2\ calc}^{(2)} \times 10^5$	Percent Error	$x_{2\ calc}^{(2)} \times 10^5$	Percent Error	$x_{2\ calc}^{(2)} \times 10^5$	Percent Error
1	Diethyl ether	3095.00	0.75	99.98	3490.59	−12.78	2695.47	12.91
2	Ethyl acetate	4416.98	10.84	99.75	4155.67	5.92	4307.10	2.49
3	Chloroform	2585.99	15.32	99.41	4014.27	−55.23	4458.72	−72.42
4	1, 4-Dioxane	7190.98	42.15	99.41	4264.61	40.70	4638.32	35.50
5	Tert-Butyl alcohol	4059.98	56.97	98.59	4421.15	−8.90	3980.67	1.95
6	Amyl alcohol	4981.01	76.58	98.46	4625.50	7.14	4393.14	11.80
7	Isobutyl alcohol	3883.99	118.48	96.95	4414.94	−13.67	3881.02	0.08
8	N-Butyl alcohol	4684.03	131.06	97.20	4395.25	6.17	4413.34	5.78
9	Isopropyl alcohol	4422.01	147.03	96.68	4146.44	6.23	4294.20	2.89
10	N-Propyl alcohol	4313.99	177.73	95.88	4026.73	6.66	4242.19	1.66
11	Acetonitrile	2593.01	178.26	93.13	3594.02	−38.60	3131.10	−20.75
12	Ethylene glycol monomethyl ether	4814.12	182.70	96.20	4061.15	15.64	4905.88	−1.91
13	Ethyl alcohol	3595.00	187.75	94.78	3459.79	3.76	3771.11	−4.90
14	Methyl alcohol	2347.99	86.21	96.33	2505.48	−6.71	2533.88	−7.92
15	Propylene glycol	2585.00	64.49	97.51	2721.77	−5.29	2616.86	−1.23
16	Ethylene glycol	1825.00	14.20	99.22	1865.78	−2.23	1831.13	−0.34
17	Glycerin	904.99	0.60	99.93	974.13	−7.64	890.01	1.66
18	Water	11.65	5.87×10^{15}	100.00	10.99	5.67	11.51	1.20

[1] Mole fraction solubilities obtained experimentally

[2] Predicted mole fraction solubilities

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Table XXII Comparison of Three Methods of Solubility Analysis for Sulfadiazine in Individual Pure Solvents at 30°C

No.	Solvents	$x_{2\,obs}^{(1)} \times 10^7$	Regular		Extended Hildebrand		Extended Hansen	
			$x_{2\,calc}^{(2)} \times 10^7$	Percent Error	$x_{2\,calc}^{(2)} \times 10^7$	Percent Error	$x_{2\,calc}^{(2)} \times 10^7$	Percent Error
1	Diethyl ether	20.48	8.79	57.10	29.61	-44.58	27.07	-32.18
2	Ethyl acetate	221.01	279.58	-26.50	106.94	51.61	255.40	-15.56
3	Chloroform	260.00	436.50	-67.88	128.45	50.59	474.62	-82.55
4	1, 4-Dioxane	239.67	1599.64	-567.43	229.49	4.24	260.10	-8.52
5	Tert-Butyl alcohol	155.77	2348.99	-1407.96	278.07	-78.51	188.41	-20.95
6	Amyl alcohol	350.44	3418.03	-875.35	340.63	2.80	382.81	-9.24
7	Sec-Butyl alcohol	557.77	4483.38	-703.81	400.07	28.27	581.43	-4.24
8	Isobutyl alcohol	274.95	5904.35	-2047.42	480.32	-74.69	311.45	-13.28
9	N-Butyl alcohol	685.34	6687.44	-875.78	527.14	23.08	696.30	-1.60
10	Isopropyl alcohol	667.27	7693.28	-1052.95	592.85	11.15	680.98	-2.05
11	N-Propyl alcohol	832.86	9612.94	-1054.21	763.42	8.34	1009.42	-21.20
12	Acetonitrile	67.97	9643.63	-14087.26	767.45	-1029.10	26.47	61.06
13	Ethylene glycol monomethyl ether	2832.11	9906.60	-249.80	804.71	71.59	1943.62	31.37
14	Ethyl alcohol	1349.82	9755.00	-622.69	1155.32	14.41	1269.70	5.94
15	Methyl alcohol	478.35	3153.39	-559.72	1758.52	-267.62	501.87	-4.92
16	Propylene glycol	3380.03	2106.59	37.68	1846.48	45.37	2806.32	16.97
17	Ethylene glycol	3437.17	262.58	92.36	2007.34	41.60	2803.31	18.44
18	Glycerin	3026.17	3.56	99.88	1690.33	44.14	2618.47	13.47
19	Water	55.48	2.70×10^{19}	100.00	68.46	-23.40	60.43	-8.92

[1] Mole fraction solubilities obtained experimentally

[2] Predicted mole fraction solubilities