CHAPTER IV

RESULTS AND DISCUSSION

Standard Curve Determination

A typical standard curve and data for indomethacin concentrations as determined using linear regression are presented in Figure 1 and Table II, respectively. The correlation coefficient of the fit to a straight line was highly significant ($r = 0.999$).

Sample Analysis

The solubility parameters of indomethacin and pure solvents are listed in Table III. Comparison of solubilities of indomethacin in various mixed solvents and their plots versus percent of nonaqueous solvents in water are shown in Table IV and Figure 2, respectively.

As can be seen (Table IV, Figure 2), solubilities of indomethacin in the systems of glycerine-water and sorbitol solution-water were less than any other systems. This is due to average solubility parameters of these two mixed solvents are relatively greater compared to that of the drug (Table III). Observed solubilities obtained using 1,4 dioxane and water system were high but there was little precipitation of the drug in some solutions upon storing for two months. Mixtures of polyethylene glycol 200 and water provided

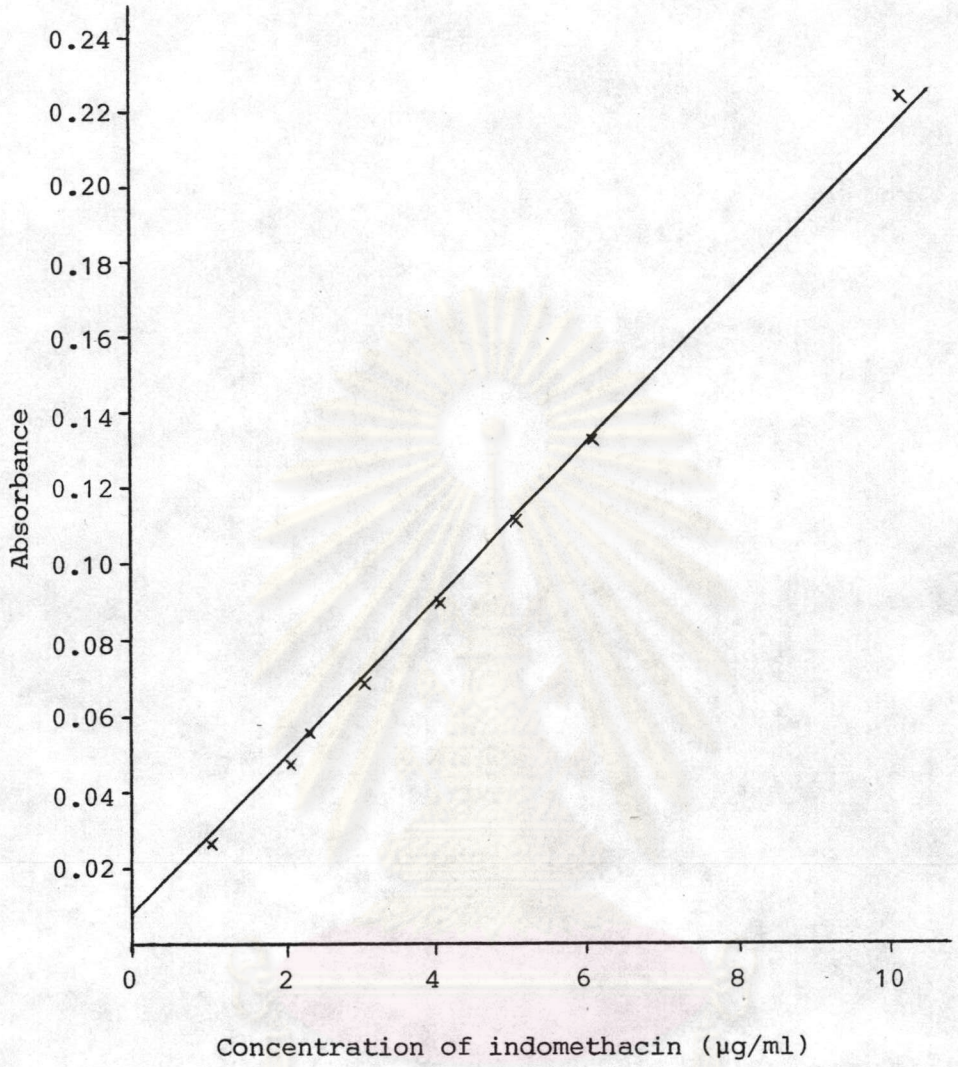


Figure 1 : Typical standard curve for indomethacin concentration.

Table II : Typical Standard Curve Data for Indomethacin Concentration Estimated Using Linear Regression[1]

Std.No.	Conc. (µg/ml)	Absorbance	Inversely estimated concentration[2]	% Theory[3]
1	1.0	0.026	1.05	104.76
2	2.0	0.047	2.05	102.38
3	2.4	0.056	2.48	103.17
4	3.0	0.068	3.05	101.59
5	4.0	0.089	4.05	101.19
6	5.0	0.110	5.05	100.95
7	6.0	0.131	6.05	100.79
8	10.0	0.220	10.28	102.86
			Mean	102.21
			S.D.	1.36
			C.V.[4]	1.33

[1] R^2 = 0.999

[2] Inversely estimated concentration = (Absorbance - 0.004)/0.021

[3] % Theory = $\frac{\text{Inversely estimated concentration}}{\text{Known concentration}} \times 100$

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

Table III : Solubility Parameters of Indomethacin and Pure Solvents

Number	Chemicals	Solubility parameter $(cal/cm^3)^{\frac{1}{2}}$
1	1, 4 Dioxane	10.00
2	Ethanol	12.70
3	Glycerine	16.50
4	Propylene Glycol	12.60
5	Water	23.40
6	Sorbitol Solution	18.60
7	Polyethylene Glycol 200	12.20
8	Polyethylene Glycol 400	10.99
9	Indomethacin	10.60

No. 1-5 obtained from Ref 19

No. 6-9 obtained using Fedor's Group Contribution Method

Table IV : Comparison of Solubilities of Indomethacin in Various Mixed Solvents

% Non aqueous solvents	Solubility of Indomethacin (µg/ml)						
	Sorbitol Sol^{n}	Glycerine	Propylene Glycol	PEG 200	Alcohol	1,4 Dioxane	PEG 400
10	18.45	33.33	428.57	380.95	488.09	495.24	30.16
20	19.05	31.75	392.86	352.38	535.71	495.24	47.62
30	17.26	43.65	357.14	400.00	523.81	623.81	109.52
40	20.24	38.09	357.14	547.62	642.86	1357.14	338.09
50	22.02	42.06	428.57	1166.67	1250.00	3404.76	904.76
60	27.38	59.52	650.79	2809.52	2761.90	11619.05	5428.57
70	30.36	67.86	1317.46	8285.71	5523.81	22857.14	10666.67
80	50.00	101.19	2571.43	11809.52	9523.81	24285.71	11904.76
90	37.50	141.67	5619.05	16952.38	18571.43	29761.90	44761.90
100	52.38	201.19	11190.48	13714.28	20952.38	27857.14	46666.67

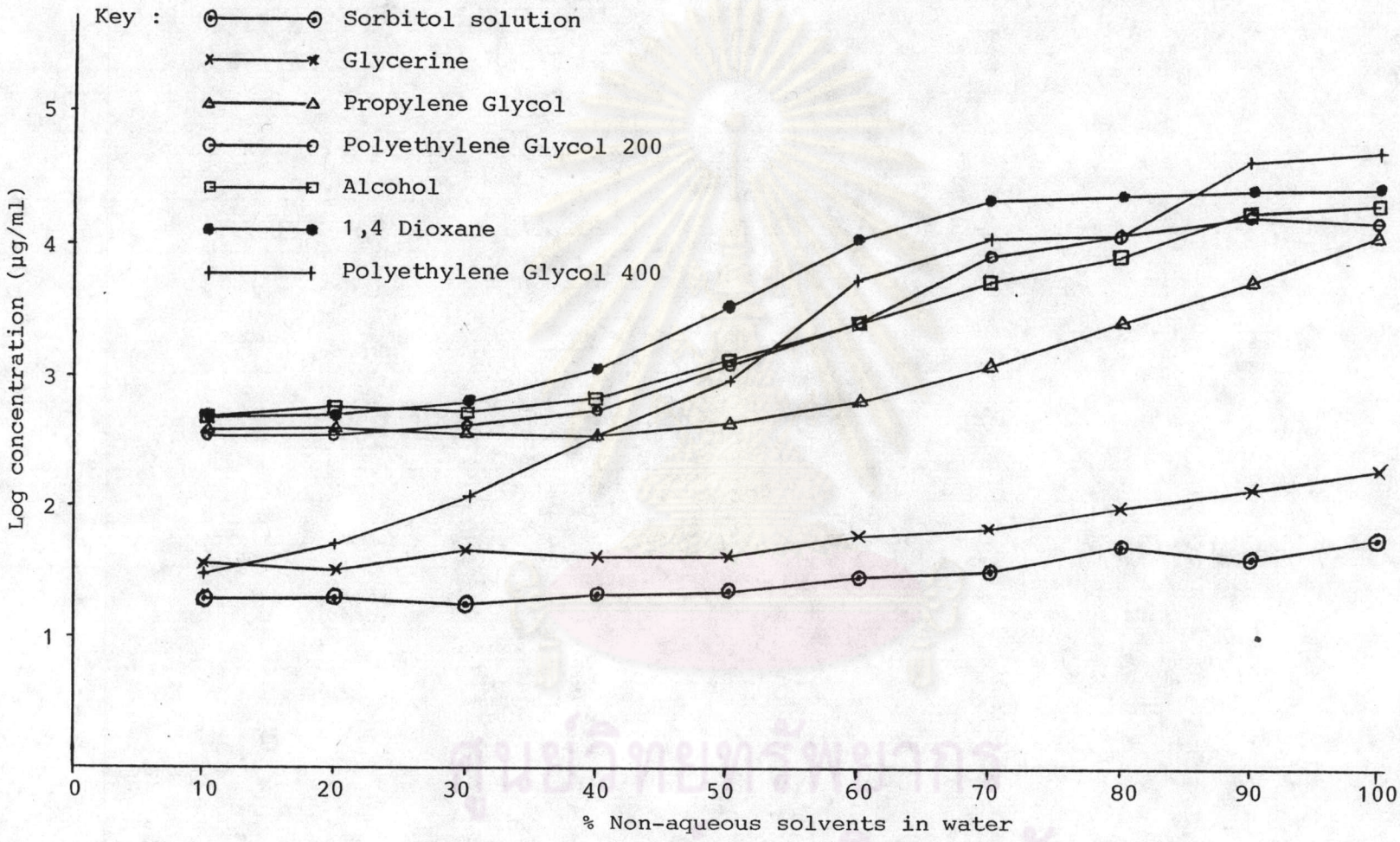


Figure 2 : Comparison of solubilities of indomethacin in various mixed solvents

good results but this solvent, especially in Thailand, is quite difficult to obtain. Solubilities of indomethacin in alcohol and water system seemed to be interesting ones. However, using alcohol at high concentration is still limited especially in some indications such as in children and in intravenous injections. The appropriate non-aqueous solvents used to form binary solvents with water appear to be polyethylene glycol 400 and propylene glycol since they provide suitable concentraitons and stability. They are used in numerous commercial parenteral preparations (Table I). Moreover, these solvents are classified as ones with low order of toxicity, irritating and wide range of compatibilities (17, 35-39). Thus, these two mixed solvents systems were chosen to be solvents of choice in this study.

The observed mole fraction solubilities of indomethacin in PEG 400-water and propylene glycol-water systems were reported in Tables V and VI, respectively, the other values were calculated using the method described in Chapter II. All experimental and calculated solubilities of indomethacin expressed as mole fraction versus the solubility parameters of mixed solvents of PEG 400 and propylene glycol systems were plotted in Figures 3 and 4, respectively. The ideal and regular solution mole fraction solubilities were also calculated and included. The ideal solubility of indomethacin, x_2^i, was 4.518039×10^{-3}. The maximum solubilities occured at 100% of each non-aqueous solvents in both systems which equalized 45.919452×10^{-3} and 2.325842×10^{-3}, respectively. These values are greater and lower than that of the ideal solubility.

Table V : Observed Solubilities of Indomethacin in PEG 400 and Water System at 30℃

PEG 400 (%)	Water (%)	δ_1 [1]	ϕ_1 [2]	A [3]	W [4]	log γ_2 [5]	log γ_v [6]	log γ_R [7]	x_2(obs) [8] x 10^{-3}
10	90	22.16	0.9999	0.23543	294.42	3.431978	31.461358	- 28.029384	0.001671
20	80	20.92	0.9999	0.23543	268.24	3.183951	25.073860	- 21.889908	0.002958
30	70	19.68	0.9998	0.23538	243.95	2.766658	19.406234	- 16.639575	0.007732
40	60	18.44	0.9996	0.23529	221.49	2.216550	14.462241	- 12.245690	0.027441
50	50	17.19	0.9991	0.23505	200.28	1.716615	10.207775	- 8.491159	0.086763
60	40	15.95	0.9949	0.23308	181.56	0.850520	6.671332	- 5.820812	0.637426
70	30	14.71	0.9900	0.23079	163.40	0.447995	3.898528	- 3.450533	1.610481
80	20	13.47	0.9890	0.23032	146.34	0.257317	1.897123	- 1.639806	2.498236
90	10	12.23	0.9591	0.21661	132.22	- 0.542796	0.575511	- 1.118308	15.766906
100	0	10.99	0.9578	0.21602	118.90	- 1.0070200	0.032857	- 1.039877	45.919452

[1] Calculated by Eq 18

[2] Calculated by Eq 19

[3] $A = V_2\phi_1^2/2.303\ RT$

[4] Calculated by Eq 17

[5] Calculated by Eq 12

[6] Calculated by Eq 14

[7] Calculated by Eq 15

[8] Mole fraction solubilities obtained experimentally

Table VI : Observed Solubilities of Indomethacin in Propylene Glycol and Water System at 30°C

Propylene Glycol(%)	Water (%)	δ_1 (1)	ϕ_1 (2)	A (3)	W (4)	log γ_2 (5)	log γ_V (6)	log γ_R (7)	x_2(obs) (8) x 10^{-3}
10	90	22.32	0.9996	0.23529	300.41	2.287054	32.319058	30.032004	0.023329
20	80	21.24	0.9996	0.23529	276.89	2.287837	26.637087	24.349250	0.023287
30	70	20.16	0.9996	0.23529	254.53	2.288714	21.504000	19.215286	0.023240
40	60	19.08	0.9996	0.23529	233.43	2.244088	16.919798	14.675709	0.025755
50	50	18.00	0.9996	0.23529	213.68	2.115492	12.884480	10.7689880	0.034632
60	40	16.92	0.9993	0.23515	195.33	1.877711	9.392455	7.514744	0.059874
70	30	15.84	0.9987	0.23486	178.42	1.506847	6.448692	4.941845	0.140638
80	20	14.76	0.9976	0.23435	162.68	1.139787	4.055567	2.915779	0.327463
90	10	13.68	0.9948	0.23303	148.23	0.708026	2.210616	1.502590	0.884937
100	0	12.60	0.9897	0.23065	134.93	0.288368	0.922600	0.634231	2.325842

[1] Calculated by Eq 18

[2] Calculated by Eq 19

[3] $A = V_2\phi_1^2/2.303\ RT$

[4] Calculated by Eq 17

[5] Calculated by Eq 12

[6] Calculated by Eq 14

[7] Calculated by Eq 15

[8] Mole fraction solubilities obtained experimentally

As can be seen, using the Extended Hildebrand Solubility Approach to calculate solubilities yields good results for both systems as observed by the fit to the calculated line to the points in Figures 3 and 4. In both systems, when comparing the regular solution curves with the observed solubility lines, the observed solubilities are larger (Figure 3 and Figure 4) than those predicted by a regular solution theory over the entire range of the solubility parameter, δ_1, values of the mixed solvents. These indicated that the mixtures do not follow regular solution theory. The ideal solubilities of indomethacin are smaller (Figure 3) and larger (Figure 4) than those obtained experimentally in all proportions of these two mixed solvents systems. Increased solubility may be due to specific interaction, such as hydrogen bonding occuring between the solute and solvont molecules. Such specific combinations of the solvent with solute are known as solvation. In addition, the intermolecular attachments consisting of charge transfer complexes, and other types of interactions may contribute. On the other hand, if specific interactions between the like molecules of one of the component (solute-solute, solvent-solvent) in solution are dominant, this may result in decreased solubility as seen in Figure 4. The specific interaction that allows increased or decreased solubility of indomethacin is unknown and cannot be predicted prior to the experimental determination. As W values, obtained from Eq. 17, are plotted against solubility parameter of mixed solvents. A nearly strainght line is obtained (Figure 5). This is suggested that W should be regressed against δ_1 as a polynomial expression over an entire range of experimental solubilities since W at present can not

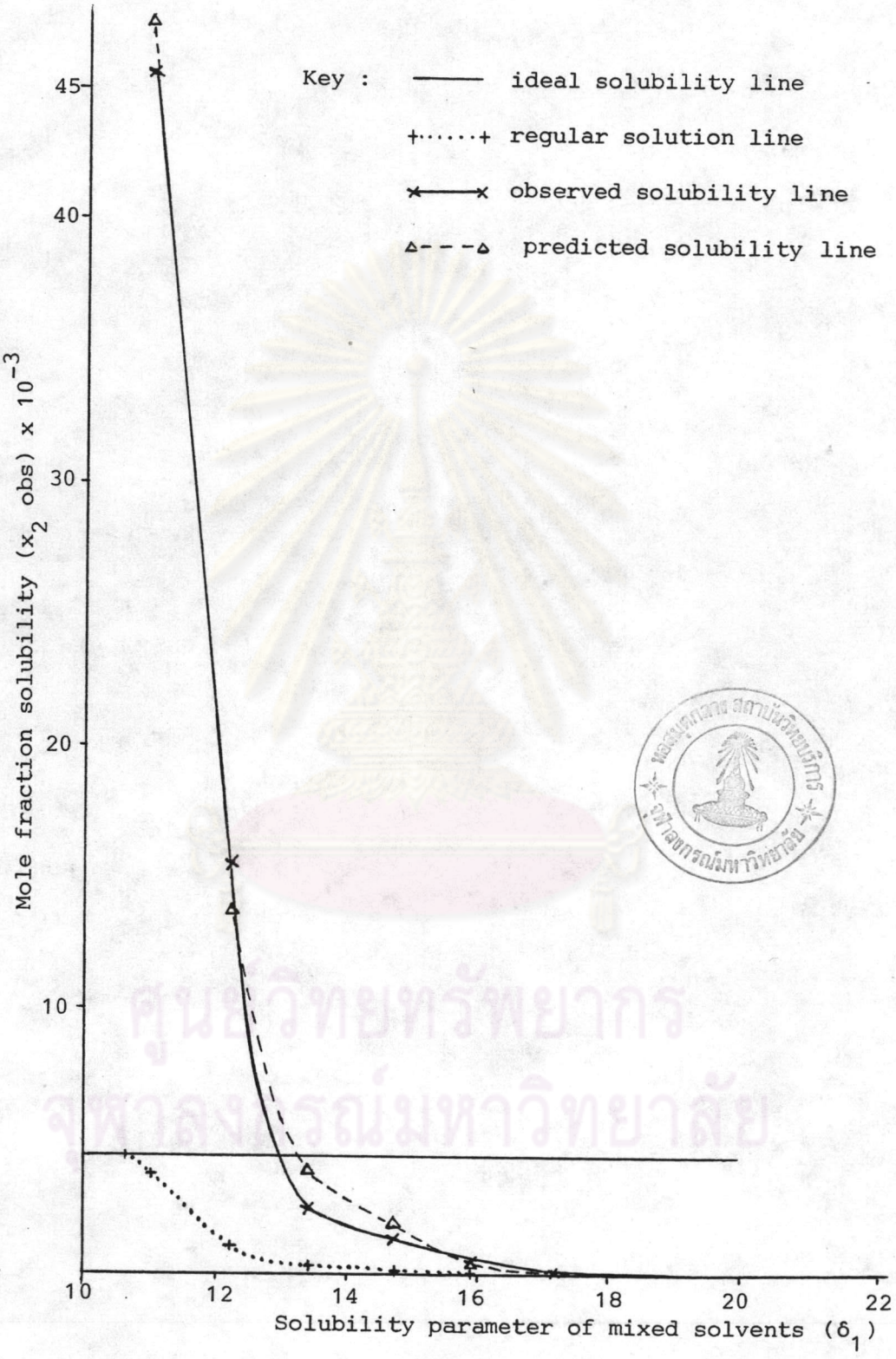


Figure 3 : Mole fraction solubility of indomethacin in PEG 400 and water system at 30°C

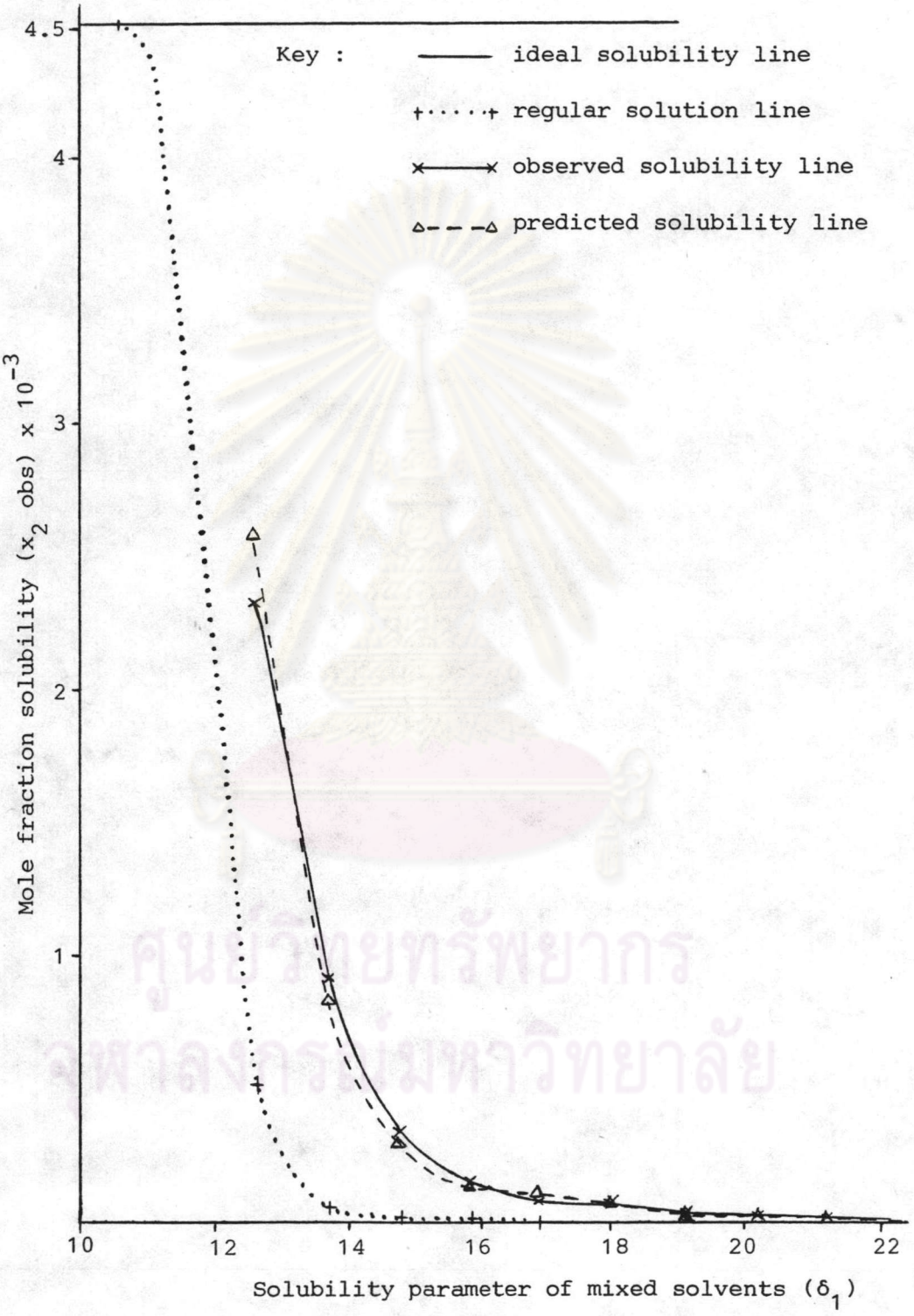


Figure 4 : Mole fraction solubility of indomethacin in propylene glycol and water system at 30°C

be obtained by a consideration of the molecular characteristics of the species in solution. It has been found (10-16), however, that when the experimentally derived W values are regressed against a power series in δ_1 for the various mixed solvents, a polynomial equation is obtained that may be used for the accurate back-calculation of solubilities. A power series in the second degree (quadratic) may be used for this purpose. Results obtained are expressed as

$$W = 71.0889 - 1.2647\ \delta_1 + 0.5113\ \delta_1^2 \qquad \text{(Eq. 22)}$$

for PEG 400 - water system, and

$$W = 79.0471 - 2.6553\ \delta_1 + 0.5634\ \delta_1^2 \qquad \text{(Eq. 23)}$$

for propylene glycol - water system. The coefficient of multiple determination, r^2, for both equations are highly significant and equal 0.9999 (n = 10).

The W values calculated using Eq. 22 and Eq. 23 are pluged into Eq. 17 to calculate the predicted indomethacin solubilities in PEG 400 - water and propylene glycol - water systems, respectively. These back-calculated solubilities, W values, and the log γ_2 values of each solvent system are shown in Tables VII and VIII, respectively.

Correlations have been made between observed solubilities and those predicted using the Extended Hildebrand Solubility Approach in these two mixed solvents. Results indicate that there are excellent linear relationship between these two values with the correlation coefficients, r = 0.998 in both systems. This implies that the method used gives satisfactory indomethacin solubility

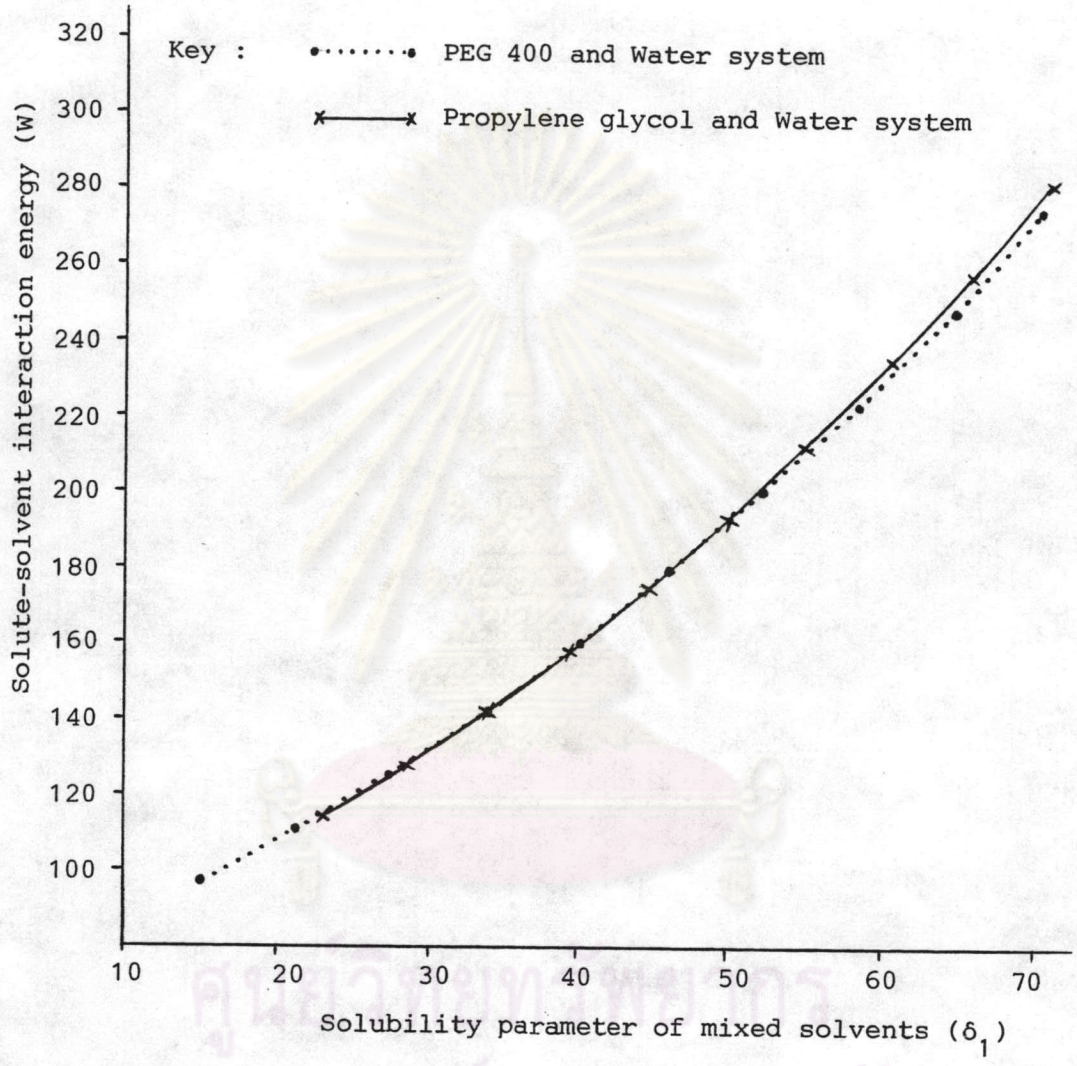


Figure 5 : Plot of W values vs the solubility parameter, δ_1, for indomethacin solubility in mixed solvents.

Table VII : Comparison of Calculated and Observed Solubilities of Indomethacin in PEG 400 and Water System

PEG 400 (%)	Water (%)	δ_1 [1]	W [2]	log γ_2 [3]	x_2(calc) [4] x 10^{-3}	x_2(obs) [5] x 10^{-3}
10	90	22.16	294.14	3.563379	0.001234	0.001671
20	80	20.92	268.39	3.109192	0.003513	0.002958
30	70	19.68	244.23	2.638082	0.010396	0.007732
40	60	18.44	221.63	2.150451	0.031952	0.027441
50	50	17.19	200.43	1.641677	0.103103	0.086763
60	40	15.95	180.99	1.114705	0.348026	0.637426
70	30	14.71	163.12	0.576835	1.197057	1.610481
80	20	13.47	146.82	0.035159	4.166686	2.498236
90	10	12.23	132.10	- 0.490315	13.972215	15.766906
100	0	10.99	118.94	- 1.025949	47.962192	45.919452

[1] Calculated by Eq 18

[2] Calculated by Eq 22

[3] Calculated by Eq 13

[4] Calculated from Eqs 17 and 22

[5] Obtained experimentally

Table VIII : Comparison of Calculated and Observed Solubilities of Indomethacin in Propylene glycol and Water System

Propylene glycol(%)	Water (%)	δ_1 (1)	W(2)	log γ_2 (3)	x_2(calc) (4) x 10^{-3}	x_2(obs) (5) x 10^{-3}
10	90	22.32	300.45	2.265575	0.024511	0.023329
20	80	21.24	276.82	2.319653	0.021641	0.023287
30	70	20.16	254.50	2.304131	0.022429	0.023240
40	60	19.08	233.49	2.219012	0.027285	0.025755
50	50	18.00	213.79	2.064293	0.038963	0.034632
60	40	16.92	195.41	1.838881	0.065473	0.059874
70	30	15.84	178.35	1.543235	0.129334	0.140638
80	20	14.76	162.60	1.177822	0.300004	0.327463
90	10	13.68	148.16	0.742236	0.817926	0.884937
100	0	12.60	135.03	0.241858	2.588762	2.325842

[1] Calculated by Eq 18

[2] Calculated by Eq 23

[3] Calculated by Eq 13

[4] Calculated from Eqs 17 and 23

[5] Obtained experimentally

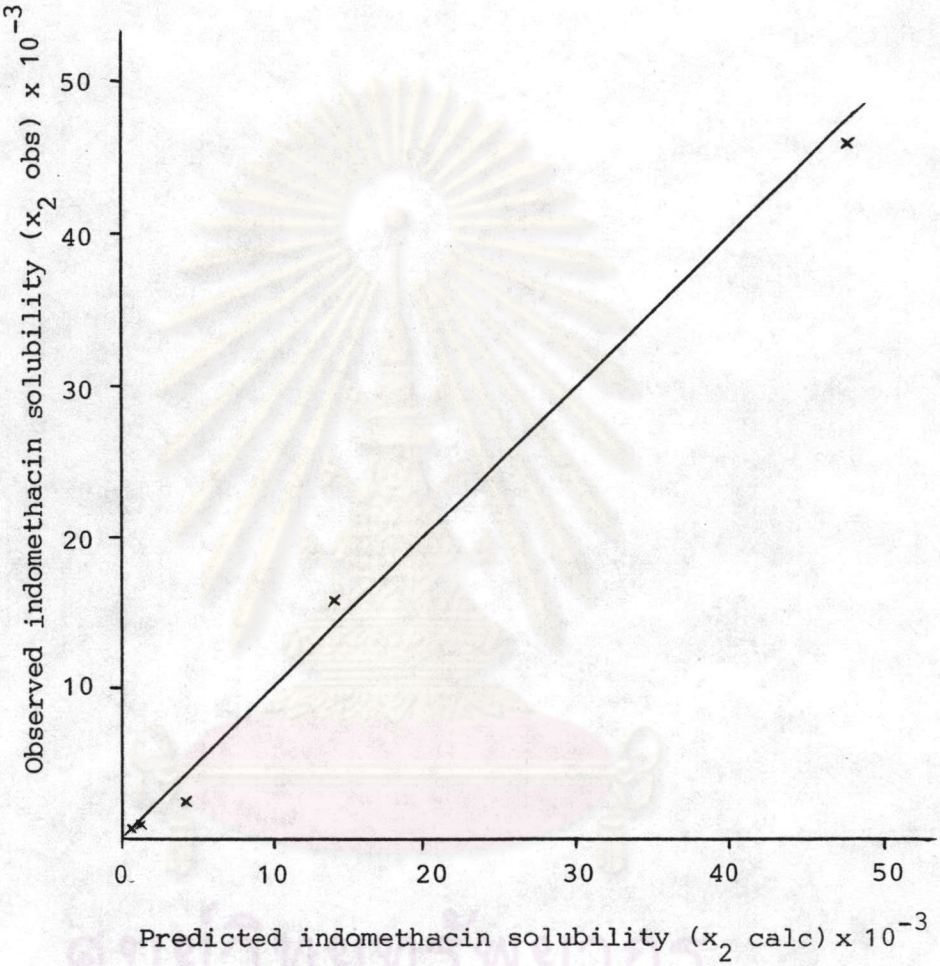


Figure 6 : Comparison of observed indomethacin solubilities in PEG 400 and water system at 30°C with solubilities predicted by the Extended Hildebrand Solubility Approach

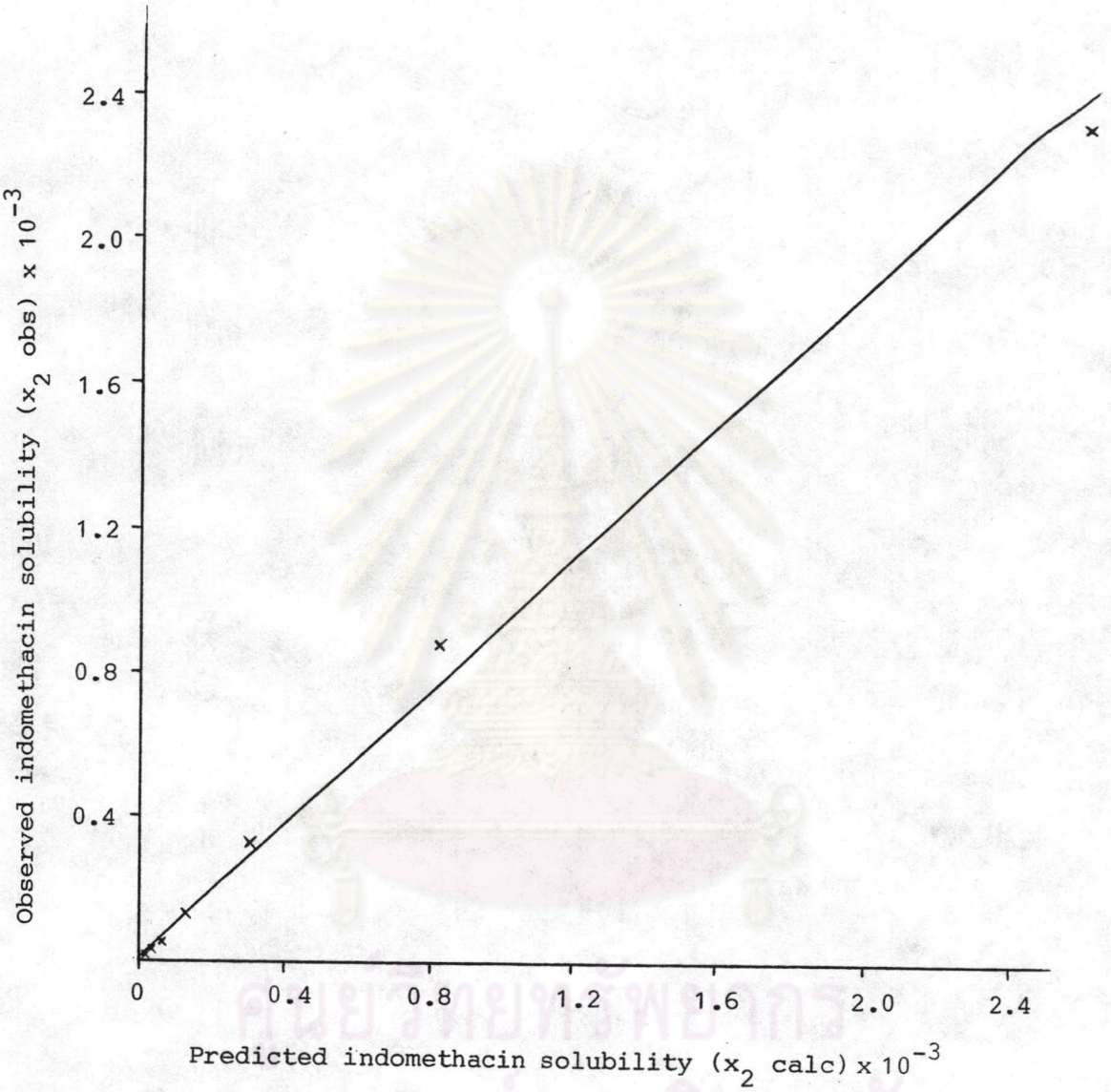


Figure 7 : Comparison of observed indomethacin solubilities in propylene glycol and water system at 30°C with solubilities predicted by the Extended Hildebrand Solubility Approach

prediction in these mixed solvents. By the same way, we can use this approach for predicting indomethacin solubility in the other binary systems.

After storing these solutions for two months, the concentrations of indomethacins in every mixed solvent systems except in 1,4 dioxane and water system are not changed (Appendix). This shows that indomethacin can be prepared and stored in these mixed solvents except 1,4 dioxane and water system for two months without problems. The mechanism of indomethacin degradation in 1,4 dioxane and water system is unknown. In summary, it can be concluded that the data obtained from this experiment is valid theoretically and is valuable in determination of drug solubility in a variety of mixed solvents. Furthermore, it is very useful for dosage form design to prepare the new formulations of indomethacin (e.g. solutions).

Molar Heat of Fusion, ΔHf, Determination

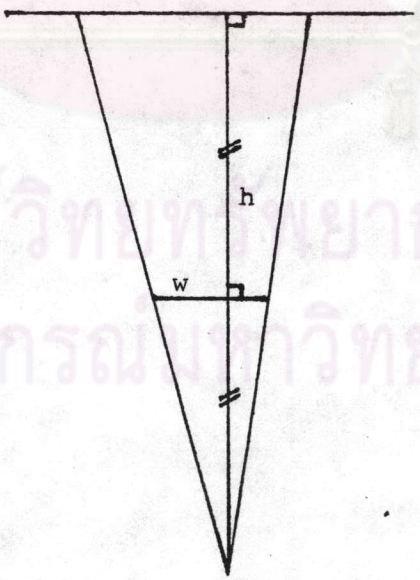
Some parameters used in ΔHf determination by differential scanning calorimeter are shown in Table IX. These parameters are substituted into equation described earlier. The molar heat of fusion of indomethacin obtained from DSC equals 11133.21 cal/mole and this value is used for calculation in this experiment.

The ΔHf value determined by solubility curve is also estimated in laboratory, the data and plot of ln mole fraction solubility versus reciprocal of temperature, ^{o}K are reported in Table X and Figure 8, respectively. Using linear regression, a straight line is obtained with slope equalizes 5481.9993.

Table IX : Some Physical Properties of Indomethacin and Indium

Parameters	Indomethacin (Sample)	Indium (Standard)
Atomic or Molecular weight	357.81	114.82
Experimental weight (gm)	0.0096	0.0159
Peak area* (cm^2)	2.90	2.10
ΔHf (cal/mole)	11133.21	781.00
Sensitivity (mcal/sec)	2.00	1.00

*Calculated by Peak height at max x Peak width at half height method (Ref. 43).



$$\text{Peak area } (cm^2) = \frac{1}{2} \times h \times w$$

Table X : Solubility of Indomethacin in Water at Various Temperatures

t (^{o}C)	T (^{o}K)	1/T(^{o}K)	x_2	ln x_2
30	303	0.0033	0.00000079	- 14.0512
40	313	0.0032	0.00000134	- 13.5215
50	323	0.0031	0.00000204	- 13.1026
60	333	0.0030	0.00000448	- 12.3151
70	343	0.0029	0.00000670	- 11.9134

Straight line equation, $\ln x_2 = 4.0134 - 5481.9993/T$

The coefficient of determination, $R^2 = 0.9950$

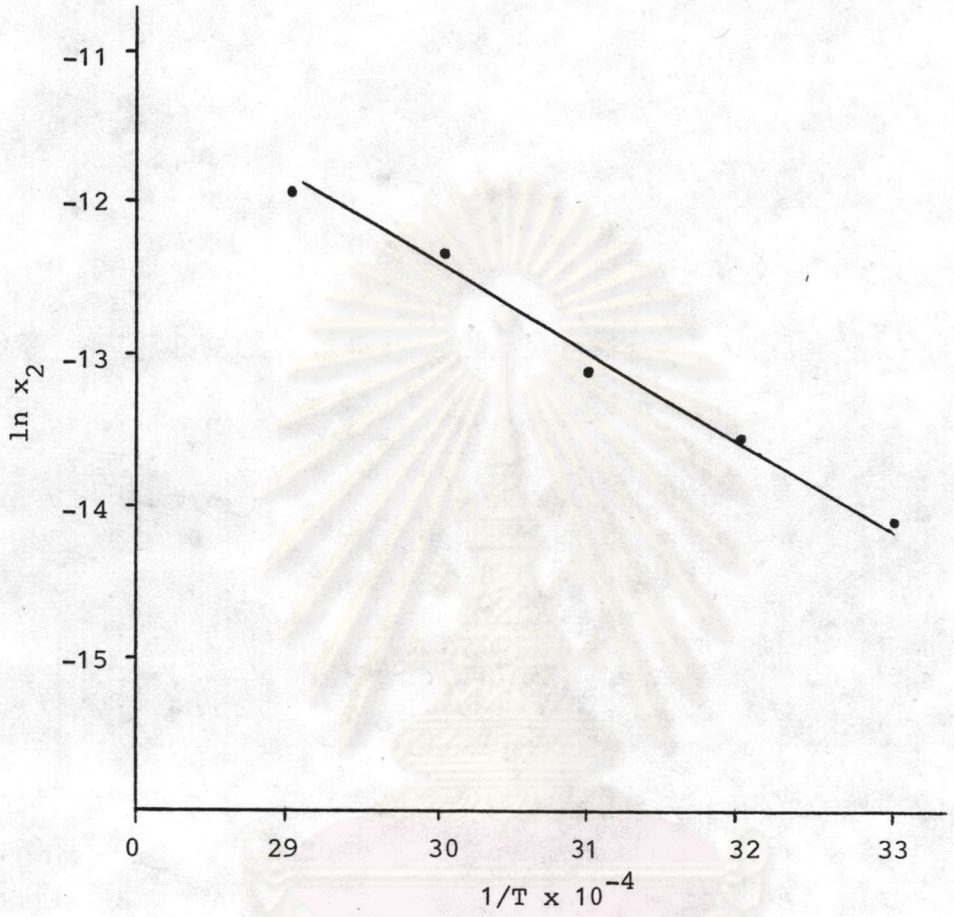


Figure 8 : Plot of the ln mole fraction solubility of indomethacin in water vs the reciprocal temperature, ^{o}K

The ΔHf value is calculated from slope of the line and equals 10892.73 cal/mole. This is an approximate value compared to that exactly determined by DSC (11133.21 cal/mole).

Compatibility and Stability Study

This study was designed to determine whether or not the proposed indomethacin in selected mixed solvents can be utilized with some buffer solutions and LVP products. Mixed solvents used in this study were PEG 400, 60% in water and propylene glycol 70% in water, these cosolvents gave suitably stability and solubility of indomethacin. Concentrations of indomethacin in these solutions were 5 mg/ml and 1.25 mg/ml, respectivety. These concentrations are reasonable for dosage adjustments (Appendix). Results obtained upon mixing both solutions with buffer and LVP systems are shown in Tables XI, XII and XIII respectively.

The pH of prepared indomethacin solutions were 4.09 in PEG 400, 60% and 4.22 in propylene glycol 70%. The data obtained agree well with previous studies (25-27) that indomethacin is soluble but not stable in alkaline solutions. As can be seen in Tables XI and XII, the concentrations of indomethacin calculated at 72 hours after mixing with buffer solutions are lower than those obtained instantly in mixed solutions at pH 7.4 and 8.0 in both solutions. However, the amounts of drug degraded are very slight between these two pH values. Owing to its high concentrations in PEG 400, 60%, indomethacin is easily precipitated when high volumes of drug solutions is added to buffer systems. The lower values of pH of buffer system used, the

lower volume of drug solution can be added compatibly, this phenomena occurs theoretically when the drug with low pKa is added to acidic media. Unlike PEG 400 system, the concentration of indomethacin in propylene glycol 70% is low enough to be compatible with buffer systems in all volumes added. These results in compatibility and stability of indomethacin solutions in buffer systems at various pH will be useful in some dosage forms formulation such as injections and ophthalmic solutions which this drug is sometime indicated.

Generally administration of drug by intravenous infusion is essential. Since it provides predictably and continuously blood levels. It is widely used today. In the case of PDA, indomethacin at very low dose (0.2 mg/kg) must be used with low birth weight infants. Predictable blood level of this drug is very necessary (36). For these reasons, compatibility and stability test of indomethacin solutions with commonly used LVP were conducted. Results are reported in Table XIII. In this test, 50 ml of LVP is used in the experiment because the acceptable flow rate of intravenous infusion is about 1000 ml/8 hr. So the drug, mixed well with 50 ml LVP, can be put into the body within 20 minutes. Results suggest that indomethacin solution in PEG 400, 60% is not recommended to be dilute with all kinds of LVP except Lactated Ringer's Solution. As reported, precipitation occurs when only 0.25 ml of solution is added to 50 ml of LVP. This is because the pH of such LVP except Lactated Ringer's Solution are low as well as that of indomethacin solution. Moreover, the concentrations of indomethacin in PEG 400, 60% are relatively high as compared to those obtained using propylene glycol 70%.

Table XI : Compatibility and Stability of Indomethacin in PEG 400, 60% in Buffer Systems

pH buffer	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
5.90	1	5.90	C	C	P	P	100	0.103	0.094	5185.71	4714.28
	2	5.88	P	P	P	P	-	-	-	-	-
6.50	1	6.48	C	C	C	C	100	0.102	0.103	5133.33	5185.71
	2	6.46	C	C	C	C	100	0.184	0.185	5142.86	5171.43
	3	6.40	T	T	T	P	-	-	-	-	-
7.00	1	7.00	C	C	C	C	100	0.103	0.103	5185.71	5185.71
	2	6.96	C	C	C	C	100	0.185	0.183	5171.43	5114.29
	3	6.92	C	C	C	C	200	0.130	0.128	5200.00	5117.46
	4	6.90	C	C	C	C	200	0.159	0.160	5166.67	5200.00
	5	6.83	T	T	T	T	-	-	-	-	-
7.40	1	7.19	C	C	C	C	100	0.102	0.096	5133.33	4819.05
	2	7.15	C	C	C	C	100	0.184	0.173	5142.86	4828.57
	3	7.03	C	C	C	C	200	0.129	0.115	5158.73	4580.95
	4	6.91	C	C	C	C	200	0.159	0.142	5166.67	4600.00
	5	6.75	C	C	C	C	200	0.187	0.165	5228.57	4600.00
	6	6.64	T	T	T	T	-	-	-	-	-

Table XI (Continue)

pH buffer	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
8.00	1	7.52	C	C	C	C	100	0.102	0.094	5133.33	4714.28
	2	7.46	C	C	C	C	100	0.183	0.175	5114.29	4885.71
	3	7.30	C	C	C	C	200	0.123	0.112	5158.73	4457.14
	4	7.16	C	C	C	C	200	0.158	0.139	5133.33	4500.00
	5	7.05	C	C	C	T	200	0.187	-	5228.57	-
	6	6.92	C	C	C	T	200	0.209	-	5206.35	-
	7	6.80	T	T	P	P	-	-	-	-	-

Key : C = Clear

T = Turbid

P = Precipitate

Table XII : Compatibility and Stability of Indomethacin in Propylene Glycol 70% in Buffer Systems

pH buffer	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
5.90	1	6.02	C	C	C	C	50	0.054	0.052	1309.52	1257.14
	2	6.01	C	C	C	C	50	0.095	0.094	1300.00	1285.71
	3	6.05	C	C	C	C	50	0.129	0.130	1289.68	1300.00
	4	6.03	C	C	C	C	50	0.158	0.158	1283.33	1283.33
	5	6.03	C	C	C	C	50	0.187	0.186	1307.14	1300.00
	6	6.02	C	C	C	C	50	0.209	0.209	1301.59	1301.59
	7	6.02	C	C	C	C	100	0.112	0.114	1248.98	1272.11
	8	6.03	C	C	C	C	100	0.126	0.124	1307.14	1285.71
	9	6.05	C	C	C	C	100	0.134	0.135	1306.88	1316.93
	10	6.05	C	C	C	C	100	0.139	0.140	1285.71	1295.24
6.50	1	6.50	C	C	C	C	50	0.053	0.052	1283.33	1257.14
	2	6.50	C	C	C	C	50	0.094	0.094	1285.71	1285.71
	3	6.52	C	C	C	C	50	0.131	0.129	1310.32	1289.68
	4	6.55	C	C	C	C	50	0.161	0.160	1308.33	1300.00
	5	6.56	C	C	C	C	50	0.187	0.185	1307.14	1292.86
	6	6.55	C	C	C	C	50	0.208	0.209	1295.23	1301.59

Table XII : (Continue)

pH buffer	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
6.50	7	6.54	C	C	C	C	100	0.112	0.113	1248.98	1260.54
	8	6.57	C	C	C	C	100	0.125	0.125	1296.43	1296.43
	9	6.54	C	C	C	C	100	0.134	0.134	1306.88	1306.88
	10	6.54	C	C	C	C	100	0.140	0.141	1295.24	1304.76
7.00	1	7.00	C	C	C	C	50	0.052	0.052	1257.14	1257.14
	2	7.00	C	C	C	C	50	0.094	0.093	1285.71	1271.43
	3	7.02	C	C	C	C	50	0.130	0.129	1300.00	1289.68
	4	7.01	C	C	C	C	50	0.157	0.159	1241.67	1291.67
	5	7.00	C	C	C	C	50	0.187	0.186	1307.14	1300.00
	6	7.03	C	C	C	C	50	0.210	0.208	1307.94	1295.23
	7	7.07	C	C	C	C	100	0.113	0.114	1260.54	1272.71
	8	7.04	C	C	C	C	100	0.124	0.124	1285.71	1285.71
	9	7.05	C	C	C	C	100	0.135	0.133	1316.93	1296.82
	10	7.04	C	C	C	C	100	0.140	0.139	1295.24	1285.71
7.40	1	7.38	C	C	C	C	50	0.053	0.052	1283.33	1257.14
	2	7.40	C	C	C	C	50	0.093	0.057	1271.43	1185.71

Table XII : (Continue)

pH buffer	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
7.40	3	7.40	C	C	C	C	50	0.132	0.128	1320.63	1279.36
	4	7.40	C	C	C	C	50	0.159	0.146	1291.67	1183.33
	5	7.41	C	C	C	C	50	0.186	0.168	1300.00	1171.43
	6	7.42	C	C	C	C	50	0.209	0.191	1301.57	1187.03
	7	7.42	C	C	C	C	100	0.115	0.105	1283.67	1168.03
	8	7.43	C	C	C	C	100	0.125	0.112	1296.43	1157.14
	9	7.41	C	C	C	C	100	0.135	0.121	1316.93	1176.19
	10	7.40	C	C	C	C	100	0.138	0.121	1276.19	1114.28
8.00	1	7.93	C	C	C	C	50	0.054	0.046	1309.52	1100.00
	2	7.92	C	C	C	C	50	0.093	0.079	1271.43	1071.43
	3	7.92	C	C	C	C	50	0.130	0.112	1300.00	1114.28
	4	7.93	C	C	C	C	50	0.159	0.131	1291.67	1058.33
	5	7.96	C	C	C	C	50	0.185	0.160	1292.86	1114.28
	6	7.98	C	C	C	C	50	0.208	0.182	1295.23	1130.16
	7	7.95	C	C	C	C	100	0.114	0.097	1272.11	1075.51
	8	7.93	C	C	C	C	100	0.125	0.107	1296.43	1103.57
	9	7.94	C	C	C	C	100	0.133	0.118	1296.82	1146.03
	10	7.94	C	C	C	C	100	0.141	0.115	1304.76	1057.14

Table XIII : Compatibility and Stability of Indomethacin in PEG 400, 60% and in Propylene Glycol 70% in LVP Systems

Original sol^{n}	Volume added (ml)	pH obtained	Compatibility				Dilution factor	Average Absorbance		Conc. of original sol^{n} (µg/ml)	
			0 hr	24 hrs	48 hrs	72 hrs		0 hr	72 hrs	0 hr	72 hrs
	D 5 N/5 (pH 4.23)										
PEG	0.25	4.12	C	C	P	P	10	0.058	-	5168.57	-
	0.50	4.10	P	P	P	P	-	-	-	-	-
PG	0.25	4.20	C	C	C	C	-	0.139	0.140	1292.14	1301.71
	0.50	4.16	C	C	C	C	10	0.031	0.031	1298.57	1298.57
	1.00	4.23	C	P	P	P	10	0.057	-	1287.14	-
	1.50	4.22	P	P	P	P	-	-	-	-	-
	D 5 W (pH 3.63)										
PEG	0.25	3.96	C	P	P	P	10	0.059	-	5264.28	-
	0.50	4.02	P	P	P	P	-	-	-	-	-
PG	0.25	4.05	C	C	C	C	-	0.139	0.138	1292.14	1282.57
	0.50	4.05	C	C	C	P	10	0.030	-	1250.08	-
	1.00	4.11	C	C	C	P	10	0.058	-	1311.42	-
	1.50	4.18	P	P	P	P	-	-	-	-	-

Table XIII : (Continue)

Original sol^{n}	Volume added (ml)	pH obtained	Compatibility 0 hr	24 hrs	48 hrs	72 hrs	Dilution factor	Average Absorbance 0 hr	72 hrs	Conc. of original sol^{n} (µg/ml) 0 hr	72 hrs
	D 5 N/2 (pH 3.78)										
PEG	0.25	3.55	P	P	P	P	-	-	-	-	-
PG	0.25	3.81	C	C	C	C	-	0.138	0.138	1282.57	1282.57
	0.50	3.82	C	P	P	P	10	0.031	-	1298.57	-
	1.00	3.83	P	P	P	P	-	-	-	-	-
	NSS (pH 6.26)										
PEG	0.25	4.17	P	P	P	P	-	-	-	-	-
PG	0.25	5.40	C	C	C	C	-	0.139	0.138	1292.14	1282.57
	0.50	5.05	C	C	C	C	10	0.031	0.030	1298.57	1250.08
	1.00	4.59	C	C	C	P	10	0.056	-	1262.86	-
	1.50	4.32	P	P	P	P	-	-	-	-	-

Table XIII : (Continue)

Original sol^{n}	Volume added (ml)	pH obtained	Compatibility 0 hr	24 hrs	48 hrs	72 hrs	Dilution factor	Average Absorbance 0 hr	72 hrs	Conc. of original sol^{n} (µg/ml) 0 hr	72 hrs
		Lactated Ringer's (pH 7.24)									
PEG	0.25	6.41	C	C	C	C	10	0.058	0.058	5168.57	5168.57
	0.50	5.88	C	C	C	C	10	0.112	0.111	5194.28	5146.19
	1.00	5.47	C	C	C	C	50	0.046	0.048	5100.00	5342.86
	1.50	5.27	P	P	P	P	-	-	-	-	-
PG	0.25	7.19	C	C	C	C	-	0.140	0.140	1301.71	1301.71
	0.50	6.84	C	C	C	C	10	0.030	0.031	1250.08	1298.57
	1.00	6.55	C	C	C	C	10	0.057	0.057	1287.14	1287.14
	5.00	6.28	C	C	C	C	50	0.053	0.054	1283.33	1309.52
	10.00	5.61	C	C	C	C	100	0.049	0.048	1285.71	1257.14
	20.00	5.33	C	C	C	C	100	0.081	0.081	1283.33	1283.33
	40.00	5.22	C	C	C	P	100	0.126	-	1307.14	-

Therefore, when LVP solutions and indomethacin solution in PEG 400, 60% are mixed, the apparent percentage of polyethylene glycol 400 becomes too low to solubilize the drug and this called precipitation on dilution. Meanwhile Lactated Ringer's Solution, its pH is so high that precipitation was not observed until 1.5 ml of drug solution was added. The results obtained from propylene glycol system are similar to those from PEG 400 system. As can be seen, volumes of indomethacin solution can be added to LVP is not more than 0.5 ml but this amount increases up to 40 ml in Lactated Ringer's Solution. This indicates that factor influencing solubility of indomethacin is acidity and basicity of solutions. In summary, it can be concluded that adding of high concentrations of indomethacin solution into LVP is not recommended. However, when low dose of this drug is used, this technique is valuable and LVP employed should be those with high pH values such as Lactated Ringer's Solution or Normal Saline Solutions.

In conclusion, on the basis of this study, the Extended Hildebrand Solubility Approach is a good mean of predicting solubilities of indomethacin in various mixed solvents. The proposed solutions of this drug in two selected mixed solvents systems may be employed as new kinds of dosage forms such as solutions, injections and ophthalmic solutions in which this drug is sometimes indicated. Additionally, the method described here may be used for estimating the solubility of other drugs which their aqueous solubilities are very low. The knowledge of solution theory is valuable in pharmaceutical and medical fields especially in preparing and adjusting the drug products to rapidly attain therapeutic efficacy. The molar heat of fusion obtained using DSC and solubility curve are nearly identical. This

shows that the method employed in a laboratory without special equipment can be used for approximate determination of this value. The study of compatibility and stability of indomethacin solution with LVP and buffer solutions demonstrate some undesirable effects which may result when inappropriate solutions are mixed. Finally, comprehensive studies of toxicity, bioavailability and pharmacokinetics of these solutions in animals and mans must be achieved for final consideration prior to use.