

CHAPTER III

RESULTS

Effect of the Carrier Types

Six types of water-soluble carriers had been used, i.e. PEG 4000, PEG 6000, PEG 20000, mannitol, urea and PVPP. The amount of the carrier used was fixed to the ratio of 1:2 as compared to the drug. The solid dispersion systems were prepared using two methods; fusion and solvent methods. The codes for all nine solid dispersion preparations and IBU used in this step were as follows:-

<u>Code</u>	<u>Solid dispersion preparations/IBU</u>
R1	1:2 IBU:PEG 4000 solid dispersion, fusion method
R2	1:2 IBU:PEG 6000 solid dispersion, fusion method
R3	1:2 IBU:PEG 20000 solid dispersion, fusion method
R4	1:2 IBU:PEG 4000 solid dispersion, solvent method
R5	1:2 IBU:PEG 6000 solid dispersion, solvent method
R6	1:2 IBU:PEG 20000 solid dispersion, solvent method
R7	1:2 IBU:mannitol solid dispersion, solvent method
R8	1:2 IBU:urea solid dispersion, solvent method
R9	1:2 IBU:PVPP solid dispersion, solvent method
R10	IBU

1. Characteristics of Ibuprofen Solid Dispersions

1.1 Fusion Method. The carriers which could be used to prepare the IBU solid dispersions by fusion method

were limited to only the PEG series owing to the low melting point of IBU. Once IBU was added to the molten carrier (except for the PEGs), evaporation occurred. The IBU-PEG melts were visually clear, homogeneous liquid. When dried, they were all white, stable masses which could be pulverized to yield dry, nonsticky white powder.

1.2 Solvent Method. All six types of water-soluble carrier mentioned above had been used to prepare IBU solid dispersions by solvent method. The IBU-mannitol and IBU-PVPP solid dispersions prepared by solvent method were nonsticky white powder which were easy to manipulate. Products yielded from the IBU-PEG systems were somewhat waxlike and more difficult to pulverized. The IBU-urea dispersion was crystalline white powder and easy to pulverized as well.

When compared, fusion method was relatively easy to be prepared, less time consuming and more economical than solvent method. Despite the fact that sublimation of IBU did occur while mixing IBU with most molten carriers except for the PEGs, the appropriate carriers could be selected and solid dispersion with good characteristic could be obtained.

2. Assay of Ibuprofen and Ibuprofen in Solid Dispersions

The percentage contents of IBU and IBU in each solid dispersion systems were shown in Table 3. The IBU contents were between 98.86 and 102.24 %

Table 3 Percentage contents of IBU and IBU in Solid Dispersions, R1 to R10

Preparation	IBU Content (percent)		
	1	2	Average \pm S.D.
R1	100.25	100.25	100.25 \pm 0.00
R2	100.15	99.90	100.03 \pm 0.13
R3	100.46	100.73	100.60 \pm 0.14
R4	99.63	99.52	99.58 \pm 0.06
R5	100.12	99.82	99.97 \pm 0.15
R6	99.96	99.93	99.95 \pm 0.02
R7	101.44	101.45	101.45 \pm 0.01
R8	98.77	98.95	98.86 \pm 0.09
R9	102.27	102.20	102.24 \pm 0.04
R10	100.22	100.31	100.27 \pm 0.05

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Table 4 Size Distribution Data of IBU and Various Solid Dispersion Systems (R1 to R9)

IBU				
Sieve Number (Passed/Retained)	Sieve Opening (mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.30	0.62	0.62
20/40	420-840	5.32	10.98	11.59
40/60	250-420	4.12	8.50	20.09
60/80	177-250	9.09	18.75	38.85
80/Receiver	<177	29.64	61.15	100.00
TOTAL		48.47	100.00	

1:2 IBU:PEG 4000, Fusion Method (R1)				
Sieve Number (Passed/Retained)	Sieve Opening (mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.36	1.46	1.46
20/40	420-840	8.50	34.44	35.90
40/60	250-420	5.22	21.15	57.05
60/80	177-250	2.51	10.17	67.22
80/Receiver	<177	8.09	32.78	100.00
TOTAL		24.68	100.00	

1:2 IBU:PEG 6000, Fusion Method (R2)				
Sieve Number (Passed/Retained)	Sieve Opening (mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.17	0.69	0.69
20/40	420-840	7.03	28.50	29.19
40/60	250-420	5.53	22.41	51.60
60/80	177-250	2.80	11.35	62.95
80/Receiver	<177	9.14	37.05	100.00
TOTAL		24.67	100.00	

Table 4 (cont.)

1:2 IBU:PEG 20000, Fusion Method (R3)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	3.51	14.27	14.27
20/40	420-840	10.51	42.72	56.99
40/60	250-420	3.74	15.20	72.20
60/80	177-250	1.47	5.98	78.17
80/Receiver	<177	5.37	21.83	100.00
TOTAL		24.60	100.00	

1:2 IBU:PEG 4000, Solvent Method (R4)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.27	1.10	1.10
20/40	420-840	6.65	26.98	28.07
40/60	250-420	4.59	18.62	46.69
60/80	177-250	2.68	10.87	57.57
80/Receiver	<177	10.46	42.43	100.00
TOTAL		24.65	100.00	

1:2 IBU:PEG 6000, Solvent Method (R5)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.06	0.24	0.24
20/40	420-840	5.15	21.00	21.24
40/60	250-420	4.34	17.69	38.93
60/80	177-250	3.03	12.35	51.28
80/Receiver	<177	11.95	48.72	100.00
TOTAL		24.53	100.00	

1:2 IBU:PEG 20000, Solvent Method (R6)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	1.38	5.56	5.56
20/40	420-840	10.79	43.51	49.07
40/60	250-420	4.64	18.71	67.78
60/80	177-250	1.92	7.74	75.52
80/Receiver	<17	6.07	24.48	100.00
TOTAL		24.80	100.00	

Table 4 (cont.)

1:2 IBU:Mannitol, Solvent Method (R7)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	0.00	0.00	0.00
20/40	420-840	0.06	0.25	0.25
40/60	250-420	0.85	3.59	3.84
60/80	177-250	1.28	5.40	9.25
80/Receiver	<177	21.51	90.76	100.00
TOTAL		23.70	100.00	

1:2 IBU:Urea, Solvent Method (R8)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	0.95	3.88	3.88
20/40	420-840	1.30	5.31	9.18
40/60	250-420	1.64	6.69	15.88
60/80	177-250	9.21	37.59	53.47
80/Receiver	<177	11.40	46.53	100.00
TOTAL		24.50	100.00	

1:2 IBU:PVPP, Solvent Method (R9)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	0.02	0.08	0.08
20/40	420-840	0.37	1.50	1.58
40/60	250-420	1.22	4.95	6.53
60/80	177-250	5.61	22.75	29.28
80/Receiver	<177	17.44	70.72	100.00
TOTAL		24.66	100.00	

3. Particle Size Determination.

Size-distribution data of IBU and IBU solid dispersion systems were presented in Table 4. The mode which is the maximum in the size-frequency curve of IBU particles occurred at the size that was less than 177 μm (passed through sieve No.80). The same results were obtained with IBU-PEG 4000 (solvent method), IBU-PEG 6000 (both method), IBU-mannitol, IBU-urea and IBU-PVPP (solvent method) systems. The mode size of IBU-PEG 4000 (fusion method) was 420-840 μm to which the percent particles in this size group was 34.44 while the percent particles in the size group of less than 177 μm , which was the next frequent-size group, was 32.78. For IBU-PEG 20000 systems, either fusion or solvent method, the mode sizes were also 420-840 μm . This may be due to the fact that the higher the molecular weight of PEGs, the harder were their characteristic. So, after pulverized, the mode of yielded products of IBU:PEG 20000 systems were somewhat larger than other systems.

4. Dissolution Tests.

The dissolution profiles of all nine preparations were depicted in Figures 1-3. The statistical comparisons of IBU dissolved from various IBU solid dispersions (R1 to R10) at various times using one-way ANOVA (Analysis of Variance) were presented in Table 5. Student's t-test were used to compare the concentrations of IBU dissolved from each solid

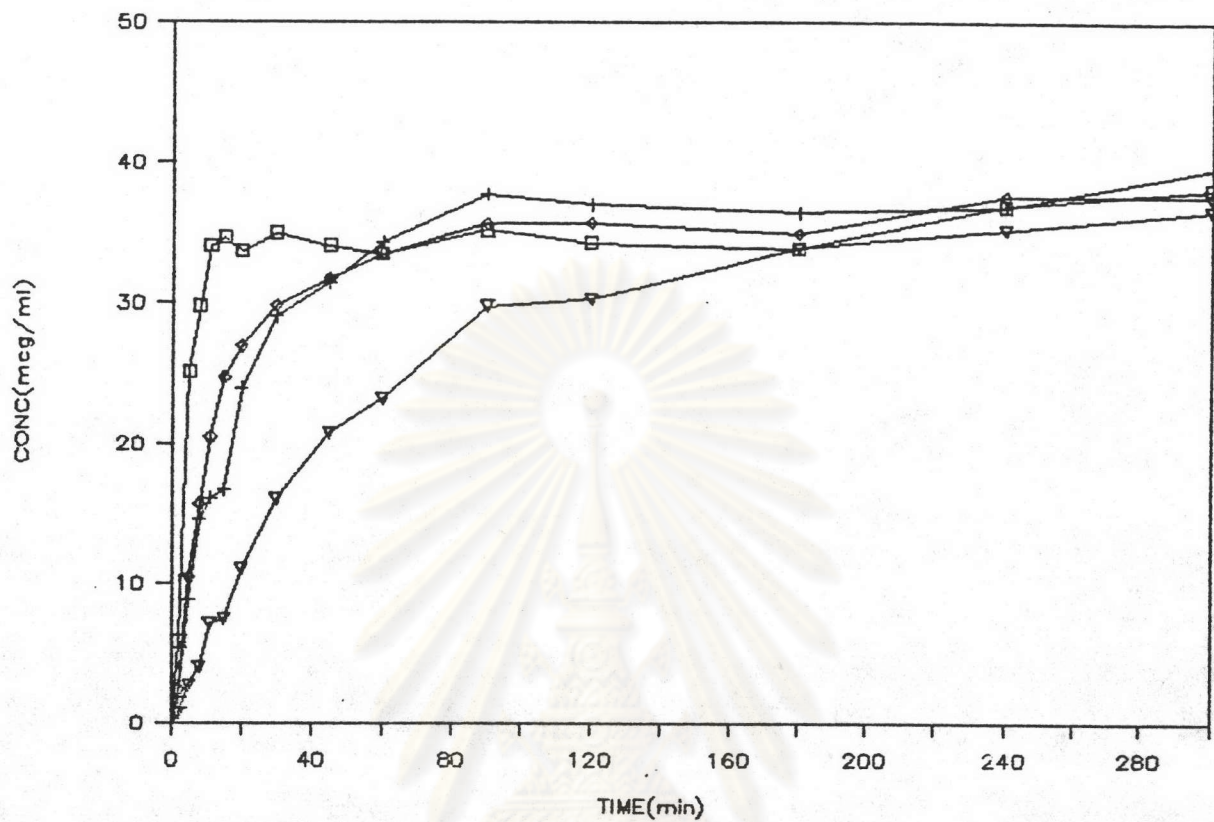


Figure 1 Dissolution profiles of ibuprofen solid dispersions, using 1:2 ratio of PEGs as the carriers, fusion method

Key: □ R1, IBU:PEG 4000
+ R2, IBU:PEG 6000
◇ R3, IBU:PEG 20000
▽ R10, IBU (control)

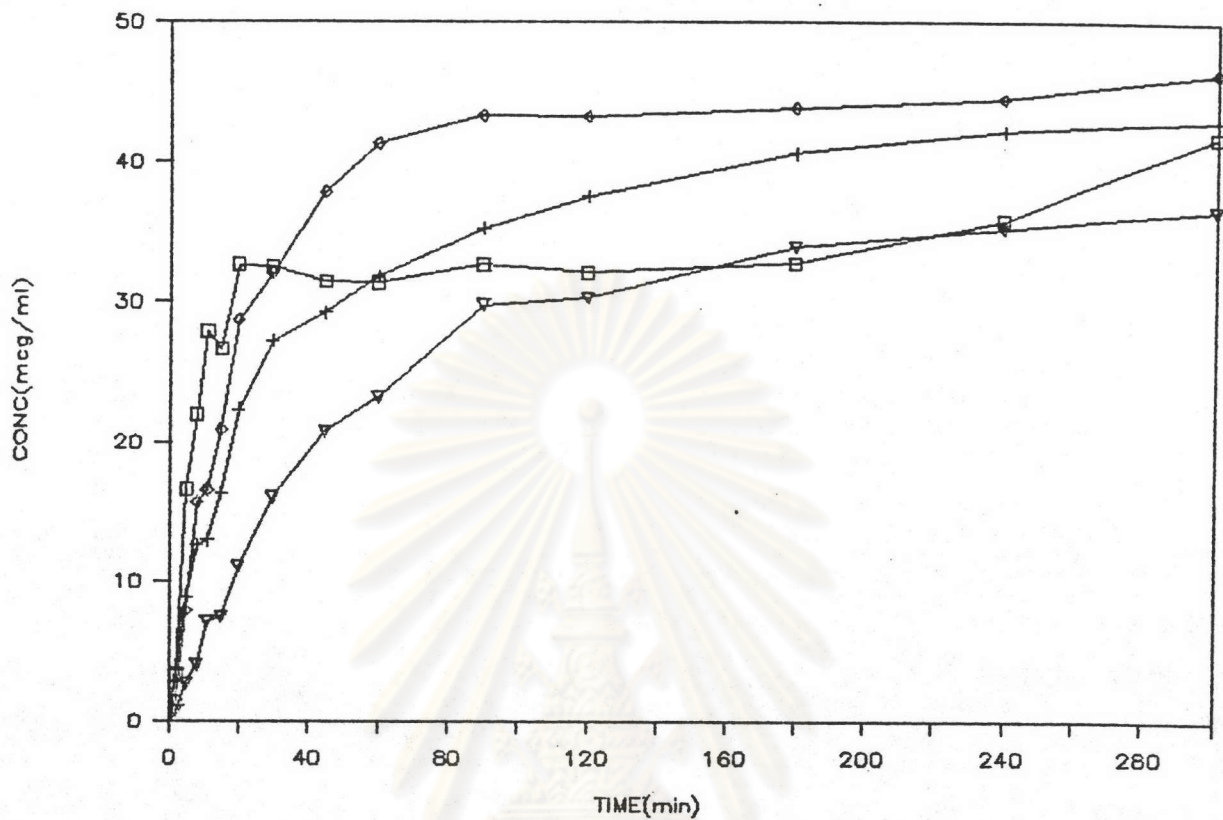


Figure 2 Dissolution profiles of ibuprofen solid dispersions, using 1:2 ratio of PEGs as the carriers, solvent method

Key: □ R4, IBU:PEG 4000
 + R5, IBU:PEG 6000
 ◇ R6, IBU:PEG 20000
 ▽ R10, IBU (control)

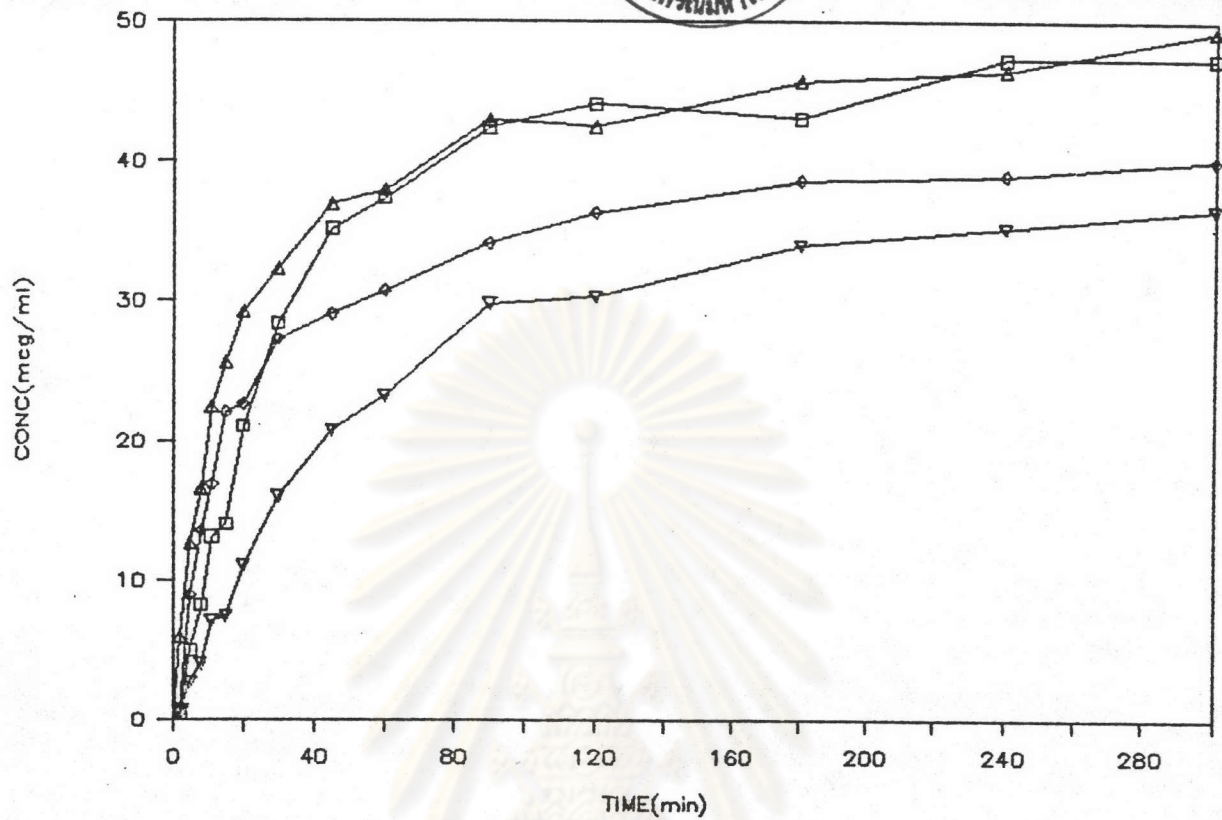


Figure 3 Dissolution profiles of ibuprofen solid dispersions, using 1:2 ratio of mannitol, urea and PVPP as the carriers, solvent method

Key: \diamond R7, IBU:Mannitol
 \triangle R8, IBU:Urea
 \square R9, IBU:PVPP
 ∇ R10, IBU (control)

Table 5 The Statistical Comparisons of IBU Concentrations Dissolved from Various IBU Solid Dispersions (R1 to R10) at Various Times Using One-way ANOVA

Time (min)	Source of variation	d.f.	SS	MS	F
5	Treatment	9	1265.0960	140.5663	8.1288
	Error	24	415.0176	17.2924	
	Total	33	1680.1140		
15	Treatment	9	2112.2830	234.6981	4.7212
	Error	24	1193.0850	49.7119	
	Total	33	3305.3680		
30	Treatment	9	1210.9490	134.5499	5.0211
	Error	24	643.1223	26.7968	
	Total	33	1854.0710		
45	Treatment	9	1015.3230	112.8137	2.3953
	Error	24	1130.3630	47.0985	
	Total	33	2145.6860		
60	Treatment	9	971.6508	107.9612	2.1953
	Error	24	1180.2910	49.1788	
	Total	33	2151.9420		
120	Treatment	9	757.0895	84.1211	1.3205
	Error	24	1528.8850	63.7036	
	Total	33	2285.9750		
180	Treatment	9	702.7247	78.0805	1.0309
	Error	24	1817.8270	75.7428	
	Total	33	2520.5520		
300	Treatment	9	670.4624	74.4958	0.8703
	Error	24	2054.4380	85.6016	
	Total	33	2724.9010		

F = 2.30
0.05 (9,24)

F = 1.91
0.10 (9,24)

Table 6 The Concentrations of IBU dissolved from IBU Solid Dispersions (R1 to R9) and Pure IBU (R10) at Various Times

Preparation	Concentration (mcg/ml) at time (min)							
	5	15	30	45	60	120	180	300
R1	25.110 (3.16)	34.649 (3.51)	34.952 (2.98)	34.079 (4.10)	33.509 (3.52)	34.268 (1.41)	33.850 (2.51)	38.104 (0.31)
R2	8.816 (3.57)	16.662 (6.22)	29.055 (1.19)	31.462 (2.88)	34.307 (7.08)	37.006 (0.09)	36.402 (6.09)	39.456 (7.63)
R3	10.442 (2.44)	24.704 (6.72)	29.836 (6.16)	31.723 (4.82)	33.470 (6.24)	35.673 (4.50)	34.909 (5.10)	37.567 (4.35)
R4	16.576 (6.05)	26.612 (9.63)	32.484 (3.37)	31.459 (3.69)	31.345 (5.79)	32.105 (3.96)	32.788 (3.79)	41.788 (6.05)
R5	8.850 (4.21)	16.305 (9.32)	27.165 (4.17)	29.200 (5.72)	31.786 (6.03)	37.492 (10.88)	40.606 (10.64)	42.961 (10.68)
R6	7.858 (4.31)	20.841 (13.07)	32.050 (9.75)	37.799 (12.72)	41.324 (12.44)	43.268 (14.02)	43.859 (14.02)	46.359 (12.48)
R7	8.932 (4.12)	21.988 (7.62)	27.233 (3.73)	29.045 (8.78)	30.716 (7.48)	36.259 (8.17)	38.575 (9.35)	40.055 (10.41)
R8	12.607 (4.56)	25.524 (5.93)	32.305 (8.16)	36.911 (9.47)	37.910 (7.42)	42.433 (9.18)	45.675 (9.89)	49.310 (12.61)
R9	4.978 (2.26)	14.019 (4.82)	28.402 (2.37)	35.129 (5.64)	37.303 (8.20)	44.101 (8.18)	43.067 (10.62)	47.301 (13.66)
R10	2.678 (4.59)	7.388 (2.53)	15.994 (3.47)	20.725 (5.11)	23.169 (4.83)	30.305 (7.54)	33.950 (7.90)	36.511 (6.64)

Average data of at least 3 determinations are represented and S.D. are given in parentheses

* = Statistically significantly higher than those of IBU (R10) (p<0.10)

** = Statistically significantly higher than those of IBU (R10) (p<0.05)

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dispersion preparations at various times to the dissolution of IBU itself. The results were presented in Table 6.

The results revealed that the IBU in all nine preparations dissolved faster than pure IBU (R10) which was used as the control. According to Figure 1 which presented the dissolution profiles of IBU solid dispersions dispersed in the PEG series prepared by the fusion method, all three preparations gave significant higher concentrations of dissolved IBU during the first 60 minutes ($p < 0.10$, t-test). R1 produced the quickest dissolution rate and the highest concentration of IBU which could be obtained within 45 minutes were 34.079 mcg/ml. The highest concentrations of IBU obtained from R3 and R2 were 31.723 and 31.462 mcg/ml respectively while the highest concentration obtained from R10 was only 20.725 mcg/ml. However, after 60 minutes these three preparations yielded nearly equal concentrations of dissolved IBU.

From Figure 2 which demonstrated the dissolution profiles of 1:2 IBU:PEGs solid dispersions prepared by solvent method, R4 gave higher concentrations of dissolved IBU than R6, R5 and R10 during the first 30 minutes of the dissolution profiles followed by subsequent lower concentrations of IBU dissolved than R6 and R5 after 60 minutes. After 30 minutes R6 showed higher concentrations of dissolved IBU than the other preparations (significantly higher than R10 at 30 and 60 minutes ($p < 0.10$, t-test)).

According to Figure 3 which illustrated the dissolution profiles of 1:2 IBU:other carriers (mannitol, urea and PVPP) solid dispersions prepared by solvent method, R8 exhibited highest concentrations of dissolved IBU among the three preparations throughout almost all the range of the study and yielded significantly ($p < 0.1$, t-test) higher IBU dissolved than R10 throughout the range of the study. Although R9 seemed to produced nearly the same average concentraion of dissolved IBU as R8, its dissolution rate within the first 30 minutes of the experiments was much slower than R8.

Due to the above dissolution results, R1, R6 and R8 were chosen for further studies by means of varying the ratio of drug:carriers in the preparation of solid dispersions in order to find the solid dispersion system which give the most promising in the improving of IBU dissolution.

Effect of the Amount of Carriers Used

Three preparations with the best dissolution properties, R1, R6 and R8 were selected and the ratio of IBU:carriers were varied as 1:2, 1:3 and 1:4. Hence, nine solid dispersion systems were prepared and compared to pure IBU at this step. The codes used for each preparations and IBU were as followed:-

<u>Code</u>	<u>Solid dispersion preparations/IBU</u>
P1	1:2 IBU:PEG 4000 solid dispersion, fusion method
P2	1:3 IBU:PEG 4000 solid dispersion, fusion method
P3	1:4 IBU:PEG 4000 solid dispersion, fusion method
P4	1:2 IBU:PEG 20000 solid dispersion, solvent method
P5	1:3 IBU:PEG 20000 solid dispersion, solvent method
P6	1:4 IBU:PEG 20000 solid dispersion, solvent method
P7	1:2 IBU:urea solid dispersion, solvent method
P8	1:3 IBU:urea solid dispersion, solvent method
P9	1:4 IBU:urea solid dispersion, solvent method
P10	IBU

All nine preparations newly prepared at this step had the same external characteristics as those obtained from the 1:2 ratio previously prepared.

The percentage content of IBU and IBU in each systems of solid dispersion were presented in Table 7. The IBU contents were between 99.40 and 101.61%

Size distribution data of IBU solid dispersion systems (P1 to P9) were shown in Table 8. The mode sizes of all preparations except P4 (1:2 IBU:PEG 20000 solid dispersion, solvent method) were less than 177 μ m (passed through No.80-mesh). The mode size of P4 was 420-840 μ m to which the percent frequency was very closed to the percent frequency of the size group of less than 177 μ m.

Dissolution studies of all nine preparations, R1 to R9, and pure IBU (P10) were performed. Table 9 presented

Table 7 Percentage Content of IBU and IBU in Solid
Dispersions, P1 to P10

Preparation	IBU Content (percent)		
	1	2	Average \pm S.D.
P1	100.94	100.60	100.77 \pm 0.17
P2	101.29	100.69	100.99 \pm 0.30
P3	99.89	100.18	100.04 \pm 0.15
P4	100.62	100.23	100.43 \pm 0.20
P5	100.30	99.76	100.03 \pm 0.27
P6	99.60	99.50	99.55 \pm 0.05
P7	100.88	101.19	101.04 \pm 0.16
P8	101.92	101.29	101.61 \pm 0.32
P9	99.45	99.55	99.40 \pm 0.08
P10	100.84	100.61	100.73 \pm 0.12

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Table 8 Size Distribution Data of Various Solid Dispersion Systems (P1 to P9)

1:2 IBU:PEG 4000, Fusion Method (P1)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency)(g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	0.47	0.95	0.95
20/40	420-840	14.65	29.54	30.49
40/60	250-420	10.74	21.66	52.15
60/80	177-250	5.63	11.35	63.50
80/Receiver	<177	18.10	36.50	100.00
TOTAL		49.59	100.00	

1:3 IBU:PEG 4000, Fusion Method (P2)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency)(g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	1.03	2.08	2.08
20/40	420-840	15.59	31.52	33.60
40/60	250-420	10.64	21.51	55.10
60/80	177-250	6.27	12.67	67.78
80/Receiver	<177	15.94	32.22	100.00
TOTAL		49.47	100.00	

1:4 IBU:PEG 4000, Fusion Method (P3)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency)(g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	0.79	1.59	1.59
20/40	420-840	13.27	26.79	28.38
40/60	250-420	10.66	21.52	49.90
60/80	177-250	6.36	12.84	62.74
80/Receiver	<177	18.46	37.26	100.00
TOTAL		49.54	100.00	

Table 8 (cont.)

1:2 IBU:PEG 20000, Solvent Method (P4)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	8.08	16.30	16.30
20/40	420-840	16.04	32.37	48.67
40/60	250-420	6.04	12.19	60.86
60/80	177-250	3.59	7.24	68.10
80/Receiver	<177	15.81	31.90	100.00
TOTAL		49.56	100.00	

1:3 IBU:PEG 20000, Solvent Method (P5)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	5.28	10.66	10.66
20/40	420-840	9.55	19.29	29.95
40/60	250-420	6.59	13.31	43.26
60/80	177-250	6.46	13.05	56.31
80/Receiver	<177	21.63	43.69	100.00
TOTAL		49.51	100.00	

1:4 IBU:PEG 20000, Solvent Method (P6)				
Sieve Number (Passed/Retained)	Sieve Opening(mcm)	Wt Retained (Frequency) (g)	Percent Frequency(%)	Cumulative %Frequency
0/20	>840	9.12	18.37	18.37
20/40	420-840	13.67	27.54	45.91
40/60	250-420	5.10	10.28	56.19
60/80	177-250	3.63	7.31	63.50
80/Receiver	<177	18.12	36.50	100.00
TOTAL		49.64	100.00	

Table 8 (cont.)

1:2 IBU:Urea, Solvent Method (P7)				
Sieve Number (Passed/Retained)	Sieve Opening (µm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.31	0.64	0.64
20/40	420-840	2.25	4.64	5.28
40/60	250-420	7.43	15.31	20.59
60/80	177-250	10.38	21.38	41.97
80/Receiver	<177	28.16	58.03	100.00
TOTAL		48.53	100.00	

1:3 IBU:Urea, Solvent Method (P8)				
Sieve Number (Passed/Retained)	Sieve Opening (µm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.05	0.10	0.10
20/40	420-840	0.97	1.97	2.07
40/60	250-420	4.22	8.58	10.65
60/80	177-250	8.58	17.43	28.08
80/Receiver	<177	35.39	71.92	100.00
TOTAL		49.21	100.00	

1:4 IBU:Urea, Solvent Method (P9)				
Sieve Number (Passed/Retained)	Sieve Opening (µm)	Wt Retained (Frequency) (g)	Percent Frequency (%)	Cumulative %Frequency
0/20	>840	0.16	0.32	0.32
20/40	420-840	0.68	1.38	1.70
40/60	250-420	2.83	5.74	7.44
60/80	177-250	7.51	15.23	22.67
80/Receiver	<177	38.13	77.33	100.00
TOTAL		49.31	100.00	

Table 9 The Concentration of IBU Dissolved from IBU Solid Dispersions (P1 to P9) and Pure IBU (P10) at Various Times

Preparation	Concentration (mcg/ml) at time (min)							
	5	11	15	30	45	60	120	180
P1	16.649 (5.25)	27.573 (4.59)	27.940 (4.05)	30.364 (3.18)	28.398 (3.21)	28.970 (3.33)	29.770 (3.43)	30.609 (4.17)
P2	27.054 (4.93)	28.246 (5.98)	29.389 (5.96)	29.580 (5.70)	29.999 (5.97)	30.113 (5.91)	30.494 (4.80)	33.200 (4.93)
P3	28.038 (4.20)	28.780 (5.68)	29.732 (5.54)	29.847 (4.46)	30.533 (4.75)	31.790 (5.26)	32.248 (4.93)	37.469 (5.95)
P4	10.200 (0.89)	14.950 (2.10)	18.334 (2.71)	22.138 (4.09)	23.725 (3.78)	28.847 (3.75)	26.531 (4.91)	32.324 (4.03)
P5	9.544 (2.17)	17.336 (0.88)	19.760 (4.52)	22.147 (2.96)	24.404 (5.72)	29.099 (5.33)	27.712 (6.15)	33.315 (5.29)
P6	11.878 (4.02)	19.257 (1.65)	21.804 (0.97)	25.798 (2.02)	27.194 (3.34)	29.084 (0.80)	29.732 (1.66)	33.734 (1.59)
P7	7.649 (1.96)	13.570 (0.62)	12.854 (2.81)	17.671 (1.84)	21.445 (1.28)	25.127 (2.16)	27.315 (3.45)	33.678 (2.26)
P8	9.865 (0.49)	13.783 (0.98)	14.539 (3.31)	18.372 (3.62)	22.893 (2.17)	25.524 (4.05)	28.572 (4.28)	32.171 (6.05)
P9	9.972 (2.30)	14.317 (1.98)	15.233 (1.06)	17.685 (2.19)	22.185 (0.99)	26.553 (1.64)	26.851 (2.34)	32.333 (2.50)
P10	1.106 (0.73)	6.099 (3.05)	7.445 (3.24)	1.761 (4.13)	15.266 (5.69)	18.974 (5.50)	19.833 (6.62)	28.154 (5.53)

Average data of at least 3 determinations are represented and S.D. are given in parentheses

Table 10 The Statistical Comparisons of IBU Concentrations Dissolved from Various IBU Solid Dispersions and Pure IBU (P1 to P10) at Various Times Using One-Way ANOVA

Time (min)	Source of variation	d.f.	SS	MS	F
5	Treatment	9	2343.4040	260.3783	29.8811
	Error	24	209.1315	8.7138	
	Total	33	2552.5360		
11	Treatment	9	1966.2530	218.4726	20.5623
	Error	24	254.9982	10.6249	
	Total	33	2221.2510		
15	Treatment	9	1957.8790	217.5421	16.4906
	Error	24	316.6049	13.1919	
	Total	33	2274.4840		
20	Treatment	9	1520.1380	168.9042	12.8027
	Error	24	316.6294	13.1929	
	Total	33	1836.7680		
30	Treatment	9	816.6403	90.7378	5.1207
	Error	24	425.2738	17.7197	
	Total	33	1241.9140		
45	Treatment	9	545.9305	60.6589	3.3533
	Error	24	434.1379	18.0891	
	Total	33	980.0683		
60	Treatment	9	481.9556	53.5506	2.3648
	Error	24	543.4698	22.6446	
	Total	33	1025.4250		
180	Treatment	9	213.0098	23.6678	1.0065
	Error	24	564.3529	23.5147	
	Total	33	777.3626		
F		= 2.30			
		0.05 (9,24)			
F		= 1.91			
		0.10 (9,24)			

Table 11 The Pairwise Statistical Comparisons of IBU Concentrations Dissolved From
IBU Solid Dispersions (P1 to P9) at Various Times Using Student's t-test

Preparation	Comparative concentration (mcg/ml) at time (min)															
	5		11		15		20		30		45		60		180	
	P2	P3	P2	P3	P2	P3	P2	P3	P2	P3	P2	P3	P2	P3	P2	P3
P1	+	++	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	P5	P6	P5	P6	P5	P6	P5	P6	P5	P6	P5	P6	P5	P6	P5	P6
P4	-	-	-	++	-	-	-	-	-	-	-	-	-	-	-	-
P5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	P8	P9	P8	P9	P8	P9	P8	P9	P8	P9	P8	P9	P8	P9	P8	P9
P7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	P4	P7	P4	P7	P4	P7	P4	P7	P4	P7	P4	P7	P4	P7	P4	P7
P1	-	++	++	++	++	++	+	++	-	++	-	-	-	-	-	-
P4	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
	P5	P8	P5	P8	P5	P8	P5	P8	P5	P8	P5	P8	P5	P8	P5	P8
P2	++	++	+	+	+	++	-	++	-	-	-	-	-	-	-	-
P5	-	-	++	-	-	-	-	-	-	-	-	-	-	-	-	-
	P6	P9	P6	P9	P6	P9	P6	P9	P6	P9	P6	P9	P6	P9	P6	P9
P3	++	++	++	++	-	++	-	++	-	+	-	-	-	-	-	-
P6	-	-	++	++	++	++	++	+	+	+	-	-	-	-	-	-

+ = Significantly different (p < 0.10)

++ = Significantly different (p < 0.05)

- = Not Significantly different (p > 0.10)

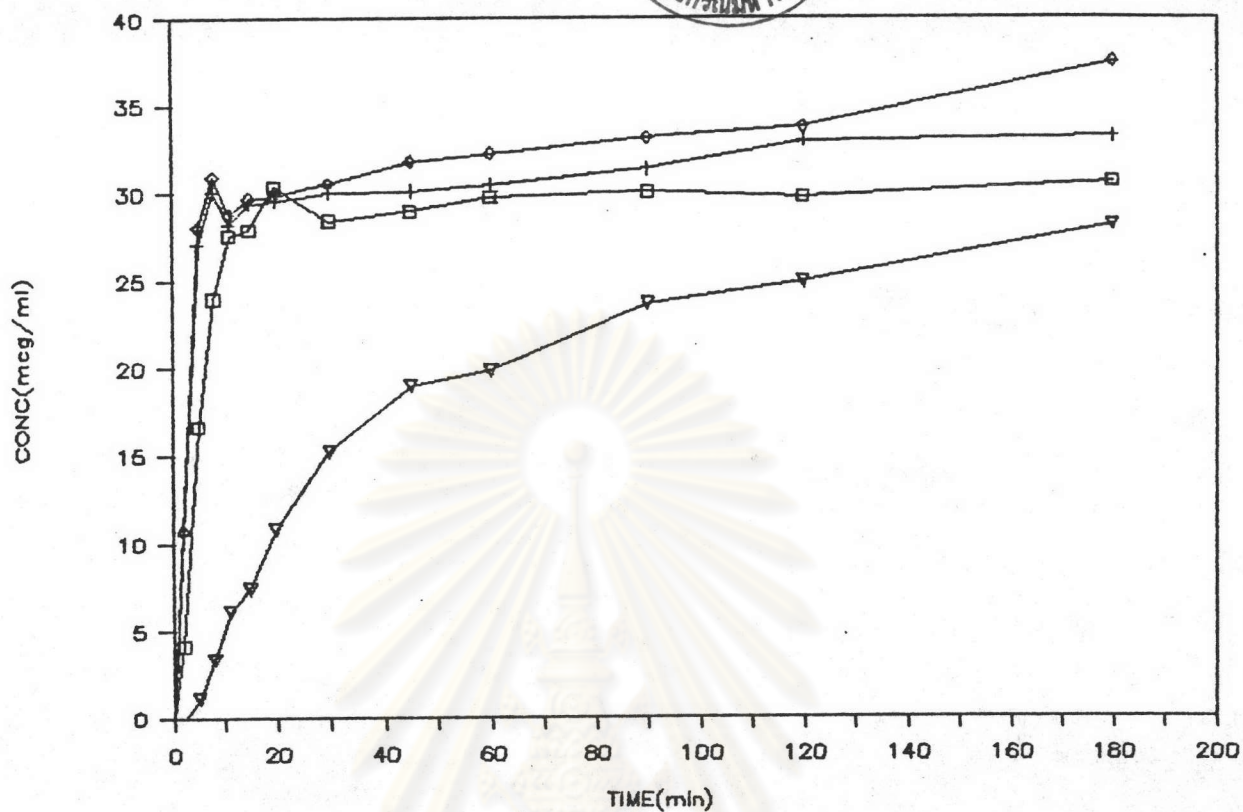


Figure 4 Dissolution profiles of ibuprofen solid dispersions, using different ratios of PEG 4000 as the carriers, fusion method

Key: □ P1, 1:2 IBU:PEG 4000
+ P2, 1:3 IBU:PEG 4000
◇ P3, 1:4 IBU:PEG 4000
▽ P10, IBU (control)

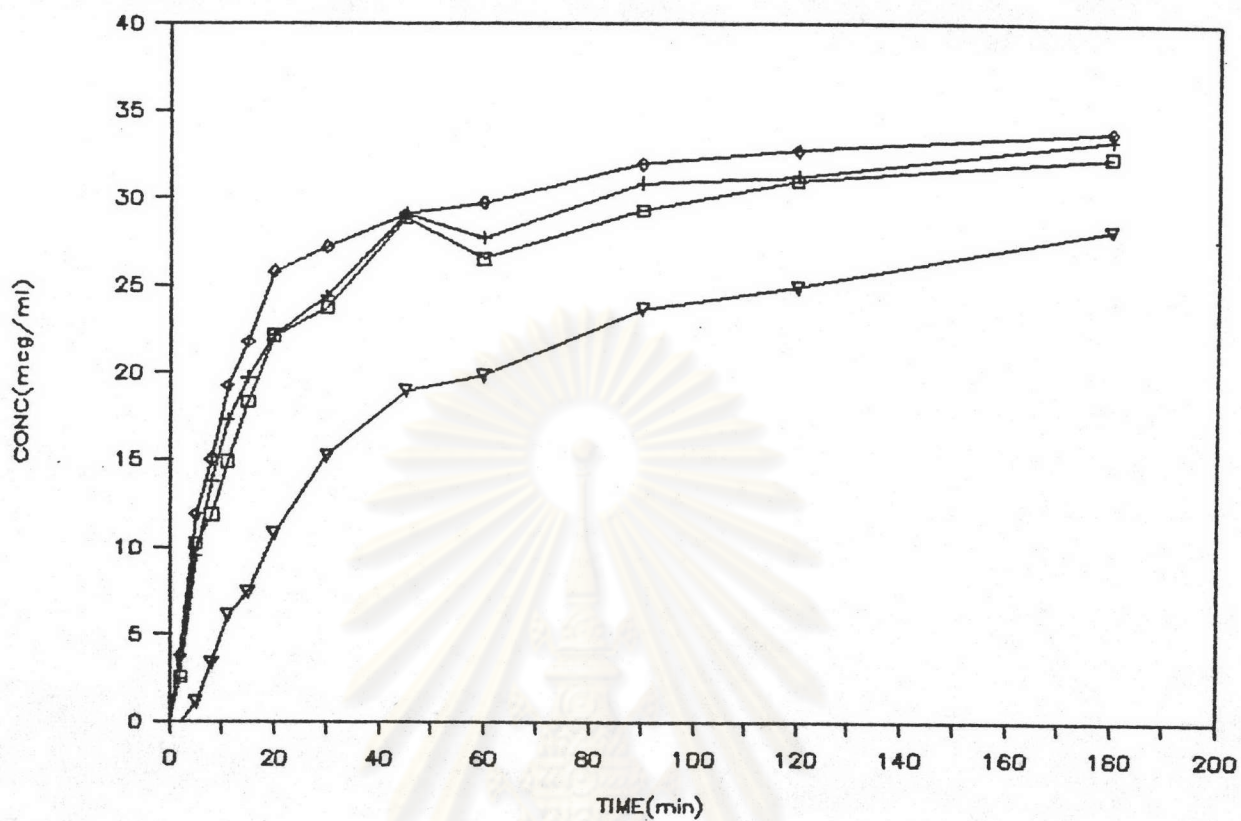


Figure 5 Dissolution profiles of ibuprofen solid dispersions, using different ratios of PEG 20000 as the carriers, solvent method

Key: □ P4, 1:2 IBU:PEG 20000
 + P5, 1:3 IBU:PEG 20000
 ◇ P6, 1:4 IBU:PEG 20000
 ▽ P10, IBU (control)

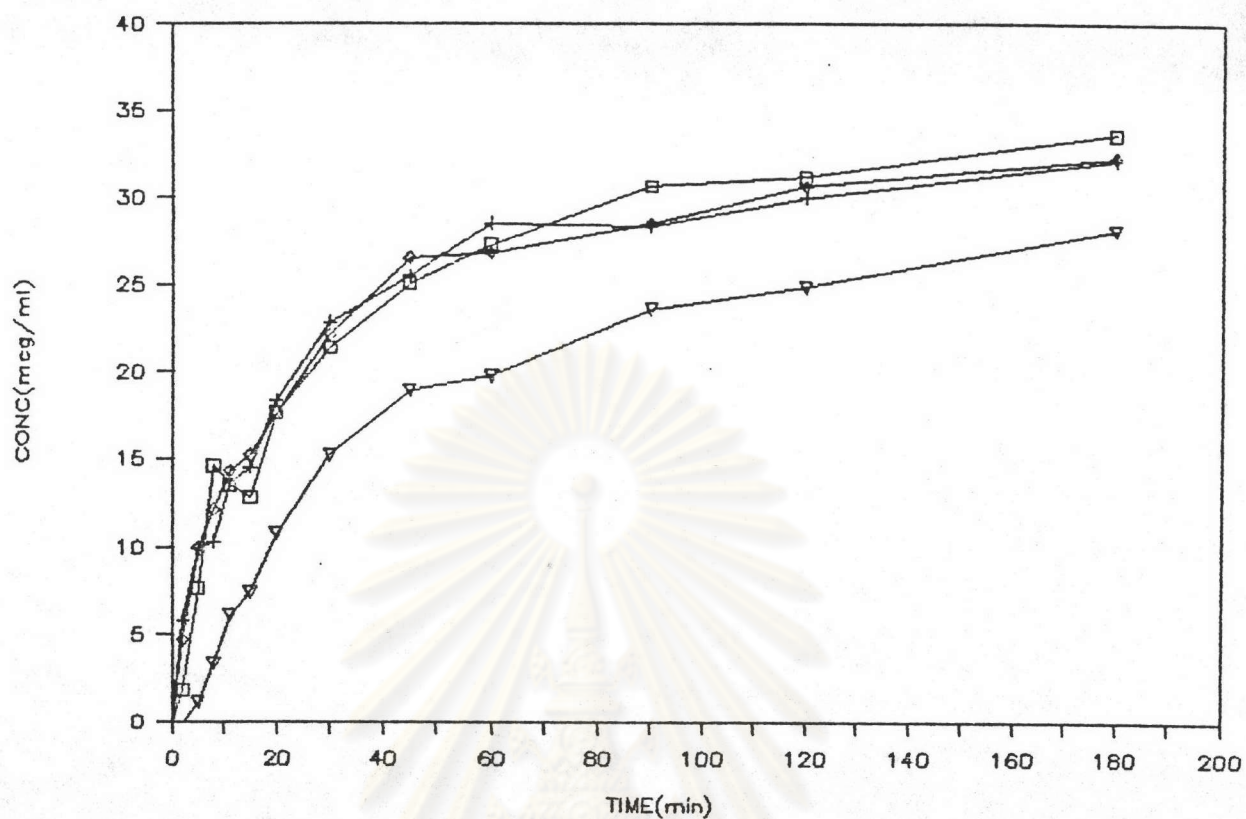


Figure 6 Dissolution profiles of ibuprofen solid dispersions, using different ratios of urea as the carriers, solvent method

Key: \square P7, 1:2 IBU:Urea
 $+$ P8, 1:3 IBU:Urea
 \diamond P9, 1:4 IBU:Urea
 ∇ P10, IBU (control)

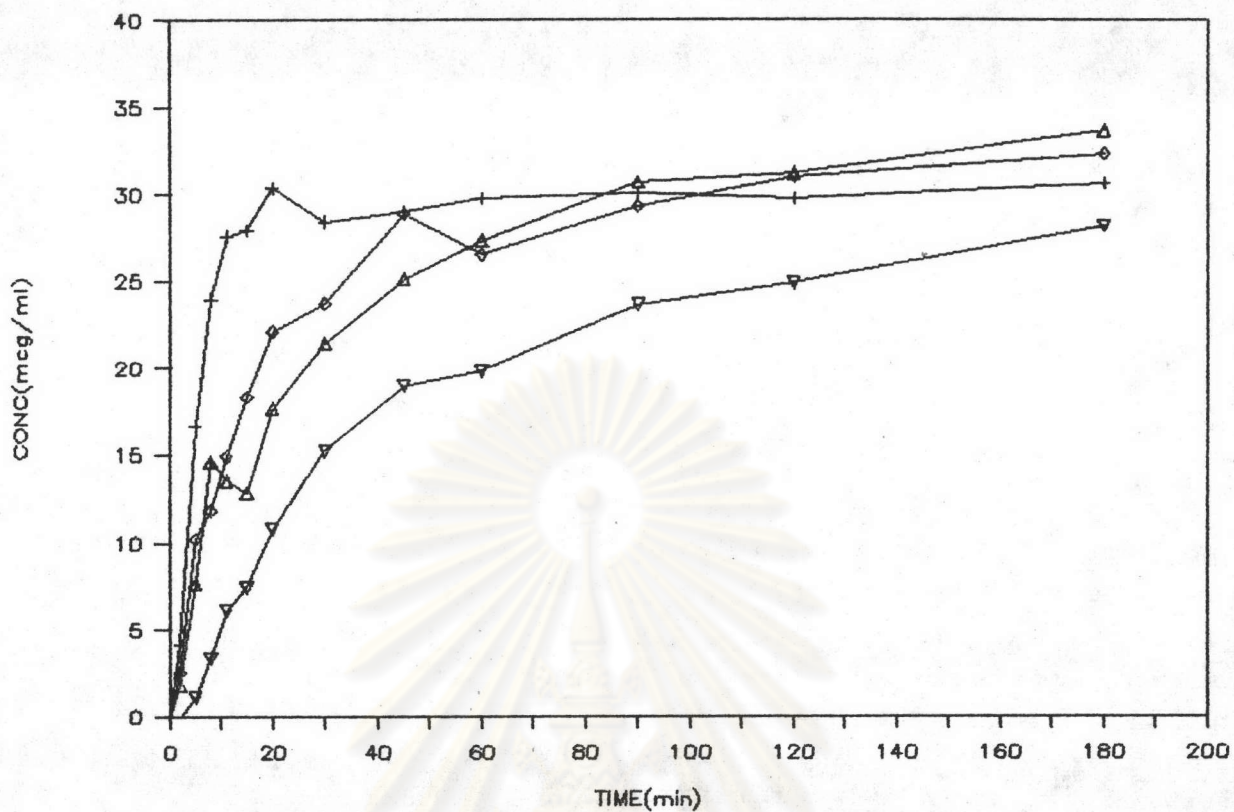


Figure 7 Comparison of the dissolution profiles of ibuprofen solid dispersions of different carriers with the same amount of carrier, 1:2

Key: + P1, IBU:PEG 4000, Fusion method
 ◇ P4, IBU:PEG 20000, Solvent method
 △ P7, IBU:Urea, Solvent method
 ▽ P10, IBU (control)

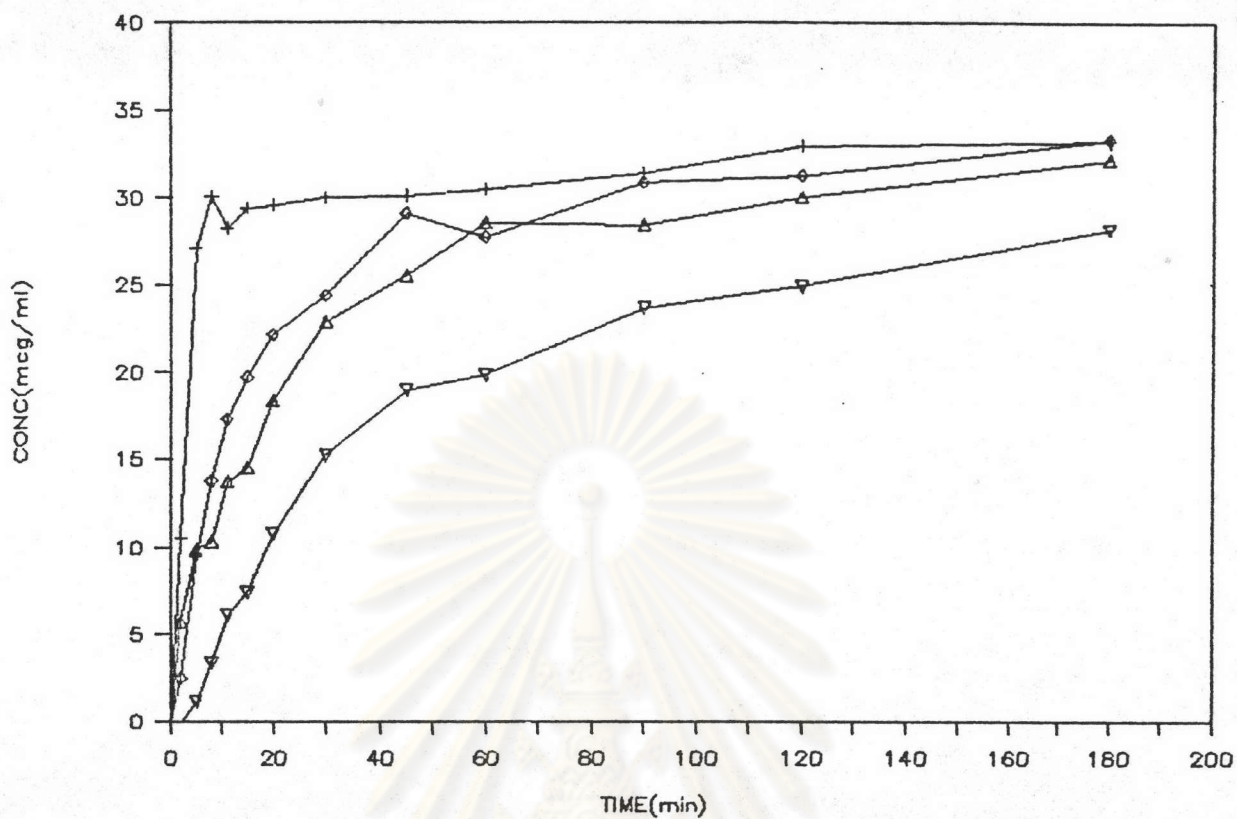


Figure 8 Comparison of the dissolution profiles of ibuprofen solid dispersions of different carriers with the same amount of carrier, 1:3

Key: + P2, IBU:PEG 4000, Fusion method
 ◇ P5, IBU:PEG 20000, Solvent method
 △ P8, IBU:Urea, Solvent method
 ▽ P10, IBU (control)

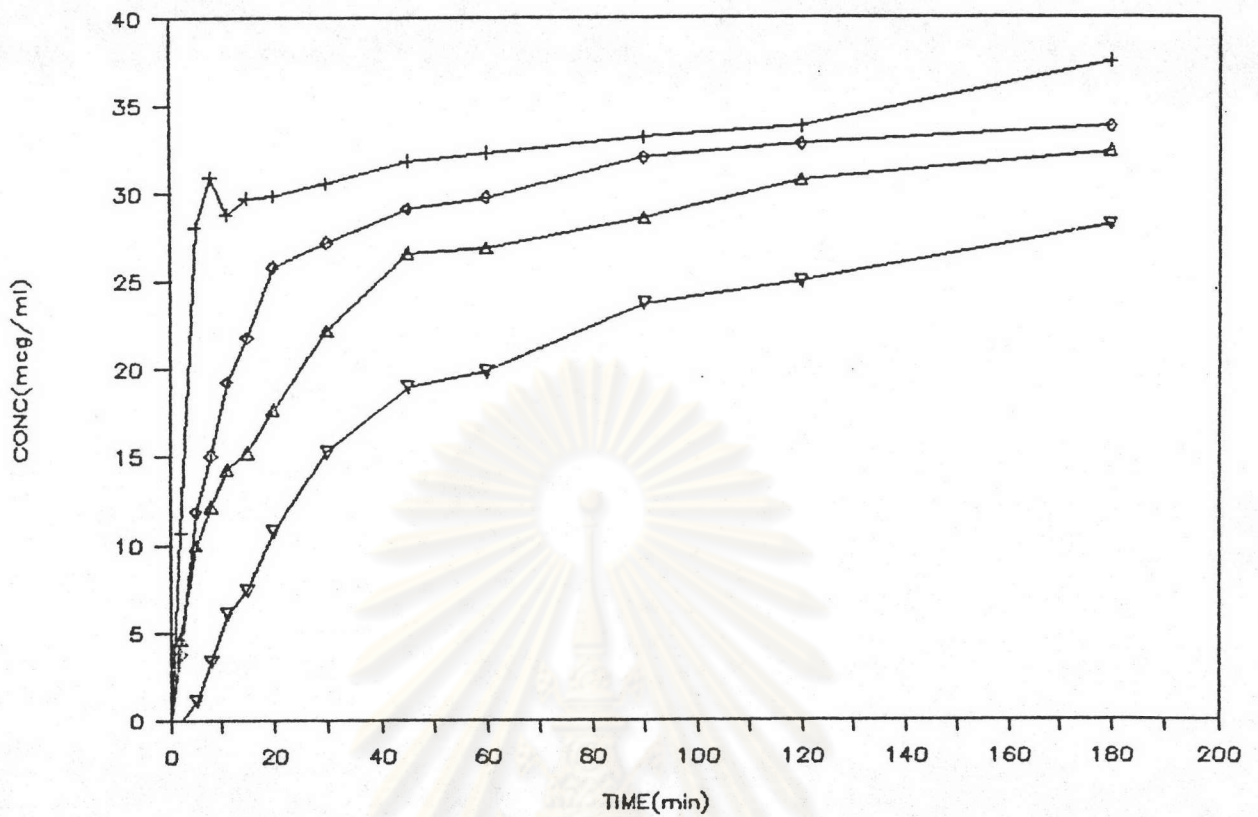


Figure 9 Comparison of the dissolution profiles of ibuprofen solid dispersions of different carriers with the same amount of carrier, 1:4

Key: + P3, IBU:PEG 4000, Fusion method

◇ P6, IBU:PEG 20000, Solvent method

△ P9, IBU:Urea, Solvent method

▽ P10, IBU (control)

the dissolution parameters of P1 to P10 in the term of concentrations of IBU dissolved at various times. Table 10 presented the statistical comparisons of IBU concentrations dissolved from various IBU solid dispersions (P1 to P10) at various times using one-way ANOVA. Table 11 demonstrated the pairwise statistical comparisons of IBU concentrations dissolved from IBU solid dispersions (P1 to P9) at various times using Student's t-test. The dissolution profiles of all preparations were illustrated in Figures 4-9.

According to Figure 4 which presented the dissolution profiles of 1:2, 1:3 and 1:4 ratios of IBU:PEG 4000 solid dispersions prepared by fusion method (P1, P2 and P3 respectively), there were significant differences ($p < 0.10$, t-test) of the dissolved IBU concentrations at 5 minutes between P1 and P2 and between P2 and P3, but no significant difference ($p > 0.10$) was found between P2 and P3. There were no statistical differences ($p > 0.10$) observed among these three preparations from 11 minutes through the end of the dissolution profiles.

From Figure 5 which illustrated the dissolution profiles of 1:2, 1:3 and 1:4 ratios of IBU:PEG 20000 solid dispersions prepared by solvent method (P4, P5 and P6 respectively), the only significant difference ($p < 0.05$) of the dissolved IBU concentrations found was between P4 and P6 at 11 minutes. After that, there were no statistical differences ($p > 0.10$) of IBU concentrations dissolved among all three preparations through 180 minutes.

Figure 6 exhibited the dissolution profiles of 1:2, 1:3 and 1:4 ratios of IBU:urea solid dispersions prepared by solvent method (P7, P8 and P9 respectively). As can be seen, there were entirely no significant difference ($p > 0.10$) of IBU concentrations dissolved from these three preparations.

Comparisons of Different Carriers Used in Solid Dispersion Preparations at the Same Ratio

The 1:2 Ratio

Figure 7 showed the dissolution profiles of IBU solid dispersions of different carriers; PEG 4000, PEG 20000 and urea, at the same 1:2 ratio (P1, P4 and P7 respectively). The results showed that the IBU concentrations obtained from P1 and P4 at 11, 15 and 20 minutes were significantly different ($p < 0.10$). There were statistical differences ($p < 0.05$) between P1 and P7 in the term of dissolved IBU concentrations throughout the first 30 minutes of the dissolution profiles. A significant difference ($p < 0.10$) of the dissolved IBU concentrations was also found between P4 and P7 at 15 minutes.

The 1:3 Ratio

Figure 8 demonstrated the dissolution profiles of IBU solid dispersions of different carriers; PEG 4000, PEG 20000 and urea, at the same 1:3 ratio (P2, P5 and P8 respectively). The data revealed that within the first 15 minutes, there were significantly differences ($p < 0.10$) of

IBU concentrations dissolved from P2 and P5. Between P2 and P8, the dissolved IBU concentrations were statistically different ($p < 0.10$) throughout the first 20 minutes of the dissolution profiles. A significant difference ($p < 0.05$) of dissolved IBU concentrations was also found between P5 and P8 at 11 minutes.

The 1:4 Ratio

Figure 9 presented the dissolution profiles of IBU solid dispersions of different carriers; PEG 4000, PEG 20000, and urea, at the same 1:4 ratio (P3, P6 and P9 respectively). The results showed significant differences ($p < 0.10$) in concentrations of IBU dissolved from P3 and P9 throughout the first 30 minutes. Statistical differences ($p < 0.05$) of the dissolved IBU concentrations were found between P3 and P6 at 5 and 11 minutes. Comparing P6 and P9, there were significant differences ($p < 0.10$) in concentrations of IBU dissolved from P6 and P9 during 11 to 45 minutes.

In conclusion, among the IBU solid dispersions with varying ratios of the drug to the carrier, there was no significant difference in concentrations of IBU dissolved among all ratios varied in all types of carriers used in this study except for the first 5 minutes of the IBU:PEG 4000 system. It was likely that among the carriers used, the PEG 4000 was found to gave the superior dissolution of IBU from solid dispersions over the other carriers, especially during the first 20 to 30 minutes. The 1:4 IBU:PEG 4000

solid dispersion prepared by fusion method (P3) was selected for stability testing due to the assumption that if there was higher amount of carrier in the solid dispersion, the effect of aging could be more clearly detected than those systems having lower amount of the carrier. If the content of IBU and the dissolution characteristics of this solid dispersion do not change with time, the solid dispersions of those systems which containing the lower amount of carriers should be stable as well. P3 was also used as a representative in the study about the effect of particle size on the dissolution rate of IBU from solid dispersion.

Effect of Particle Size on Dissolution Rate

The effect of particle size on dissolution rate was studied using 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method (P3). Dissolution profile of the portion which pass through No.80-mesh was compared to that of the unseived portion. As a reference, dissolution tests of IBU, sieved through No.80-mesh and unsieved, were also performed. Codes for each portion were as follow:-

<u>Code</u>	<u>Solid dispersion preparations/IBU</u>
S1	IBU, passed through No.80-mesh
S2	IBU
S3	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method, passed through No.80-mesh
S4	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method

Table 12 showed the dissolution parameters of S1 to S4 in the term of concentrations of IBU dissolved at various times and the results of the Student's t-test. The dissolution profiles of all portions tested were presented in Figure 10. There was no significant difference in the dissolution profiles between S1 and S2, except for the concentrations of IBU dissolved at 180 minutes which was significantly different ($p < 0.05$, t-test). IBU concentrations dissolved from S3 were significantly higher ($p < 0.10$, t-test) than those dissolved from S4 within the first 30 minutes followed by insignificant different ($p > 0.10$) through the end of the dissolution profile.

It can be concluded that for pure IBU, the dissolution rates were not significantly different whether the drug particles were sieved through No.80-mesh sieve or unsieved. But in the case of 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method, the portion which passed through No.80-mesh gave higher dissolution rate and concentrations dissolved of IBU than the unsieved portion in the first part of the dissolution profile.

Aging of the Best Preparation.

Effect of storage on dissolution of 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method (P3) was studied. The percentage content of IBU and P3 after kept outside the desiccator for a period of time were presented in Table 13 and 14 respectively. Very little decreasing of the IBU

Table 12 Concentrations of IBU Dissolved from Pure IBU and IBU Solid
Dispersions (S1 to S4) at Various Times

Preparation	Concentration (mcg/ml) at time (min)					
	5	15	30	60	120	180
S1	0.954 (1.18)	5.932 (2.92)	13.265 (4.62)	20.804 (5.79)	24.030 (3.64)	28.664 (1.55)
S2	1.251 (0.80)	7.692 (2.11)	14.073 (2.01)	20.805 (1.52)	24.952 (1.45)	25.273 (1.30) ++
S3	26.528 (1.53)	31.028 (2.12)	35.487 (3.42)	36.859 (3.92)	38.688 (3.98)	39.717 (4.35)
S4	19.523 (1.56)	23.635 (1.60)	29.123 (2.03)	32.591 (0.91)	35.982 (1.49)	36.059 (1.15)

Average data of 3 determinations are represented and S.D. are given in parentheses

++ = Significantly different ($p < 0.05$), compared to S1

* = Significantly different ($p < 0.10$), compared to S3

** = Significantly different ($p < 0.05$), compared to S3



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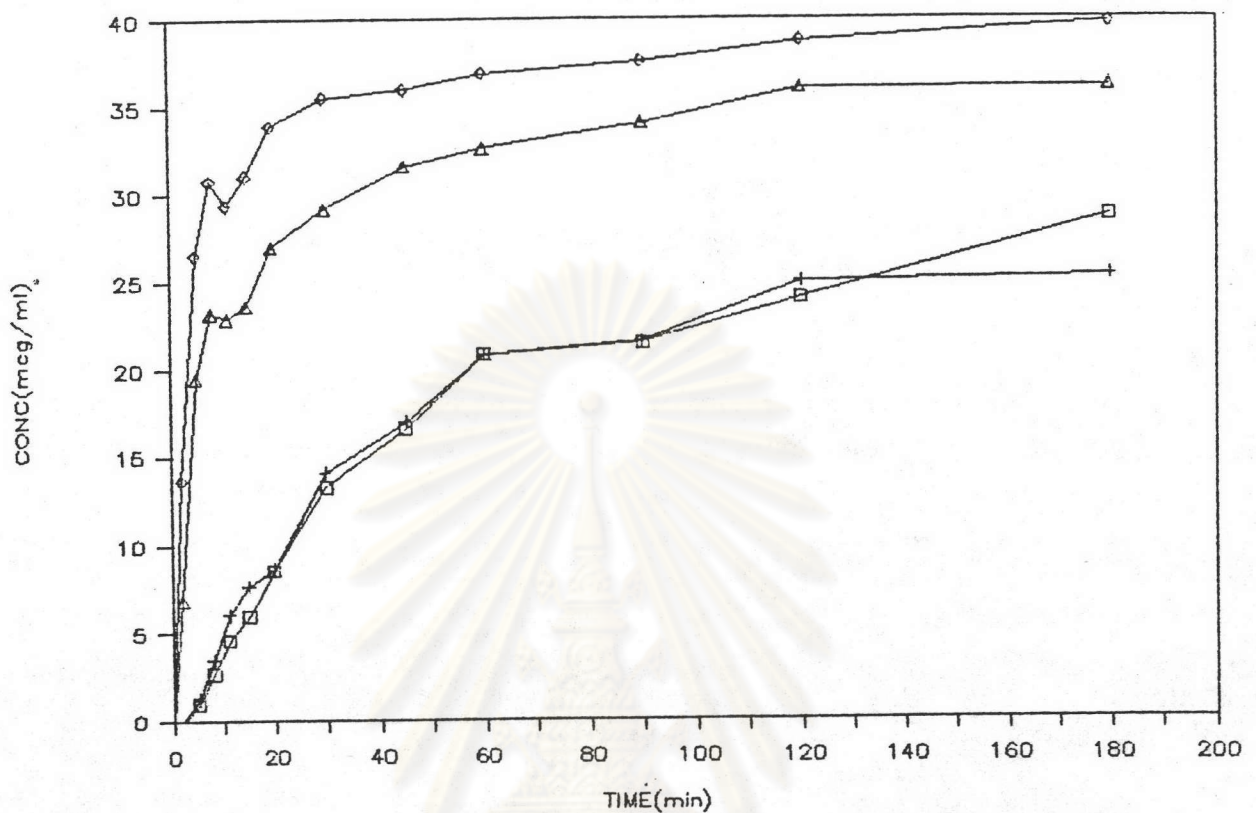


Figure 10 Comparison of the dissolution profiles of ibuprofen solid dispersions with different particle sizes, using 1:4 ratio of PEG 4000 as the carrier, fusion method

Key: □ S1, IBU, passed through No.80-mesh
 + S2, IBU
 ◇ S3, 1:4 IBU:PEG 4000 solid dispersion, passed through No.80-mesh
 △ S4, 1:4 IBU:PEG 4000 solid dispersion

Table 13 Percentage Content of IBU after Kept Outside the Desiccator for a Period of Times

Time (wk)	IBU content (percent)		
	1	2	Average \pm S.D.
0	100.84	100.61	100.73 \pm 0.12
2	100.48	100.81	100.65 \pm 0.17
6	100.41	100.79	100.60 \pm 0.19
10	100.19	100.55	100.37 \pm 0.18

Table 14 Percentage Content of IBU in P3 (1:4 IBU:PEG 4000 Solid Dispersion Prepared by Fusion Method) after Kept Outside the Desiccator for a Period of Time

Time (wk)	IBU Content		
	1	2	Average \pm S.D.
0	99.89	100.18	100.04 \pm 0.15
2	99.75	99.76	99.76 \pm 0.01
6	100.04	99.79	99.92 \pm 0.13
10	99.19	99.59	99.39 \pm 0.20

Table 15 Statistical Comparisons of Percentage Content of
IBU and IBU in P3 after Kept Outside the Desiccator
for a Period of Time Using One-Way ANOVA

Ibuprofen				
Source	D.F.	SS	MS	F
Treatment	3	0.1406	0.0460	0.8533
Error	4	0.2197	0.0549	
Total	7	0.3604		

1:4 IBU:PEG 4000 solid dispersion, Fusion method				
Source	D.F.	SS	MS	F
Treatment	3	0.4727	0.1576	4.1104
Error	4	0.1533	0.0383	
Total	7	0.6260		

$$F = 6.59$$

0.05 (3, 4 D.F.)

$$F = 4.19$$

0.10 (3, 4 D.F.)

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content were detected at the 2nd, 6th and 10th weeks of storage outside the desiccator for both pure IBU and P3. Their statistical comparisons using ANOVA were shown in Table 15. There was no significant difference ($p > 0.10$) of IBU content at the mentioned time from the beginning. The same result was obtained for P3.

Dissolution test of IBU and P3 were performed at the same time as that their percentage contents were determined. Codes of each preparations or IBU after kept outside the desiccator for a certain time were as follow:-

<u>Code</u>	<u>Solid dispersion preparations/IBU</u>
T1	IBU
T2	IBU, kept outside the desiccator for 2 weeks
T3	IBU, kept outside the desiccator for 6 weeks
T4	IBU, kept outside the desiccator for 10 weeks
T5	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method (P3)
T6	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method, kept outside the desiccator for 2 weeks
T7	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method, kept outside the desiccator for 6 weeks
T8	1:4 IBU:PEG 4000 solid dispersion prepared by fusion method, kept outside the desiccator for 10 weeks

Figures 11 and 12 showed dissolution of IBU and of P3 after kept outside the dessiccator for a period of time. Table 16 showed the dissolution parameters of T1 to T8 in term of concentrations of IBU dissolved at various times. The statistical comparisons of IBU concentrations dissolved from T1 to T4 and T5 to T8 at various times using ANOVA were presented in Table 17 and 18 respectively. There were no statistical difference ($p > 0.10$, ANOVA) for both IBU and P3 dissolution parameters. The Student's t-test in Table 16 indicated that there were no significant difference between IBU concentrations dissolved at various times between T1 and T2, T3, T4 and between T5 and T6, T7, T8 except for the IBU concentrations dissolved at 180 minutes from T1 and T4 ($p < 0.10$).

In conclusion, the storage for 10 weeks did not affect the content and dissolution characteristic of IBU and 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method.

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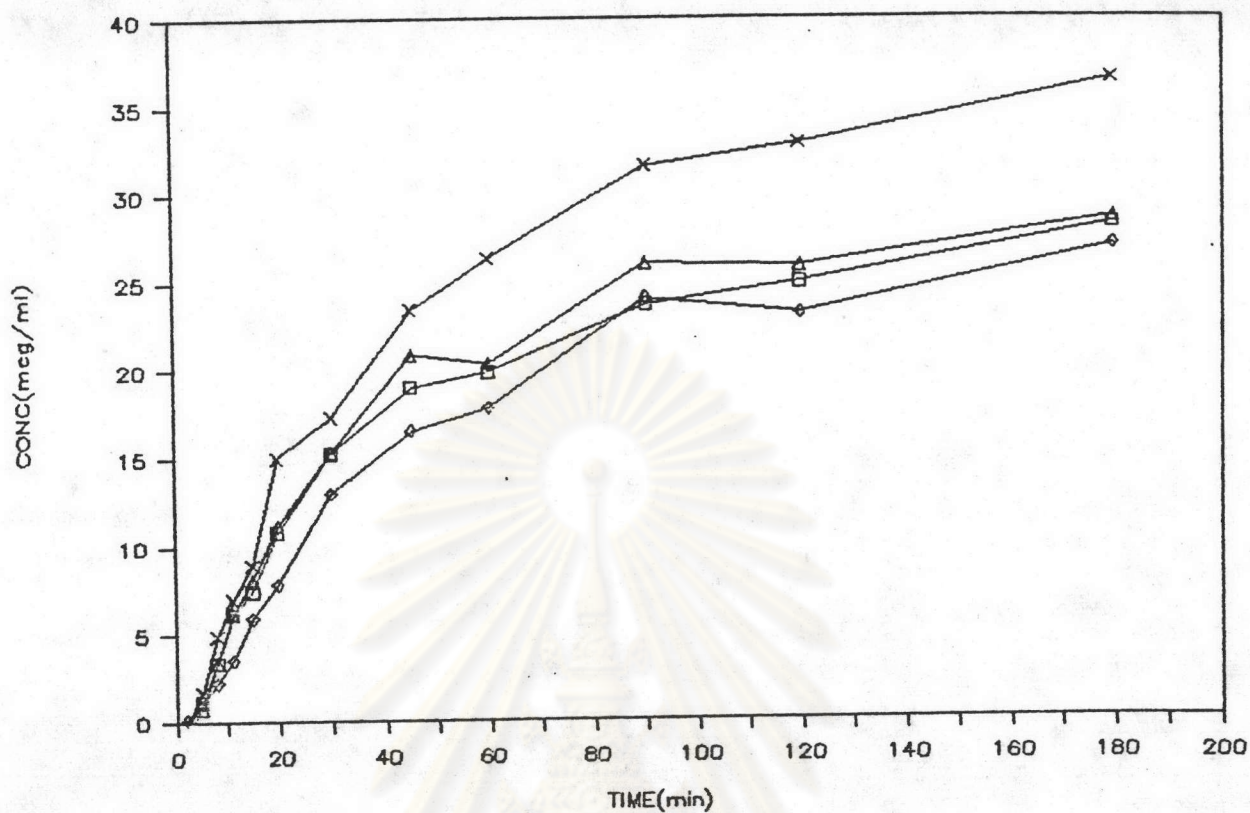


Figure 11 Dissolution profiles of ibuprofen after kept outside the desiccator for a period of time

Key: □ T1, 0 week
 ◇ T2, 2nd week
 △ T3, 6th week
 × T4, 10th week

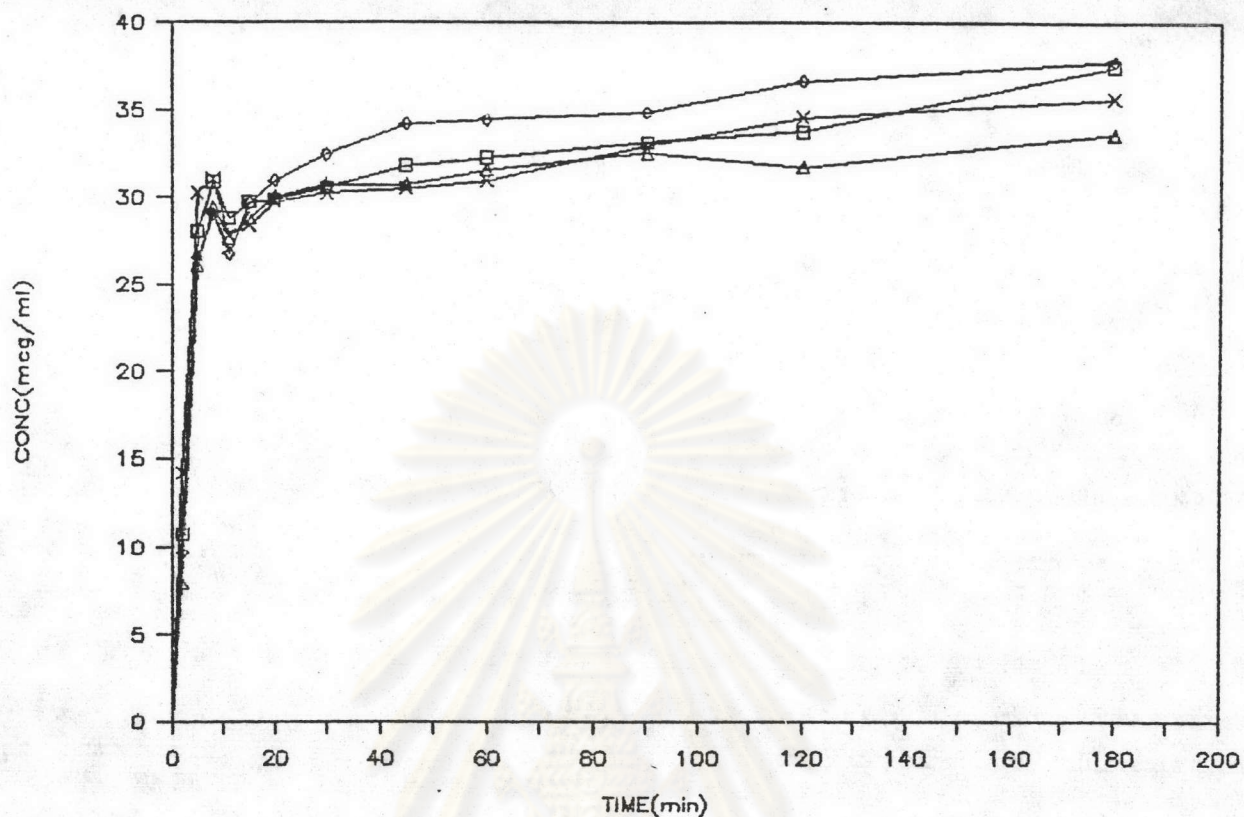


Figure 12 Dissolution profiles of 1:4 IBU:PEG 4000 solid dispersions, fusion method, after kept outside the desiccator for a period of time

Key: □ T5, 0 week
 ◇ T6, 2nd week
 △ T7, 6th week
 × T8, 10th week

Table 16 Concentrations of IBU Dissolved from Pure IBU and IBU Solid
Dispersions (T1 to T8) at Various Times

Preparation	Concentration ($\mu\text{cg/ml}$) at time (min)					
	5	15	30	60	120	180
T1	1.106 (0.73)	7.445 (3.24)	15.266 (5.69)	19.833 (6.62)	24.891 (6.41)	28.154 (5.53)
T2	1.010 (1.02)	5.899 (3.94)	12.958 (6.39)	17.803 (5.55)	23.144 (3.34)	26.964 (3.17)
T3	0.763 (0.75)	8.044 (1.31)	15.291 (1.97)	20.327 (2.34)	25.817 (1.73)	28.521 (2.53)
T4	1.672 (1.11)	8.897 (3.59)	17.274 (9.91)	26.307 (4.22)	32.831 (7.85)	36.439 (7.52)
T5	28.038 (4.20)	29.732 (5.54)	30.533 (4.75)	32.248 (4.93)	33.734 (4.60)	37.469 (5.95)
T6	26.541 (2.05)	29.646 (0.92)	32.434 (0.94)	34.420 (1.16)	36.635 (0.67)	37.742 (0.89)
T7	26.137 (2.66)	28.790 (4.42)	30.708 (4.26)	31.552 (3.64)	31.706 (3.62)	33.586 (3.96)
T8	30.300 (3.18)	28.356 (3.13)	30.202 (3.77)	30.940 (4.69)	34.533 (6.44)	35.626 (4.49)

Average data of at least 3 determinations are represented and S.D. are given
in parentheses

* = Significantly higher ($p < 0.10$), compared to T1

There was no significant difference between T5 and T6, T7, T8 ($p > 0.10$)

Table 17 The Statistical Comparisons of IBU Concentrations Dissolved from
Various IBU Solid Dispersions (T1 to T4) at Various Times Using
One-way ANOVA

Time (min)	Source of variation	d.f.	SS	MS	F
5	Treatment	3	1.3333	0.4444	0.5874
	Error	11	8.3221	0.7566	
	Total	14	9.6554		
15	Treatment	3	14.4220	4.8073	0.4685
	Error	11	112.8753	10.2614	
	Total	14	127.2973		
30	Treatment	3	28.0412	9.3471	0.2294
	Error	11	448.1925	40.7448	
	Total	14	476.2337		
60	Treatment	3	124.1900	41.3967	1.3915
	Error	11	327.2438	29.7494	
	Total	14	451.4338		
120	Treatment	3	170.4309	56.8103	1.7506
	Error	11	356.9730	32.4521	
	Total	14	527.4039		
180	Treatment	3	177.1830	59.0610	2.1719
	Error	11	299.1285	27.1935	
	Total	14	476.3115		

$$F = 3.59$$

0.05 (3,11)

$$F = 2.66$$

0.10 (3,11)

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Table 18 The Statistical Comparisons of IBU Concentrations Dissolved from
Various IBU Solid Dispersions (T5 to T8) at Various Times Using
One-way ANOVA

Time (min)	Source of variation	d.f.	SS	MS	F
5	Treatment	3	31.9521	10.6507	1.0899
	Error	8	78.1784	9.7723	
	Total	11	110.1305		
15	Treatment	3	4.0327	1.3443	0.0883
	Error	8	121.8267	15.2283	
	Total	11	125.8594		
30	Treatment	3	8.9775	2.9925	0.2144
	Error	8	111.6622	13.9578	
	Total	11	120.6397		
60	Treatment	3	20.7126	6.9042	0.4541
	Error	8	121.6390	15.2049	
	Total	11	142.3516		
120	Treatment	3	37.4061	12.4687	0.6537
	Error	8	152.5988	19.0748	
	Total	11	190.0048		
180	Treatment	3	33.3495	11.1165	0.6171
	Error	8	144.1107	18.0138	
	Total	11	177.4603		

$$F_{0.05 (3,8)} = 4.07$$

$$F_{0.10 (3,8)} = 2.92$$

