CHAPTER IV

RESULTS AND DISCUSSION

In Vitro Studies

The nine commercial brands of naproxen tablets were first tested for uniformity of weight and content of active ingredient. Each of them met the B.P. requirement (25) for uniformity of weight within the range of limitation. The content of active ingredient of all brands were within the 90–110% limits as specified by the USP XXI monograph (26). These results supported the assumption that all various brands were pharmaceutically equivalent.

The hardness of naproxen tablets were presented in Table 2. The rank orders of hardness, maximum to minimum, were brand I > A > F > G > H > B > E > C > D. They were statistical difference at $p < 0.05$ as seen in Table 3. When compared with brand A, the hardness of all except brand I were significantly lower as seen in Table 4. However, there were no standard requirement for tablet hardness in both the B.P. and the U.S.P., the tablet hardness, in general, was not less than 4 kg (29).

All of these nine brands of naproxen tablets met the USP XXI requirement for disintegration time in distilled water within 30 minutes. The rank orders of disintegration time, maximum to minimum, were F > H > A > D > E > G > B > I > C as shown in Table 2. Results in Table 5 showed significantly different among all brands studied ($p < 0.05$). When compared with brand A, the disintegration times of

Table 2 Physical Characteristics of In Vitro Studies of 9 Commercial Brands of Naproxen Tablets

Brand	Weight[a] (g)	% Labelled amount[b]	Hardness[c] (kp)	Disintegration time[d] (min)
A	0.383 ± 0.003	96.67 ± 0.14	17.03 ± 0.96	6.39 ± 0.61
B	0.372 ± 0.011	95.92 ± 0.18	6.90 ± 1.13	1.44 ± 0.35
C	0.378 ± 0.002	95.81 ± 1.54	6.53 ± 0.51	0.36 ± 0.02
D	0.364 ± 0.007	99.20 ± 2.36	4.52 ± 0.39	2.26 ± 0.27
E	0.372 ± 0.005	95.03 ± 1.79	6.83 ± 0.15	2.00 ± 0.37
F	0.421 ± 0.006	101.36 ± 1.47	11.33 ± 1.33	13.73 ± 3.85
G	0.373 ± 0.004	98.89 ± 5.08	8.55 ± 0.41	1.80 ± 0.16
H	0.349 ± 0.012	96.64 ± 2.03	8.40 ± 1.45	7.27 ± 5.26
I	0.371 ± 0.006	96.64 ± 0.47	> 20	1.03 ± 0.24

a = Values are mean ± standard deviation (n = 20)

b = Values are mean ± standard deviation (n = 3)

c = Values are mean ± standard deviation (n = 6)

d = Values are mean ± standard deviation (n = 6)

Table 3 Analysis of Variance for Hardness (kp) of 8 Brands of Naproxen Tablets (A-H)

Source of Variance	D.F.	S.S.	M.S.	F Test
Among Groups	7	630.79	90.11	156.33
Within Groups	40	23.06	0.58	
Total	47			

$^{a}F_{0.95,\ (7,\ 40)} = 2.25$

D.F. = Degree of Freedom

S.S. = Sum of Squares

M.S. = Mean of Squares

F = Variation Ratio

a = F-value from the table

Table 4 Comparison of Hardness (kp) of Naproxen Tablets Brand A with Other Brands Using T-Test

Brand	t-value
B	19.700*
C	31.116*
D	39.888*
E	35.187*
F	9.949*
G	25.717*
H	13.640*

$t^{a}_{0.05,\ 10} = 2.228$

* = Statistically Difference at $p < 0.05$

a = t-value from the table

Table 5 Analysis of Variance for Disintegration Time (min) of 9 Brands of Naproxen Tablets (A-I)

Source of Variance	D.F.	S.S.	M.S.	F Test
Among Groups	8	909.37	113.67	23.63
Within Groups	45	216.48	4.81	
Total	53	1125.86		

$$F_{0.95,\ (8,\ 45)} = 2.15$$

Table 6 Comparison of Disintegration Time (min) of Brand A with Other Brands Using T-Test

Brand	t-value
B	15.665*
C	21.931*
D	13.781*
E	13.707*
F	-4.203*
G	16.183*
H	-0.372
I	18.199*

$$t_{0.05,10} = 2.228$$

* = Statistically Difference at $p < 0.05$

brands B C, D, E, G and I were lower and of brand F was higher ($p < 0.05$), while brand H was not differ significantly ($p > 0.05$) as shown in Table 6.

Neither the USP XXI nor the B.P. 1980 contains a dissolution specification for naproxen tablets. The dissolution test was carried out using the USP method II with dissolution media like the biological fluid in the gastrointestinal tract. In simulated gastric fluid, the amount of naproxen dissolved at various times was shown in Table 7 and Figure 2. The mean dissolution rate constants obtained from the sigma-minus plot (Figure 3) of naproxen tablets were summarized in Table 8. The rank orders of mean dissolution rate constant, maximum to minimum, were B > G > A > C > F > H > E > I > D. They were statistically different at $p < 0.05$ (Table 9). When compared with brand A, the mean dissolution rate constant of brands D E, H and I were lower and of brand B was higher whereas the others were not differ significantly (Table 10).

In simulated intestinal fluid, the amount of naproxen dissolved at various times was shown in Table 11 and Figure 4. The mean dissolution rate constants obtained from the sigma-minus plot (Figure 5) of all brands were presented in Table 8. Rank orders in term of mean dissolution rate constant were A, C > F > E > G > H > B > I > D. Analysis of variance indicated that there were statistically different among nine different brands as shown in Table 12 and Student's -t-statistic showed that brands B, D, H and I were significantly different from brand A while brands C, E, F, G, were not (Table 13). The slower dissolution rates for brand I, and especially brand D in both dissolution

Table 7 Dissolution Data of Nine Brands of Naproxen Tablets in Simulated Gastric Fluid pH 1.2

Time (min) \ Brand	Percent Naproxen Dissolved[a]								
	A	B	C	D	E	F	G	H	I
5	1.21 ± 0.11	2.63 ± 0.12	2.80 ± 0.23	1.24 ± 0.14	1.51 ± 0.08	1.45 ± 0.23	1.72 ± 0.18	1.93 ± 0.18	1.46 ± 0.25
10	2.06 ± 0.30	4.51 ± 0.23	3.97 ± 0.24	1.17 ± 0.06	2.60 ± 0.29	1.59 ± 0.23	2.84 ± 0.42	2.66 ± 1.16	1.46 ± 0.22
15	2.87 ± 0.53	6.00 ± 0.23	5.18 ± 0.38	1.25 ± 0.02	3.90 ± 0.36	2.28 ± 0.32	4.23 ± 0.44	3.53 ± 1.35	1.60 ± 0.28
20	3.80 ± 0.57	7.17 ± 0.21	6.16 ± 0.37	1.35 ± 0.08	4.73 ± 0.34	3.21 ± 0.77	5.31 ± 0.32	3.94 ± 1.50	1.75 ± 0.27
25	4.62 ± 0.58	7.83 ± 0.23	6.62 ± 0.39	1.45 ± 0.12	5.32 ± 0.46	3.91 ± 0.74	6.24 ± 0.26	4.46 ± 1.46	2.05 ± 0.26
30	5.41 ± 0.63	8.29 ± 0.29	7.16 ± 0.34	1.65 ± 0.20	5.85 ± 0.49	4.69 ± 0.70	6.90 ± 0.26	4.87 ± 1.56	2.62 ± 0.40
45	7.13 ± 0.60	8.78 ± 0.12	8.21 ± 0.35	2.16 ± 0.42	7.30 ± 0,89	6.14 ± 0.74	8.09 ± 0.09	5.99 ± 1.50	3.81 ± 0.73
60	8.08 ± 0.56	8.99 ± 0.16	8.53 ± 0.24	2.75 ± 0.57	8.01 ± 0.65	6.82 ± 0.76	8.53 ± 0.11	6.56 ± 1.53	4.56 ± 0.86
80	8.62 ± 0.42	9.08 ± 0.12	8.84 ± 0.16	3.29 ± 0.77	8.25 ± 0.48	7.39 ± 0.81	8.81 ± 0.08	7.09 ± 1.37	5.69 ± 0.83
100	8.86 ± 0.44	9.38 ± 0.24	9.06 ± 0.12	3.95 ± 0.79	8.27 ± 0.39	7.74 ± 0.64	9.38 ± 0.27	7.76 ± 1.27	6.60 ± 0.71
120	9.14 ± 0.38	9.27 ± 0.08	9.28 ± 0.20	5.01 ± 0.88	8.58 ± 0.40	7.96 ± 0.69	9.65 ± 0.49	7.99 ± 1.16	7.18 ± 0.56
150	8.70 ± 0.30	9.51 ± 0.21	9.40 ± 0.19	5.38 ± 0.71	8.91 ± 0.26	8.51 ± 0.83	9.39 ± 0.19	8.29 ± 1.21	7.92 ± 0.42
180	8.99 ± 0.28	9.66 ± 0.16	9.69 ± 0.24	5.97 ± 0.73	9.57 ± 0.54	8.48 ± 0.70	9.51 ± 0.24	8.30 ± 1.17	8.29 ± 0.31
210	9.23 ± 0.25	9.79 ± 0.12	9.72 ± 0.20	6.23 ± 0.65	9.22 ± 0.24	8.68 ± 0.69	9.42 ± 0.12	8.73 ± 1.11	8.67 ± 0.17
240	9.38 ± 0.29	9.47 ± 0.20	9.76 ± 0.19	6.46 ± 0.65	9.12 ± 0.20	8.94 ± 0.79	9.47 ± 0.27	8.81 ± 1.17	8.85 ± 0.15

a = Values are mean ± standard deviation (n = 6)

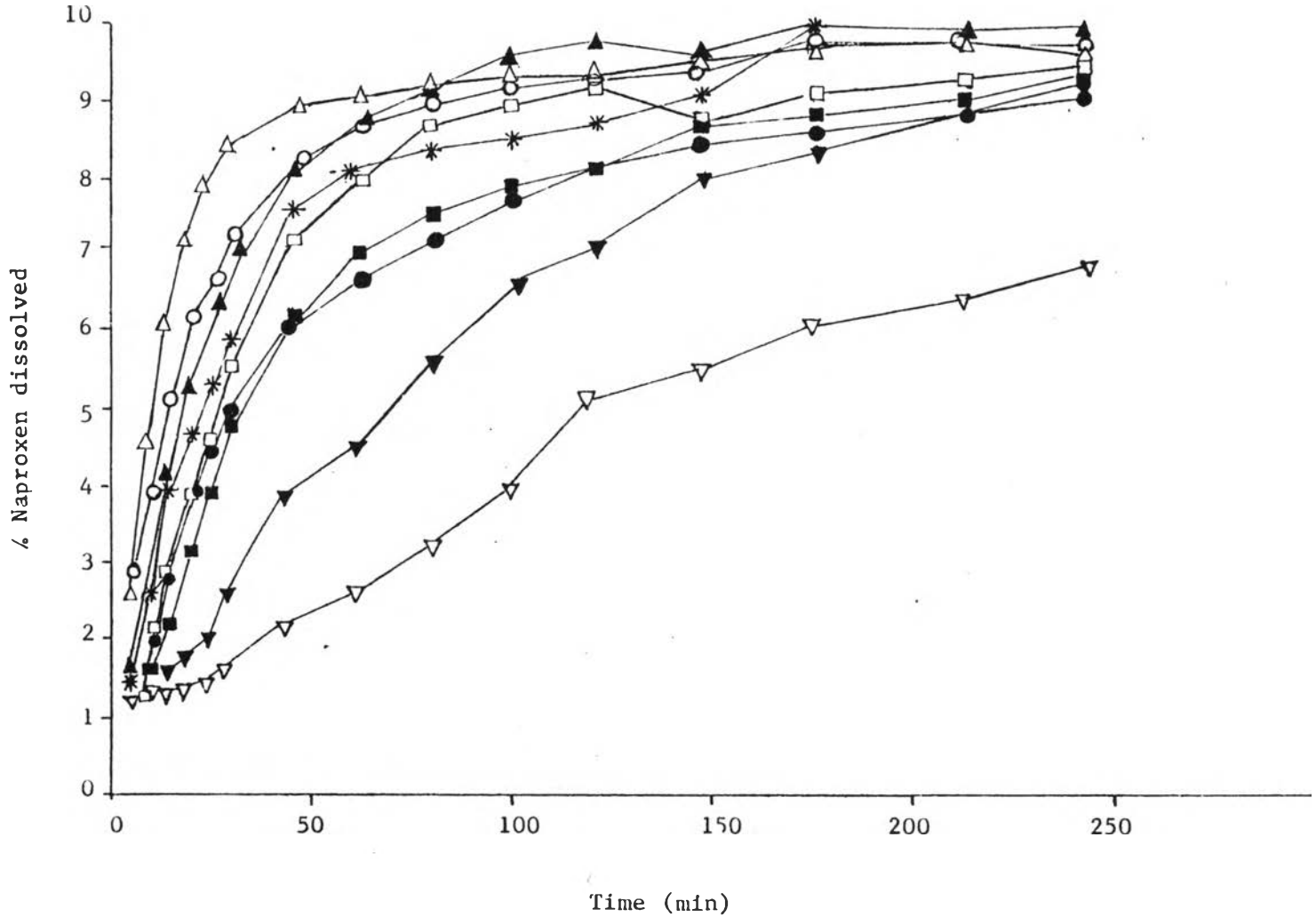

Figure 2 Dissolution profile of nine commercial brands of naproxen tablets in simulated gastric fluid pH 1.2

Key : Brand A (□), Brand B (Δ), Brand C (o), Brand D (∇), Brand E (*), Brand F (■), Brand G (▲), Brand H (●), Brand I (▼)

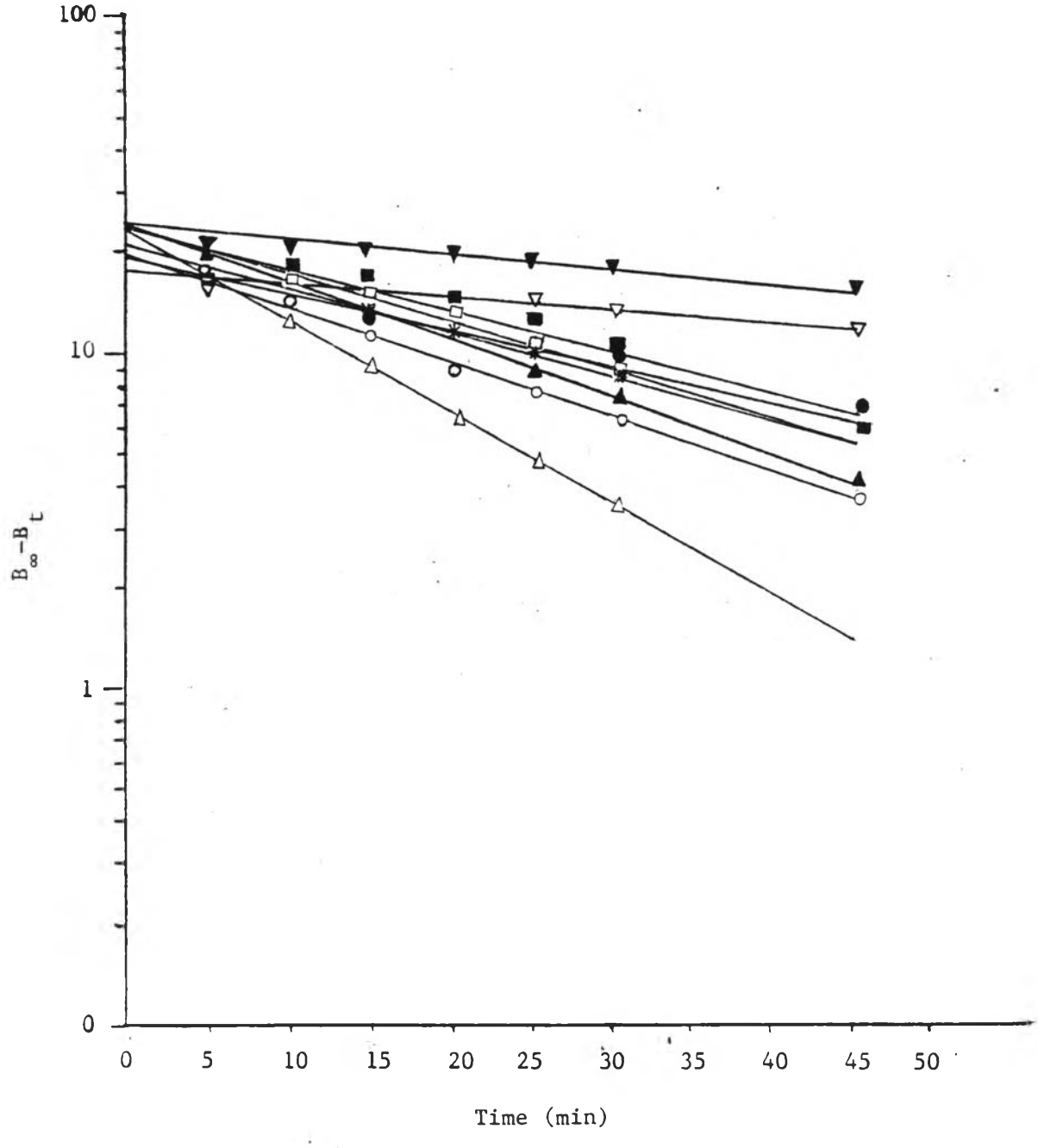

Figure 3 The sigma-minus plot between amount of undissolved naproxen in simulated gastric fluid versus time for nine brands of naproxen tablets

Key : Brand A (□), Brand B (Δ), Brand C (o), Brand D (▽)
Brand E (*), Brand F (■), Brand G (▲), Brand H (●)
Brand I (▼)

Table 8 Mean Dissolution Rate Constant (hr^{-1}) of 9 Brands of Naproxen Tablets in Simulated Gastric Fluid (pH 1.2) and in Simulated Intestinal Fluid (pH 7.5)

Brand	Dissolution Rate Constant (hr^{-1}) [a]	
	Simulated Gastric Fluid	Simulated Intestinal Fluid
A	1.39 ± 0.25	6.22 ± 1.96
B	2.03 ± 0.35	2.29 ± 0.43
C	1.15 ± 0.14	6.22 ± 1.51
D	0.55 ± 0.09	0.76 ± 0.20
E	1.00 ± 0.11	4.51 ± 0.97
F	1.13 ± 0.12	4.81 ± 0.53
G	1.79 ± 0.36	4.06 ± 1.82
H	1.08 ± 0.16	3.99 ± 0.95
I	0.62 ± 0.20	1.19 ± 0.30

a = Values are mean ± standard deviation (n = 6)

Table 9 Analysis of Variance for Dissolution Rate Constant (hr^{-1}) of 9 Brands of Naproxen Tablets in Simulated Gastric Fluid (pH 1.2)

Source of Variance	D.F.	S.S.	M.S.	F Test
Among Groups	8	11.32	1.41	29.43
Within Groups	45	2.16	0.05	
Total	53	13.48		

$$F_{0.95,\ (8,\ 45)} = 2.15$$

Table 10 Comparison of Dissolution Rate Constant (hr^{-1}) in Simulated Gastric Fluid (pH 1.2) of Brand A with Other Brands Using T-Test

Brand	t-value
B	-3.327*
C	1.894
D	7.181*
E	3.211*
F	2.062
G	-2.105
H	2.314*
I	5.470*

$$t_{0.05,\ 10} = 2.228$$

* = Statistically Difference at $p < 0.05$

Table 11 Dissolution Data of Nine Brands of Naproxen Tablets in Simulated Intestinal Fluid pH 7.5

Time (min) \ Brand	Percent Naproxen Dissolved[a]								
	A	B	C	D	E	F	G	H	I
5	17.67 ± 2.70	35.40 ± 4.57	52.18 ± 9.08	4.06 ± 0.51	46.26 ± 6.13	15.60 ± 2.77	38.40 ± 5.44	18.35 ± 9.25	6.30 ± 0.75
10	36.23 ± 4.35	57.96 ± 4.43	76.05 ± 10.64	11.32 ± 1.49	71.73 ± 4.70	35.67 ± 5.85	59.94 ± 8.05	35.55 ± 16.25	16.10 ± 1.95
15	57.51 ± 6.14	70.85 ± 3.98	86.12 ± 8.95	17.97 ± 3.30	84.53 ± 4.28	66.25 ± 6.61	72.90 ± 9.67	52.78 ± 16.15	24.12 ± 2.66
20	74.41 ± 6.70	77.82 ± 3.87	90.31 ± 7.07	24.18 ± 4.40	90.10 ± 3.80	82.23 ± 2.21	80.06 ± 10.20	66.24 ± 16.10	31.55 ± 3.93
25	87.53 ± 6.20	82.55 ± 3.83	94.22 ± 6.22	29.66 ± 5.35	93.37 ± 3.10	87.98 ± 1.66	83.99 ± 9.56	75.08 ± 13.78	37.75 ± 5.34
30	95.17 ± 2.65	85.54 ± 3.34	94.93 ± 4.55	34.31 ± 6.13	94.33 ± 2.51	92.01 ± 1.84	87.36 ± 8.92	83.57 ± 12.71	43.04 ± 6.72
45	97.10 ± 2.10	90.76 ± 2.81	97.43 ± 1.97	45.22 ± 7.07	96.97 ± 1.79	96.77 ± 0.65	93.17 ± 6.90	93.35 ± 3.89	55.69 ± 9.82
60	99.58 ± 1.02	94.43 ± 2.27	97.26 ± 2.32	53.77 ± 7.01	98.92 ± 1.55	98.71 ± 0.83	95.61 ± 5.02	97.38 ± 0.99	65.70 ± 11.03
80	97.86 ± 1.06	96.26 ± 2.18	97.75 ± 2.24	61.49 ± 7.65	98.86 ± 1.80	99.96 ± 0.08	97.65 ± 3.54	98.60 ± 1.50	75.72 ± 11.87
100	98.00 ± 1.63	97.41 ± 2.28	98.28 ± 1.44	69.16 ± 6.94	96.84 ± 2.07	98.98 ± 0.61	97.33 ± 2.02	99.31 ± 0.92	83.93 ± 9.25
120	97.59 ± 1.47	97.21 ± 1.99	98.14 ± 1.68	78.27 ± 6.89	97.62 ± 2.30	98.32 ± 0.40	98.12 ± 2.05	98.93 ± 0.83	88.52 ± 6.57
150	95.78 ± 1.10	98.65 ± 2.42	95.25 ± 1.04	84.29 ± 6.53	96.05 ± 1.78	97.61 ± 1.21	97.93 ± 1.76	98.81 ± 1.76	93.39 ± 4.62
180	95.29 ± 1.25	99.38 ± 0.73	94.34 ± 1.25	90.07 ± 6.79	96.57 ± 1.89	97.62 ± 3.36	98.46 ± 1.91	99.14 ± 0.92	96.32 ± 2.79
210	94.83 ± 1.33	97.42 ± 1.76	93.92 ± 1.14	93.53 ± 4.45	96.29 ± 1.94	97.72 ± 1.62	96.86 ± 2.03	99.04 ± 0.81	97.40 ± 2.40
240	94.68 ± 1.29	96.79 ± 1.89	93.18 ± 1.13	96.38 ± 3.68	96.12 ± 2.11	98.21 ± 0.69	96.92 ± 1.87	98.29 ± 1.09	99.03 ± 1.71

a = Values are mean ± standard deviation (n = 6)

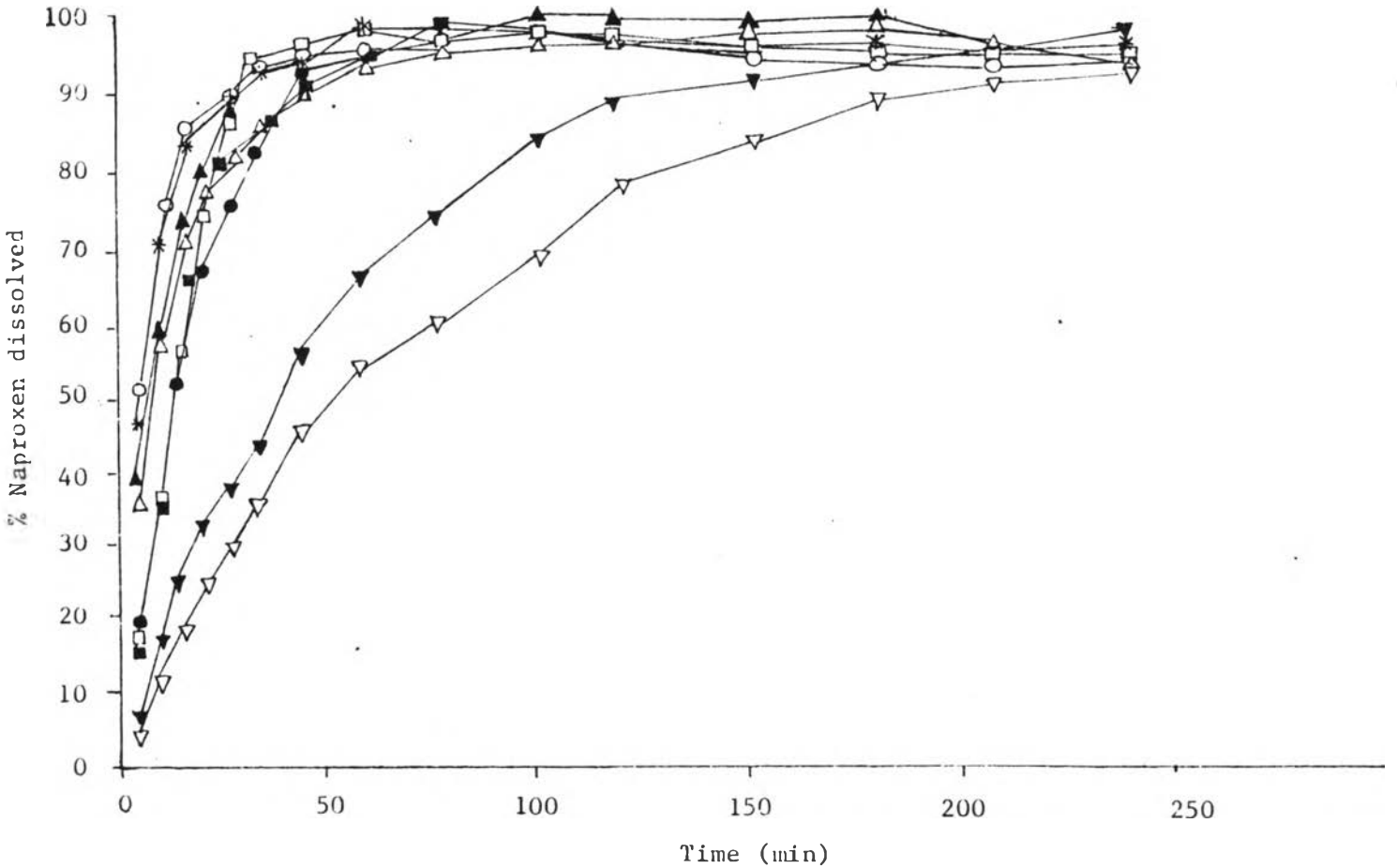

Figure 4 Dissolution profile of nine commercial brands of naproxen tablets in simulated intestinal fluid pH 7.5

Key : Brand A (□), Brand B (Δ), Brand C (○), Brand D (▽), Brand E (*), Brand F (■), Brand G (▲), Brand H (●), Brand I (▼)

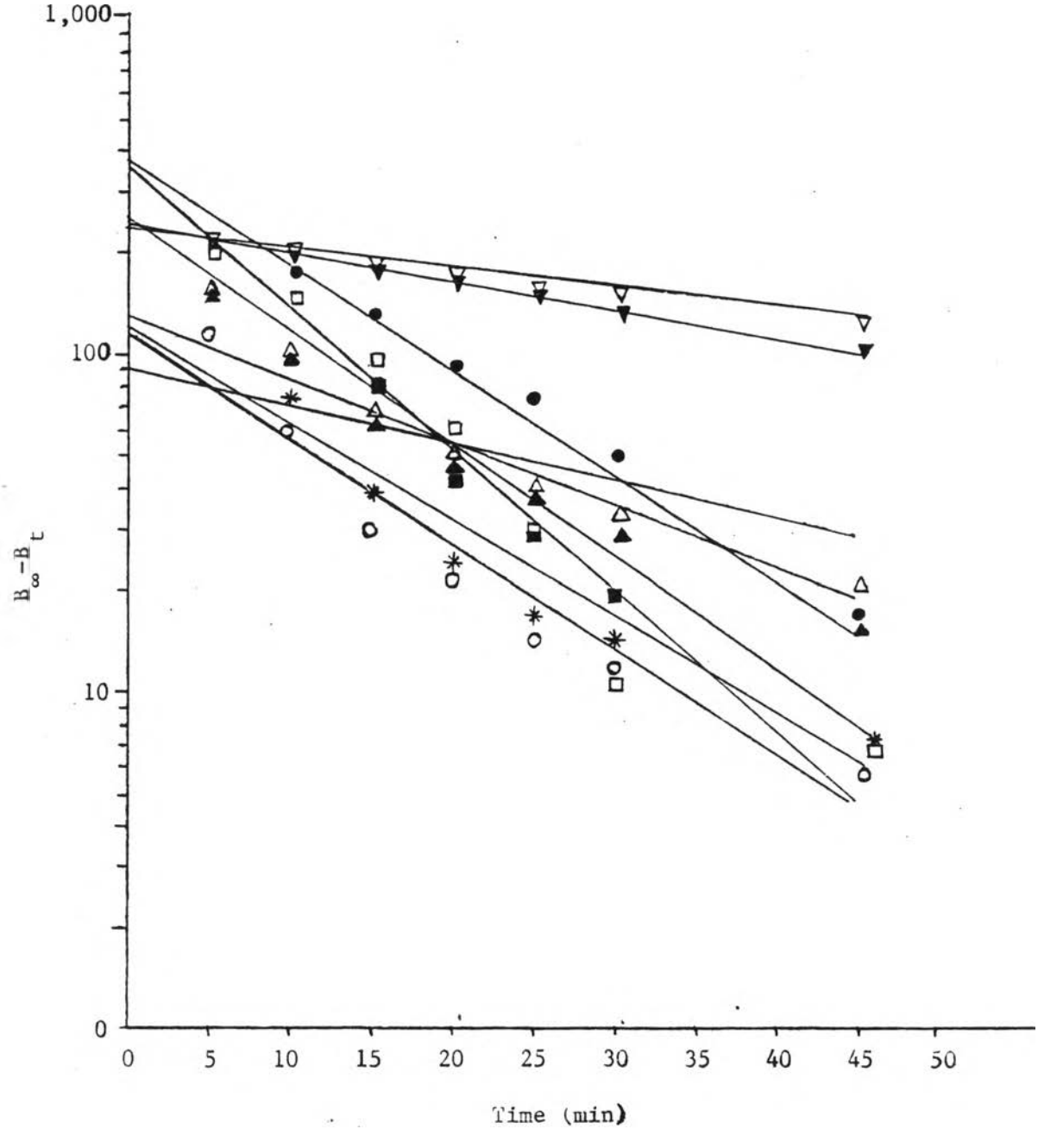

Figure 5 The sigma-minus plot between amount of undissolved naproxen in simulated intestinal fluid versus time for nine brands of naproxen tablets

Key : Brand A (□), Brand B (Δ), Brand C (o), Brand D (▽) Brand E (*), Brand F (■), Brand G (▲), Brand H (●) Brand I (▼)

Table 12 Analysis of Variance for Dissolution Rate Constant (hr^{-1}) of 9 Brands of Naproxen Tablets in Simulated Intestinal Fluid (pH 7.5)

Source of Variance	D.F.	S.S.	M.S.	F Test
Among Groups	8	189.60	23.70	18.00
Within Groups	45	59.23	1.32	
Tatal	53	248.83		

$$F_{0.95,\ (8,\ 45)} = 2.15$$

Table 13 Comparison of Dissolution Rate Constant (hr^{-1}) in Simulated Intestinal Fluid (pH 7.5) of Brand A with Other Brands Using T-Test

Brand	t-value
B	4.385*
C	0.006
D	6.204*
E	1.755
F	1.563
G	1.805
H	2.294*
I	5.682*

$$t_{0.05,\ 10} = 2.228$$

* = Statistically Difference at $p < 0.05$

media obviously seen in Figure 2 and 4 might be due to the formulation factors such as disintegrants, lubricant, aging of tablets, and manufacturing methods (30) eventhough they were rapidly disintegrated.

According to dissolution rate constant, only five brands were chosen to performed in vivo study. They were

brand A, the reference standard for the local brands

brand B, the maximum dissolution rate in simulated gastric fluid

brand C, the maximum dissolution rate in simulated intestinal fluid

brand D, the minimum dissolution rate in both dissolution media and brand E was included in the study because it was fabricated by the Government Pharmaceutical Organization which was the important manufacturer for providing drug products to all government hospitals in Thailand.

Using linear correlation test, there was poor linear correlation between hardness and disintegration time ($p > 0.05$) of the eight brands of naproxen tablets (Table 14 and Figure 6). Results from Tables 15-16 and Figures 7-8 showed that the hardness and dissolution rate constant in both dissolution media were not correlated ($p > 0.05$).

Tables 17-18 and Figures 9-10 also represented the poor correlation between the disintegration time and the dissolution rate constant of all brands studied in both dissolution media. These results indicated that the physical properties of naproxen tablets had no correlation between each other.

Table 14 Correlation between Hardness (k p) and Disintegration Time (min) of 8 Brands of Naproxen Tablets

Brand	Hardness (k p)	Disintegration time (min)
A	17.03	6.39
B	6.89	1.44
C	6.53	0.36
D	4.52	2.26
E	6.90	2.00
F	11.33	13.73
G	8.60	1.80
H	8.41	7.27

correlation coefficient (r) = 0.5573

t-value = 1.644

$t_{0.05,.6}$ = 2.447

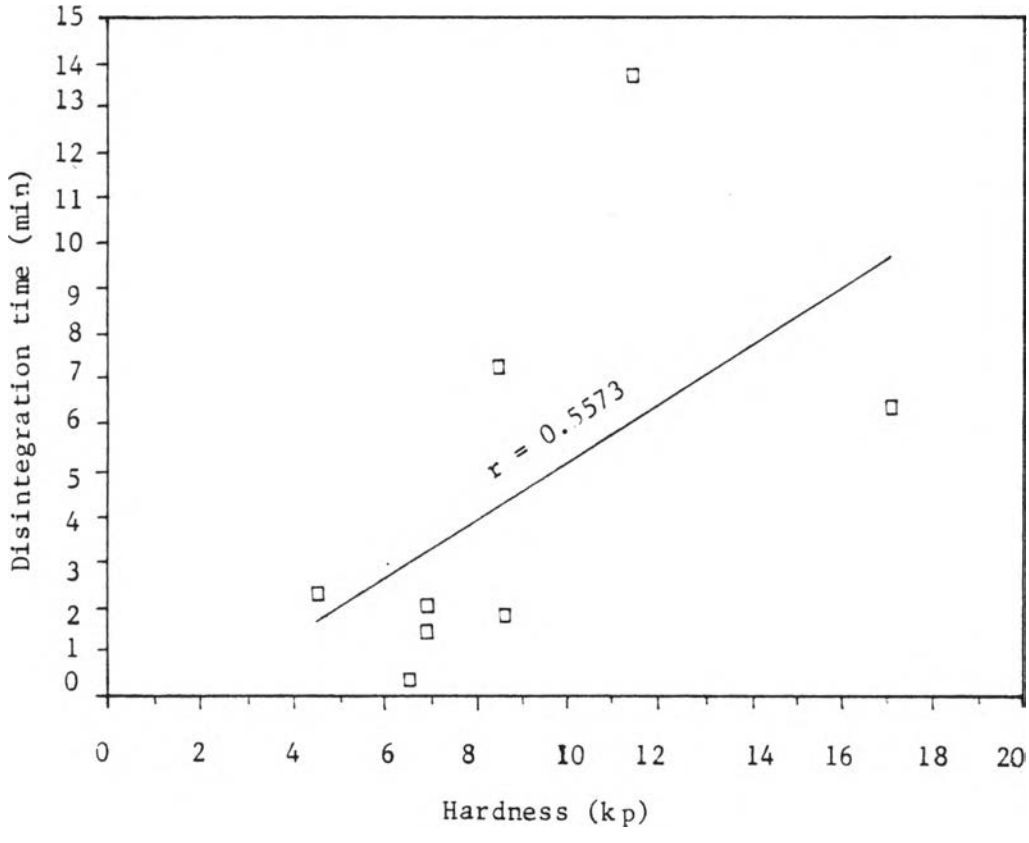

Figure 6 Correlation between hardness and disintegration time.

Table 15 Correlation between Hardness (kp) and Dissolution Rate Constant (hr^{-1}) of 8 Brands of Naproxen Tablets in Simulated Gastric Fluid (pH 1.2)

Brand	Hardness (kp)	Dissolution rate constant (hr^{-1})
A	17.03	1.39
B	6.89	2.03
C	6.53	1.15
D	4.52	0.55
E	6.90	1.00
F	11.33	1.13
G	8.60	1.79
H	8.41	1.08

correlation coefficient (r) = 0.2385

t-value = 0.602

$t_{0.05, 6}$ = 2.447

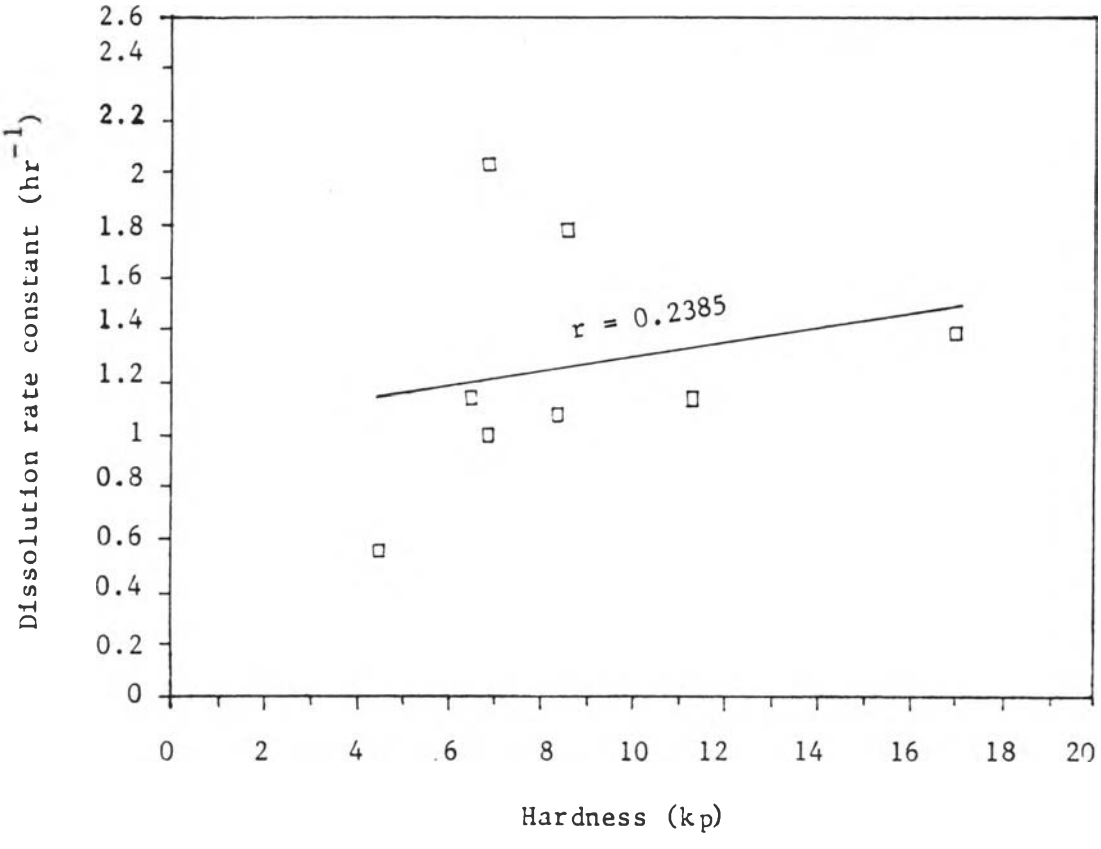

Figure 7 Correlation between hardness and dissolution rate constant in simulated gastric fluid

Table 16 Correlation between Hardness (kp) and Dissolution Rate Constant (hr^{-1}) of 8 Brands of Naproxen Tablets in Simulated Intestinal Fluid (pH 7.5)

Brand	Hardness (kp)	Dissolution rate constant (hr^{-1})
A	17.03	6.22
B	6.89	2.29
C	6.53	6.22
D	4.52	0.76
E	6.90	4.51
F	11.33	4.81
G	8.60	4.06
H	8.41	3.99

correlation coefficient (r) = 0.6251

t-value = 1.962

$t_{0.05, 6}$ = 2.447

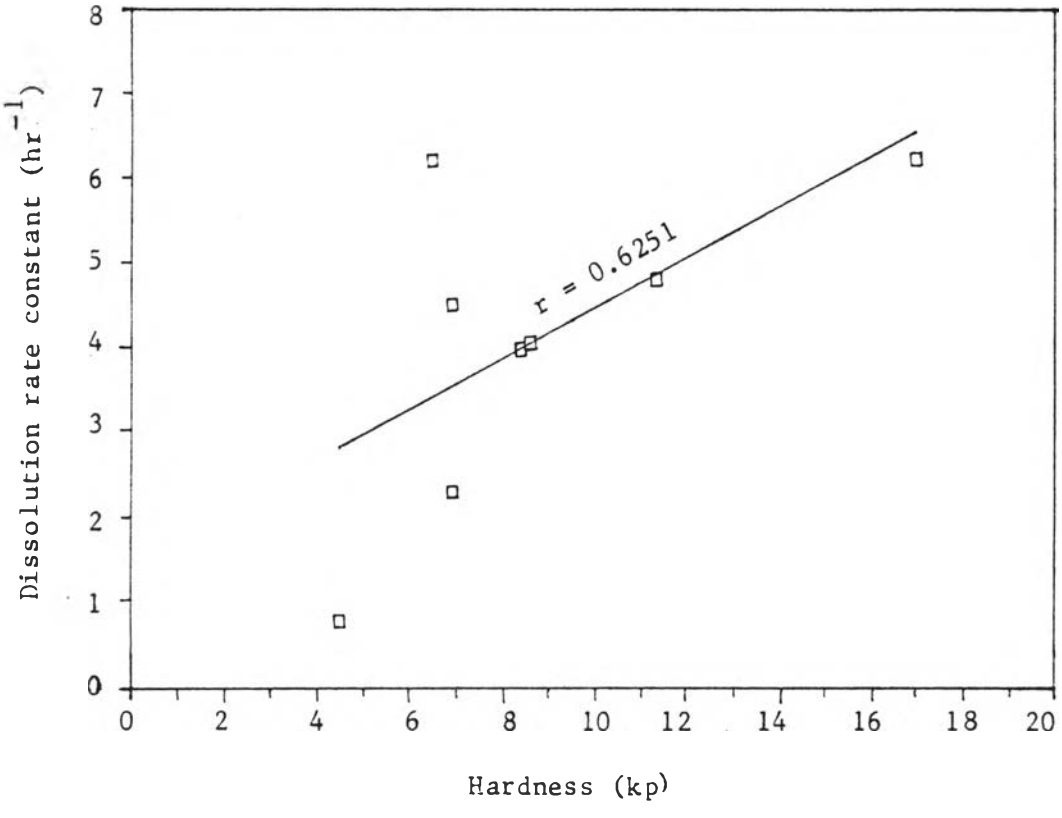

Figure 8 Correlation between hardness and dissolution rate constant in simulated intestinal fluid

Table 17 Correlation between Disintegration Time (min) and Dissolution Rate Constant (hr^{-1}) of 9 Brands of Naproxen Tablets in Simulated Gastric Fluid (pH 1.2)

Brand	Disintegration time (min)	Dissolution rate constant (hr^{-1})
A	6.39	1.39
B	1.44	2.03
C	0.36	1.15
D	2.26	0.55
E	2.00	1.00
F	13.73	1.13
G	1.80	1.79
H	7.27	1.08
I	1.03	0.62

correlation coeffieicnt (r) = -0.0334

t-value = -0.088

$t_{0.05,\ 7}$ = 2.365

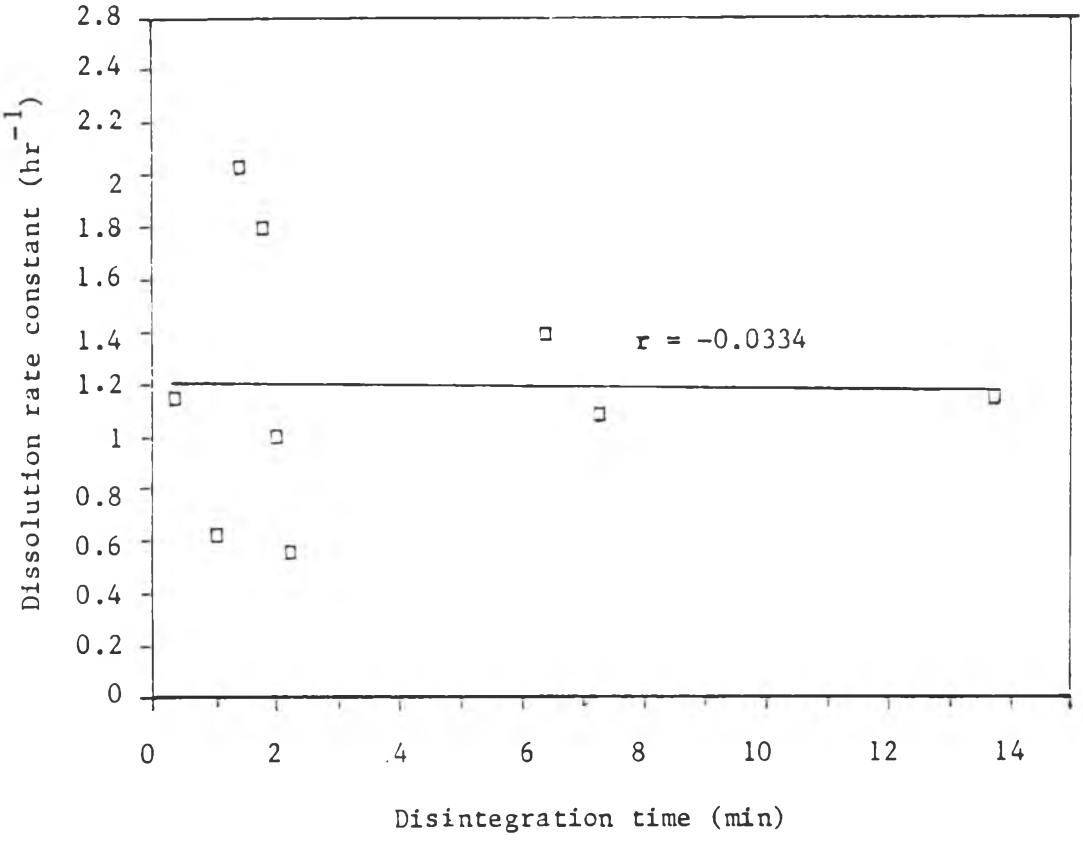

Figure 9 Correlation between disintegration time and dissolution rate constant in simulated gastric fluid

Table 18 Correlation between Disintegration Time (min) and Dissolution Rate Constant (hr^{-1}) of 9 Brands of Naproxen Tablets in Simulated Intestinal Fluid (pH 7.5)

Brand	Disintegration time (min)	Dissolution rate constant (hr^{-1})
A	6.39	6.22
B	1.44	2.29
C	0.36	6.22
D	2.26	0.76
E	2.00	4.51
F	13.73	4.81
G	1.30	4.06
H	7.27	3.99
I	1.03	1.19

correlation coefficient (r) = 0.3223

t-value = 0.901

$t_{0.05,\ 7}$ = 2.365

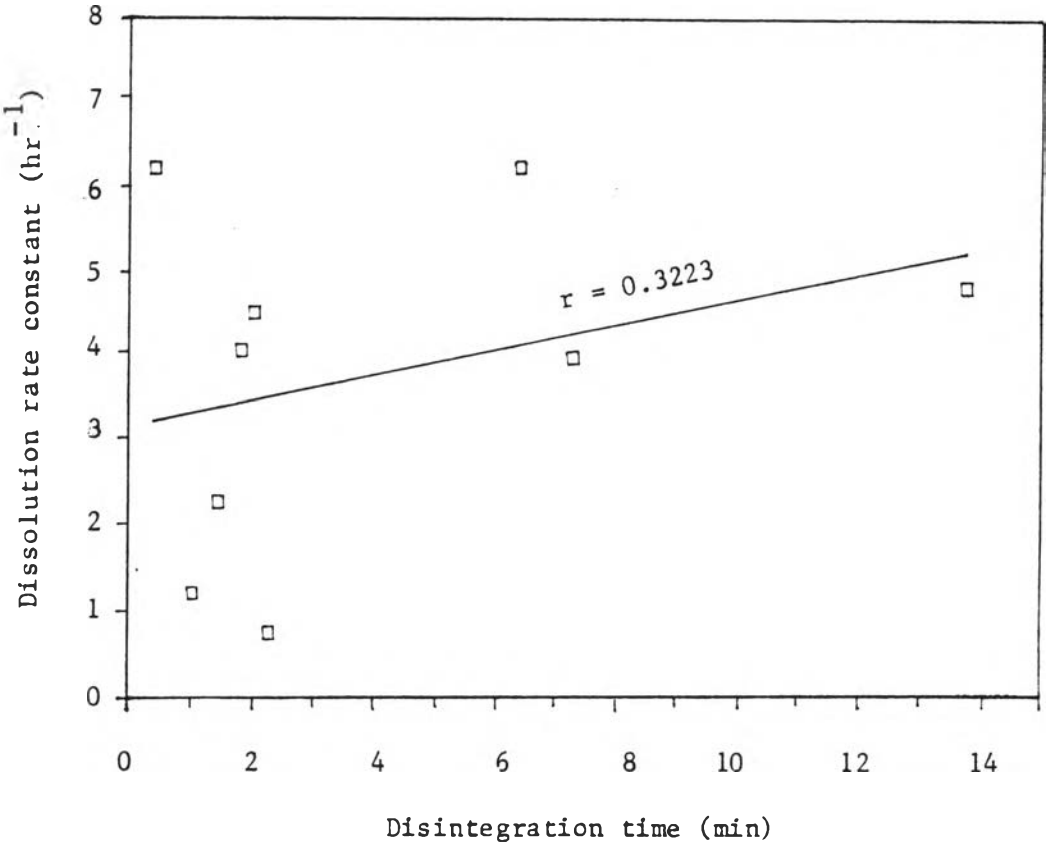

Figure 10 Correlation between disintegration time and dissolution rate constant in simulated intestinal fluid

In Vivo Studies

Analysis of Naproxen in Plasma

Plasma naproxen concentrations were analyzed using high performance liquid chromatography. Typical chromatograms of naproxen and internal-standard, phenylbutazone, were illustrated in Figure 11. Retention times for naproxen and internal standard were 5.08 and 8.66 minutes, respectively. The sensitivity of detection for naproxen in plasma was 5 μg/ml.

Clinical Observations

No side effects and/or any indication of intoxication were associated following oral administration of naproxen tablets throughout the study.

Plasma Naproxen Level

Plasma naproxen concentrations at each sampling time (0 to 24 hours) after administration of brands A, B, C, D and E were presented in Tables 19-23 respectively. The mean plasma naproxen concentration profile for each product from eight subjects were illustrated in Figures 12-15.

Pharmacokinetics of Naproxen Tablets

The derived pharmacokinetic parameters of naproxen based on the model independent analysis of the plasma concentration-time data were reported in Tables 24-41. The area under the plasma concentration-time curve, AUC_0^{24} and AUC_0^{∞}, calculated from individual plasma data for five different brands were presented in Tables 24 and 26. As seen in Tables

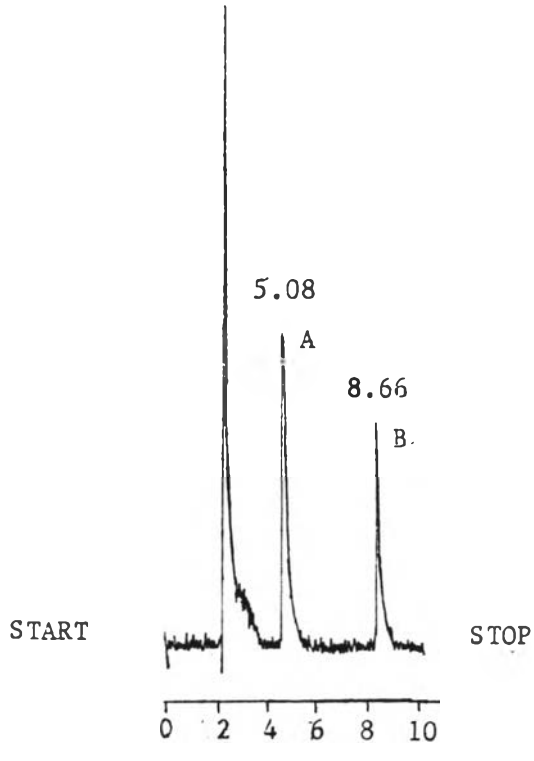

Figure 11 High pressure liquid chromatogram of naproxen (A) and internal standard (B).

Table 19 Plasma Naproxen Concentration at Various Times Following Oral Administration of 250 mg. Naproxen Tablet, Brand A, to 8 Subjects.

Time (hr.) \ Subject No.	Plasma Naproxen Concentration (μg/ml.)									
	1	2	3	4	5	6	7	8	MEAN [a]	SEM [b]
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	21.56	10.64	17.82	12.01	15.15	2.42	13.55	10.47	12.95	2.01
1	25.20	18.25	28.54	31.03	29.84	7.99	18.84	18.84	22.32	2.76
1.5	23.93	28.67	25.20	40.62	28.16	28.00	30.54	19.58	28.09	2.16
2	22.66	27.62	22.53	34.90	24.03	23.85	30.60	29.14	26.92	1.57
3	19.98	20.11	18.51	27.90	20.57	19.83	23.25	23.99	21.77	1.09
4	17.92	18.25	17.16	26.05	18.25	18.13	20.30	20.55	19.53	1.01
6	14.28	15.94	14.49	19.83	16.73	13.14	18.84	16.96	16.27	0.81
8	12.47	13.62	14.18	18.56	13.09	10.46	15.89	15.89	14.27	0.88
12	11.86	12.47	11.48	14.86	9.45	9.93	15.11	14.40	12.44	0.77
24	5.27	8.60	7.10	8.83	5.52	5.09	10.21	9.34	7.50	0.71

a = mean values obtained from 8 subjects, b = standard error of the mean

Table 20 Plasma Naproxen Concentration at Various Times Following Oral Administration of 250 mg Naproxen Tablet, Brand B, to 8 Subjects.

Time (hr) \ Subject No.	Plasma Naproxen Concentration (μg/ml)									
	1	2	3	4	5	6	7	8	MEAN[a]	SEM[b]
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	8.22	7.80	18.62	11.48	18.20	0.00	6.44	4.23	9.37	2.29
1	17.11	22.47	25.46	12.19	33.91	6.11	21.18	19.22	19.71	2.97
1.5	19.14	26.67	33.10	14.07	28.31	14.49	30.30	22.20	23.53	2.54
2	18.25	26.00	30.41	32.84	23.85	20.52	25.89	22.38	25.02	1.72
3	16.73	21.96	27.14	26.19	22.53	18.84	19.83	18.13	21.42	1.33
4	13.09	19.24	21.47	23.25	20.24	18.66	15.81	15.30	18.38	1.21
6	12.47	18.83	20.50	18.84	14.49	15.81	14.49	13.87	16.16	1.01
8	11.25	15.89	17.72	16.24	12.47	15.02	13.14	11.76	14.19	0.83
12	9.67	13.20	14.17	15.11	10.46	11.20	11.05	8.94	11.73	0.78
24	5.09	11.18	9.34	9.99	6.44	7.38	7.79	6.82	8.00	0.71

a = mean values obtained from 8 subjects, b = standard error of the mean

Table 21 Plasma Naproxen Concentration at Various Times Following Oral Administration of 250 mg Naproxen Tablet, Brand C, to 8 Subjects.

Time (hr) \ Subject No.	Plasma Naproxen Concentration (µg/ml)									
	1	2	3	4	5	6	7	8	MEAN [a]	SEM [b]
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	8.85	4.00	17.28	8.66	26.55	5.84	3.05	6.11	10.04	2.82
1	11.41	4.71	27.69	9.11	26.48	33.50	20.77	16.29	19.75	3.56
1.5	29.33	6.11	34.30	13.14	25.20	33.72	19.68	25.20	23.34	3.50
2	27.33	6.26	30.60	23.78	23.93	30.29	22.99	23.93	23.64	2.70
3	21.96	17.46	28.40	18.51	22.53	29.59	22.38	18.84	22.46	1.58
4	20.37	17.11	22.24	17.16	20.11	23.81	18.56	17.57	19.61	0.98
6	16.56	15.25	19.42	13.75	17.57	22.02	15.26	14.49	16.79	0.98
8	15.25	12.47	17.25	9.93	13.14	17.46	14.13	13.14	14.10	0.89
12	13.20	10.16	14.40	8.66	12.47	16.06	10.87	11.81	12.20	0.84
24	10.90	7.84	9.53	6.11	7.38	8.94	7.48	7.20	3.17	0.54

a = mean values obtained from 8 subjects, b = standard error of the mean

Table 22 Plasma Naproxen Concentration at Various Times Following Oral Administration of 250 mg Naproxen Tablet, Brand D, to 8 Subjects.

Time (hr) \ Subject No.	Plasma Naproxen Concentration (μg/ml)									
	1	2	3	4	5	6	7	8	MEAN [a]	SEM [b]
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	8.22	0.00	17.57	0.00	8.64	7.04	0.00	6.75	6.03	2.14
1	22.75	11.76	25.20	5.24	11.13	8.53	4.38	7.48	12.06	2.76
1.5	21.99	25.15	25.84	18.51	18.59	9.53	21.56	8.60	18.72	2.31
2	20.78	24.45	23.93	20.52	22.04	9.76	20.77	22.99	20.65	1.64
3	20.78	24.45	18.38	18.51	34.76	22.50	20.57	19.91	22.48	1.89
4	18.56	24.45	16.73	18.13	31.14	22.30	17.92	18.56	20.97	1.71
6	16.48	20.78	12.47	16.27	29.17	16.96	16.73	13.54	17.80	1.85
8	15.86	17.62	11.20	14.49	25.36	16.66	13.09	13.03	15.91	1.54
12	14.11	15.24	8.66	11.81	19.44	12.94	11.86	11.66	13.21	1.12
24	10.57	9.74	6.11	7.51	11.75	8.95	6.39	8.22	8.65	0.70

a = mean values obtained from 8 subjects, b = standard error of the mean

Table 23 Plasma Naproxen Concentration at Various Times Following Oral Administration of 250 mg. Naproxen Tablet, Brand E, to 8 Subjects.

Time (hr) \ Subject No.	Plasma Naproxen Concentration (µg/ml)									
	1	2	3	4	5	6	7	8	MEAN [a]	SEM [b]
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	8.15	4.88	18.20	14.79	23.80	0.00	6.32	10.16	10.79	2.73
1	32.61	9.75	30.30	26.30	45.97	6.11	9.86	13.62	21.81	4.99
1.5	28.05	18.45	27.88	25.20	46.10	19.14	13.40	13.62	23.98	3.77
2	24.88	24.24	25.20	20.77	38.58	17.92	34.89	24.03	26.32	2.46
3	22.96	28.10	20.95	18.56	37.99	18.84	29.94	19.98	24.67	2.42
4	20.40	20.80	17.16	15.78	26.45	17.57	26.28	17.11	20.19	1.47
6	15.24	18.45	15.15	15.25	22.82	15.02	23.42	15.94	17.66	1.26
8	14.94	17.91	13.14	14.69	18.84	14.64	18.89	13.62	15.83	0.83
12	12.02	13.94	10.46	10.82	15.89	9.93	17.67	12.47	12.90	0.97
24	8.80	10.07	5.80	7.84	10.47	6.11	10.28	5.52	8.11	0.74

a = mean values obtained from 8 subjects, b = standard error of the mean

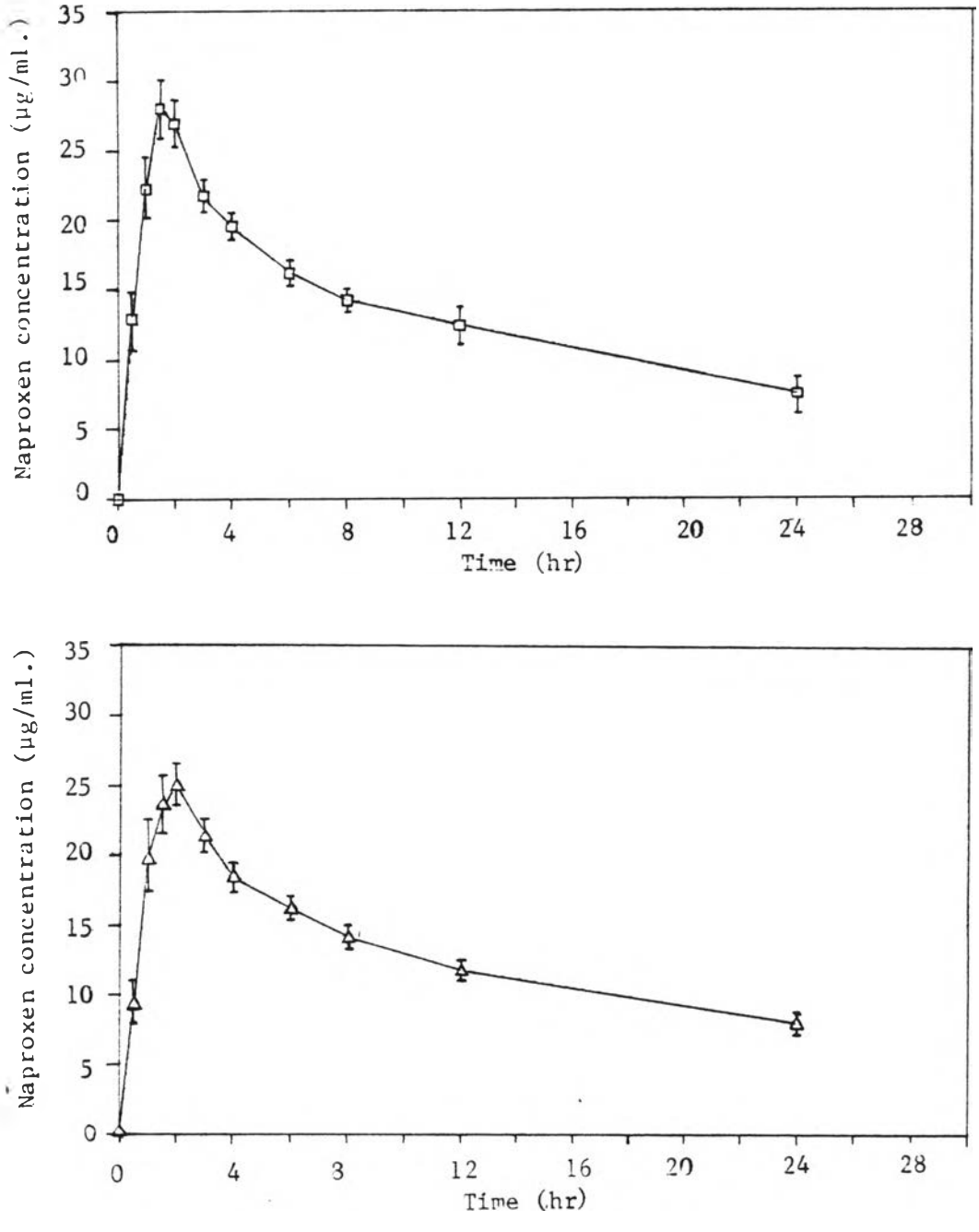

Figure 12 Mean plasma naproxen concentration-time profile from 8 subjects following oral administration of 250 mg. naproxen tablet, brand A (above), and brand B (below) (vertical lines indicate standard error of the mean)

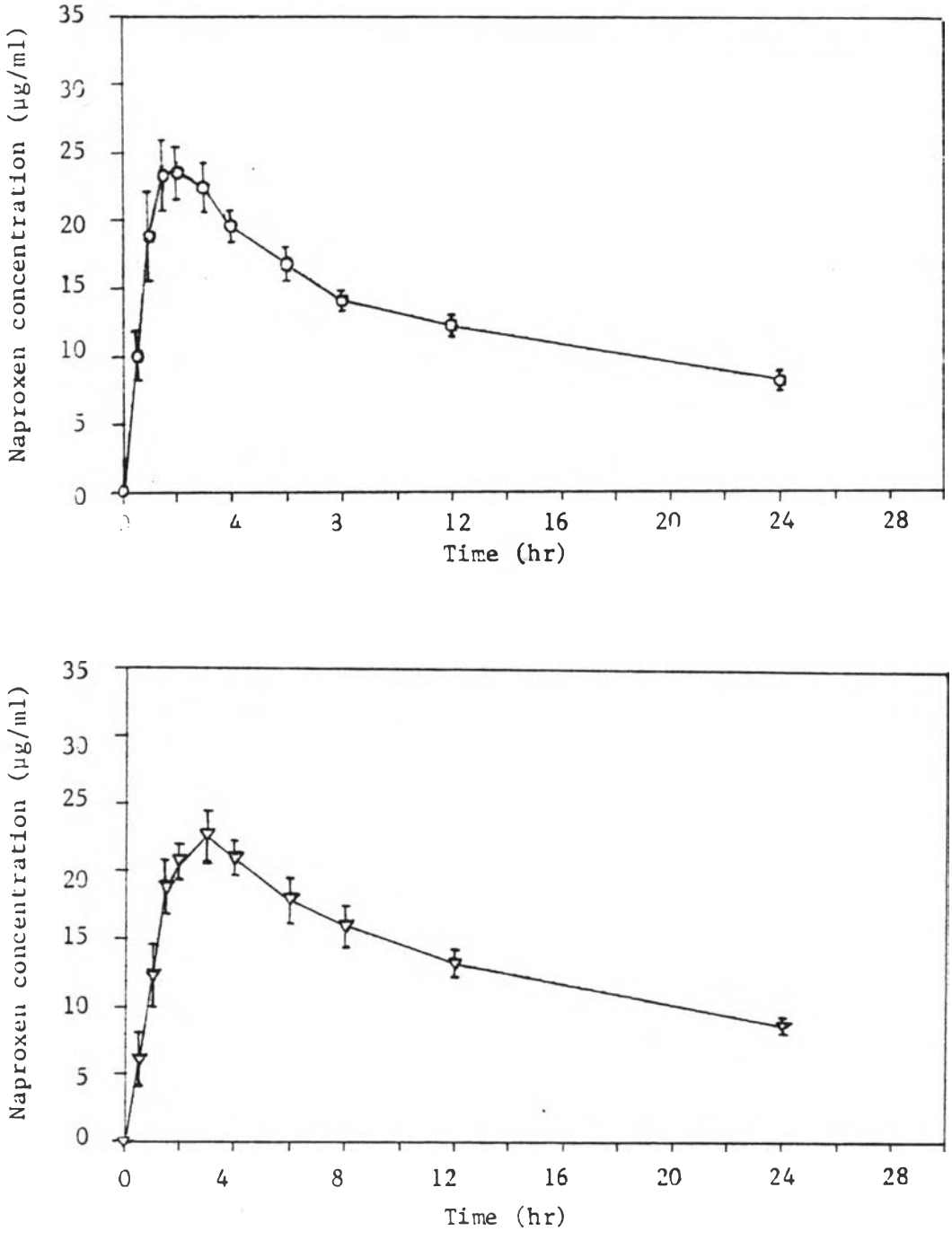

Figure 13 Mean plasma naproxen concentration-time profile from 8 subjects following oral administration of 250 mg naproxen tablet, brand C (above) and brand D (below) (vertical lines indicate standard error of the mean)

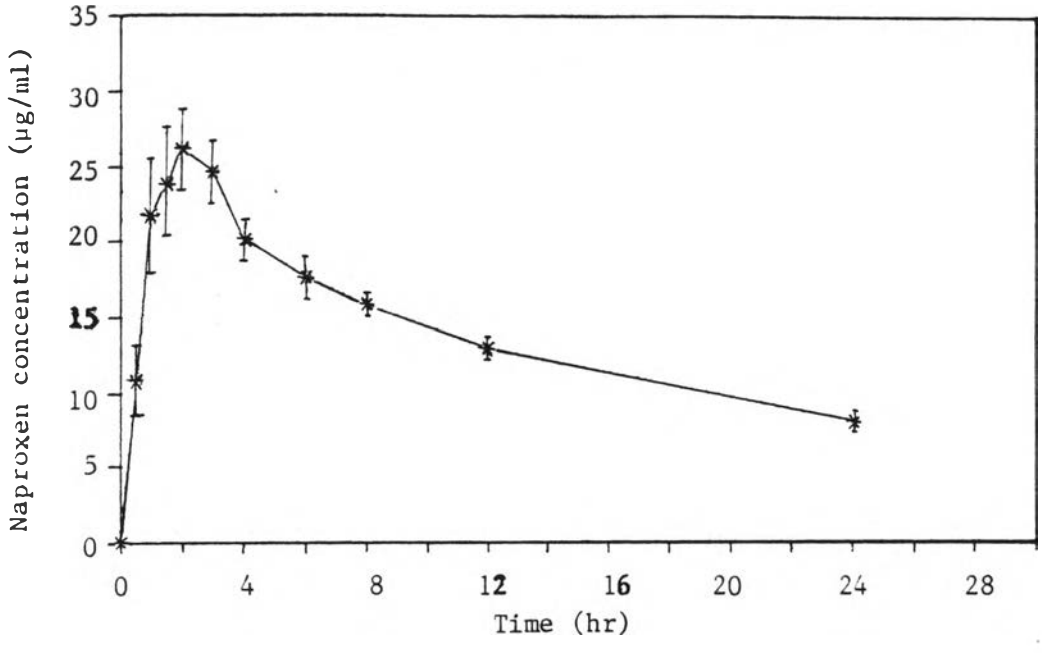

Figure 14 Mean plasma naproxen concentration-time profile from 8 subjects following oral administration of 250 mg naproxen tablet, brand E (vertical lines indicate standard error of the mean)

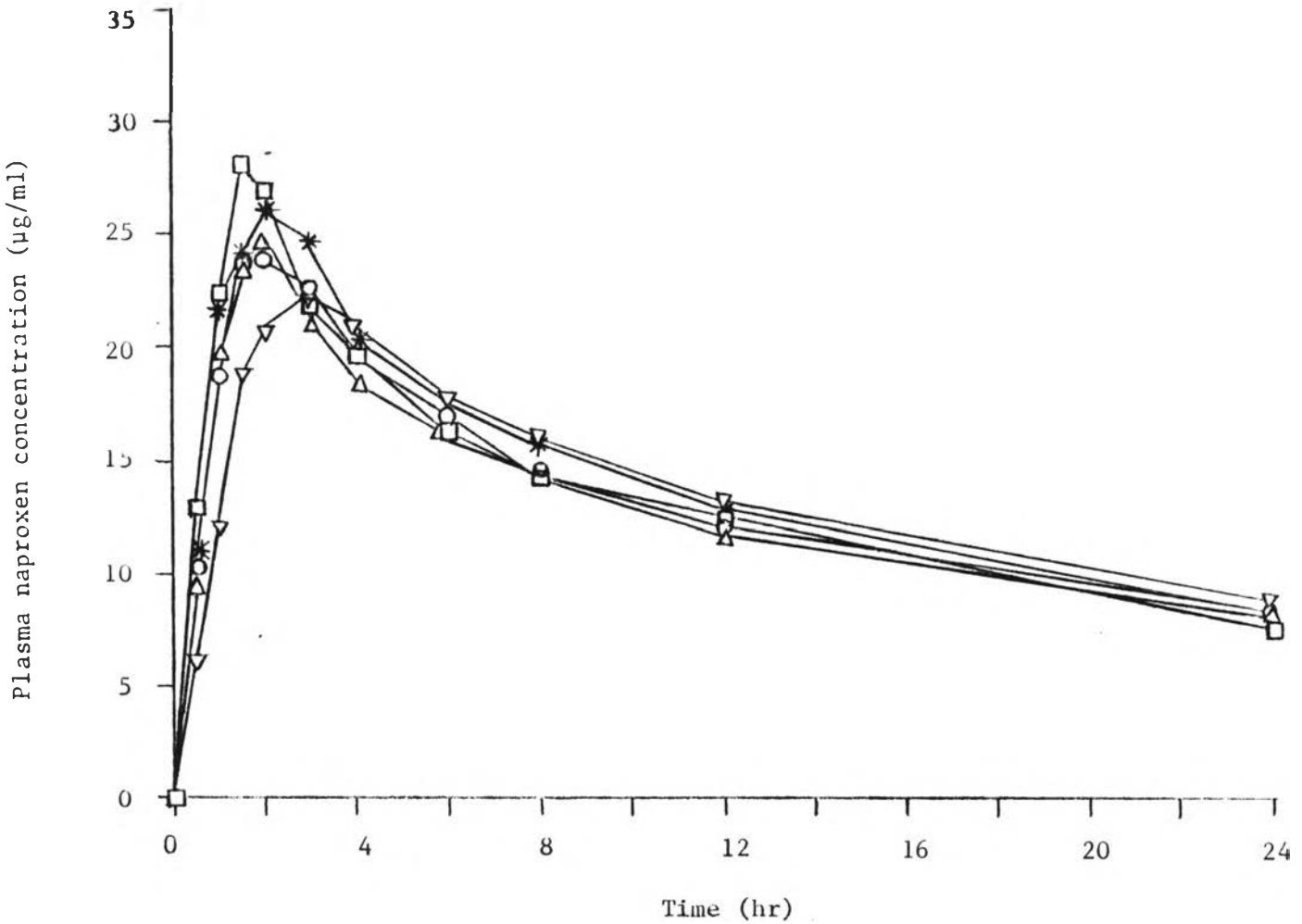

Figure 15 Comparison of the mean plasma naproxen concentration-time profile of five different brands following oral administration of 250 mg naproxen tablet to 8 subjects.

Key : Brand A (□), Brand B (Δ), Brand C (o), Brand D (V), Brand E (*)

25 and 27, there were no statistically significant difference among AUC_o^{24} and AUC_o^{∞} from five commercial brands. This indicated that all brands were equally absorbed. The values of AUC_o^{24} and AUC_o^{∞} in this study were lower than those previously presented by Runkel et al. (18) 417 µg.hr/ml for AUC_o^{24}, and Anttila et al. (20), 797 µg.hr/ml for AUC_o^{∞}.

The mean residence times after oral and intravenous administration (MRT_{oral}, MRT_{iv}) were shown in Tables 28, 30. MRT_{oral} was obtained from the ratio of AUMC and AUC (Appendix E) and MRT_{iv} was approximately calculated from the reciprocal of elimination rate constant which determined from a least-square linear regression fit of the terminal region of the semilogarithmic plasma concentration-time curve of individual oral data. Results from Tables 29, 31 showed that there were no statistically significant difference among these parameters from five treatments ($p > 0.05$) except for brands A and D ($A < D$ at $p < 0.05$).

The mean absorption time, MAT, which was the product of the difference of MRT_{oral} and MRT_{iv} for each brand was presented in Table 32. The first-order absorption rate constants (Ka), the reciprocal of MAT, from five different brands were shown in Table 34. Statistical analysis of difference among MAT and Ka in Tables 33, 35 indicated that these two parameters from brands A, B, C, D, and E were not different among each other ($p > 0.05$).

The peak plasma naproxen concentration (Cp_{max}) observed directly from individual plasma concentration-time curve was summarized in Table 36. The mean Cp_{max} for brands A, B, C, D, and E were 30.08 ± 1.60, 27.36 ± 2.13, 26.67 ± 2.00, 24.51 ± 1.59, and 30.18 ± 2.87 µg/ml, respectively. Statistically significant difference

Table 24 Area Under the Plasma Concentration-Time Curve (AUC_o^{24}) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	AUC_o^{24} (µg.hr/ml)				
	A	B	C	D	E
1	291.73	238.94	347.65	347.56	330.88
2	321.15	356.81	251.46	372.67	356.60
3	302.91	384.33	387.28	260.19	292.91
4	402.18	371.74	240.72	288.52	299.13
5	283.96	299.74	328.40	477.59	456.62
6	251.76	283.11	403.07	317.00	261.30
7	375.58	295.43	293.97	281.97	422.32
8	353.88	256.14	293.05	285.21	288.05
MEAN	322.89	310.78	318.20	328.84	338.36
SEM	17.92	19.14	20.97	25.00	24.49

Table 25 Analysis of Variance and Student's T-Statistical Comparison of AUC_o^{24} (μg.hr/ml) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	3,513.00	873.38	0.23
Within groups	35	131,666.00	3,761.89	
Total	39	135,179.00		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	0.395	0.000			
C	0.153	-0.242	0.000		
D	-0.194	-0.589	-0.347	0.000	
E	-0.504	-0.899	-0.657	-0.310	0.000

$$t_{0.05,\ 14} = 2.145$$

Table 26 Area Under the Plasma Concentration-Time Curve (AUC_o^∞) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	AUC_o^∞ (μg.hr/ml)				
	A	B	C	D	E
1	371.70	329.54	612.85	668.92	295.42
2	495.34	652.57	452.00	594.45	594.73
3	431.12	557.88	563.82	355.36	375.88
4	543.51	579.78	346.80	455.78	457.22
5	360.47	394.60	460.47	707.94	617.00
6	323.79	441.20	557.39	521.79	377.68
7	617.59	442.41	441.61	399.65	621.55
8	558.22	393.15	431.61	476.00	378.46
MEAN	462.72	473.89	483.32	522.49	489.74
SEM	37.72	39.16	30.85	44.46	38.63

Table 27 Analysis of Variance and Student's T-Statistical Comparison of AUC_0^∞ (µg.hr/ml)

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	16,321.70	4,080.42	0.34
Within groups	35	413,163.00	11,804.70	
Total	39	429,484.00		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	-0.206	0.000			
C	-0.379	-0.174	0.000		
D	-1.100	-0.895	-0.721	0.000	
E	-0.497	-0.292	-0.118	0.603	0.000

$$t_{0.05,\ 14} = 2.145$$

Table 28 Mean Residence Time after Oral Administration (MRT_{oral}) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	MRT_{oral} (hr)				
	A	B	C	D	E
1	15.44	18.36	26.88	31.65	20.07
2	22.02	28.59	28.10	23.88	25.30
3	19.16	19.83	19.89	17.23	15.45
4	17.25	22.63	11.35	23.50	21.66
5	14.87	16.08	18.64	21.06	16.95
6	15.66	22.85	18.30	24.84	20.07
7	24.85	20.80	21.14	19.48	20.71
8	23.20	21.71	20.57	25.21	16.85
MEAN	19.06	21.36	21.61	23.36	19.71
SEM	1.36	1.31	1.33	1.53	1.12

Table 29 Analysis of Variance and Student's T-Statistical Comparison of MRT_{oral} (hr) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	91.80	22.95	1.59
Within groups	35	503.33	14.38	
Total	39	595.13		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	-1.210	0.000			
C	-1.342	-0.131	0.000		
D	-2.263*	-1.053	-0.921	0.000	
E	-0.342	0.868	1.000	1.921	0.000

$$t_{0.05,\ 14} = 2.145$$

* = Statistically difference at $p < 0.05$

Table 30 Mean Residence Time after Intravenous Administration (MRT_{iv}) of Naproxen Approximately Calculated from the Reciprocal of Elimination Rate Constant ($^{1}/Kel$) from the Plasma Concentration Time Curve Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	MRT_{iv} (hr)				
	A	B	C	D	E
1	15.17	17.79	24.33	30.39	18.69
2	20.24	26.45	25.57	22.78	23.69
3	18.05	18.59	18.52	15.58	14.45
4	16.00	20.83	17.36	22.27	20.16
5	13.85	14.73	17.89	19.61	15.31
6	14.14	21.41	17.27	22.88	19.05
7	23.70	18.87	19.72	18.42	19.38
8	21.88	20.08	19.23	23.20	16.37
MEAN	17.88	19.84	19.99	21.89	18.38
SEM	1.31	1.19	1.13	1.54	1.05

Table 31 Analysis of Variance and Student's T-Statistical Comparison of MRT_{iv} (hr) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	79.25	19.81	1.57
Within groups	35	442.33	12.64	
Total	39	521.58		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	-1.101	0.000			
C	-1.185	-0.084	0.000		
D	-2.253*	-1.152	-1.067	0.000	
E	-0.281	0.820	0.904	1.972	0.000

$$t_{0.05,\ 14} = 2.145$$

* = Statistically difference at $p < 0.05$

Table 32 Mean Absorption Time (MAT) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	MAT (hr)				
	A	B	C	D	E
1	0.27	0.57	2.55	1.26	2.01
2	1.78	2.14	2.53	1.10	1.66
3	1.11	1.24	1.37	1.65	1.00
4	1.25	1.80	1.99	1.23	1.50
5	1.02	1.35	0.75	1.45	1.64
6	1.52	1.44	1.03	1.96	1.02
7	1.15	1.93	1.42	1.06	1.33
8	1.32	1.63	1.34	2.01	0.48
MEAN	1.18	1.51	1.61	1.46	1.33
SEM	0.15	0.17	0.23	0.13	0.17

Table 33 Analysis of Variance and Student's T-Statistical Comparison of MAT (hr) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	0.95	0.24	0.95
Within groups	35	8.73	0.25	
Total	39	9.68		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	-1.320	0.000			
C	-1.720	-0.400	0.000		
D	-1.120	0.200	0.600	0.000	
E	-0.600	0.720	1.120	0.520	0.000

$$t_{0.05,\ 14} = 2.145$$

Table 34 Absorption Rate Constant (Ka) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets

Brand / Subject No.	Ka (hr^{-1})				
	A	B	C	D	E
1	3.70	1.75	0.39	0.79	0.50
2	0.56	0.47	0.39	0.91	0.60
3	0.90	0.81	0.73	0.61	1.00
4	0.80	0.55	0.50	0.81	0.67
5	0.98	0.74	1.33	0.69	0.61
6	0.66	0.69	0.97	0.51	0.98
7	0.87	0.52	0.70	0.94	0.75
8	0.76	0.61	0.75	0.50	2.08
MEAN	1.15	0.77	0.72	0.72	0.90
SEM	0.37	0.15	0.11	0.06	0.18

Table 35 Analysis of Variance and Student's T-Statistical Comparison of Ka (hr^{-1}) of 5 Brands of Naproxen Tablets

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	1.08	0.27	0.83
Within groups	35	11.45	0.33	
Total	39	12.54		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	1.310	0.000			
C	1.483	0.172	0.000		
D	1.483	0.172	0.000	0.000	
E	0.862	-0.448	-0.621	-0.621	0.000

$$t_{0.05,\ 14} = 2.145$$

among these parameters from five brands studied were not observed ($p > 0.05$) as shown in Table 37. The values of Cp_{max} varied greatly among previously published data such as Brogden et al. (1) reported the peak plasma concentration obtained from healthy volunteers after a single oral dose of 250 mg. naproxen was about 34 µg/ml., approximately 44.3 µg/ml. of Cp_{max} was found by Anttila et al. (20). The Cp_{max} ranging from 39 to 58 µg/ml. and 50 to 60 µg/ml. have been published by Calvo et al. (21), and Aarbakke et al. (19), respectively. The value obtained from present study was lower than those previous reports. This may be due to intersubject variation.

The time to peak plasma level (T_{max}) was also obtained from the plasma concentration-time curve of each individual as seen in Table 38. The mean T_{max} values were 1.44 ± 0.15, 1.62 ± 0.13, 1.69 ± 0.29, 1.94 ± 0.25, and 1.62 ± 0.25 hours for brands A, B, C, D, and E, respectively. Statistical comparison as presented in Table 39 indicateed that all five commercial brands were not significantly different. There was a good agreement of this value from this study and other reports (15, 17, 19-21, 31). The time to peak plasma level in previous studies was within 2 hours (15, 17, 21, 31) and Aarbakke et al. (19) also reported that the T_{max} ranged from 1.5 to 3 hours in healthy volunteers after 250 mg. oral administration.

The plasma half-life ($t_{\frac{1}{2}}$) for brands A, B, C, D, and E were 12.39 ± 0.91, 13.75 ± 0.83, 13.85 ± 0.73, 15.17 ± 1.07, and 12.74 ± 0.72 hours, respectively (Table 40). Statistical result in Table 41 showed significantly difference between brand A and D ($A < D$ at $p < 0.05$) whereas the others were not. However, all values obtained were the same as that in the previous studies. The half-life of naproxen ranged from

Table 36 Peak Plasma Concentration (Cp_{max}) of Naproxen Reading Directly from the Plasma Concentration Time Curve of Each Individual Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets.

Brand / Subject No.	Cp_{max} (µg/ml)				
	A	B	C	D	E
1	25.20	19.14	29.33	22.75	32.61
2	23.67	26.67	17.46	25.15	28.10
3	28.54	33.10	34.30	25.84	30.29
4	40.62	32.84	23.78	20.52	26.30
5	29.84	33.91	26.55	34.76	46.10
6	28.00	20.52	33.72	22.50	19.14
7	30.60	30.29	22.99	21.56	34.89
8	29.14	22.38	25.20	22.99	24.03
MEAN	30.08	27.36	26.67	24.51	30.18
SEM	1.60	2.13	2.00	1.59	2.87

Table 37 Analysis of Variance and Student's T-Statistical Comparison of Cp_{max} (µg/ml) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	185.31	46.33	1.32
Within groups	35	1,224.73	34.99	
Total	39	1,410.04		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	0.919	0.000			
C	1.152	0.233	0.000		
D	1.882	0.963	0.730	0.000	
E	-0.034	-0.953	-1.186	-1.915	0.000

$$t_{0.05,\ 14} = 2.145$$

Table 38 Time to Peak Plasma Level (T_{max}) of Naproxen Reading Directly from the Plasma Concentration Time Curve of Each Individual Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets.

Brand / Subject No.	T_{max} (hr)				
	A	B	C	D	E
1	1.00	1.50	1.50	1.00	1.00
2	1.50	1.50	3.00	1.50	3.00
3	1.00	1.50	1.50	1.50	1.00
4	1.50	2.00	2.00	2.00	1.00
5	1.00	1.00	0.50	3.00	1.50
6	1.50	2.00	1.50	3.00	1.50
7	2.00	1.50	2.00	1.50	2.00
8	2.00	2.00	1.50	2.00	2.00
MEAN	1.44	1.62	1.69	1.94	1.62
SEM	0.15	0.13	0.29	0.25	0.25

Table 39 Analysis of Variance and Student's T-Statistical Comparison of T_{max} (hr) of 5 Brands of Naproxen Tablets

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	1.04	0.26	0.72
Within groups	35	12.66	0.36	
Total	39	13.69		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statistic

Brand	A	B	C	D	E
A	0.000				
B	-0.600	0.000			
C	-0.833	-0.233	0.000		
D	-1.667	-1.067	-0.833	0.000	
E	-0.600	0.000	0.233	1.067	0.000

$$t_{0.05,\ 14} = 2.145$$

Table 40 Plasma Half-life ($t_{\frac{1}{2}}$) of Naproxen from 8 Subjects Following 250 mg Oral Administration of Five Different Brands of Naproxen Tablets.

Brand / Subject No.	$t_{\frac{1}{2}}$ (hr)				
	A	B	C	D	E
1	10.51	12.33	16.89	21.06	12.95
2	14.03	18.33	17.72	15.79	16.38
3	12.51	12.88	12.83	10.80	10.01
4	11.09	14.43	12.03	15.43	13.97
5	9.60	10.21	12.40	13.59	10.61
6	9.80	14.84	11.97	15.85	13.20
7	16.42	13.08	13.66	12.76	13.43
8	15.16	13.91	13.33	16.08	11.34
MEAN	12.39	13.75	13.85	15.17	12.74
SEM	0.91	0.83	0.78	1.07	0.72

Table 41 Analysis of Variance and Student's T-Statistical Comparison of $t_{\frac{1}{2}}$ (hr) of 5 Brands of Naproxen Tablets.

Source of Variance	D.F.	S.S.	M.S.	F-test
Among groups	4	38.07	9.52	1.57
Within groups	35	212.35	6.07	
Total	39	250.42		

$$F_{0.95,\ (4,\ 35)} = 2.64$$

Student's T-Statiscal

Brand	A	B	C	D	E
A	0.000				
B	-1.106	0.000			
C	-1.187	-0.081	0.000		
D	-2.260*	-1.154	-1.073	0.000	
E	-0.284	0.821	0.902	1.976	0.000

$$t_{0.05,\ 14} = 2.145$$

* = Statistically difference at $p < 0.05$

Table 42 The Mean Value of Pharmacokinetic Parameters of Naproxen from 8 Subjcets following 250 mg Oral Administration. (Values in Parenthesis were the SEM)

Parameter	Brand					Statistical Significance[a]
	A	B	C	D	E	
Area under the plasma concentration time curve, AUC_0^∞ (μg.hr/ml)	462.72 (37.72)	473.89 (39.16)	483.32 (30.85)	522.49 (44.46)	489.74 (38.63)	NS
The absorption rate constant, Ka (hr^{-1})	1.15 (0.37)	0.77 (0.15)	0.72 (0.11)	0.72 (0.06)	0.90 (0.18)	NS
Peak plasma concentration, Cp_{max} (μg/ml)	30.08 (1.60)	27.36 (2.13)	26.67 (2.00)	24.51 (1.59)	30.18 (2.87)	NS
Time to peak plasma level, T_{max} (hr)	1.44 (0.15)	1.62 (0.13)	1.69 (0.29)	1.94 (0.25)	1.62 (0.25)	NS
Plasma half-life, $t_{\frac{1}{2}}$ (hr)	12.39 (0.91)	13.75 (0.83)	13.85 (0.78)	15.17 (1.07)	12.74 (0.72)	A < D

a = significant difference at $p < 0.05$

NS = no significant difference at $p < 0.05$

12 to 15 hours (1, 18, 32). Anttila et al. (20) reported the half-life of naproxen was 17.7 hours. Runkel et al. (16) and Thomson et al. (31) found that naproxen half-life ranged from 10 to 17 and from 9.5 to 21.9 hours, respectively.

The mean values of pharmacokinetic parameters of naproxen from 8 subjects following 250 mg. oral administration were summarized in Table 42. These results obtained from the in vivo study indicated that brands A, B, C, D, and E were bioequivalent according to both the rate and the extent of drug absorption into the general circulation.

In Vitro - In Vivo Correlation

Due to the disintegration and dissolution of solid dosage from could affect the bioavailability of the drug product, the correlation between the disintegration time as well as the dissolution rate of the drug and the corresponding pharmacokinetic parameters were tested. Results from Tables 43-47 and Figures 16-20 exhibited poor linear correlations between the disintegration time and the in vivo parameters (AUC_0^∞, Cp_{max}, T_{max}) meanwhile statistically significant of correlation between disintegration time and absorption rate constant was found ($p < 0.05$). The linear correlation found between the disintegration time and the absorption rate constant seemed to be meaningless because the absorption rate constant increased proportional to the increase of disintegration time. This evidence may be attributed to the disintegration characteristic of each brand. According to the observations during tablet disintegrations, naproxen tablets for brands B, C, D, and E disintegrated into granules and then passed through the mesh of the basket while tablets for brand A gradually disintegrated into finer

particles and the tablets disappeared bit by bit which brought on the maximum disintegration time. If brand A was excluded from the correlation test, no statistically significant ($p > 0.05$) of this correlation was obserbed as shown in Table 45 and Figure 18. Gibaldi, M. (33) reported that it was unlikely that disintegration would be the rate limiting step in the absorption of drugs from tablets. The test for tablet disintegration following the standard requirement of pharmacopoeia is useful for quality control in manufacturing but it does not grarantee adequately drug absorption. Also, it is generally recognized that the in vitro disintegration test is a poor index of drug bioavailability (33). Generally, the correlation between disintegration and drug absorption was happened especially with sugar-coated or enteric-coated tablets (33).

Tables 48-55 and Figures 21-28 showed the correlation results between dissolution rate constant in both simulated gastric fluid and simulated intestinal fluid and in vivo parameters, AUC_o^∞, Ka, Cp_{max}, T_{max}, respectively. All tests indicated that the linear correlations were not statistically significant ($p > 0.05$). This suggested that the dissolution of drug was not the factor affecting the biovailability of naproxen.

Table 43 Correlation between Disintegration Time (min) and AUC_o^∞ (µg.hr/ml)' of 5 Brands of Naproxen Tablets.

Brand	Disintegration Time (min)	AUC_o^∞ (µg.hr/ml)
A	6.39	462.72
B	1.44	473.89
C	0.36	483.32
D	2.26	522.49
E	2.00	489.74

correlation coefficient (r) = -0.3977

t-value = -0.751

$t_{0.05, 3}$ = 3.182

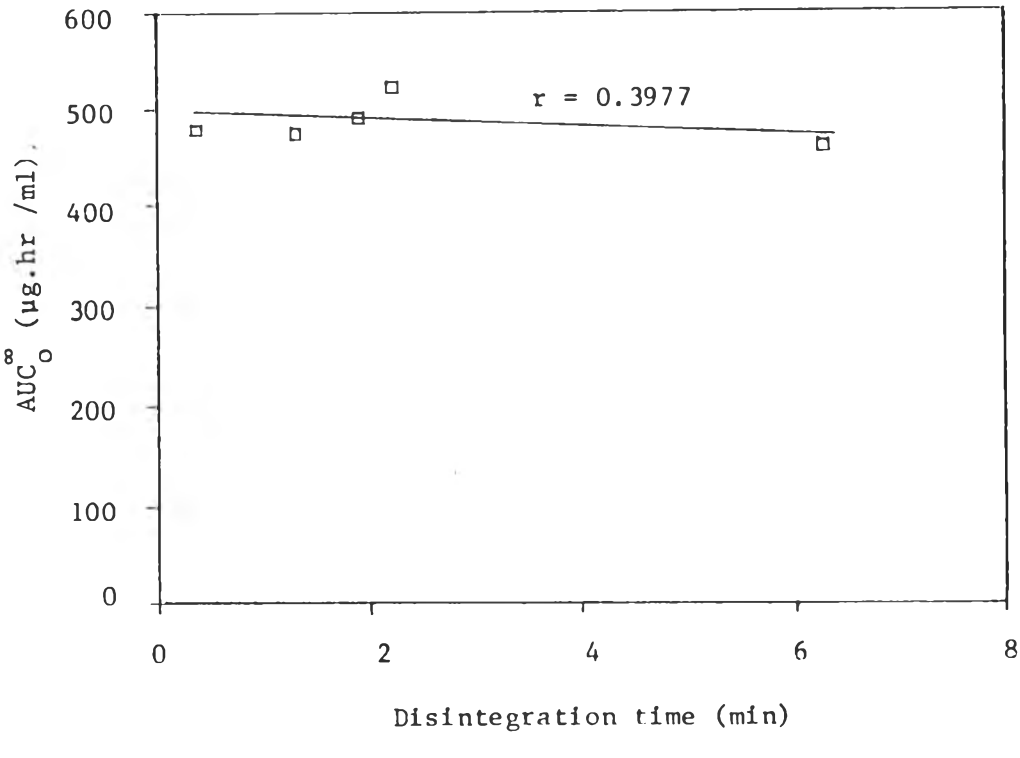

Figure 16 Correlation between disintegration time and AUC_o^∞

Table 44 Correlation between Disintegration Time (min) and Ka (hr^{-1}) of 5 Brands of Naproxen Tablets.

Brand	Disintegration time (min)	Ka (hr^{-1})
A	6.39	1.15
B	1.44	0.77
C	0.36	0.72
D	2.26	0.72
E	2.00	0.90

correlation coefficient (r) = 0.9173

t-value = 3.989

$t_{0.05, 3}$ = 3.182

$t_{0.01, 3}$ = 5.841

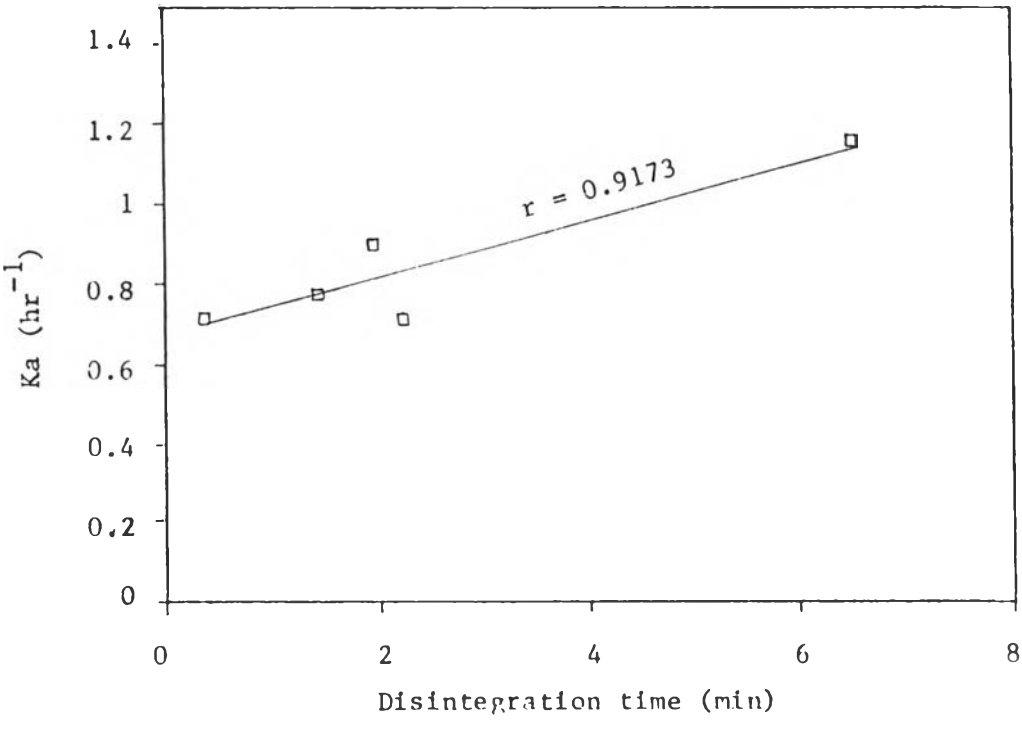

Figure 17 Correlation between disintegration time and Ka

Table 45 Correlation Disintegration Time (min) and Ka (hr^{-1}) of 4 Brands of Naproxen Tablets

Brand	Disintegration time (min)	Ka (hr^{-1})
B	1.44	0.77
C	0.36	0.72
D	2.26	0.72
E	2.00	0.90

correlation coefficient (r) = 0.3888

t-value = 0.597

$t_{0.05,\ 2}$ = 4.303

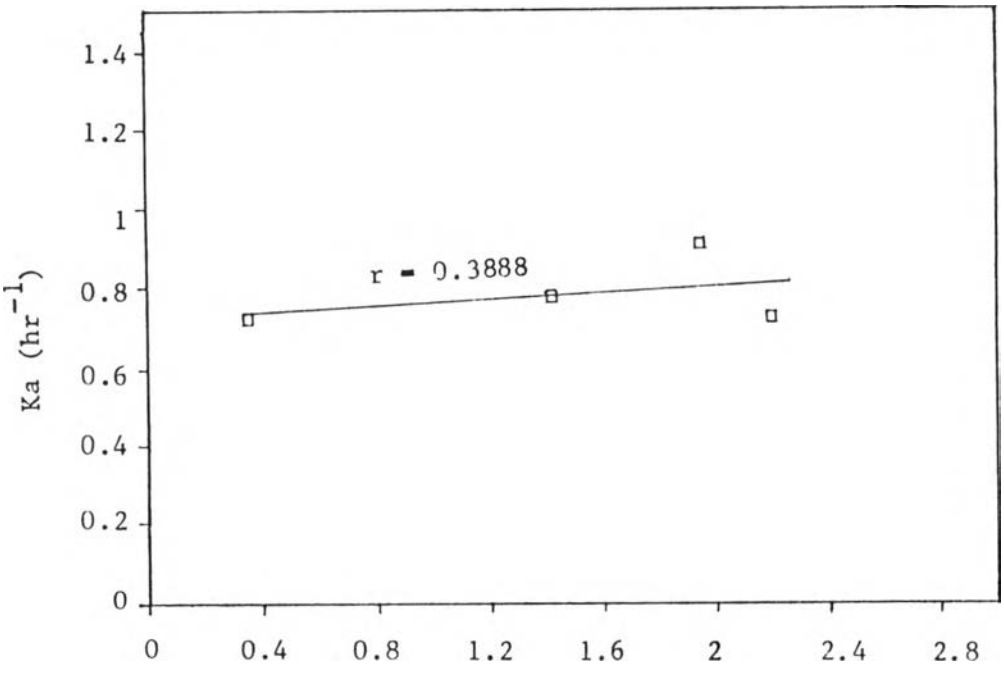

Figure 18 Correlation between disintegration time and Ka (When brand A was excluded)

Table 46 Correlation between Disintegration Time (min) and Cp_{max} (μg/ml) of 5 Brands of Naproxen Tablets.

Brand	Disintegration time (min)	Cp_{max} (μg/ml.)
A	6.39	30.08
B	1.44	27.36
C	0.36	26.67
D	2.26	24.51
E	2.00	30.18

correlation coefficient (r) = 0.5131

t-value = 1.035

$t_{0.05, 3}$ = 3.182

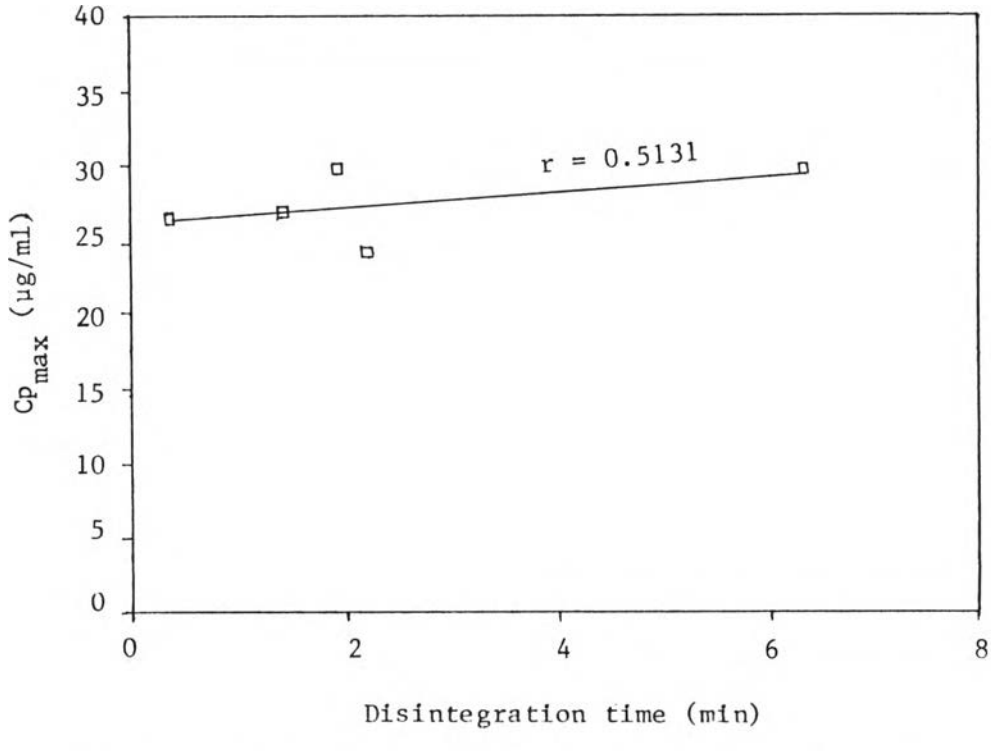

Figure 19 Correlation between disintegration time and Cp_{max}

Table 47 Correlation between Disintegration Time (min) and T_{max} (hr)) of 5 Brands of Naproxen Tablets

Brand	Disintegration time (min)	T_{max} (hr))
A	6.39	1.44
B	1.44	1.62
C	0.36	1.69
D	2.26	1.94
E	2.00	1.62

correlation coefficient (r) = -0.5559

t-value = -1.158

$t_{0.05, 3}$ = 3.182

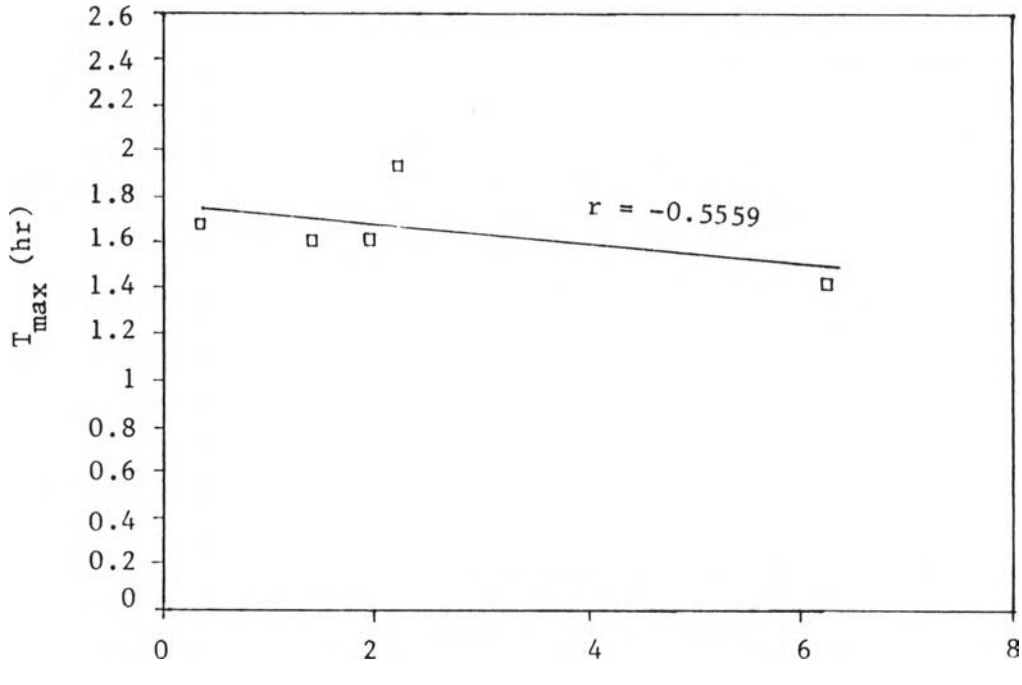

Figure 20 Correlation between disintegration time and T_{max}

Table 48 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Gastric Fluid (pH 1.2) and AUC_o^∞ (µg.hr/ml) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	AUC_o^∞ (µg.hr/ml)
A	1.39	462.72
B	2.03	473.89
C	1.15	483.32
D	0.55	522.49
E	1.00	489.74

correlation coefficient (r) = -0.7896

t-value = -2.228

$t_{0.05, 3}$ = 3.182

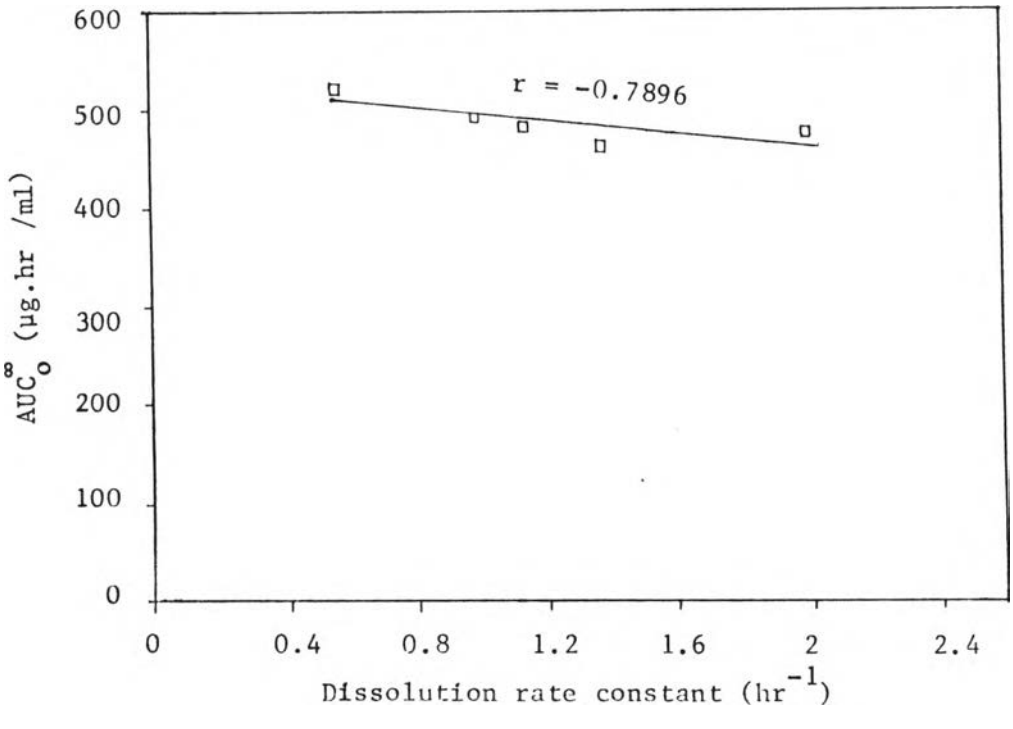

Figure 21 Correlation between dissolution rate constant in simulated gastric fluid and AUC_o^∞

Table 49 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Gastric Fluid (pH 1.2)) and Ka (hr^{-1}) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	Ka (hr^{-1})
A	1.39	1.15
B	2.03	0.77
C	1.15	0.72
D	0.55	0.72
E	1.00	0.90

correlation coefficient (r) = 0.1798

t-value = 0.316

$t_{0.05, 3}$ = 3.182

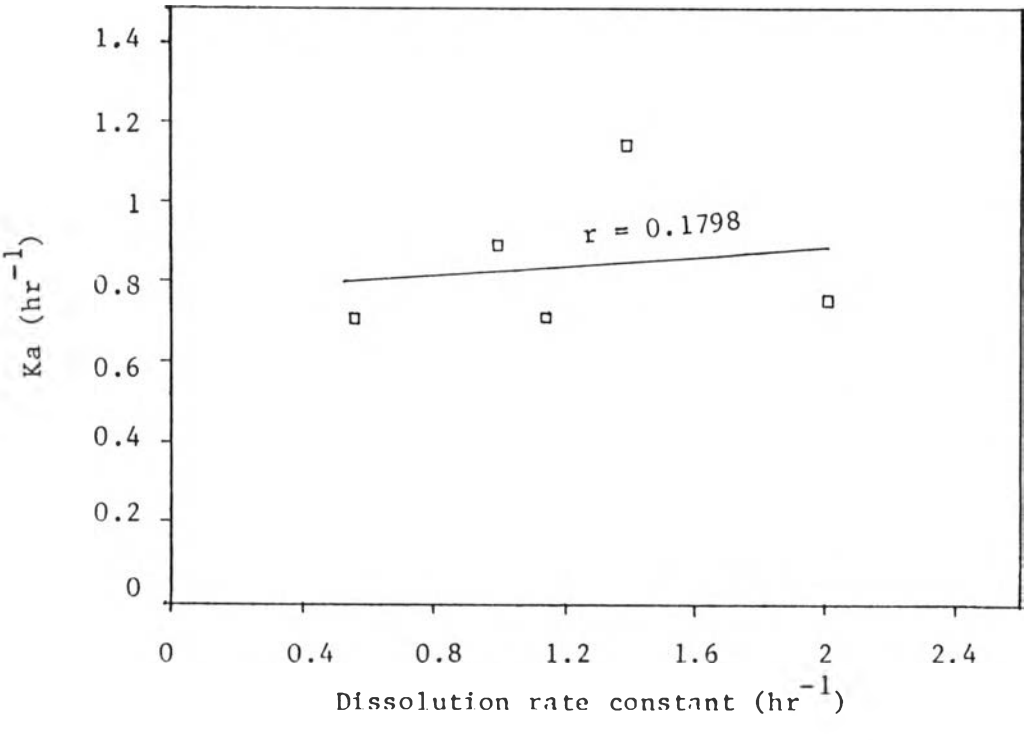

Figure 22 Correlation between dissolution rate constant in simulated gastric fluid and Ka.

Table 50 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Gastric Fluid (pH 1.2) and Cp_{max} (µg/ml) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	Cp_{max} (µg/ml)
A	1.39	30.08
B	2.03	27.36
C	1.15	26.67
D	0.55	24.51
E	1.00	30.18

correlation coefficient (r) = 0.3418

t-value = 0.630

$t_{0.05, 3}$ = 3.182

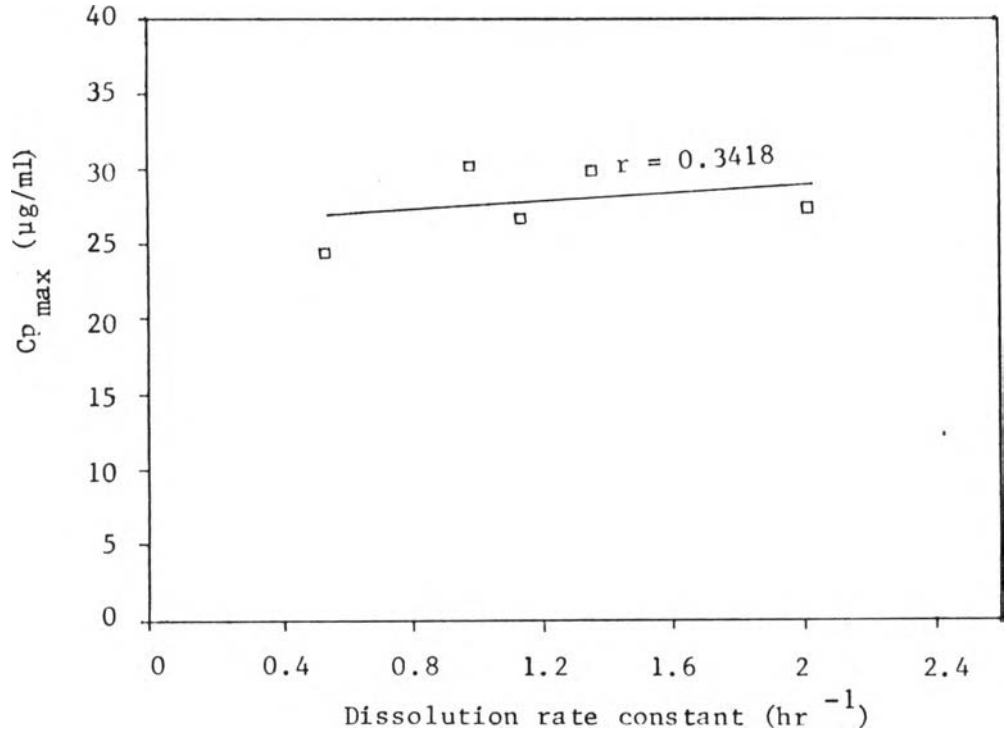

Figure 23 Correlation between dissolution rate constant in simulated gastric fluid and Cp_{max}

Table 51 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Gastric Fluid (pH 1.2) and T_{max} (hr) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	T_{max} (hr)
A	1.39	1.44
B	2.03	1.62
C	1.15	1.69
D	0.55	1.94
E	1.00	1.62

correlation coefficient (r) = -0.6361

t-value = -1.428

$t_{0.05, 3}$ = 3.182

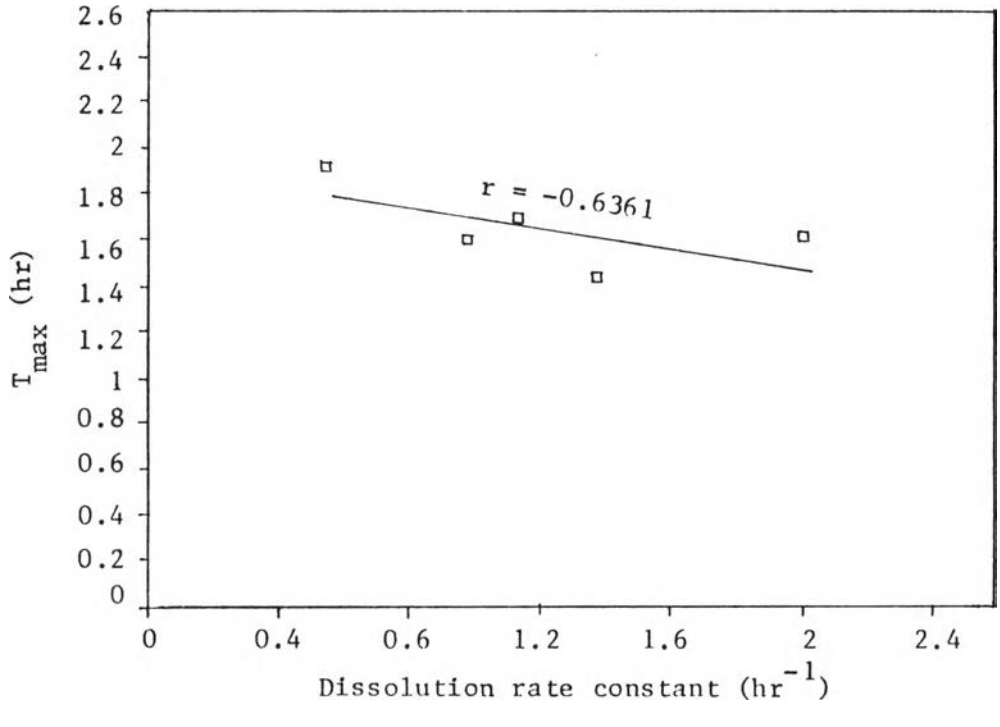

Figure 24 Correlation between dissolution rate constant in simulated gastric fluid and T_{max}

Table 52 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Intestinal Fluid (pH 7.5) and AUC_o^∞ (µg.hr/ml) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	AUC_o^∞ (µg.hr/ml)
A	6.22	462.72
B	2.29	473.89
C	6.22	483.32
D	0.76	522.49
E	4.51	489.74

correlation coefficient (r) = -0.6992

t-value = -1.694

$t_{0.05, 3}$ = 3.182

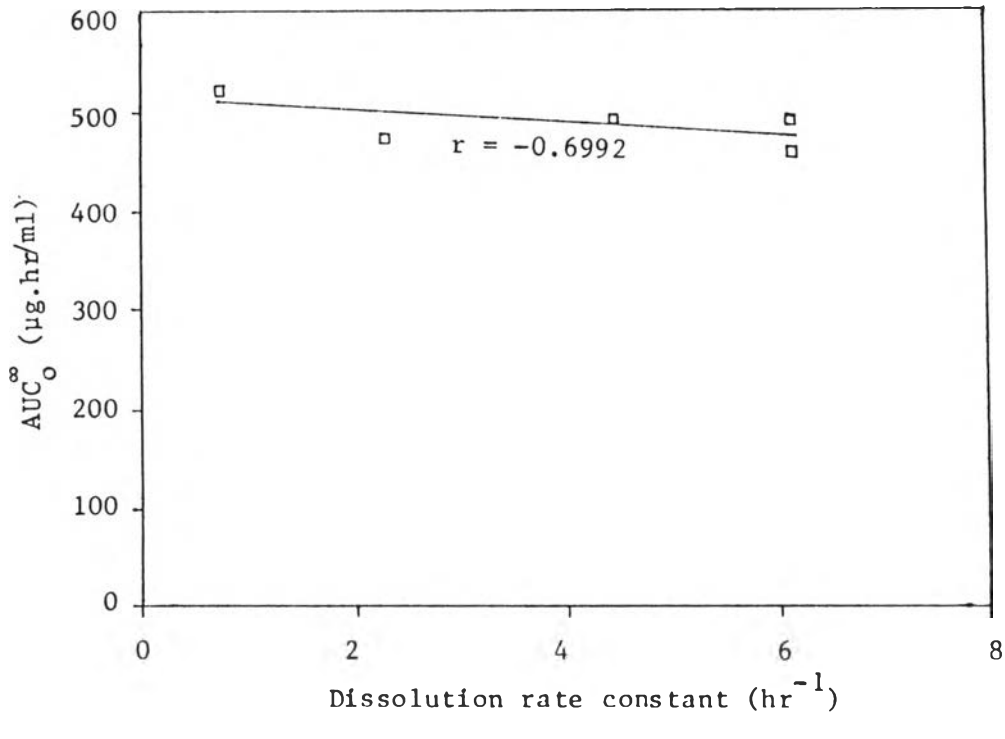

Figure 25 Correlation between dissolution rate constant in simulated intestinal fluid and AUC_o^∞

Table 53 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Intestinal Fluid (pH 7.5) and Ka (hr^{-1}) of 5 Brands of Naproxen Tablets

Brand	Dissolution Rate Constant (hr^{-1})	Ka (hr^{-1})
A	6.22	1.15
B	2.29	0.77
C	6.22	0.72
D	0.76	0.72
E	4.51	0.90

correlation coefficient (r) = 0.5437

t-value = 1.122

$t_{0.05, 3}$ = 3.182

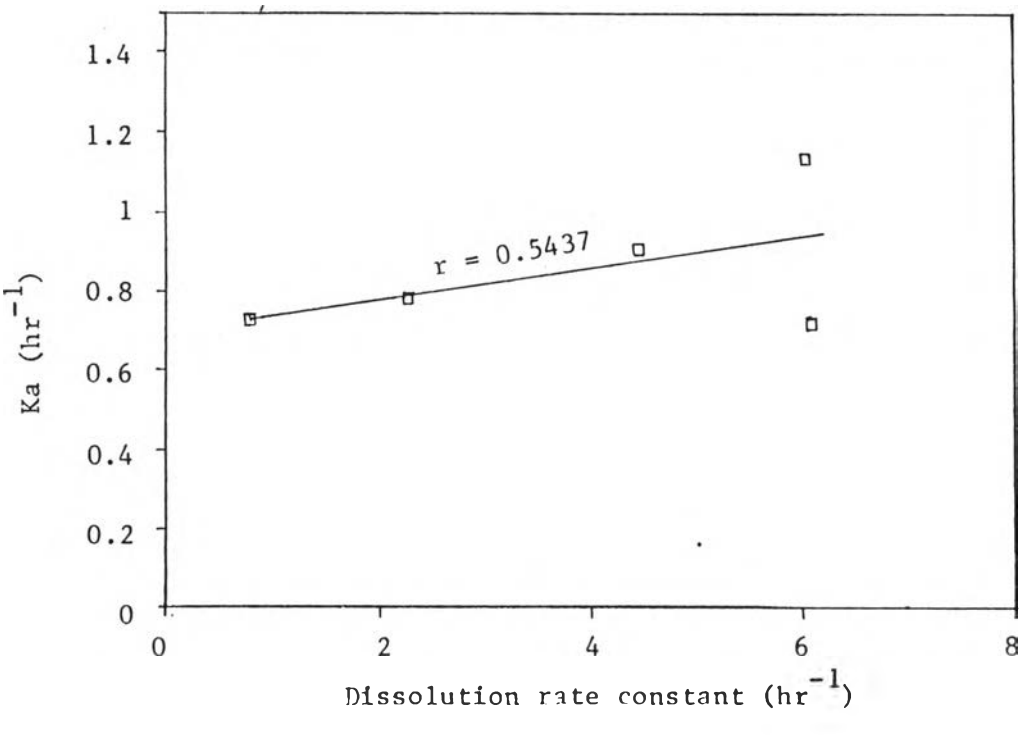

Figure 26 Correlation between dissolution rate constant in simulated intestinal fluid and Ka.

Table 54 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Intestinal Fluid (pH 7.5) and Cp_{max} (µg/ml) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant ($hr.^{-1}$)	Cp_{max} (µg/ml),
A	6.22	30.08
B	2.29	27.36
C=	6.22	26.67
D	0.76	24.51
E	4.51	30.18

correlation coefficient (r) = 0.6502

t-value = 1.482

$t_{0.05, 3}$ = 3.182

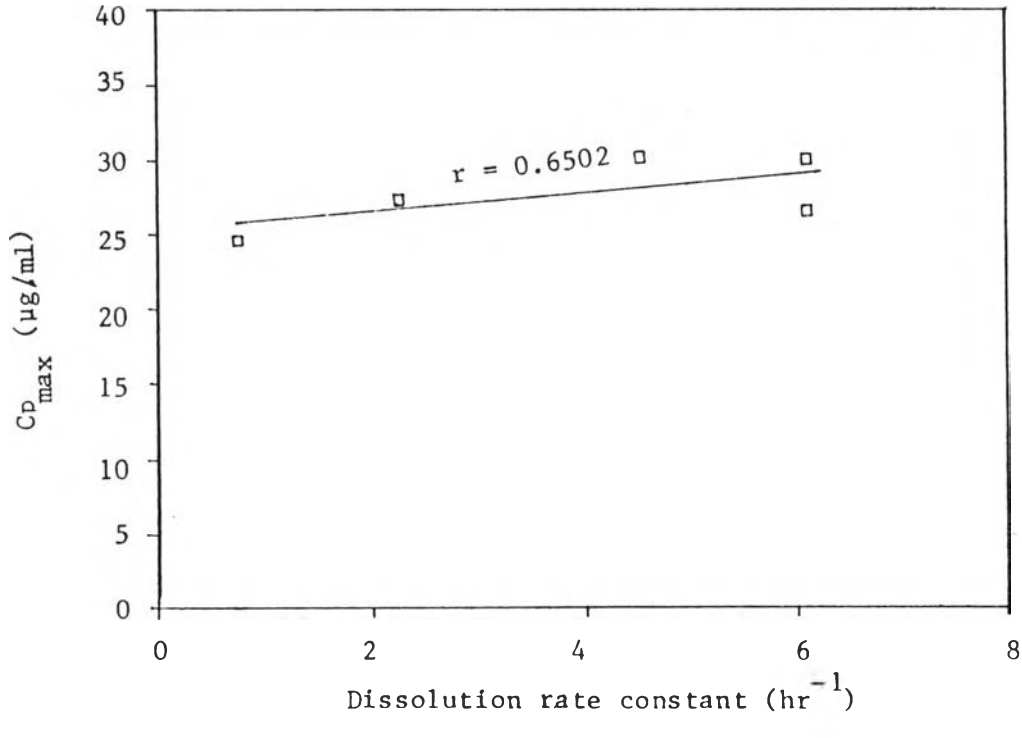

Figure 27 Correlation between dissolution rate constant in simulated intestinal fluid and Cp_{max}

Table 55 Correlation between Dissolution Rate Constant (hr^{-1}) in Simulated Intestinal Fluid (pH 7.5) and T_{max} (hr) of 5 Brands of Naproxen Tablets.

Brand	Dissolution Rate Constant (hr^{-1})	T_{max} (hr)
A	6.22	1.44
B	2.29	1.62
C	6.22	1.69
D	0.76	1.94
E	4.51	1.62

correlation coefficient (r) = -0.7298

t-value = -1.849

$t_{0.05, 3}$ = 3.182

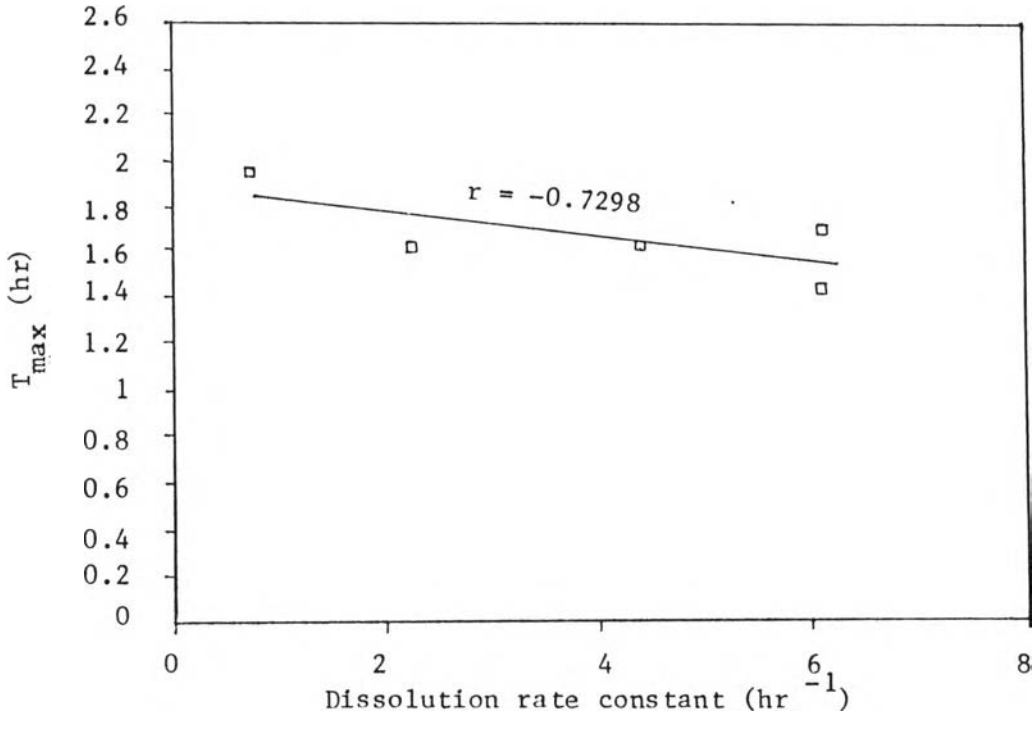

Figure 28 Correlation between dissolution rate constant in simulated simulated intestinal fluid and T_{max}

The correlation between in vitro and in vivo parameters in this study revealed that neither disintegration time nor dissolution rates in both simulated gastric fluid and simulated intestinal fluid had the relations to the in vivo parameters. This result was thus concluded that both the disintegration and the dissolution were not the rate-limited naproxen bioavailability.