CHAPTER III

RESULTS AND DISCUSSION

In Vitro Study

The original brand of paracetamol elixir and four brands of paracetamol suspensions were tested for content of active ingredient and were studied for the in vitro absorption through Sartorius Absorption Simulator SM16750. Table 2 summarizes the findings of the in vitro studies. Results indicated that the elixir was within the range of limit content ,95-105 %, existing standard in the B.P.1980(11) and all of the four brands of paracetamol suspensions met the U.S.P. XXI (9) requirement for the percent labeled amount, 90-110 %.

Of all the five products tested , one brand of paracetamol suspensions (Brand S3) was removed from the in vitro absorption study. The reason was that , its vehicle was hardly passed the filter making the circulation of the system erratic and inconsistent.

Figure 1 illustrates the increasing of average paracetamol concentrations in phase II of Brands E, S1, S2 and S4 in both simulated gastric and intestinal conditions. Tables 3-6 list results of the in vitro absorption studies for Brands E, S1, S2 and S4, respectively.

Table 2 In Vitro Study of the Paracetamol Elixir and the Paracetamol Suspensions.

Brand	Assayed , %of labeled amount	Diffusion Rate Constant (/hr)		Absorption Rate Constant (/hr)	
		Stomach	Intestine	Stomach	Intestine
E	100.70[a] (0.14)[b]	0.0624 (0.0020)	0.1508 (0.0008)	0.2503 (0.0085)	1.4003 (0.0079)
S1	100.56 (0.88)	0.0661 (0.0004)	0.1479 (0.0034)	0.2661 (0.0012)	1.3715 (0.0339)
S2	100.97 (0.79)	0.0679 (0.0009)	0.1421 (0.0085)	0.2739 (0.0037)	1.3130 (0.0848)
S3	99.54 (0.35)	-	-	-	-
S4	99.54 (0.13)	0.0630 (0.0015)	0.1523 (0.0009)	0.2527 (0.0065)	1.4152 (0.0090)

a. Mean , n=3 .
b. Standard error

Most drugs are absorbed from gastrointestinal tract by passive diffusion which absorption occurs more rapidly in small intestine than in stomach , and so does the paracetamol (17). In this study the diffusion rate constants, Kd and absorption rate constants, Ki were higher in intestinal experiments than those in gastric conditions. This is not surprising since environmental conditions in the intestine are more obviously suitable for absorption of any drugs than those in the stomach such as ; larger surface areas, etc. However, there were no statistically significant difference in Kd or Ki values obtained from stomach and intestine among Brands E, S1, S2 and S4 ($p>0.05$)(Tables 7-8).

Table 3 In Vitro Absorption Study of Paracetamol Elixir, Brand E Using Sartorius Absorption Simulator SM 16750.

Concentration of Paracetamol in phase II (mg%)										
	Absorption from Stomach					Absorption from Intestine				
Time(hr)	1	2	3	Mean	SE[b]	1	2	3	Mean	SE[b]
0.5	1.53	1.57	1.51	1.54	0.02	4.70	4.14	4.14	4.32	0.19
1.0	3.07	3.05	3.00	3.04	0.02	8.50	7.82	7.88	8.07	0.22
1.5	4.61	4.34	4.51	4.49	0.08	12.64	11.23	11.46	11.78	0.44
2.0	5.93	5.69	5.97	5.87	0.09	15.41	14.97	14.88	15.09	0.16
3.0	8.76	8.03	8.23	8.34	0.22	20.96	20.43	20.39	20.59	0.18
4.0	12.00	10.79	10.90	11.23	0.39	25.39	24.76	24.71	24.96	0.22
5.0	14.16	11.86	13.34	13.12	0.67	28.47	27.86	27.76	28.03	0.22
C_{io}[a](mg%)	61.88	55.61	56.22	57.90	2.00	60.72	59.20	59.09	59.67	0.53
Kd(/hr)	0.0596	0.0614	0.0662	0.0624	0.0020	0.1493	0.1517	0.1516	0.1508	0.0008
Ki(/hr)	0.2383	0.2459	0.2667	0.2503	0.0085	1.3846	1.4088	1.4076	1.4003	0.0079

a. The starting concentration

b. Standard error

Table 4 In Vitro Absorption Study of Paracetamol Suspension, Brand S1 Using Sartorius Absorption Simulator SM 16750.

	Concentration of Paracetamol in phase II (mg%)									
	Absorption from Stomach					Absorption from Intestine				
Time(hr)	1	2	3	Mean	SE[b]	1	2	3	Mean	SE[b]
0.5	1.41	1.37	1.58	1.45	0.06	3.91	3.97	3.47	3.78	0.16
1.0	3.05	2.89	3.35	3.10	0.13	7.51	7.61	7.55	7.56	0.03
1.5	4.68	4.36	5.14	4.73	0.22	10.77	11.29	11.29	11.12	0.18
2.0	6.15	5.78	6.55	6.16	0.22	13.92	14.48	14.66	14.35	0.22
3.0	9.33	8.21	9.36	8.97	0.38	19.79	19.56	20.11	19.82	0.16
4.0	11.56	10.88	11.65	11.36	0.24	23.88	23.76	24.85	24.17	0.35
5.0	14.16	13.15	14.91	14.07	0.51	27.30	27.26	27.41	27.32	0.04
Cio[a](mg%)	60.62	57.06	61.08	59.59	1.27	58.89	58.59	61.28	59.59	2.00
Kd(/hr)	0.0654	0.0644	0.0684	0.0661	0.0004	0.1413	0.1503	0.1523	0.1479	0.0034
Ki(/hr)	0.2632	0.2588	0.2762	0.2661	0.0012	1.3046	1.3951	1.4148	1.3715	0.0339

a. The starting concentration

b. Standard error

Table 5 In Vitro Absorption Study of Paracetamol Suspension, Brand S2 Using Sartorius Absorption Simulator SM 16750.

	Concentration of Paracetamol in phase II (mg%)									
	Absorption from Stomach					Absorption from Intestine				
Time(hr)	1	2	3	Mean	SE[b]	1	2	3	Mean	SE[b]
0.5	1.66	1.65	1.80	1.70	0.05	4.39	4.46	4.54	4.47	0.05
1.0	3.41	3.32	3.56	3.43	0.07	8.64	8.51	7.65	8.27	0.31
1.5	5.05	4.99	5.14	5.06	0.04	12.42	12.06	10.57	11.68	0.57
2.0	6.55	6.39	6.58	6.51	0.06	16.13	15.50	13.25	14.96	0.87
3.0	8.65	8.89	8.93	8.82	0.09	20.91	20.30	18.60	19.94	0.69
4.0	10.96	10.88	10.66	10.83	0.09	24.86	25.71	21.29	23.95	1.36
5.0	13.96	14.37	12.83	13.72	0.46	28.42	29.49	24.24	27.38	1.60
Cio(mg%)[a]	58.76	60.16	58.49	59.13	0.52	60.50	59.63	57.81	59.31	0.79
Kd(/hr)	0.0693	0.0664	0.0680	0.0679	0.0009	0.1536	0.1256	0.1471	0.1421	0.0085
Ki(/hr)	0.2801	0.2673	0.2741	0.2739	0.0037	1.4284	1.1477	1.3629	1.3130	0.0848

a. The starting concentration

b. Standard error

Table 6 In Vitro Absorption Study of Paracetamol Suspension, Brand S4 Using Sartorius Absorption Simulator SM 16750.

	Concentration of Paracetamol in phase II (mg%)									
	Absorption from Stomach					Absorption from Intestine				
Time(hr)	1	2	3	Mean	SE[b]	1	2	3	Mean	SE[b]
0.5	1.54	1.54	1.60	1.56	0.02	4.27	4.50	4.39	4.38	0.07
1.0	3.21	2.94	3.46	3.21	0.15	8.08	8.18	8.60	8.29	0.16
1.5	4.81	4.40	4.66	4.62	0.12	11.90	11.59	12.10	11.86	0.15
2.0	6.32	5.66	6.07	6.02	0.19	15.36	14.92	15.19	15.16	0.13
3.0	9.11	8.11	8.62	8.61	0.29	20.59	19.88	20.11	20.19	0.21
4.0	11.68	9.88	10.98	10.85	0.52	25.39	23.86	24.66	24.64	0.44
5.0	13.91	12.33	13.38	13.21	0.46	28.57	27.31	28.05	27.98	0.37
Cio(mg%)[a]	60.64	57.06	58.26	58.65	1.05	59.37	57.63	58.66	58.55	0.50
Kd(/hr)	0.0657	0.0605	0.0627	0.0630	0.0015	0.1505	0.1531	0.1533	0.1523	0.0009
Ki(/hr)	0.2646	0.2422	0.2515	0.2527	0.0065	1.3973	1.4230	1.4253	1.4152	0.0090

a. The starting concentration

b. Standard error

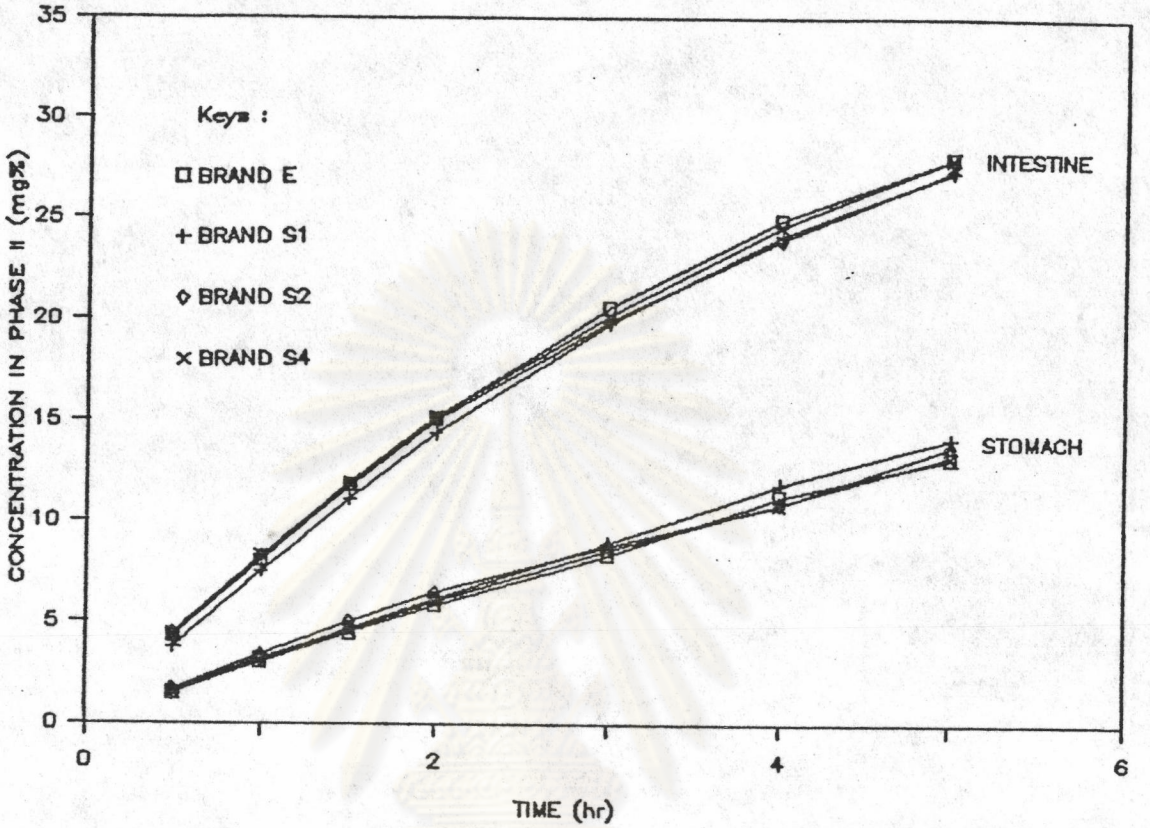


Figure 1 In vitro representative increasing of mean paracetamol concentrations in phase II after 60 mg dose of paracetamol from paracetamol elixir and paracetamol suspensions using the Sartorius Absorption Simulator SM16750.

Table 7 Analysis of Variance for In Vitro Absorption Rate Constants ,Ki of the Paracetamol Elixir (Brand E) and Paracetamol Suspensions(Brands S1,S2 and S4).

Parameters	Source of Variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Ki (Stomach)	Among groups	3	0.0039	0.0013	1.00
	Within groups	8	0.0105	0.0013	
	Total	11	0.0144		
Ki (Intestine)	Among groups	3	0.0183	0.0061	0.96
	Within groups	8	0.0509	0.0064	
	Total	11	0.0692		

$$F^{e}_{0.95(4,35)} = 2.65$$

[a] Degree of freedom

[b] Sum of square

[c] Mean square

[d] Variation ratio

[e] F obtained from the table

Table 8 Comparison of In Vitro Absorption Rate Constants, Ki of Commercial Brands of Paracetamol Suspensions with Paracetamol Elixir, Brand E and the Original Brand of Paracetamol Suspension, Brand S1 Using t-test.

Parameters	Comparison with	t (Calculated)	
		Brand E	Brand S1
Ki (Stomach)	Brand S1	0.6819	-
	Brand S2	0.8257	0.7664
	Brand S4	-0.9794	-1.0106
Ki (Intestine)	Brand S1	0.6759	-
	Brand S2	0.8374	0.5230
	Brand S4	-1.0167	-1.0166

$t_{(0.05,14)} = 2.1448^{a}$

[a] A t-value from the table

In Vivo Study

Standard curve of paracetamol in pooled urine was constructed to determine concentrations of total paracetamol excreted into the urine (Appendix D, Table 27, Figure 13). Since very low concentrations in urine samples at the time 32 hour postadministration, some of the results were determined by extrapolation of the standard curve . Table 9 illustrates the amount of drug excreted into the urine for each brand as a function of time .

The cumulative amount of drug excreted into the urine is directly related to the total amount of drug absorbed. Table 10 presents the cumulative amount of drug excreted into the urine as a function of time for Brands E, S1, S2, S3 and S4 (Figure 2). In this study , the cumulative amount of drug excreted into the urine at the time 32 hour postdose was read as the maximum cumulative amount of drug excreted into the urine, $[Du]_{\infty}$ (Table 11). No statistically significant difference in the maximum cumulative amount of drug excreted into the urine among the five brands was observed ($p>0.05$) (Tables 12-13). The total paracetamol recovery studied here was about 70-75 % of the dose. The value is less than those of approximately 80-90 % reported by Miller, R.P. et al (18) and Holt, S. et al (19). However, the total recovery of paracetamol in urine of about 67-80 % was published by McGilveray,I.J. and Mattok,G.L.(20).

Table 9 Individual Amount of Paracetamol Excreted into the Urine from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol Elixir and Paracetamol Suspensions.

Brand	Time(hr)	Amount of Paracetamol Excreted into the Urine (mg)									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[b]
E	0.5	5.96	8.17	7.78	7.77	9.88	10.72	5.79	5.68	7.72	0.67
	1.0	26.78	27.49	32.26	19.60	29.00	20.12	23.55	21.84	25.08	1.60
	1.5	29.61	28.07	28.56	29.62	31.24	29.34	23.46	27.53	28.43	0.81
	2.0	30.89	34.08	36.85	35.28	32.15	33.04	30.12	29.85	32.78	0.89
	3.0	53.96	66.27	70.48	65.87	61.51	55.76	47.48	53.31	59.33	2.80
	4.0	52.64	60.03	66.40	50.16	52.48	60.11	41.50	55.61	54.87	2.67
	6.0	73.03	78.59	79.03	88.05	82.15	72.55	78.53	87.17	79.89	2.03
	8.0	46.11	63.03	44.38	40.48	54.18	44.14	54.55	57.66	50.57	2.79
	12.0	43.14	59.37	41.52	51.35	65.44	69.88	62.55	55.73	56.12	3.62
	16.0	18.87	22.87	30.58	22.37	36.80	27.35	23.29	25.59	25.96	1.99
	24.0	14.20[a]	14.65	19.80	26.76[a]	27.19[a]	20.41[a]	21.03[a]	18.95[a]	20.37	1.69
	32.0	7.67[a]	9.44	6.66	7.93[a]	9.28[a]	9.53[a]	8.61[a]	12.65[a]	8.97	0.63
S1	0.5	6.25	7.09	5.48	3.70	6.22	3.89	4.80	4.94	5.30	0.42
	1.0	28.00	19.34	20.98	18.29	29.07	12.94	13.54	19.46	20.20	2.08
	1.5	31.76	24.62	29.67	27.46	27.70	26.81	24.03	24.72	27.10	0.95
	2.0	31.65	26.83	31.87	32.72	32.88	27.53	24.35	25.74	29.20	1.22
	3.0	57.30	57.07	65.67	59.63	59.81	47.87	46.88	56.98	56.40	2.21
	4.0	49.53	54.69	53.33	48.92	54.79	49.62	49.48	46.94	50.91	1.04
	6.0	73.63	77.29	65.59	77.77	83.41	71.79	67.43	75.15	74.01	2.04
	8.0	41.35	65.61	46.66	50.56	57.18	61.19	47.94	56.00	53.31	2.86
	12.0	38.15	64.14	38.85	66.98	64.17	58.03	54.58	59.28	55.52	3.97
	16.0	16.77	28.17	15.73	34.05	32.82	27.37	22.20	26.12	25.40	2.39
	24.0	13.22[a]	22.17	11.54	33.65[a]	32.03[a]	18.22	18.05	23.96	21.61	2.85
	32.0	12.16[a]	10.88	7.44	13.38[a]	13.14[a]	14.58	11.09	12.84	11.94	0.77

a. Determined by extrapolation of the standard curve.

b. Standard error

Table 9 (continued)

Brand	Time(hr)	Amount of Paracetamol Excreted into the Urine (mg)									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[b]
S2	0.5	8.53	5.00	2.89	7.80	5.55	8.41	6.49	2.71	5.92	0.82
	1.0	25.33	23.04	17.68	26.34	22.74	26.04	10.36	10.27	20.22	2.37
	1.5	27.73	29.26	42.23	32.21	32.51	29.94	17.43	20.54	28.98	2.69
	2.0	33.90	31.65	38.34	38.08	32.74	29.33	16.63	26.43	30.89	2.49
	3.0	74.41	59.81	72.72	70.11	62.42	59.43	38.98	48.13	60.75	4.34
	4.0	60.43	57.78	67.98	60.69	54.40	57.46	37.78	53.54	56.26	3.08
	6.0	88.27	94.68	92.31	93.61	85.71	89.55	59.48	91.95	86.94	4.06
	8.0	50.59	60.11	55.24	53.34	59.87	64.62	44.57	53.76	55.26	2.21
	12.0	50.19	65.11	47.86	64.75	63.30	60.49	46.72	66.13	58.07	2.95
	16.0	18.08	21.28	18.21	26.67	36.56	31.59	21.76	27.36	25.19	2.33
	24.0	18.91	21.66	18.35	27.34	34.82	21.78	15.06	20.42	22.29	2.18
	32.0	7.67[a]	7.93[a]	10.21	13.35[a]	5.96	4.80[a]	5.62	10.60	8.27	1.03
S3	0.5	8.26	8.64	7.61	7.21	9.99	4.49	2.20	10.01	7.30	0.96
	1.0	23.52	22.34	24.40	22.74	26.09	21.96	10.72	27.94	22.46	1.82
	1.5	27.51	25.24	26.98	29.36	31.01	27.96	18.41	32.06	27.32	1.49
	2.0	30.11	27.21	29.15	28.56	30.97	27.56	24.62	30.30	28.56	0.73
	3.0	50.37	61.07	59.61	63.49	61.50	48.61	43.94	59.75	56.04	2.57
	4.0	40.95	62.31	49.68	60.53	51.80	46.84	37.60	51.49	50.15	3.03
	6.0	80.24	96.42	76.57	82.70	70.90	68.16	62.35	64.32	75.21	3.98
	8.0	41.48	48.27	43.07	56.17	53.57	50.48	44.11	57.81	49.37	2.18
	12.0	42.33	62.58	42.99	57.87	60.85	66.02	64.14	57.46	56.78	3.25
	16.0	18.83	20.85	18.73	23.84	26.55	35.33	27.84	26.37	24.79	1.96
	24.0	16.10	18.61[a]	14.64[a]	26.67[a]	27.32[a]	17.06[a]	25.98	20.11	20.81	1.81
	32.0	11.21[a]	10.11[a]	5.26	20.48	16.95[a]	5.82	6.53	6.80[a]	10.39	1.98

a. Determined by extrapolation of the standard curve.

b. Standard error

Table 9 (continued)

Brand	Time(hr)	Amount of Paracetamol Excreted into the Urine (mg)									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[b]
	0.5	7.23	3.82	5.77	2.77	5.58	8.25	2.29	7.79	5.44	0.81
	1.0	29.80	19.63	24.27	12.67	19.85	22.91	14.04	24.23	20.92	2.00
	1.5	30.06	26.47	29.87	20.68	29.59	29.49	16.59	31.62	26.80	1.89
	2.0	28.36	26.77	30.59	29.67	36.56	27.79	19.31	29.02	28.51	1.68
	3.0	54.02	52.58	59.10	51.16	67.36	48.97	37.71	58.24	53.64	3.05
S4	4.0	49.52	52.68	48.18	50.37	58.18	47.57	36.53	55.70	49.84	2.30
	6.0	73.41	78.52	75.56	74.30	91.00	89.74	54.76	90.50	78.47	4.31
	8.0	41.24	53.53	37.73	61.22	56.59	53.42	40.54	57.23	50.19	3.17
	12.0	42.03	55.23	38.57	57.26	46.44	63.27	54.18	64.10	52.64	3.34
	16.0	23.12	31.44	13.00	28.89	26.52	29.52	25.16	24.68	25.29	2.01
	24.0	16.51	20.30[a]	12.00[a]	27.16[a]	23.26	25.67[a]	23.94	24.32[a]	21.64	1.81
	32.0	9.91	5.70[a]	4.34[a]	13.06[a]	11.99	7.10[a]	6.16	15.16[a]	9.18	1.39

a. Determined by extrapolation of the standard curve.

b. Standard error

Table 10 Individual Cumulative Amount of Paracetamol Excreted into the Urine from 8 Subjects Following Oral Single Dose of Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Brand	Time(hr)	Cumulative Amount of Paracetamol Excreted into the Urine									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[a]
E	0.5	5.96	8.17	7.78	7.77	9.88	10.72	5.79	5.68	7.72	0.67
	1.0	32.74	35.66	40.04	27.36	38.88	30.83	29.34	27.53	32.80	1.75
	1.5	62.35	63.73	68.60	56.98	70.12	60.17	52.80	55.06	61.23	2.19
	2.0	93.24	97.81	105.46	92.26	102.27	93.21	82.92	84.91	94.01	2.75
	3.0	147.21	164.08	175.94	158.13	163.78	148.98	130.40	138.22	153.34	5.29
	4.0	199.84	224.11	242.34	208.29	216.26	209.08	171.90	193.83	208.21	7.41
	6.0	272.88	302.70	321.37	296.34	298.41	281.64	250.43	281.01	288.10	7.60
	8.0	318.99	365.73	365.76	336.82	352.59	325.78	304.98	338.66	338.66	7.74
	12.0	362.13	425.10	407.27	388.17	418.03	395.66	367.53	394.39	394.78	7.87
	16.0	381.00	447.97	437.85	410.54	454.83	423.01	390.83	419.98	420.75	9.24
	24.0	395.20	462.61	457.65	437.30	482.01	443.41	411.85	438.94	441.12	9.82
	32.0	402.87	472.05	464.31	445.23	491.30	452.94	420.46	451.58	450.09	9.93
S1	0.5	6.25	7.09	5.48	3.70	6.22	3.89	4.80	4.94	5.30	0.42
	1.0	34.25	26.43	26.46	21.99	35.29	16.83	18.34	24.40	25.50	2.37
	1.5	66.01	51.05	56.12	49.45	62.99	43.64	42.38	49.13	52.59	3.02
	2.0	97.66	77.88	87.99	82.17	95.87	71.16	66.72	74.87	81.79	3.99
	3.0	154.96	134.95	153.66	141.80	155.68	119.04	113.60	131.84	138.19	5.77
	4.0	204.49	189.64	206.98	190.72	210.47	168.65	163.08	178.79	189.10	6.29
	6.0	278.11	266.93	272.58	268.49	293.88	240.45	230.51	253.94	263.11	7.28
	8.0	319.46	332.54	319.24	319.05	351.06	301.64	278.46	309.94	316.42	7.54
	12.0	357.61	396.68	358.09	386.03	415.22	359.67	333.04	369.22	371.94	9.21
	16.0	374.37	424.86	373.82	420.08	448.04	387.03	355.24	395.34	397.35	11.03
	24.0	387.60	447.02	385.36	453.73	480.08	405.26	373.30	419.30	418.95	13.44
	32.0	399.75	457.91	392.81	467.11	493.21	419.84	384.39	432.14	430.89	13.78

a. Standard error

Table 10 (continued)

Brand	Time(hr)	Cumulative Amount of Paracetamol Excreted into the Urine									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[a]
S2	0.5	8.43	5.00	2.89	7.80	5.55	8.41	6.49	2.71	5.91	0.81
	1.0	33.75	28.04	20.57	34.14	28.29	34.44	16.85	12.98	26.13	2.96
	1.5	61.48	57.29	62.80	66.35	60.80	64.39	34.28	33.53	55.12	4.72
	2.0	95.38	88.94	101.15	104.43	93.54	93.72	56.45	59.96	86.70	6.45
	3.0	159.16	148.75	173.86	174.55	155.96	145.27	95.44	108.09	145.13	10.23
	4.0	219.59	206.53	241.85	235.24	210.36	199.55	133.22	161.63	201.00	12.99
	6.0	307.86	301.21	334.16	328.85	296.07	289.10	192.70	253.58	287.94	16.20
	8.0	358.45	361.31	389.40	382.19	355.94	353.72	237.27	307.34	343.20	17.42
	12.0	408.64	426.42	437.25	446.94	419.24	414.20	283.99	373.48	401.27	18.46
	16.0	426.72	447.71	455.47	473.61	455.80	445.79	305.75	400.84	426.46	18.89
	24.0	445.62	469.37	473.82	500.96	490.62	467.58	320.81	421.26	448.75	20.28
	32.0	453.30	477.30	484.03	514.31	496.58	472.37	326.43	431.86	457.02	20.67
S3	0.5	8.26	8.64	7.61	7.21	9.99	4.49	2.20	10.01	7.30	0.96
	1.0	32.16	30.98	32.01	29.94	36.08	26.45	12.92	37.95	29.81	2.72
	1.5	59.67	56.22	58.99	59.31	67.09	54.41	31.34	70.01	57.13	4.13
	2.0	89.79	83.43	88.14	87.86	98.06	81.97	55.96	100.30	85.69	4.81
	3.0	140.16	144.50	147.74	151.35	159.56	130.59	99.90	160.05	141.73	6.90
	4.0	181.11	206.81	197.42	211.88	211.36	177.43	137.50	211.54	191.88	9.16
	6.0	261.35	303.23	274.00	294.59	282.27	245.59	199.86	275.86	267.09	11.52
	8.0	302.83	351.50	317.07	350.75	335.84	296.07	243.97	333.67	316.46	12.63
	12.0	345.17	414.08	360.06	408.62	396.69	362.09	308.11	391.13	373.24	12.76
	16.0	363.99	434.92	378.79	432.46	423.23	397.42	335.95	417.50	398.03	12.64
	24.0	380.10	453.53	393.43	459.14	450.55	414.48	361.93	437.61	418.85	13.09
	32.0	391.31	463.64	398.68	479.61	467.50	420.30	368.46	444.41	429.24	14.37

a. Standard error

Table 10 (continued)

Brand	Time(hr)	Cumulative Amount of Paracetamol Excreted into the Urine									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[a]
S4	0.5	7.23	3.82	5.77	2.77	5.58	8.25	8.25	7.79	6.18	0.73
	1.0	28.90	23.46	30.04	15.43	25.43	31.16	16.33	32.02	25.35	2.30
	1.5	54.05	49.93	59.91	36.11	55.02	60.65	32.92	63.64	51.53	4.02
	2.0	82.41	76.70	90.51	65.79	91.58	88.44	52.23	92.66	80.04	5.12
	3.0	136.43	129.28	149.60	116.94	158.94	137.40	89.94	150.90	133.68	7.82
	4.0	185.95	181.97	197.78	167.31	217.11	184.98	126.47	206.60	183.52	9.81
	6.0	259.36	260.48	273.34	241.61	308.11	274.72	181.23	297.10	261.99	13.76
	8.0	300.61	314.01	311.07	302.82	364.71	328.14	221.76	354.33	312.18	15.35
	12.0	342.64	369.24	349.64	360.08	411.15	391.41	275.95	418.43	364.82	16.03
	16.0	365.76	400.68	362.64	388.97	437.67	420.94	301.11	443.11	390.11	16.58
	24.0	382.27	420.98	374.64	416.13	460.93	446.60	325.05	467.42	411.75	17.22
	32.0	392.18	426.68	378.98	429.19	472.91	453.70	331.21	482.59	420.93	18.08

a. Standard error

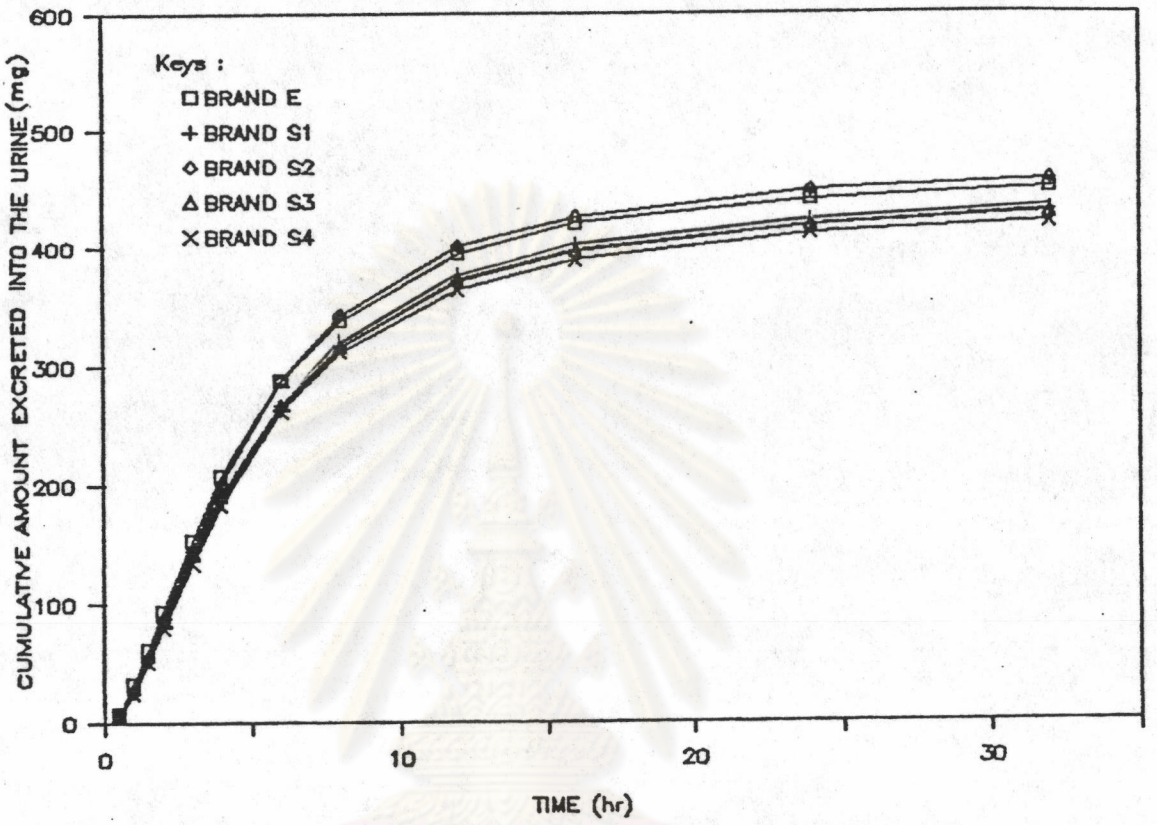


Figure 2 Mean cumulative amount of paracetamol excreted into the urine from 8 subjects following oral single dose of 600 mg paracetamol from paracetamol elixir and paracetamol suspensions.

Table 11 Individual Maximum Cumulative Amount of Paracetamol Excreted into the Urine ($[Du]_{\infty}$) from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Maximum Cumulative Amount of Paracetamol Excreted into the Urine (mg)				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	402.87	399.75	453.30	391.31	392.18
2	472.05	457.91	477.30	463.64	426.68
3	464.31	392.81	484.03	398.69	378.98
4	445.23	467.11	514.31	479.61	429.19
5	491.30	493.21	496.58	467.50	472.91
6	452.94	419.84	472.37	420.30	453.70
7	420.46	384.39	326.43	368.46	331.21
8	451.58	432.14	431.86	444.41	482.59
Mean	450.09	430.89	457.02	429.24	420.93
SE[a]	9.93	13.78	20.67	14.37	18.08

[a] Standard error

Table 12 Analysis of Variance for Maximum Amount of Paracetamol Excreted into the Urine, $[Du]_\infty$ of Paracetamol Elixir (Brand E) and Paracetamol Suspensions (Brands S1,S2,S3 and S4).

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	7408.28	1852.07	0.93
Within groups	35	69956.80	1998.77	
Total	39	77365.18		

$$F^{e}_{0.95(4,35)} = 2.65$$

a Degree of freedom

b Sum of square

c Mean square

d Variation ratio

e F obtained from the table

Table 13 Comparison of Maximum Amount of Paracetamol Excreted into the Urine, $[Du]_{\infty}$ of Commercial Brands of Paracetamol Suspensions with Paracetamol Elixir, Brand E and the Original Brand of Paracetamol Suspension, Brand S1 Using t-test

Comparison with	t (Calculated)	
	Brand E	Brand S1
Brand S1	1.0573	-
Brand S2	-0.0827	-0.9839
Brand S3	1.1167	0.0777
Brand S4	1.3221	0.4099

$t_{(0.05,14)} = 2.1448^{a}$

[a] A t-value from the table

The rate of drug excretion, dDu/dt could not be determined experimentally for any given instance. Therefore, an average urinary excretion was calculated for the collection period. The rate of drug excretion, as a function of time , of Brands E, S1, S2, S3 and S4 were shown in Table 14. The average rate of drug excretion of each brand was plotted on a semilogarithmic scale against the time at midpoint of the collection period (Figure 3).

Since most drugs are eliminated by a first order process , the rate of drug excretion is dependent on the concentration of drug in plasma (14). Thus, the maximum rates of drug excretion for the five brands or (dDu/dt)max , as shown in Table 15, were analyzed. The analysis of variance indicated no statistically significant difference among the five brands ($p>0.05$) (Table 16). Whereas, the t-test showed statistically significant difference in the maximum rate of drug excretion between Brand E and Brand S3 ($p<0.05$) (Table 17).

According to the semilogarithmic plots of the individual rate of paracetamol excreted into the urine-time data for eight subjects, the data were well described by a mean of one compartment open model with first-order absorption and elimination. The individual excretion data was estimated for the pharmacokinetic parameters utilizing CSTRIP computer program.

Table 14 Individual Rate of Paracetamol Excretion from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol Elixir and Paracetamol Suspensions.

Brand	Tmid(hr)[a]	Rate of Paracetamol Excretion (mg/hr)									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[b]
E	0.25	11.93	16.34	15.57	15.53	19.76	21.43	11.58	11.37	15.44	1.33
	0.75	53.56	54.97	64.52	39.20	58.00	40.23	47.10	43.69	50.16	3.20
	1.25	59.22	56.14	57.12	59.23	62.47	58.67	46.93	55.06	56.86	1.63
	1.75	61.78	68.16	73.71	70.56	64.31	66.08	60.24	59.70	65.57	1.78
	2.50	53.96	66.27	70.48	65.87	61.51	55.76	47.48	53.31	59.33	2.80
	3.50	52.64	60.03	66.40	50.16	52.48	60.11	41.50	55.61	54.87	2.67
	5.00	36.52	39.30	39.52	44.02	41.08	36.28	39.26	43.59	39.94	1.01
	7.00	23.06	31.51	22.19	20.24	27.09	22.07	27.28	28.83	25.28	1.39
	10.00	10.79	14.84	10.38	12.84	16.36	17.47	15.64	13.93	14.03	0.90
	14.00	4.72	5.72	7.65	5.59	9.20	6.84	5.82	6.40	6.49	0.50
	20.00	1.78	1.83	2.47	3.34	3.40	2.55	2.63	2.37	2.55	0.21
	28.00	0.96	1.18	0.83	0.99	1.16	1.19	1.08	1.58	1.12	0.08
S1	0.25	12.50	14.19	10.95	7.40	12.44	7.77	9.59	9.74	10.57	0.84
	0.75	56.00	38.67	41.96	36.58	58.15	25.89	27.09	39.51	40.48	4.16
	1.25	63.52	49.23	59.33	54.91	55.40	53.61	48.07	48.21	54.04	1.95
	1.75	63.30	53.66	63.73	65.45	65.76	55.06	48.69	51.96	58.45	2.41
	2.50	57.30	57.07	65.67	59.63	59.81	47.87	46.88	56.08	56.29	2.21
	3.50	49.53	54.69	53.33	48.92	54.79	49.62	49.48	46.69	50.88	1.06
	5.00	36.81	38.64	32.80	38.89	41.70	35.90	33.72	37.58	37.00	1.02
	7.00	20.67	32.81	23.33	25.28	28.59	30.60	23.97	27.79	26.63	1.43
	10.00	9.54	16.03	9.71	16.75	16.04	14.51	13.65	14.29	13.81	0.98
	14.00	4.19	7.04	3.93	8.51	8.21	6.84	5.55	6.32	6.32	0.60
	20.00	1.65	2.77	1.44	4.21	4.00	2.28	2.26	2.97	2.70	0.36
	28.00	1.52	1.36	0.93	1.67	1.64	1.82	1.39	1.54	1.48	0.10

a. Time at midpoint of the collection period

b. Standard error

Table 14 (continued)

Brand	Tmid(hr)[a]	Rate of Paracetamol Excretion (mg/hr)									
		Subject No.								Mean	SE[b]
		1	2	3	4	5	6	7	8		
S2	0.25	17.06	10.00	5.78	15.60	11.10	16.81	12.98	5.43	11.84	1.63
	0.75	50.65	46.08	35.37	52.68	45.48	52.07	20.73	20.53	40.45	4.74
	1.25	55.45	58.51	84.46	64.41	65.02	59.89	34.86	41.09	57.96	5.38
	1.75	67.80	63.30	76.68	76.17	65.48	58.66	44.34	52.86	63.16	3.92
	2.50	63.78	59.81	72.72	70.11	62.42	51.55	38.98	48.13	58.44	4.05
	3.50	60.43	57.78	67.98	60.69	54.40	54.29	37.78	53.54	55.86	3.08
	5.00	44.13	47.34	46.16	46.81	42.85	44.77	29.74	45.98	43.47	2.09
	7.00	25.29	30.05	27.62	26.67	29.93	32.31	22.28	26.88	27.63	1.11
	10.00	12.55	16.28	11.96	16.19	15.83	15.12	11.68	16.53	14.52	0.74
	14.00	4.52	5.32	4.55	6.67	9.14	7.90	5.44	6.84	6.30	0.58
	20.00	2.22	2.71	2.29	3.42	4.35	2.72	1.88	2.55	2.77	0.28
	28.00	0.96	0.99	1.28	1.67	0.75	0.60	0.70	1.32	1.09	0.13
S3	0.25	16.51	17.29	15.21	14.41	19.98	8.98	4.41	20.03	14.60	1.91
	0.75	47.04	44.67	48.81	45.48	52.18	43.91	21.44	55.87	44.93	3.65
	1.25	55.02	50.48	53.95	58.73	62.02	55.93	36.83	64.12	54.63	2.98
	1.75	60.23	54.42	58.30	57.11	61.94	55.12	49.24	60.59	57.12	1.46
	2.50	50.37	61.07	59.61	63.49	61.50	48.61	43.94	59.75	56.04	2.57
	3.50	40.95	62.31	49.68	60.53	51.80	46.84	37.60	51.49	50.15	3.03
	5.00	40.12	48.21	38.29	41.35	35.45	34.08	31.18	32.16	37.60	1.99
	7.00	20.74	24.13	21.54	28.08	26.79	25.24	22.05	28.90	24.68	1.09
	10.00	10.58	15.64	10.75	14.47	15.21	16.51	16.04	14.36	14.19	0.81
	14.00	4.71	5.21	4.68	5.96	6.64	8.83	6.96	6.59	6.20	0.49
	20.00	2.01	2.33	1.83	3.33	3.41	2.13	3.25	2.51	2.60	0.23
	28.00	1.40	1.26	0.66	2.56	2.12	0.73	0.82	0.85	1.30	0.25

a. Time at midpoint of the collection period

b. Standard error

Table 14 (continued)

Brand	Tmid(hr)[a]	Rate of Paracetamol Excretion (mg/hr)									
		Subject No.									
		1	2	3	4	5	6	7	8	Mean	SE[b]
S4	0.25	14.46	7.65	11.55	5.53	11.16	16.50	4.58	15.58	10.88	1.61
	0.75	43.34	39.27	48.54	25.34	39.70	45.82	28.08	48.46	39.82	3.13
	1.25	50.30	52.94	59.74	41.35	59.18	58.97	33.18	63.24	52.36	3.68
	1.75	56.71	53.54	61.19	59.35	73.11	55.58	38.63	58.04	57.02	3.37
	2.50	54.02	52.58	59.10	51.16	67.36	48.97	37.71	58.24	53.64	3.05
	3.50	49.52	52.68	48.18	50.37	58.18	47.57	36.53	55.70	49.84	2.30
	5.00	36.71	39.26	37.78	37.15	45.50	44.87	27.38	45.25	39.24	2.16
	7.00	20.62	26.77	18.86	30.61	28.30	26.71	20.27	28.61	25.09	1.58
	10.00	10.51	13.81	9.64	14.31	11.61	15.82	13.55	16.02	13.16	0.83
	14.00	5.78	7.86	3.25	7.22	6.63	7.38	6.29	6.17	6.32	0.50
	20.00	2.06	2.54	1.50	3.40	2.91	3.21	2.99	3.04	2.71	0.23
	28.00	1.24	0.71	0.54	1.63	1.50	0.89	0.77	1.90	1.15	0.17

a. Time at midpoint of the collection period

b. Standard error

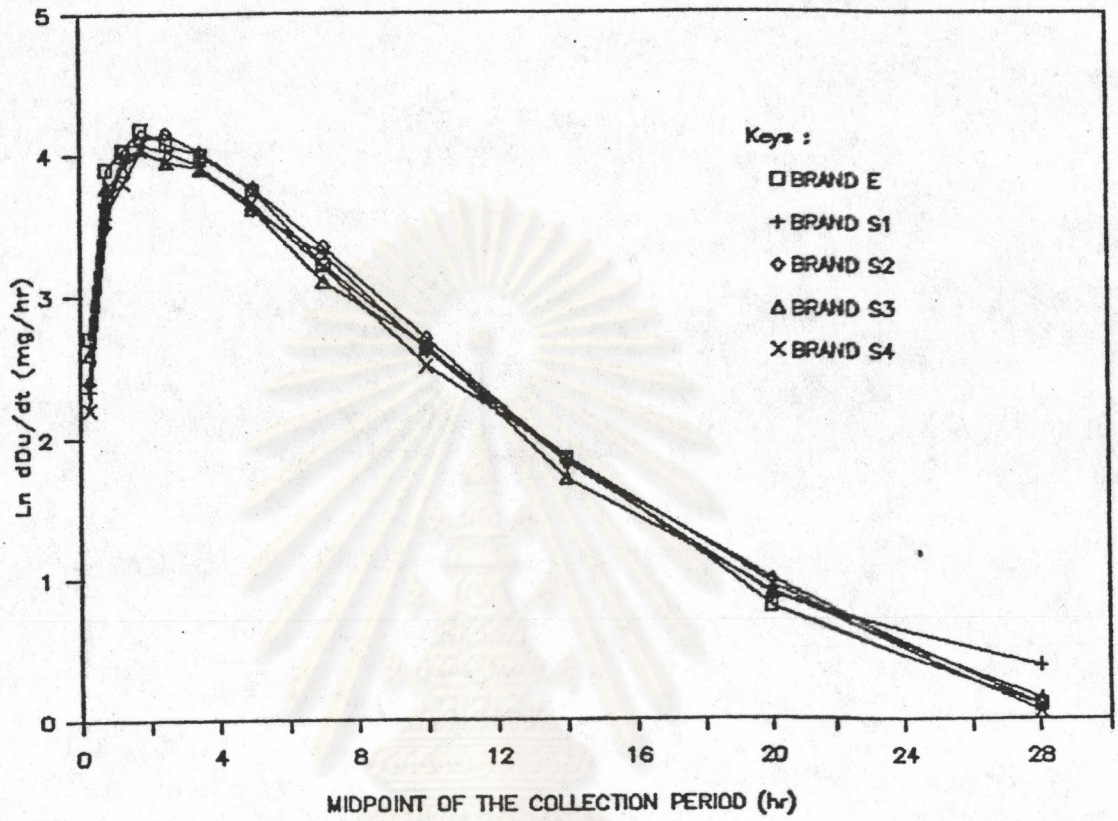


Figure 3 Mean rate of paracetamol excretion from 8 subjects following oral single dose of 600 mg paracetamol from paracetamol elixir and paracetamol suspensions.

Table 15 Individual Maximum Rate of Paracetamol Excretion, (dDu/dt)max, from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Maximum Rate of Paracetamol Excretion ($mg.hr^{-1}$)				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	61.78	63.52	67.80	60.23	56.71
2	68.16	57.07	63.30	62.31	53.54
3	73.71	65.45	84.46	59.61	61.19
4	70.56	65.45	76.17	63.49	59.35
5	64.31	65.76	65.48	62.02	73.11
6	66.08	55.06	59.89	55.93	58.97
7	60.24	49.48	44.34	49.24	38.63
8	59.70	56.08	53.54	60.59	63.24
Mean	65.57	59.73	64.37	59.18	58.09
SE[a]	1.18	2.17	4.42	1.63	3.45

[a] Standard error

Table 16 Analysis of Variance for Maximum Rate of Paracetamol Excretion,(dDu/dt)max of Paracetamol Elixir(Brand E) and Paracetamol Suspensions(Brands S1,S2,S3 and S4).

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	358.85	89.71	1.34
Within groups	35	2350.26	67.15	
Total	39	2709.10		

$$F^{e}_{0.95(4,35)} = 2.65$$

a Degree of freedom

b Sum of square

c Mean square

d Variation ratio

e F obtained from the table·pa

Table 17 Comparison of the Maximum Rate of Paracetamol Excretion, (dDu/dt)max of the Commercial Brands of Paracetamol Suspensions with Paracetamol Elixir, Brand E and the Original Brand of Paracetamol Suspension,Brand S1 Using t-test

Comparison with	t (Calculated)	
	Brand E	Brand S1
Brand S1	1.9462	-
Brand S2	-0.2345	-0.8809
Brand S3	2.4771[a]	0.1915
Brand S4	1.8026	0.3769

$t_{(0.05,14)} = 2.1448$[b]

[a] Significant ($p<0.05$)

[b] A t-value from the table

The individual absorption rate constant of paracetamol for each brand , Ka are listed in Table 18. The order of magnitude of the five brands in term of Ka were Brand E > Brand S1 > Brand S3 > Brand S4 > Brand S2. There was statistically significant difference between the Ka of Brand E versus that of Brand S2,and the Ka of Brand E versus that of Brand S4 ($p<0.05$) (Tables 19-20).

The individual overall elimination rate constants,K, and the half lives, $t_{1/2}$, of each brand were shown in Tables 21 and 22, respectively. No statistically significant difference among the five brands was observed in terms of K and $t_{1/2}$ values ($p>0.05$). The average overall elimination rate constant was 0.1615 hr^{-1} with a range 0.1591-0.1679 hr^{-1}. The average half-life for paracetamol of 4.32 hours with a range of 4.14-4.43 hours studied here is longer than those of approximately 1.62-2.83 hours as reported by Nelson,E. and Morioka,T (21). and 2.67±0.43 hours (Mean±SD) as reported by Holt, S. et al (19). However, the half-lives from excretion data of upto 4 hours in adults have been published by Miller, R.P. et al (18) and Sotiropouslus,J.B. (22).

Table 18 Individual Absorption Rate constant (Ka) of Paracetamol from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Absorption Rate constant of Paracetamol (hr^{-1})				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	3.0670	4.6100	1.4057	2.7366	2.0085
2	2.2776	1.3202	1.7493	1.1887	1.2938
3	3.3173	1.5390	1.1278	1.7405	2.2860
4	2.0246	1.9827	1.9983	2.0443	1.1923
5	2.6101	1.6846	1.6955	2.6723	1.8005
6	1.9098	2.5504	1.5450	1.9484	1.8005
7	2.5457	2.0494	1.2667	1.2034	1.3249
8	1.9098	3.0391	1.0865	2.3693	2.0831
Mean	2.4577	2.3469	1.4843	1.9879	1.7267
SE[a]	0.1871	0.3782	0.1135	0.2111	0.1445

[a] Standard error

Table 19 Analysis of Variance for Absorption Rate Constant,Ka of Paracetamol Elixir (Brand E) and Paracetamol Suspensions (Brands S1,S2,S3 and S4).

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	5.36	1.34	3.27
Within groups	35	14.36	0.41	
Total	39	19.72		

$$F^{e}_{0.95(4,35)} = 2.65$$

[a] Degree of freedom

[b] Sum of square

[c] Mean square

[d] Variation ratio

[e] F obtained from the table

Table 20 Comparison of Absorption Rate Constants of Paracetamol,Ka of Commercial Brands of Paracetamol Suspensions with Paracetamol Elixir, Brand E and the Original Brand of Paracetamol Suspension, Brand S1 Using t-test

Comparison with	t (Calculated)	
	Brand E	Brand S1
Brand S1	0.2456	-
Brand S2	4.1598[a]	2.0436
Brand S3	1.5579	0.7754
Brand S4	2.8923[a]	1.4331

$t_{(0.05,14)} = 2.1448$[b]

[a] Significant ($p<0.05$)

[b] A t-value from the table

Table 21 Individual Elimination Rate Constant (K) of Paracetamol from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Elimination Rate Constant of Paracetamol(hr^{-1})				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	0.1725	0.1614	0.1760	0.1566	0.1596
2	0.1694	0.1551	0.1634	0.1667	0.1740
3	0.1738	0.2208	0.1739	0.1825	0.1917
4	0.1654	0.1426	0.1552	0.1380	0.1452
5	0.1558	0.1467	0.1687	0.1407	0.1596
6	0.1613	0.1464	0.1785	0.1680	0.1606
7	0.1562	0.1518	0.1683	0.1551	0.1538
8	0.1550	0.1478	0.1595	0.1699	0.1471
Mean	0.1637	0.1591	0.1679	0.1597	0.1615
SE[a]	0.0027	0.0091	0.0029	0.0054	0.0054

[a] Standard error

Table 22 Individual Half Life ($t_{1/2}$) of Paracetamol from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Half Life of Paracetamol (hr)				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	4.02	4.30	3.94	4.43	4.34
2	4.09	4.47	4.24	4.16	3.98
3	3.99	3.86	3.14	3.80	3.61
4	4.19	4.86	4.46	5.02	4.77
5	4.45	4.73	4.11	4.93	4.34
6	4.30	4.73	3.88	4.13	4.32
7	4.44	4.57	4.12	4.47	4.51
8	4.47	4.69	4.34	4.08	4.71
Mean	4.24	4.43	4.14	4.38	4.32
SE[a]	0.07	0.20	0.07	0.15	0.13

[a] Standard error

The time for maximum urinary excretion, t_{∞} refers to the total time required for the drug to be absorbed and completely excreted after drug administration. In this study, this time was approximately set to be seven times of the half life of the drug. This is because the drug in urine samples at the time 24-32 hours postdose was too low to be correctly determined with the analytical prosedure used here.

The individual time for maximum urinary excretion of the five brands were shown in Table 23. Results indicated that there were no statistically significant difference among the products tested in the t_{∞} values using one way analysis of variance and t-test ($p>0.05$) (Tables 24-25).

Table 23 Individual Time for Maximum Urinary Excretion (t_{∞}) of Paracetamol from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Subject No.	Time for Maximum Urinary Excretion of Paracetamol(hr)				
	Brand E	Brand S1	Brand S2	Brand S3	Brand S4
1	28.12	30.06	27.56	30.98	30.40
2	28.64	31.28	29.68	29.10	27.87
3	27.92	21.27	27.89	26.59	25.30
4	29.32	34.02	31.28	35.15	33.41
5	31.13	33.07	28.75	34.48	30.40
6	30.08	33.14	27.18	28.88	30.22
7	31.06	31.96	28.85	31.29	31.55
8	31.31	32.81	30.41	28.56	32.98
Mean	29.70	30.95	28.95	30.63	30.27
SE[a]	0.49	1.45	0.50	1.05	0.94

[a] Standard error

Table 24 Analysis of Variance for Time for Maximum Urinary Excretion, t_{∞} of Paracetamol Elixir(Brand E) and Paracetamol Suspensions (Brands S1,S2,S3 and S4).

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	20.21	5.05	0.69
Within groups	35	256.67	77.33	
Total	39	276.89		

$$F^{e}_{0.95(4,35)} = 2.65$$

a Degree of freedom

b Sum of square

c Mean square

d Variation ratio

e F obtained from the table

Table 25 Comparison of Time for Maximum Urinary Excretion, t_{∞} of Commercial Brands of Paracetamol Suspensions with Paracetamol Elixir, Brand E and the Original Brand of Paracetamol Suspension, Brand S1 Using t-test.

Comparison with	t (Calculated)	
	Brand E	Brand S1
Brand S1	-0.7663	-
Brand S2	0.9977	1.2218
Brand S3	-0.7510	0.1691
Brand S4	-0.5032	0.3709

$$t_{(0.05,14)} = 2.1448^{a}$$

[a] A t-value from the table

Bioequivalent evaluation

Relative bioavailabilities of paracetamol suspensions (Brands S1, S2, S3 and S4) to paracetamol elixir were studied. Results indicated that Brand S1 and Brand E were bioequivalent according to four parameters : $[Du]_{\infty}$, (dDu/dt)max, t_{∞} and Ka. Although there were statistically significant difference ($p<0.05$) in Ka between Brand S2 and Brand E, and Brand S4 and Brand E, these three brands were bioequivalent regarding to the following parameters : $[Du]_{\infty}$, (dDu/dt)max and t_{∞} . In spite of the statistically significant difference ($p<0.05$) between Brand S3 and Brand E in (dDu/dt)max , they were also bioequivalent with respect to $[Du]_{\infty}$, t_{∞} and Ka. The relative bioavailabilities of paracetamol suspensions with respect to paracetamol elixir were 104.31,98.35,104.12 and 106.74 % for Brand S1, S2, S3 and S4, respectively.

Comparative bioavailability of paracetamol suspensions was also evaluated. Paracetamol suspension `Brand S1´ was assigned as a reference standard against Brands S2, S3 and S4. Results demonstrated that Brand S1, Brand S2, Brand3 and Brand S4 were bioequivalent regarding to the four parameters :$[Du]_{\infty}$, (dDu/dt)max, t_{∞} and Ka.

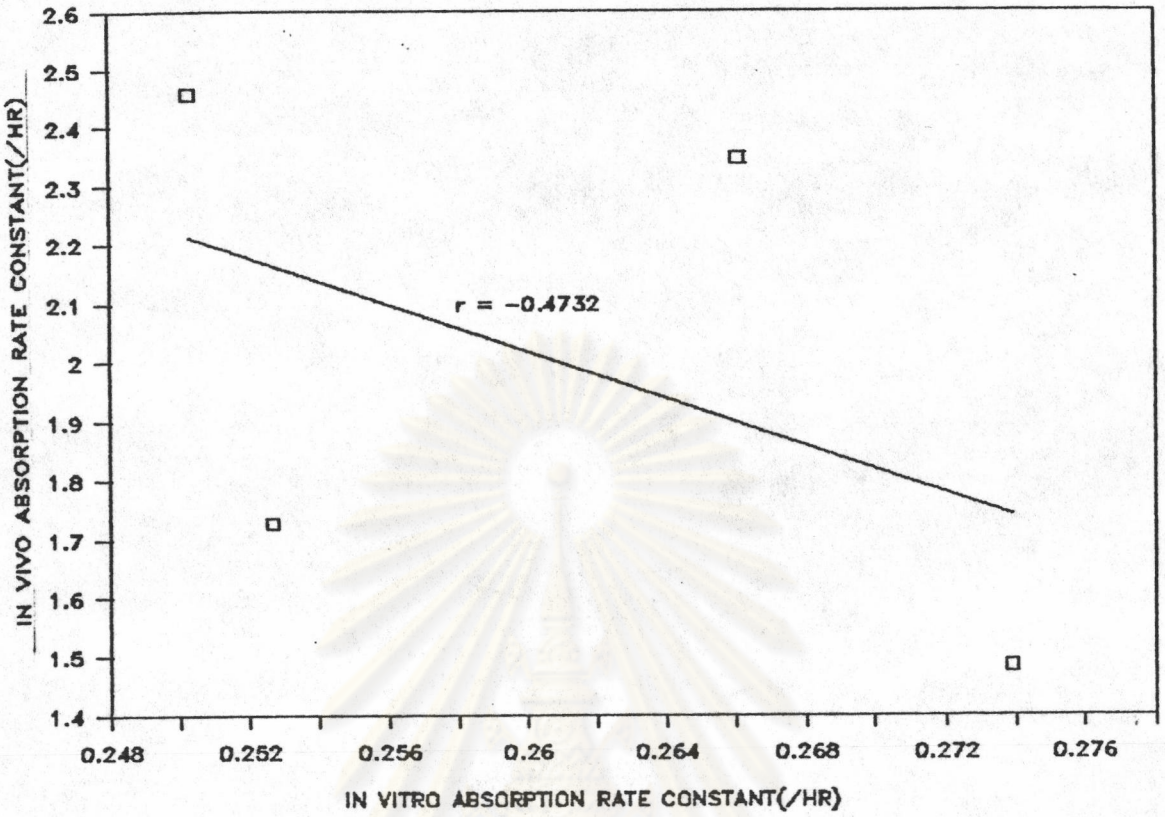
Table 26 Estimated Pharmacokinetic Parameters from 8 Subjects Following Oral Single Dose of 600 mg Paracetamol from Paracetamol Elixir and Paracetamol Suspensions.

Parameters	Brands					Statistic
	E	S1	S2	S3	S4	significa
Maximum cumulative amount excreted into the urine ,[Du] (mg)	450.09 (9.93)	430.89 (13.78)	457.02 (20.67)	429.24 (14.37)	420.93 (18.08)	NS
Maximum rate of drug excretion, (dDu/dt)max (mg/hr)	65.57 (1.78)	59.73 (2.17)	64.37 (4.42)	59.18 (1.63)	58.09 (3.45)	S (E>S3)
Time for maximum urinary excretion,t (hr)	29.70 (0.49)	30.95 (1.45)	28.95 (0.50)	30.63 (1.05)	30.27 (0.94)	NS
Absorption rate constant,Ka (/hr)	2.4577 (0.1871)	2.3469 (0.3782)	1.4843 (0.1135)	1.9890 (0.2111)	1.7270 (0.1445)	S (E>S2 ; E>S4
Overall elimination rate constant,K (/hr)	0.1637 (0.0027)	0.1591 (0.0091)	0.1679 (0.0029)	0.1597 (0.0054)	0.1615 (0.0054)	NS
Half life,t1/2 (hr)	4.24 (0.07)	4.43 (0.20)	4.14 (0.07)	4.38 (0.15)	4.32 (0.13)	NS
Lag time,Tlag (hr)	0.17 (0.01)	0.16 (0.04)	0.14 (0.03)	0.12 (0.02)	0.15 (0.02)	NS

a. Mean and standard error (value in parenthesis).
b. NS = not significant ($p>0.05$)
c. S = significant ($p<0.05$)

In Vitro-In Vivo Correlation

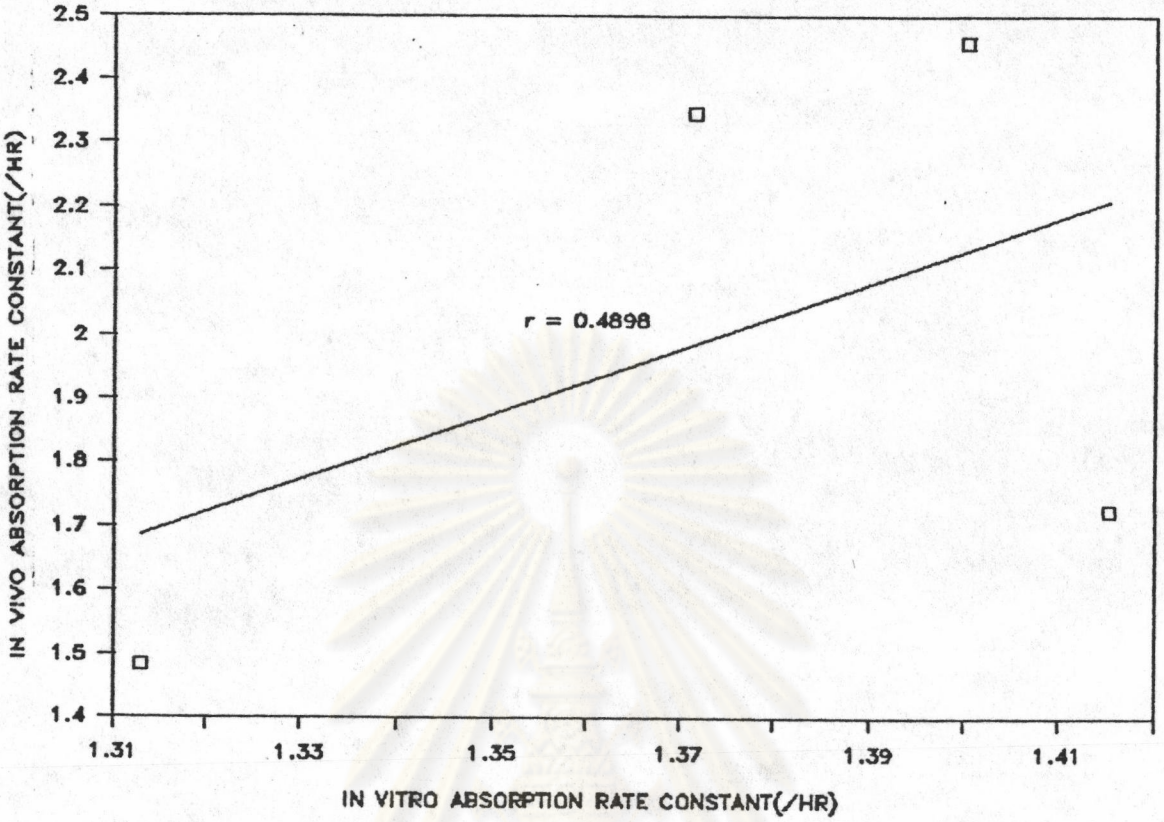
An attempt to correlate the mean absorption rate constants, Ki of paracetamol in the stomach and in the intestine predicted by the Sartorius Absorption Simulator SM 16750, with the mean absorption rate constants, Ka of the drug in in vivo study was performed. There were poor correlation between the Ki values (both in simulated gastric and in intestinal simulated conditions) and the Ka values with correlation coefficients of -0.4732 and 0.4898, respectively (Figures 4-5). The results obtained indicated that the in vivo absorption rate constants of paracetamol suspensions and/or elixir could not be predicted by the in vitro model study ($p>0.05$). These results were not agree with that previously report (17). This may be due to the in vitro Absorption Simulator used in this study is not suitable for suspension dosage forms. However, the in vitro Absorption Simulator should be continuously studied and developed for a valuable aid to investigate the absorption of new drugs or new preparations.



Brand	Ki(hr^{-1})	Ka(hr^{-1})
E	0.2503	2.4577
S1	0.2661	2.3469
S2	0.2739	1.4843
S4	0.2527	1.7267

correlation coefficient	-0.4732
t value	-0.7596
$t_{(0.05,2)}$	±4.3027

Figure 4 Correlation between in vitro absorption rate constant, Ki, in simulated gastric condition and in vivo absorption rate constant, Ka.



Brand	Ki(hr^{-1})	Ka(hr^{-1})
E	1.4003	2.4577
S1	1.3715	2.3469
S2	1.3130	1.4843
S4	1.4152	1.7267

correlation coefficient	0.4898
t value	-0.7596
$t_{(0.05,2)}$	±4.3027

Figure 5 Correlation between in vitro absorption rate constant, Ki, in simulated intestinal condition and in vivo absorption rate constant, Ka.