RESULTS

1. Screening for theophylline clearance

Thirteen healthy male volunteers were in this study. The serum theophylline concentrations at various time points after administration of 400 mg Franol® are shown in Table 3. The serum theophylline concentrations-time curves of each subject and the mean concentration-time curves are depicted in Figure 3 and 4, respectively. A summary of calculated pharmacokinetic parameters derived from Topfit 2.0 are shown in Table 4. Figure 5 and 6 illustrate the mean amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) and mean amount (%) of drug remaining to be absorbed with time, respectively.

Following an oral dose of 400 mg Franol®, the absorption was rapid with the average time to reach the peak concentration (T_{max}, hr) of 2.54 ± 1.23 (range 0.5-4.0). The average peak concentration (C_{max}, μg/ml) was 14.24 ± 2.69 (range 9.74–18.69). The average elimination half-life ($T_{1/2}$, hr), volume of distribution (V_d, l/kg) and clearance (CL, ml/min/kg) were 10.33 ± 2.97 (range 5.72-14.1), 0.40 ± 0.04 (range 0.34–0.47) and 0.49 ± 0.16 (range 0.30–0.80), respectively.

The 1st and the 5th subject were excluded from the multiple dose study, although their pharmacokinetic parameters were normal, because of adverse experiences (nausea, tremor, palpitation, headache, and insomnia). The 8th subject was withdrawn because of poor compliance. Therefore ten subjects were enrolled and completed the study.

Table 3. Serum theophylline concentrations (μg/ml) after a single oral dose of 400 mg Franol®

Subj. No.	Hours after dose										
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	6.00	8.00	12.00	24.00
1	0.00	17.77	17.29	15.72	15.57	13.90	12.84	11.65	10.27	8.23	4.70
2	0.00	4.76	10.01	11.83	12.47	13.19	13.00	11.97	10.50	8.04	3.26
3	0.00	16.88	16.62	16.41	16.25	13.11	12.55	10.55	8.83	6.79	2.37
4	0.00	0.39	4.04	6.96	7.66	9.64	9.74	9.55	8.70	6.85	2.06
5	0.00	2.76	6.76	9.73	10.58	14.73	14.12	13.94	12.90	10.87	5.64
6	0.00	0.25	2.09	6.84	9.35	13.02	13.69	10.84	8.67	6.27	2.40
7	0.00	0.69	3.28	5.16	6.60	10.51	9.91	8.89	7.11	4.23	1.01
8	0.00	10.72	11.88	12.90	13.54	13.14	12.13	9.60	7.99	5.27	-
9	0.00	7.27	10.04	10.72	11.69	11.88	12.06	10.80	9.27	7.31	2.91
10	0.00	1.19	3.25	6.48	12.41	12.86	12.43	11.74	10.89	10.11	4.93
11	0.00	11.35	15.05	15.43	14.97	13.42	12.99	10.73	10.24	8.82	4.43
12	0.00	11.51	11.67	15.13	17.50	18.69	18.12	15.57	13.34	11.74	5.92
13	0.00	10.02	12.40	16.09	15.77	14.05	13.97	11.81	9.99	8.11	3.21
Mean	0.00	7.35	9.57	11.49	12.64	13.24	12.89	11.36	9.90	7.90	3.57
SD	0.00	6.19	5.26	4.13	3.40	2.15	2.06	1.81	1.79	2.14	1.54

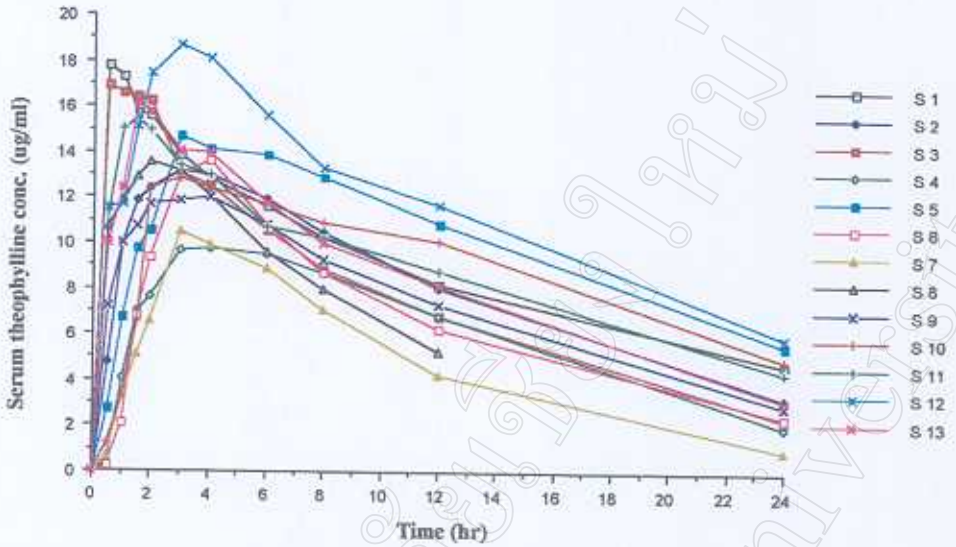

Figure 3. Serum concentration-time curves after a single oral dose of 400 mg Franol® in 13 healthy Thai male subjects.

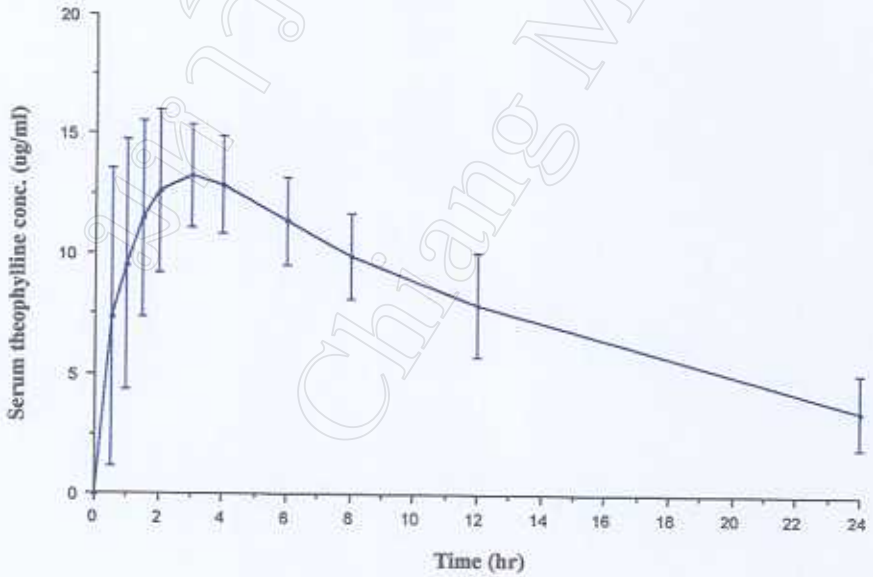

Figure 4. Mean serum concentration-time curve after a single oral dose of 400 mg Franol® in 13 healthy Thai male subjects.

Table 4. Pharmacokinetic parameters of theophylline after a single oral dose of 400 mg Franol®

Subj. No.	C_{max} (μg/ml)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{(0-24)}$ (μg.hr/ml)	$AUC_{(0-inf)}$ (μg.hr/ml)	CL (ml/min/kg)	V_d (l/kg)
1	17.77	0.50	13.90	218.38	312.88	0.33	0.40
2	13.19	3.00	9.54	194.62	239.48	0.51	0.42
3	16.88	0.50	8.37	185.21	213.82	0.48	0.35
4	9.74	4.00	7.93	148.05	171.61	0.65	0.45
5	14.73	3.00	13.60	240.85	351.57	0.35	0.41
6	13.69	4.00	8.42	157.41	186.55	0.55	0.40
7	10.51	3.00	5.72	113.90	122.23	0.80	0.40
8	13.54	2.00	6.72	112.95	164.05	0.70	0.41
9	12.06	4.00	9.52	178.10	218.07	0.51	0.42
10	12.86	3.00	14.10	212.88	313.39	0.39	0.47
11	15.43	1.50	13.70	214.37	301.93	0.33	0.39
12	18.69	3.00	13.10	278.75	391.00	0.30	0.34
13	16.09	1.50	9.63	203.82	248.40	0.45	0.37
Mean	14.24	2.54	10.33	189.18	248.84	0.49	0.40
SD	2.69	1.23	2.97	47.70	80.19	0.16	0.04

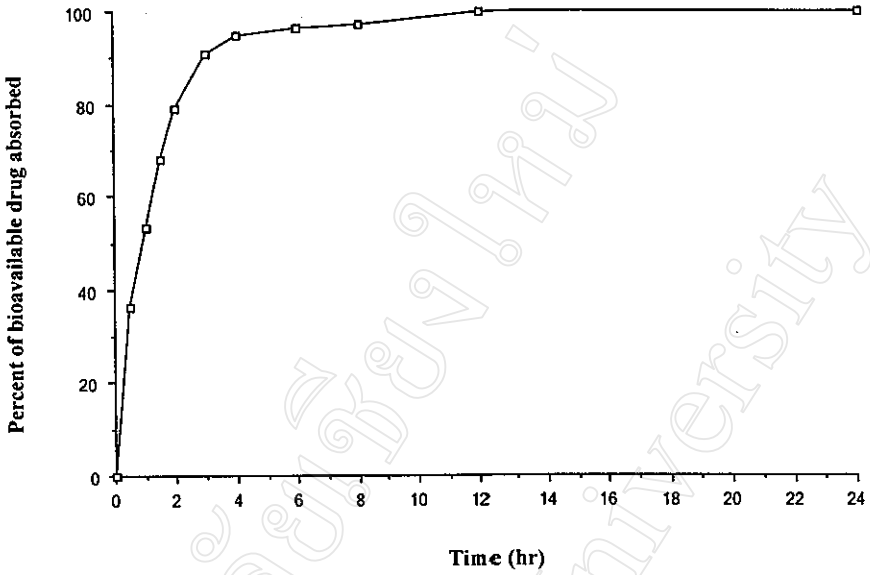

Figure 5. Mean amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose of Franol®.

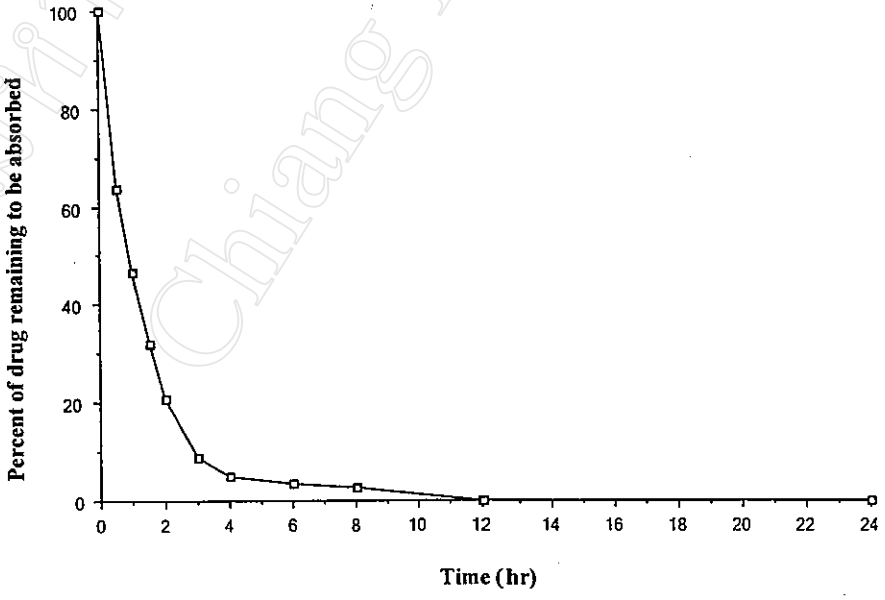

Figure 6. Mean amount (%) of drug remaining to be absorbed with time after 400 mg oral dose of Franol®.

2. Steady-state bioavailability study of Uni-Dur®, Theo-Dur® and Xanthium®

Ten subjects participated and completed the study without any serious adverse effects. The individual steady-state serum theophylline concentrations at various time points after once daily dosing of 400 mg SRT preparations (Uni-Dur®, Theo-Dur® and Xanthium®) of Day 4, 5, 6 and 7 are shown in Table 5-7, respectively. The comparative serum concentration-time curves of individual subject on Day 6 and Day 7 as well as their average serum concentration-time curves are depicted in Figure 7 and 8, respectively. The individual of bioavailable drug absorbed (%) with time derived from Wagner-Nelson method and mean amount (%) of bioavailable drug absorbed with time after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol® are shown in Figure 9, 10, 12, and 14, respectively. Similarly, mean amount (%) of drug remaining to be absorbed with time after oral doses of Uni-Dur®, Theo-Dur® and Xanthium® are shown in Figure 11, 13, and 15, respectively. The summary of mean amount (%) of bioavailable drug absorbed with time are shown in Figure 16. Figure 17 illustrates the comparison of mean amount (%) of drug remaining to be absorbed with time.

Steady-state pharmacokinetic parameters of Uni-Dur®, Theo-Dur® and Xanthium® are shown in Table 8-10, respectively. Comparison of steady-state pharmacokinetic parameters of Uni-Dur®, Theo-Dur® and Xanthium® are shown in Table 11. The mean ± SD of Css_{min} (μg/ml) of Uni-Dur®, Theo-Dur®, and Xanthium® were 5.07 ± 2.67 (range 0.40-10.16), 4.29 ± 2.34 (range 0.49-9.25), and 4.18 ± 2.23 (range 1.08-7.58), respectively. Bioequivalence analysis revealed the parametric 90%CI of the Css_{min} ratios of μUni-Dur®/μXanthium®, μUni-Dur®/μTheo-Dur®, and μXanthium®/μTheo-Dur® were 1.07-1.39, 1.06-1.33 and 0.92-1.13, respectively. These values were well within the bioequivalence range of 0.7-

1.43 for the mean ratios ($\frac{\text{Test}}{\text{Reference}}$), therefore the three SRT products achieved equivalent minimum theophylline concentrations at their steady states.

Parametric 90%CI of the Css_{max} ratios of μUni-Dur®/μXanthium®, μUni-Dur®/μTheo-Dur®, μXanthium®/μThe-Dur® were 0.99-1.22, 0.67-0.84 and 0.64-0.73, respectively. The results demonstrated that the Css_{max} (μg/ml) of Uni-Dur® [8.51 ± 2.88 (range 2.88-13.23)] and Xanthium® [7.65 ± 2.71 (range 3.56-12.38)] were equivalent and were significantly less than that of Theo-Dur® [11.02 ± 3.33 (range 4.45-19.44)].

The average peak trough fluctuation (%) of Uni-Dur® [137 ± 174 (range 30-620)] and Xanthium® [113 ± 67 (range 47-244)] were not significantly different (p=0.30, Wilcoxon Singed Rank test) and were statistically less than that of Theo-Dur® [232 ± 187 (range 71-808)] (p<0.01). The Tss_{max} (hr) of Theo-Dur® [7.8 ± 1.54 (range 6-11)] and Xanthium® [7.7 ± 1.69 (range 6-11)] were bioequivalent, however, they were significantly faster than that of Uni-Dur® [10.05 ± 4.63 (range 4-15)].

Parametric 90%CI of the $AUCss_{0-24}$ ratios of μUni-Dur®/μXanthium®, μ Uni-Dur®/μTheo-Dur®, μXanthium®/μThe-Dur® were 0.81-1.25, 0.60-1.01 and 0.69-0.86, respectively. The extent of absorption assessed by $AUCss_{0-24}$ (μg.hr/ml) of Theo-Dur® [188.97 ± 67.24 (range 57.84-338.26)] was significantly greater than those of Uni-Dur® [165.73 ± 68.83 (range 29.95-288.83)] and Xanthium® [150.5 ± 62.34 (range 61.23-260.25)].

The parametric 90% confidencial intervals (90%CI) of the mean steady-state pharmacokinetic parameters of Uni-Dur®, Theo-Dur® and Xanthium® were compared and summarized in Table 12.

The Wagner Nelson absorption method showed that during the first 6 hours where 76% of drug was absorbed, the absorption process of Theo-Dur® was closed to

zero-order (8.6% per hr), thereafter, followed by first-order absorption rate. The absorption profile of Xanthium® complied with the first-order process ($Tabs_{1/2}$ of 5 hours). The absorption profile of Uni-Dur® was characterized by a zero-order process for 0-4 hr, 4-15 hr and 15-24 hr with the rate of approximately 7.5 % per hr, 2.5 % per hr and 1% per hr, where 60%, 90% and >90% of drug was absorbed, respectively.

Table 5. Steady-state serum theophylline concentrations (μg/ml) after once daily doses of 400 mg Uni-Dur®.

Day/time(hr)	Subj. no.2	3	4	6	7	9	10	11	12	13	Mean	SD	SE
Day 4/ 0	6.42	6.66	0.62	4.10	1.70	5.34	7.63	6.87	10.40	5.91	5.57	2.85	0.90
Day 5/ 0	7.04	4.76	0.76	4.66	3.20	5.22	9.18	7.42	6.29	5.67	5.42	2.34	0.74
Day 6 / 0	6.90	5.57	0.45	5.27	1.46	4.72	10.51	6.77	10.16	4.89	5.67	3.21	1.02
2	7.48	7.57	2.41	6.37	2.96	6.07	11.21	7.62	12.21	6.76	7.07	3.06	0.97
4	7.64	8.71	2.98	6.49	3.56	8.18	11.25	8.45	12.56	6.59	7.64	2.98	0.94
6	7.62	7.68	3.01	6.12	3.82	8.27	10.10	8.87	13.02	6.96	7.55	2.90	0.92
7	6.85	7.51	3.16	5.93	3.77	7.70	10.26	9.22	12.70	6.91	7.40	2.86	0.90
8	6.91	6.91	2.84	5.91	3.65	7.55	10.10	9.42	12.29	6.56	7.21	2.85	0.90
9	8.62	7.08	2.82	5.80	3.84	7.39	9.56	9.80	11.82	6.62	7.34	2.76	0.87
10	10.16	6.33	2.61	5.93	4.47	7.09	9.93	9.69	11.63	6.65	7.45	2.84	0.90
11	10.44	6.19	2.28	5.99	5.00	6.98	10.24	9.73	11.36	6.27	7.45	2.89	0.91
12	10.67	5.83	2.07	5.89	5.36	6.98	10.81	9.93	12.08	6.21	7.58	3.15	1.00
13	11.17	5.78	1.85	6.19	5.18	6.74	11.48	9.45	11.83	6.56	7.62	3.25	1.03
15	11.15	5.45	1.52	6.99	4.80	6.55	11.54	9.16	13.23	6.64	7.70	3.56	1.13
Day 7/ 0	6.59	4.73	0.61	5.31	1.76	4.67	8.60	7.37	10.30	4.45	5.44	2.94	0.93
2	7.13	8.04	1.22	7.10	2.86	5.85	9.35	7.65	11.29	6.13	6.66	2.92	0.92
4	7.14	8.88	2.88	6.88	4.49	6.59	10.44	8.70	11.54	6.91	7.45	2.59	0.82
6	7.28	8.07	2.44	6.61	4.21	6.31	10.34	9.78	11.15	7.20	7.34	2.70	0.85
7	6.57	7.90	2.04	6.20	3.91	6.29	10.55	9.80	10.70	7.30	7.13	2.80	0.88
8	7.14	7.48	1.83	6.02	3.45	6.38	10.27	9.86	10.64	7.37	7.04	2.85	0.90
9	7.74	7.49	1.71	6.02	3.32	6.47	10.24	10.45	10.96	7.53	7.19	3.01	0.95
10	9.29	6.69	1.48	6.38	3.22	6.39	10.09	10.04	10.12	8.40	7.21	3.00	0.95
11	9.77	6.43	1.40	6.73	3.03	6.42	10.16	10.13	9.73	8.94	7.27	3.09	0.98
12	10.00	6.09	1.19	7.19	2.87	6.16	10.56	10.02	9.43	8.62	7.21	3.18	1.01
13	10.32	5.86	1.01	7.68	2.66	6.96	11.08	10.09	9.30	9.06	7.40	3.36	1.06
15	9.87	5.65	0.82	8.28	2.54	7.48	11.44	10.41	8.15	7.96	7.26	3.38	1.07
24	6.14	4.89	0.40	4.90	1.26	5.55	9.00	8.99	5.76	5.48	5.24	2.77	0.88

Table 6. Steady-state serum theophylline concentrations (μg/ml) after once daily doses of 2 X 200 mg Theo-Dur®.

Day/time(hr)	Subj. no.2	3	4	6	7	9	10	11	12	13	Mean	SD	SE
Day 4/ 0	4.52	4.30	1.16	3.31	1.97	4.45	7.44	5.80	8.20	3.19	4.43	2.23	0.70
Day 5/ 0	5.96	5.88	1.97	3.02	1.74	3.85	7.87	4.84	8.67	2.95	4.68	2.40	0.76
Day 6 / 0	4.77	4.87	1.87	2.62	0.49	3.91	6.79	5.65	10.00	3.06	4.40	2.71	0.86
2	6.83	6.76	4.58	4.65	2.53	6.16	9.78	7.56	12.82	5.63	6.73	2.89	0.91
4	6.87	6.99	5.84	6.95	3.18	8.24	11.23	9.40	13.99	7.19	7.99	2.99	0.94
6	9.92	9.88	7.42	8.97	3.63	10.90	12.85	12.51	12.33	9.71	9.81	2.76	0.87
7	10.75	10.79	7.09	8.93	4.00	10.68	12.93	11.90	11.57	11.15	9.98	2.65	0.84
8	11.45	11.36	7.27	8.84	4.45	10.53	13.31	12.07	12.60	11.42	10.33	2.72	0.86
9	11.45	11.61	6.89	8.13	4.01	10.38	12.48	11.54	13.10	10.68	10.03	2.84	0.90
10	11.64	11.73	6.56	7.97	3.75	10.06	12.25	11.43	14.00	10.51	9.99	3.06	0.97
11	11.17	11.12	6.23	7.32	3.29	9.45	12.08	11.10	15.83	9.50	9.71	3.47	1.10
12	10.62	10.70	5.83	7.01	2.75	9.31	11.65	10.69	15.67	9.10	9.33	3.53	1.12
13	10.73	10.86	5.48	6.75	2.49	8.44	10.81	9.61	15.59	8.39	8.92	3.56	1.13
15	9.66	9.57	4.71	5.74	1.99	7.55	9.63	8.82	14.04	7.45	7.92	3.29	1.04
Day 7/ 0	5.66	5.54	2.12	2.72	0.79	4.30	6.48	5.68	9.25	3.69	4.62	2.44	0.77
2	7.48	5.85	4.20	4.91	2.83	6.44	9.04	8.16	12.61	6.57	6.81	2.75	0.87
4	9.44	7.68	3.36	7.98	4.39	7.93	10.50	9.52	18.12	7.78	8.67	3.99	1.26
6	13.37	8.68	6.34	9.83	5.58	10.26	12.39	12.31	19.44	9.89	10.81	3.94	1.25
7	13.38	8.93	6.79	9.61	5.77	10.37	12.33	12.44	17.81	10.14	10.76	3.46	1.09
8	13.56	8.59	8.61	8.94	5.94	9.84	12.67	12.44	17.57	10.17	10.83	3.29	1.04
9	13.10	8.47	8.93	8.88	5.70	9.68	12.13	12.46	18.32	9.61	10.73	3.46	1.09
10	12.65	8.44	8.43	8.04	5.75	9.84	12.05	12.13	17.03	8.66	10.30	3.21	1.02
11	11.88	8.30	7.51	7.59	5.83	9.34	11.53	11.45	15.73	8.40	9.76	2.90	0.92
12	11.05	7.79	6.93	7.08	5.58	8.81	11.50	10.92	15.80	8.00	9.35	3.01	0.95
13	10.62	7.41	6.10	6.37	5.46	8.18	10.42	10.47	15.07	7.78	8.79	2.90	0.92
15	9.04	6.55	5.06	6.95	5.02	7.43	11.62	9.47	13.71	7.21	8.21	2.79	0.88
24	5.46	3.26	1.98	2.80	2.31	4.21	6.97	6.02	8.47	4.02	4.55	2.13	0.67

Table 7. Steady-state serum theophylline concentrations (μg/ml) after once daily doses of 400 mg Xanthium®.

Day/time(hr)	Subj. no.2	3	4	6	7	9	10	11	12	13	Mean	SD	SE
Day 4/ 0	3.75	4.47	1.66	2.51	2.60	4.30	7.21	6.94	9.58	5.81	4.88	2.49	0.79
Day 5/ 0	2.32	3.51	1.25	2.46	1.26	4.70	7.88	7.71	7.93	5.17	4.42	2.68	0.85
Day 6 / 0	2.94	4.36	1.38	2.80	1.48	4.96	7.35	7.04	5.34	4.94	4.26	2.09	0.66
2	3.68	5.33	2.38	3.87	1.99	6.21	8.31	7.72	6.53	6.12	5.21	2.16	0.68
4	5.34	6.47	3.76	5.41	3.13	7.72	9.64	8.62	8.53	7.94	6.66	2.19	0.69
6	6.39	6.78	3.77	5.68	3.37	9.21	10.59	9.03	9.41	8.48	7.27	2.47	0.78
7	6.52	6.80	3.92	5.46	3.56	9.01	10.64	9.51	9.47	8.84	7.37	2.49	0.79
8	6.36	6.74	4.03	5.25	3.49	9.05	10.97	10.04	9.17	8.75	7.39	2.59	0.82
9	6.23	6.48	3.77	5.07	3.37	8.87	10.75	10.07	9.70	8.36	7.27	2.66	0.84
10	6.32	6.47	3.79	4.73	3.21	7.54	10.53	10.14	9.41	7.91	7.01	2.58	0.82
11	6.24	6.25	3.77	4.55	3.01	8.02	10.52	10.32	9.39	7.70	6.98	2.67	0.84
12	6.05	6.25	3.51	4.45	2.95	7.27	10.59	10.19	9.21	8.07	6.85	2.70	0.85
13	5.82	5.75	3.24	4.36	2.74	6.80	10.37	10.13	9.22	8.09	6.65	2.75	0.87
15	5.50	5.72	3.04	3.98	2.40	6.67	10.39	9.44	9.11	7.87	6.41	2.77	0.88
Day 7/ 0	3.80	3.42	1.67	2.17	1.08	4.65	8.71	7.58	7.19	5.14	4.54	2.62	0.83
2	4.43	4.03	3.32	3.28	2.01	4.79	8.88	8.24	8.03	4.92	5.19	2.37	0.75
4	6.05	5.47	4.41	4.77	3.26	5.43	10.30	9.02	10.90	5.76	6.54	2.60	0.82
6	7.04	5.96	4.88	5.85	3.71	6.52	11.20	10.16	11.39	6.18	7.29	2.68	0.85
7	7.18	6.02	4.75	5.63	3.52	6.84	10.93	10.04	11.48	6.56	7.30	2.67	0.84
8	7.49	6.08	4.48	5.74	3.43	6.68	10.65	10.80	11.85	7.19	7.44	2.81	0.89
9	6.84	5.91	4.46	5.79	3.24	6.67	10.51	11.13	11.71	7.39	7.37	2.86	0.91
10	7.35	5.84	4.14	5.75	3.21	6.69	10.14	11.26	12.38	7.63	7.44	3.00	0.95
11	6.97	5.84	3.93	5.78	3.25	6.61	10.60	11.31	12.26	7.61	7.42	3.06	0.97
12	7.00	5.64	3.88	5.68	2.93	6.53	10.13	10.94	11.71	7.50	7.19	2.93	0.93
13	6.55	5.56	3.70	5.69	2.82	6.37	9.48	11.03	12.06	7.38	7.06	3.00	0.95
15	6.30	5.65	3.30	5.31	2.55	6.07	8.95	11.02	11.44	6.80	6.74	2.95	0.93
24	4.36	3.81	1.48	3.36	1.38	4.62	6.97	9.27	10.18	5.30	5.07	2.97	0.94

Table 8. Steady-state pharmacokinetic parameters of theophylline after once-daily doses of 400 mg Uni-Dur®.

Day Subj. no.	C_{min} (μg/ml)	C_{max} (μg/ml)	T_{max} (hr)	$MRT_{(0-24)}$ (hr)	* FI %	$AUC_{(0-24)}$ (μg.hr/ml)	** F %
(Day 6) 2	6.59	11.17	13.00	12.1	69.50	209.96	107.88
3	4.73	8.71	4.00	10.8	84.14	149.43	80.68
4	0.45	3.16	7.00	9.56	602.22	45.41	30.67
6	5.27	6.99	15.00	11.8	32.64	147.25	93.55
7	1.46	5.36	12.00	11.5	267.12	88.41	77.62
9	4.67	8.27	6.00	11.2	77.09	156.47	87.86
10	8.60	11.54	15.00	11.6	34.19	250.76	117.79
11	6.77	9.93	12.00	11.9	46.68	207.73	96.90
12	10.16	13.23	15.00	11.8	30.22	288.38	103.45
13	4.45	6.96	6.00	11.3	56.40	147.64	72.44
Mean D6	5.32	8.53	10.50	11.36	130.02	169.14	86.88
SD	2.94	3.05	4.30	0.74	179.92	72.54	24.29
(Day 7) 2	6.14	10.32	13.00	12	68.08	193.96	99.66
3	4.73	8.88	4.00	10.8	87.74	154.63	83.49
4	0.40	2.88	4.00	8.99	620.00	29.95	20.23
6	4.90	8.28	15.00	11.7	68.98	160.84	102.18
7	1.26	4.49	4.00	10.1	256.35	66.21	58.13
9	4.67	7.48	15.00	12	60.17	153.68	86.29
10	8.60	11.44	15.00	11.9	33.02	245.60	115.37
11	7.37	10.45	9.00	12.2	41.79	227.89	106.31
12	5.76	11.54	4.00	10.5	100.35	218.96	78.55
13	4.45	9.06	13.00	11.9	103.60	171.52	84.15
Mean D7	4.83	8.48	9.60	11.21	144.01	162.32	83.44
SD	2.49	2.87	5.13	1.07	178.60	68.66	27.54
Mean D6+D7	5.07	8.51	10.05	11.28	137.01	165.73	85.16
SD	2.67	2.88	4.63	0.90	174.63	68.83	25.33

* FI = Fluctuation index = [(Cmax-Cmin)/Cmin] x 100

** F = Relative bioavailability compared to Franol®

Table 9. Steady-state pharmacokinetic parameters of theophylline after once daily doses of 2 x 200 mg Theo-Dur®.

Day Subj. no.	C_{min} (μg/ml)	C_{max} (μg/ml)	T_{max} (hr)	$MRT_{(0-24)}$ (hr)	* FI %	$AUC_{(0-24)}$ (μg.hr/ml)	** F %
(Day 6) 2	4.77	11.64	10.00	11.60	144.03	208.83	107.30
3	4.87	11.73	10.00	11.60	140.86	208.36	112.50
4	1.87	7.42	6.00	10.50	296.79	117.38	79.28
6	2.62	8.97	6.00	10.60	242.37	141.41	89.84
7	0.49	4.45	9.00	9.90	808.16	57.84	50.78
9	3.91	10.90	6.00	11.00	178.77	183.00	102.75
10	6.48	13.31	8.00	11.00	105.40	241.13	113.27
11	5.65	12.51	6.00	11.10	121.42	215.55	100.55
12	9.25	15.83	11.00	11.50	71.14	307.12	110.18
13	3.06	11.42	8.00	11.00	273.20	175.79	86.25
Mean D6	4.30	10.82	8.00	10.98	238.21	185.64	95.27
SD	2.51	3.19	1.94	0.54	213.59	68.99	19.49
(Day 7) 2	5.46	13.56	8.00	11.00	148.35	225.39	115.81
3	3.26	8.93	7.00	10.60	173.93	157.95	85.28
4	1.98	8.93	9.00	10.80	351.01	119.84	80.95
6	2.72	9.83	6.00	10.70	261.40	153.77	97.69
7	0.79	5.94	8.00	11.40	651.90	104.36	91.62
9	4.21	10.37	7.00	11.00	146.32	178.39	100.16
10	6.48	12.67	8.00	11.40	95.52	247.26	116.15
11	5.68	12.46	9.00	11.20	119.37	226.23	105.53
12	8.47	19.44	6.00	10.90	129.52	338.26	121.35
13	3.69	10.17	8.00	10.90	175.61	171.62	84.20
Mean D7	4.27	11.23	7.60	10.99	225.29	192.31	99.87
SD	2.29	3.63	1.07	0.27	167.86	68.99	14.54
Mean D6+D7	4.29	11.02	7.80	10.99	231.75	188.97	97.57
SD	2.34	3.33	1.54	0.41	187.09	67.24	16.90

* FI = Fluctuation index = [(Cmax-Cmin)/Cmin] x 100

** F = Relative bioavailability compared to Franol®

Table 10. Steady-state pharmacokinetic parameters of theophylline after once daily doses of 400 mg Xanthium®.

Day Subj. no.	C_{min} (μg/ml)	C_{max} (μg/ml)	T_{max} (hr)	$MRT_{(0-24)}$ (hr)	* FI %	$AUC_{(0-24)}$ (μg.hr/ml)	** F %
(Day 6) 2	2.94	6.52	7.00	11.7	121.77	124.37	63.90
3	3.42	6.80	7.00	11	98.83	132.60	71.59
4	1.38	4.03	8.00	11	192.03	71.20	48.09
6	2.17	5.68	6.00	10.6	161.75	97.46	61.91
7	1.08	3.56	7.00	10.5	229.63	58.54	51.40
9	4.65	9.21	6.00	11.1	98.06	164.21	92.20
10	7.35	10.97	8.00	12	49.25	235.03	110.40
11	7.04	10.32	11.00	11.9	46.59	214.76	100.18
12	5.34	9.70	9.00	11.5	81.65	202.22	72.55
13	4.94	8.84	7.00	11.5	78.95	173.96	85.35
Mean D6	4.03	7.56	7.60	11.28	115.85	147.43	75.76
SD	2.20	2.62	1.51	0.52	60.79	60.70	20.76
(Day 7) 2	3.80	7.49	8.00	11.6	97.11	142.25	73.09
3	3.42	6.08	8.00	11.6	77.78	123.25	66.55
4	1.48	4.88	6.00	10.4	229.73	80.54	54.40
6	2.17	5.85	6.00	11.8	169.59	114.18	72.54
7	1.08	3.71	6.00	10.9	243.52	61.23	53.76
9	4.62	6.84	7.00	11.7	48.05	138.62	77.83
10	6.97	11.20	6.00	11.2	60.69	221.64	104.11
11	7.58	11.31	11.00	12.2	49.21	241.69	112.74
12	7.19	12.38	10.00	12.2	72.18	260.35	93.40
13	4.92	7.63	10.00	12	55.08	151.97	74.56
Mean D7	4.32	7.74	7.80	11.56	110.29	153.57	78.30
SD	2.37	2.94	1.93	0.58	75.52	67.07	19.63
Mean D6+D7	4.18	7.65	7.70	11.42	113.07	150.50	77.03
SD	2.23	2.71	1.69	0.55	66.78	62.34	19.70

* FI = Fluctuation index = [(Cmax-Cmin)/Cmin] x 100

** F = Relative bioavailability compared to Franol®

Table 11. Comparison of steady-state pharmacokinetic (PK) parameters of Uni-Dur®, Theo-Dur® and Xanthium®

PK Parameters	Uni-Dur® (U)	Theo-Dur® (T)	Xanthium® (X)	90% CI (U:X)	90% CI (U:T)	90% CI (X:T)
C_{min} (D6) (μg/ml)	5.32 ± 2.94	4.30 ± 2.51	4.03 ± 2.2	1.09-1.66 (U>X)	1.06-1.43 (U=T)	0.86-1.22 (X=T)
C_{min} (D7) (μg/ml)	4.83 ± 2.49	4.27 ± 2.29	4.32 ± 2.37	0.94-1.38 (U=X)	0.9-1.41 (U>T)	0.87-1.14 (X=T)
Average C_{min} (μg/ml)	**5.07 ± 2.67**	**4.29 ± 2.34**	**4.18 ± 2.23**	**1.07-1.39 (U=X)**	**1.06-1.33 (U=T)**	**0.92-1.13 (X=T)**
C_{max} (D6) (μg/ml)	8.53 ± 3.05	10.82 ± 3.19	7.56 ± 2.62	0.96-1.31 (U=X)	0.66-0.91 (U<T)	0.62-0.77 (X<T)
C_{max} (D7) (μg/ml)	8.48 ± 2.87	11.23 ± 3.63	7.74 ± 2.94	0.92-1.28 (U=X)	0.6-0.89 (U<T)	0.6-0.75 (X<T)
Average C_{max} (μg/ml)	**8.51 ± 2.88**	**11.02 ± 3.33**	**7.65 ± 2.71**	**0.99-1.22 (U=X)**	**0.67-0.84 (U<T)**	**0.64-0.73 (X<T)**
T_{max} (D6) (hr)	10.50 ± 4.3	8.00 ± 1.94	7.60 ± 1.51	1.02-4.78 (U>X)	0.09-4.9 (U>T)	(-1.88)-1.08 (X<T)
T_{max} (D7) (hr)	9.60 ± 5.13	7.60 ± 1.07	7.80 ± 1.93	(-1.06)-4.66 (U>X)	(-0.48)-4.48 (U>T)	(-1.53)-1.13 (X=T)
Average T_{max} (hr)	**10.05 ± 4.63**	**7.8 ± 1.54**	**7.70 ± 1.69**	**0.82-3.87 (U>X)**	**0.70-3.80 (U>T)**	**(-1.0)-0.8 (X=T)**
AUC_{0-24} (D6) (μg.hr/ml)	169.14 ± 72.54	185.64 ± 68.99	147.43 ± 60.7	0.95-1.33 (U>X)	0.72-1.09 (U<T)	0.68-0.90 (X<T)
AUC_{0-24} (D7) (μg.hr/ml)	162.32 ± 68.66	192.31 ± 68.99	153.57 ± 67.07	0.8-1.25 (U=X)	0.60-1.01 (U<T)	0.69-0.86 (X<T)
Average AUC_{0-24} (μg.hr/ml)	**165.73 ± 68.83**	**188.97 ± 67.24**	**150.50 ± 62.34**	**0.94-1.21 (U=X)**	**0.71-0.96 (U<T)**	**0.72-0.84 (X<T)**
% F (D6)	86.88 ± 24.29	95.27 ± 19.49	5.76 ± 20.76	1.0-1.33	0.79-1.04	0.68-0.91
% F (D7)	83.44 ± 27.54	99.87 ± 14.54	78.30 ± 19.63	0.92-1.22	0.70-0.97	0.69-0.87
Average % F	**85.16 ± 25.33**	**97.57 ± 16.90**	**77.03 ± 19.70**	**1.01-1.21**	**0.79-0.96**	**0.73-0.85**
Wilcoxon Signed Rank test						
% FI (D6)	130.02 ± 179.92	238.21 ± 213.59	115.85 ± 60.79	P=0.1509 (NS)	P= 0.0156 P<0.05	P=0.0494 P<0.05
% FI (D7)	144.01 ± 178.6	225.29 ± 167.86	110.29 ± 75.52	P=0.9397 (NS)	P= 0.0156 (p<0.05)	P= 0.0233 (p<0.05)
Average % FI	**137.01 ± 174.63**	**231.75 ±187.09**	**113.07 ± 66.78**	**P= 0.3040 (NS)**	**P= 0.005 (P<0.01)**	**P=0.0024 (p<0.01)**

Table 12. Summary of parametric 90%CI of the mean steady-state pharmacokinetic parameters of Uni-Dur®, Theo-Dur® and Xanthium®

PK Parameters	90% CI (U:X)	90% CI (U:T)	90% CI (X:T)
C_{min}	1.07-1.39 (U=X)	1.06-1.33 (U=T)	0.92-1.13 (X=T)
C_{max}	0.99-1.22 (U=X)	0.67-0.84 (U<T)	0.64-0.73 (X<T)
T_{max}	0.82-3.87 (U>X)	0.70-3.80 (U>T)	(-1.0)-0.8 (X=T)
AUC_{0-24}	0.94-1.21 (U=X)	0.71-0.96 (U<T)	0.72-0.84 (X<T)
Wilcoxon Signed Rank test			
Average % FI	U & X	U & T	X & T
	NS	P<0.01	P<0.01

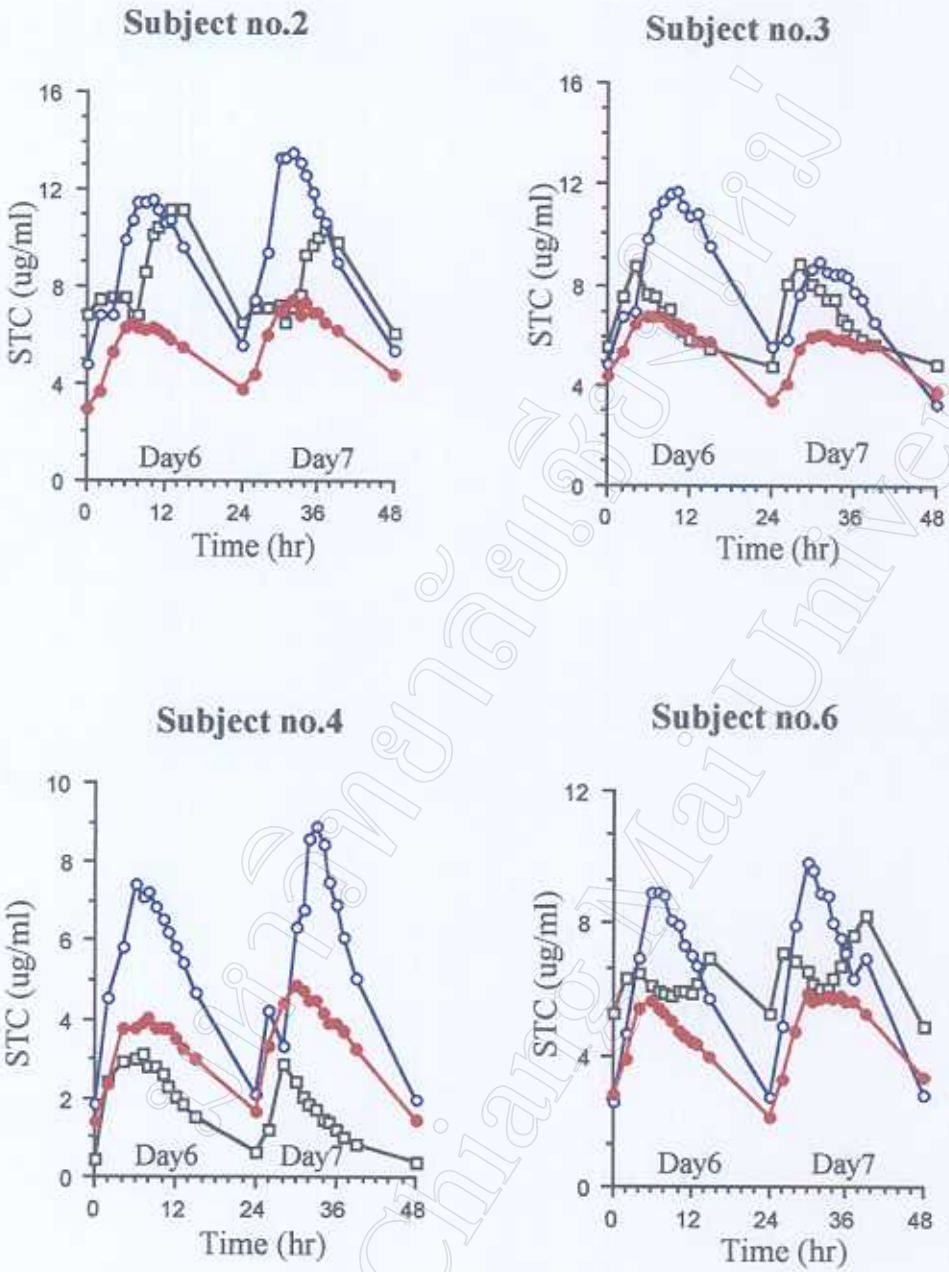

Figure 7. Individual profiles of steady-state (Day6-Day7) serum concentration-time curves after once daily doses of 400 mg Uni-Dur®(□), Theo-Dur®(O) and Xanthium®(●).

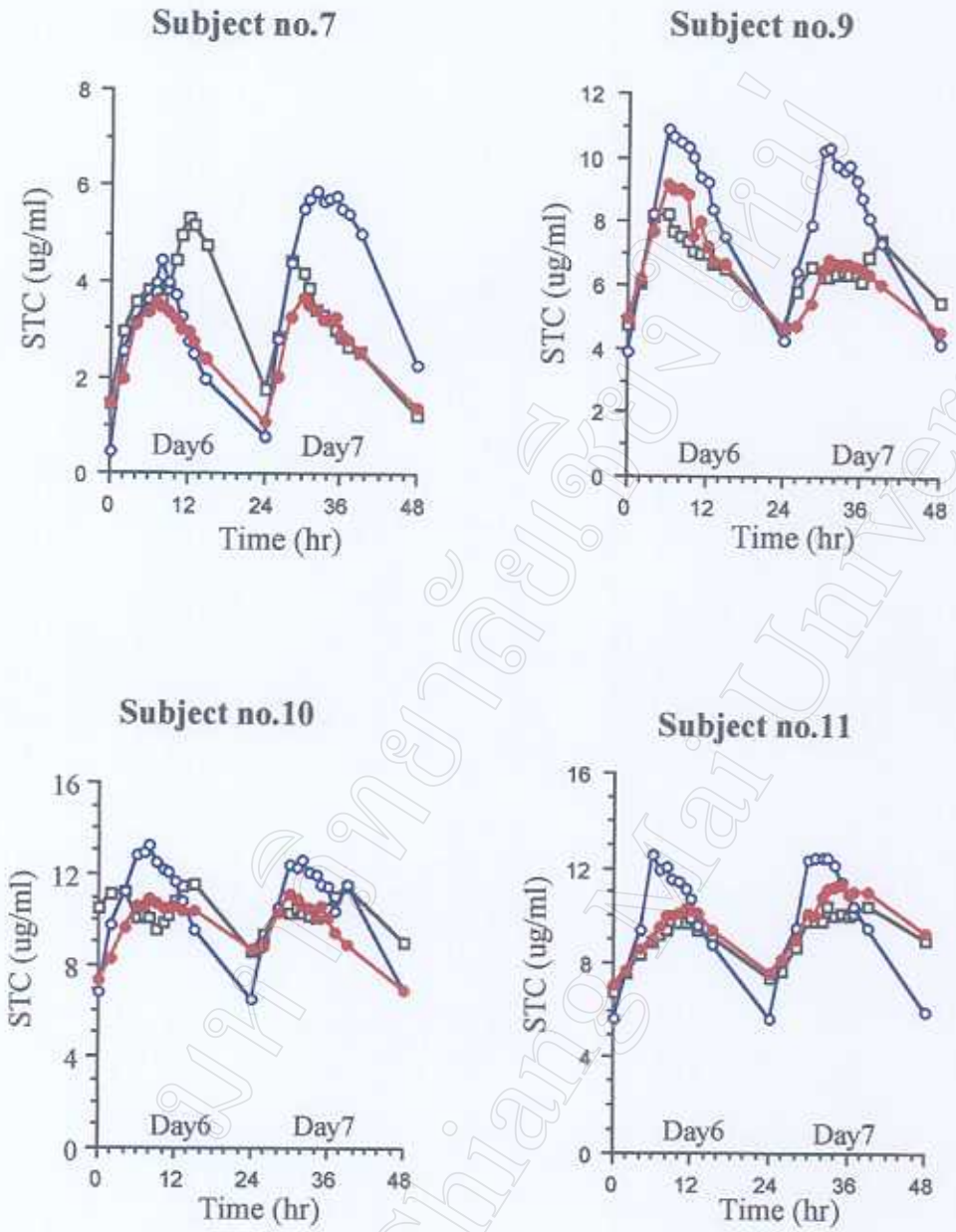

Figure 7 (cont.) Individual profiles of steady-state (Day6-Day7) serum concentration-time curves after once daily doses of 400 mg Uni-Dur® (□), Theo-Dur® (O) and Xanthium® (●)

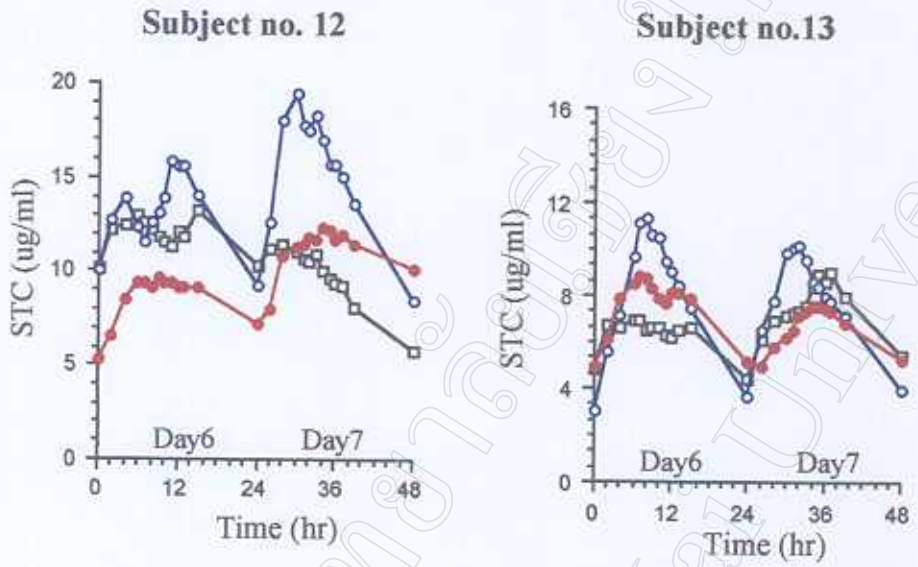

Figure 7 (cont.) Individual profiles of steady-state (Day6-Day7) serum concentration-time curves after once daily doses of 400 mg Uni-Dur® (□), Theo-Dur® (O) and Xanthium® (●)

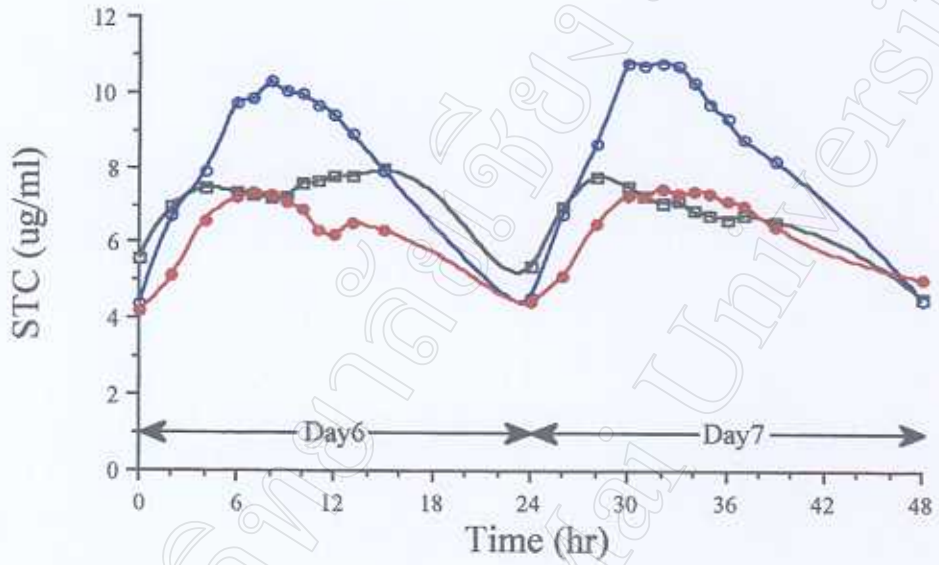

Figure 8. Mean steady-state (Day6-Day7) serum theophylline concentration-time curves after once daily dose of 400 mg Uni-Dur® (□),Theo-Dur® (O) and Xanthium® (•).

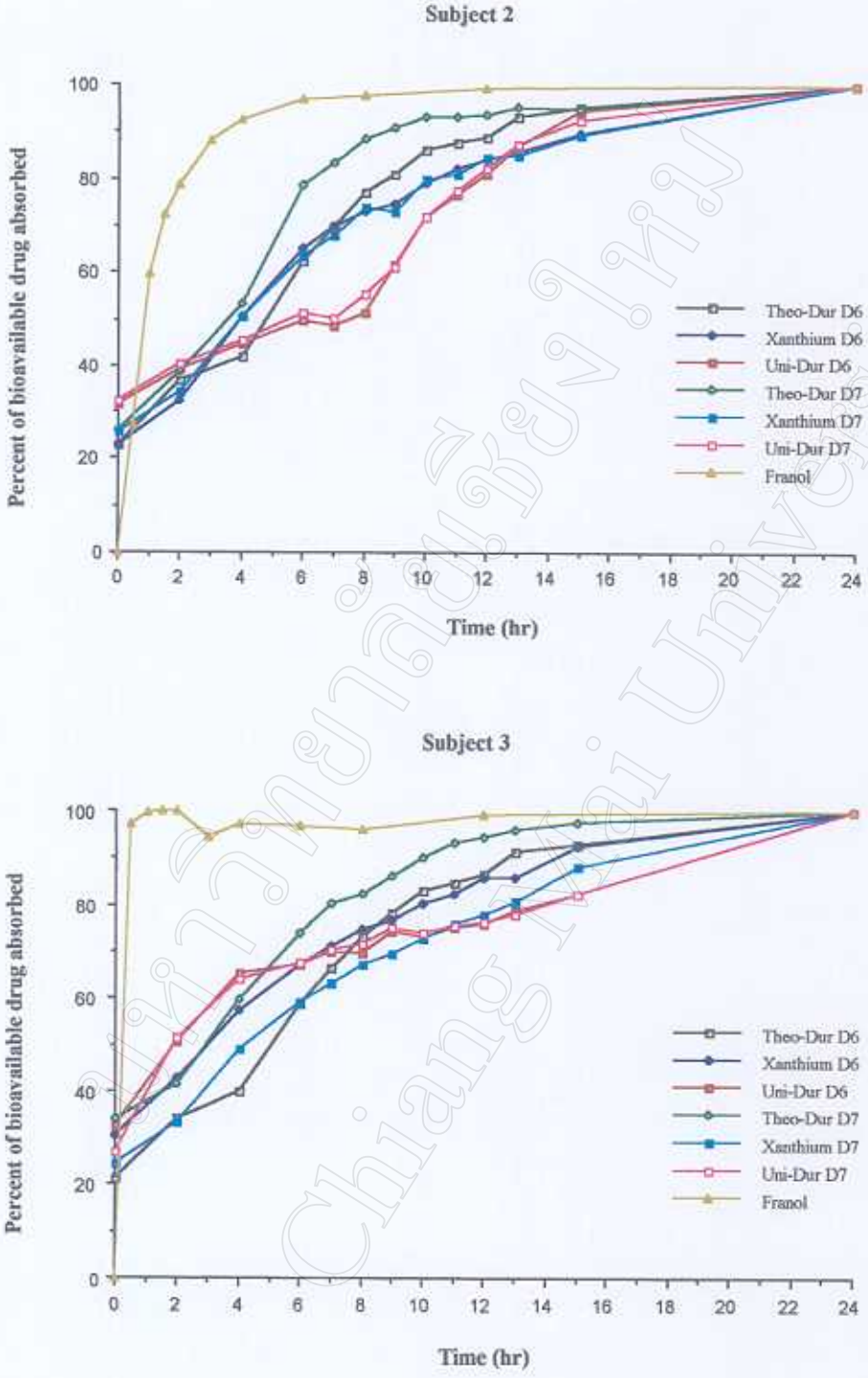

Figure 9. Amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

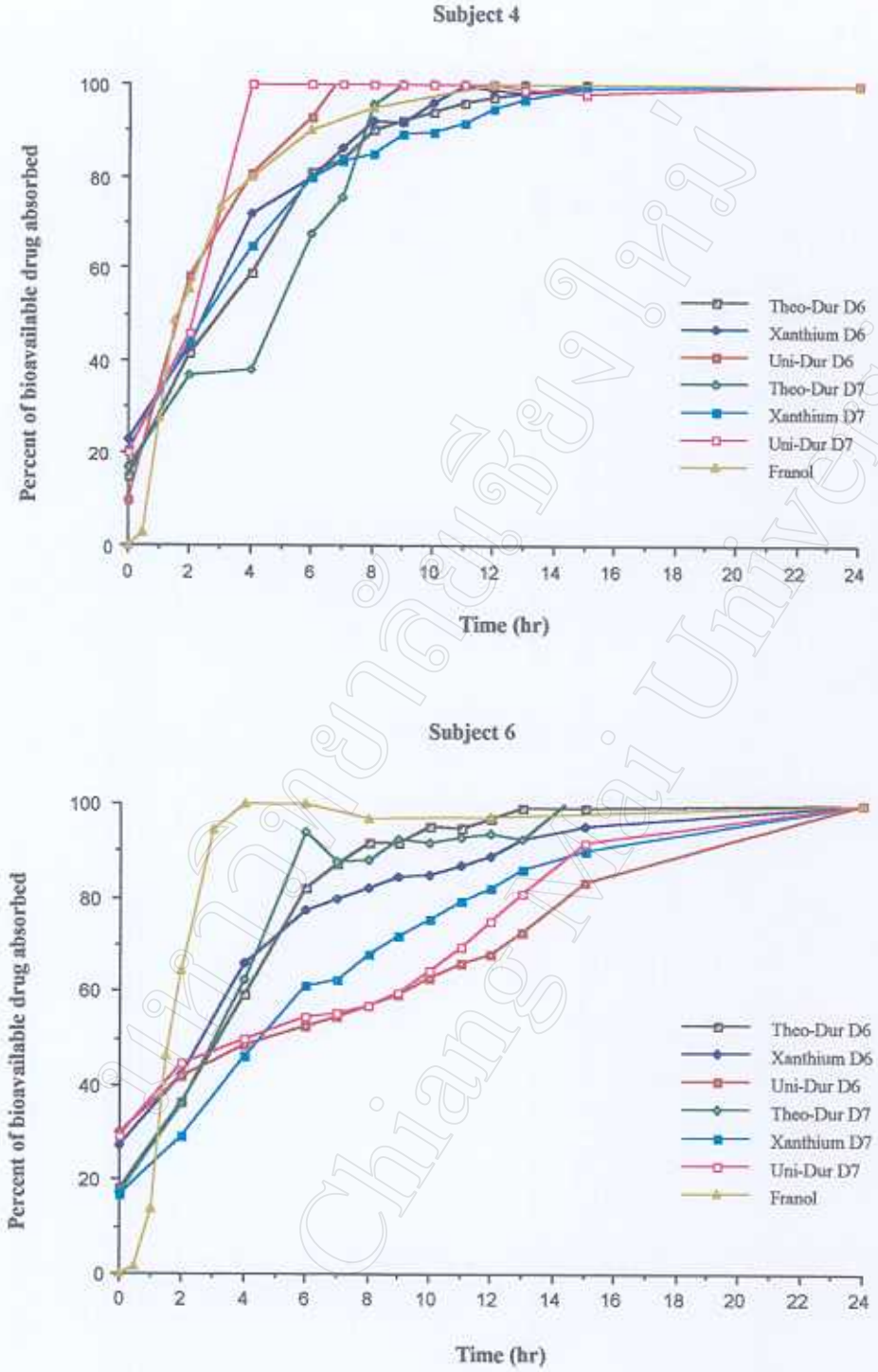

Figure 9. (cont.) Amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

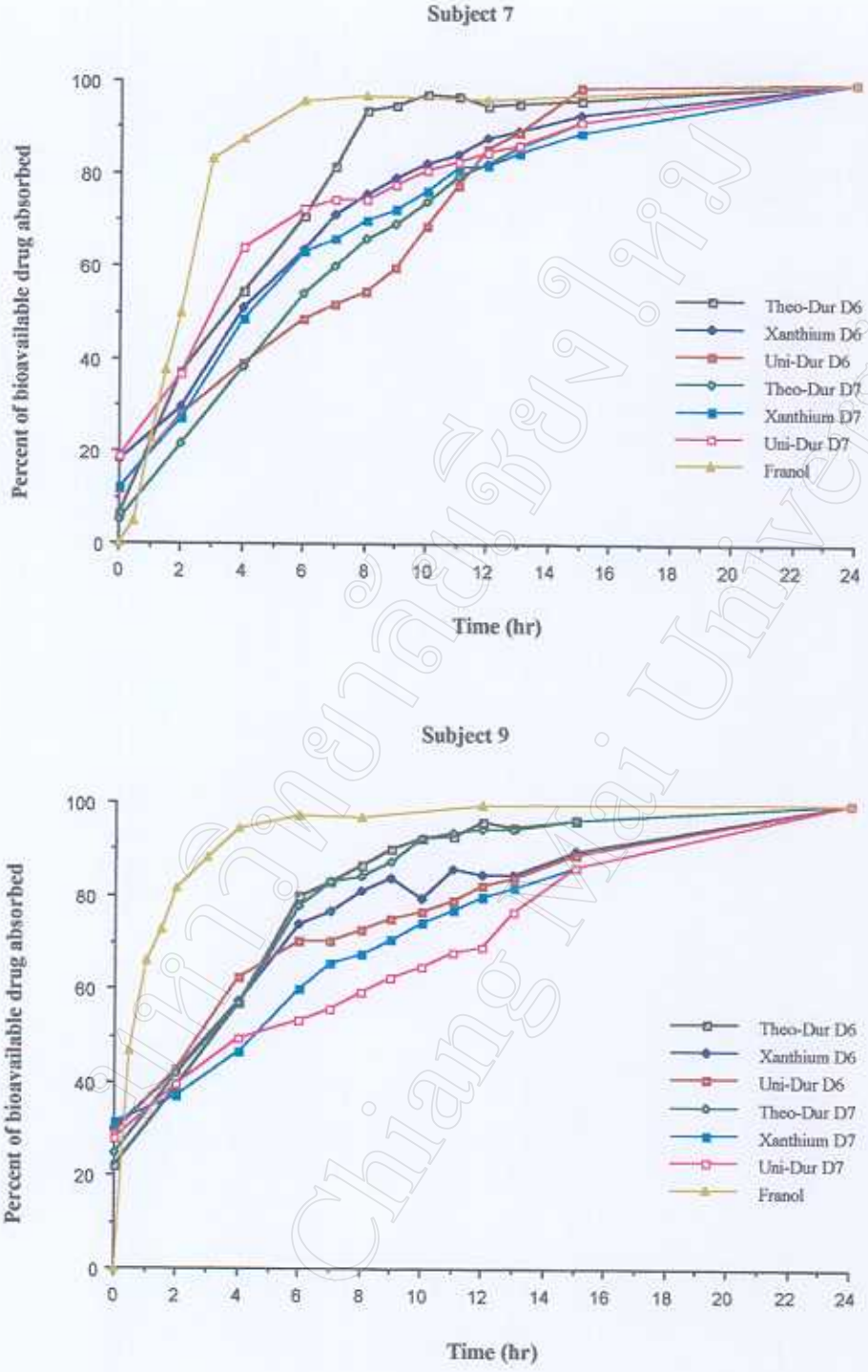

Figure 9. (cont.) Amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

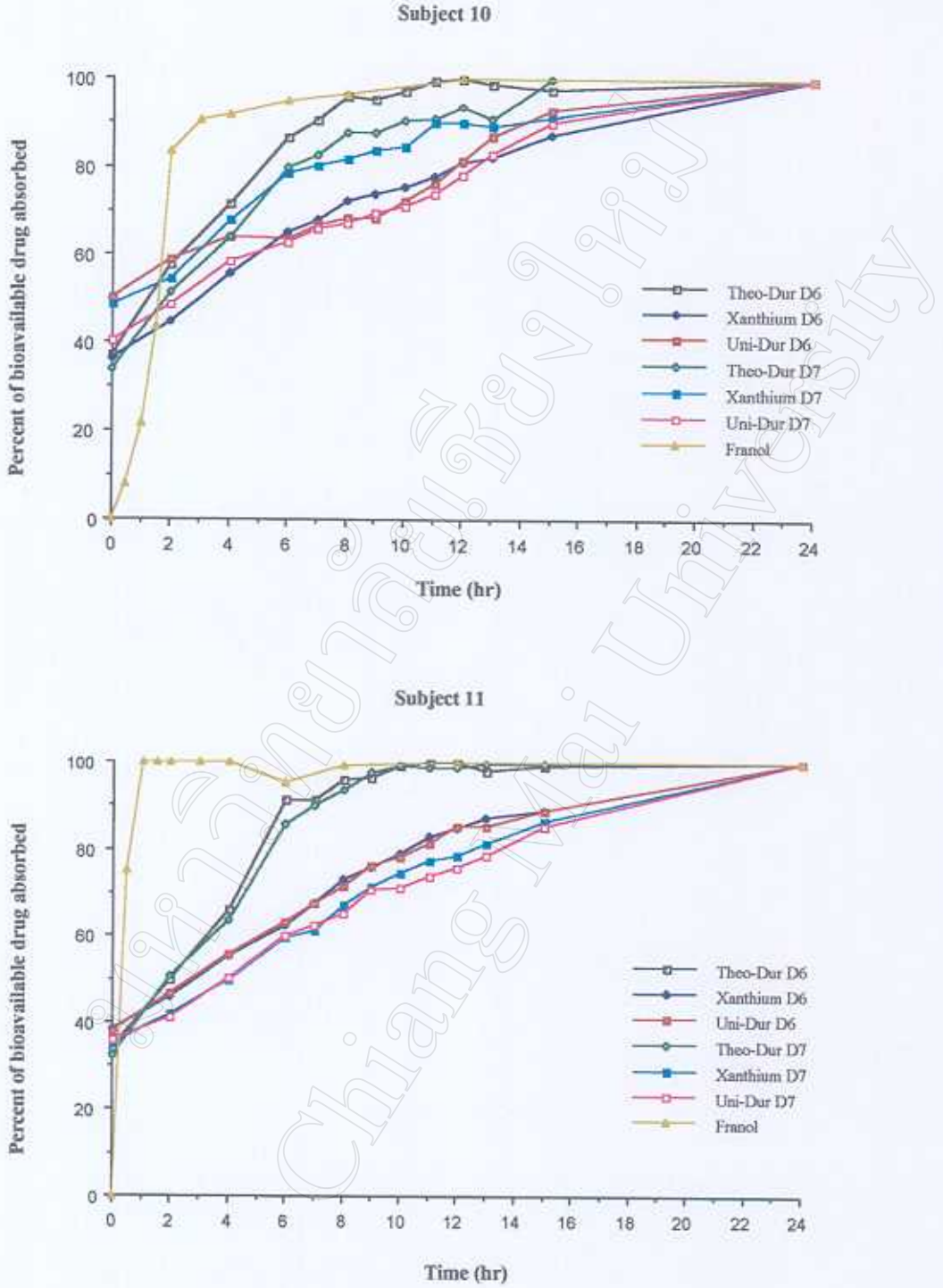

Figure 9. (cont.) Amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

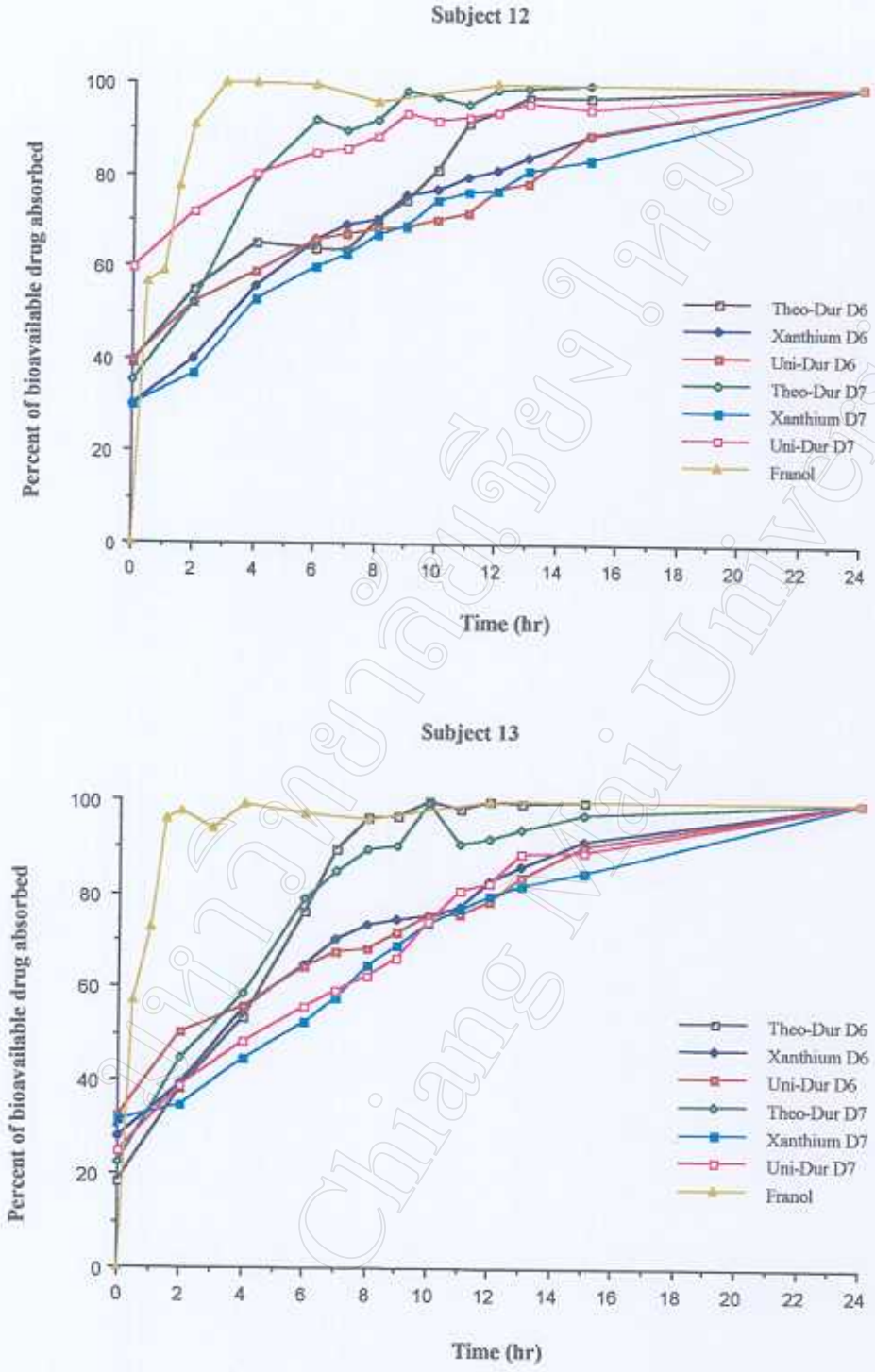

Figure 9. (cont.) Amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

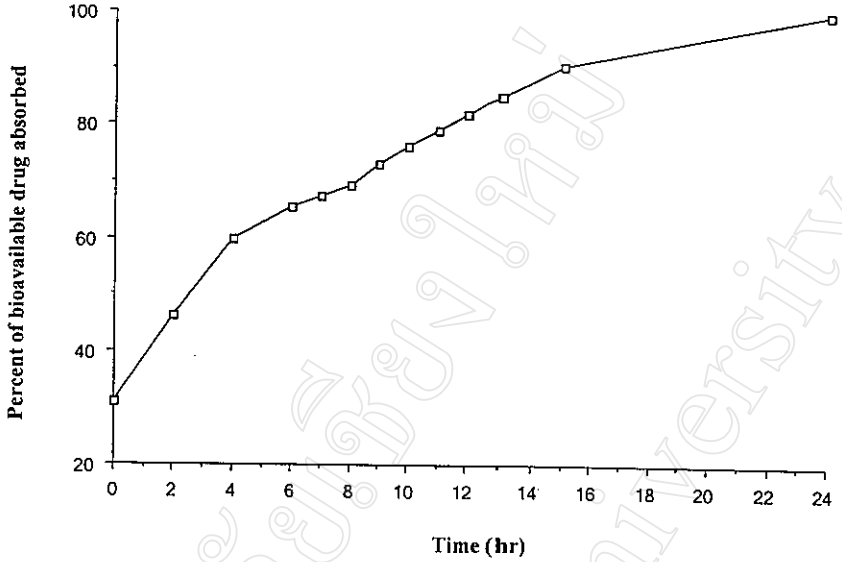

Figure 10. Mean amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral doses of Uni-Dur®.

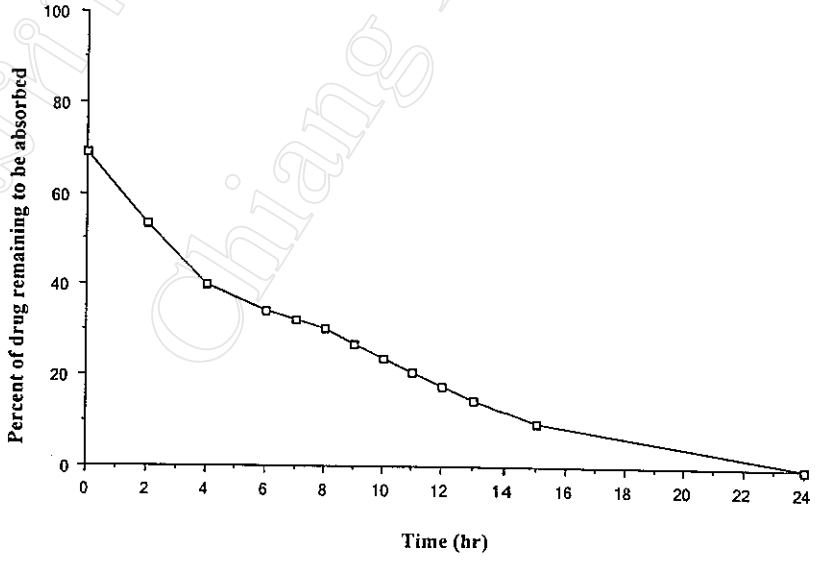

Figure 11. Mean amount (%) of drug remaining to be absorbed with time after 400 mg oral doses of Uni-Dur®.

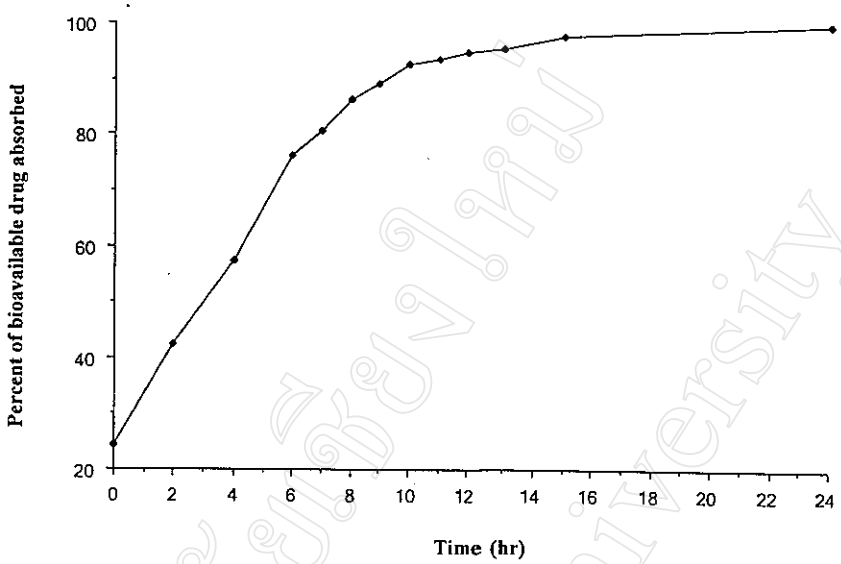

Figure 12. Mean amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral doses of Theo-Dur®.

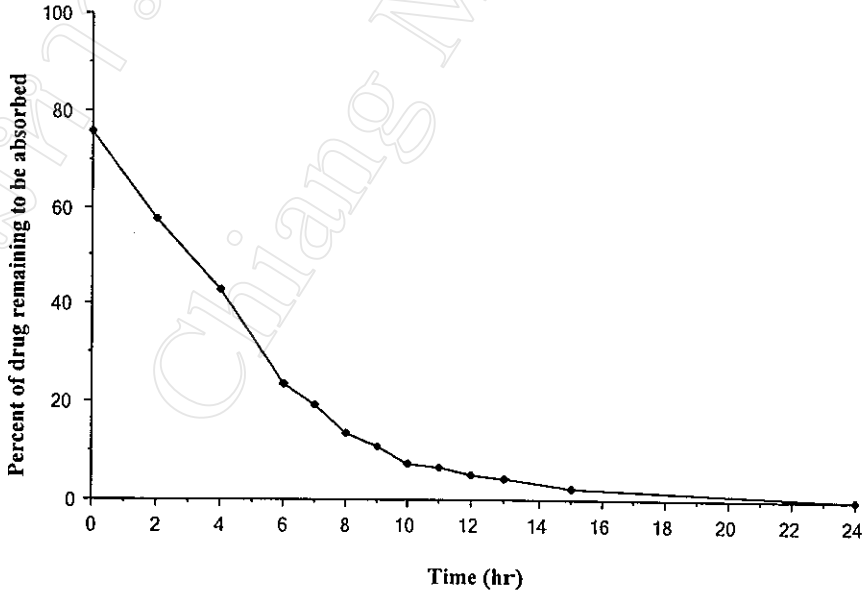

Figure 13. Mean amount (%) of drug remaining to be absorbed with time after 2 x 200 mg oral doses of Theo-Dur®.

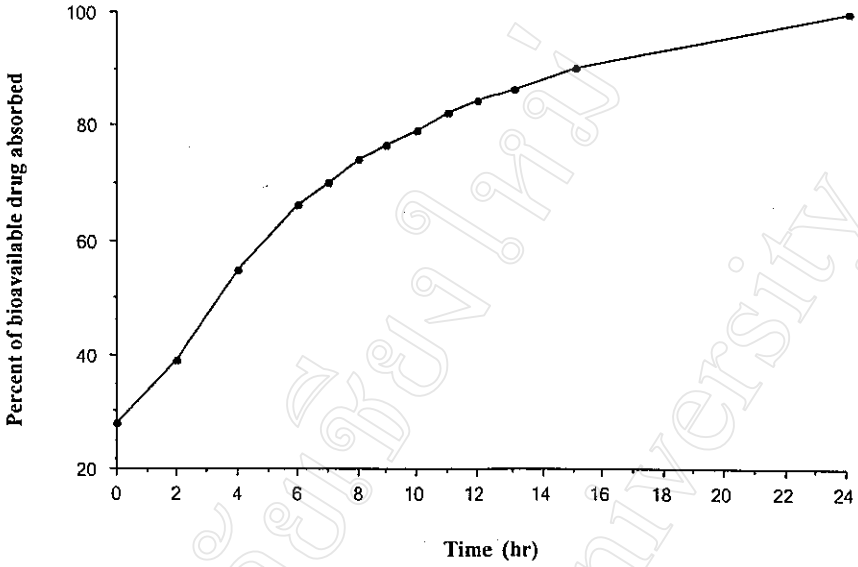

Figure 14. Mean amount (%) of bioavailable drug absorbed with time (Wagner-Nelson method) after 400 mg oral doses of Xanthium®.

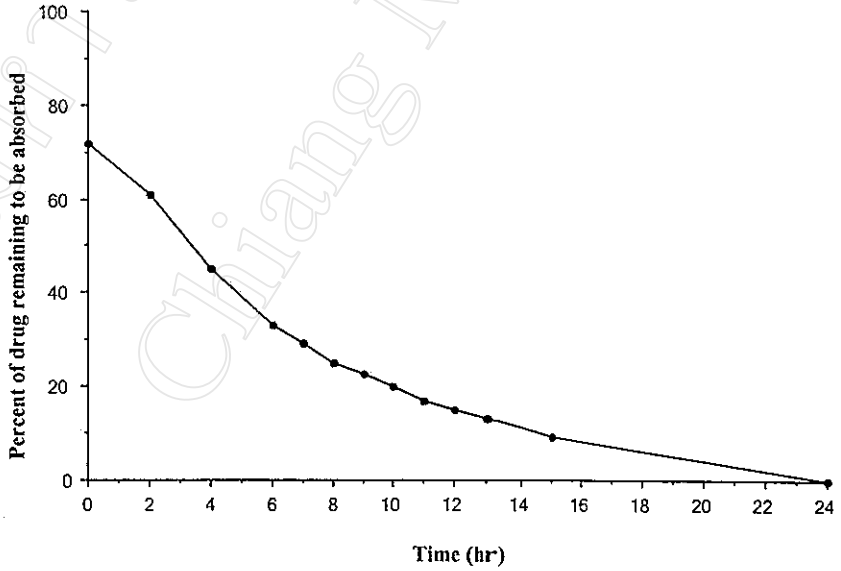

Figure 15. Mean amount (%) of drug remaining to be absorbed with time after 400 mg oral doses of Xanthium®.

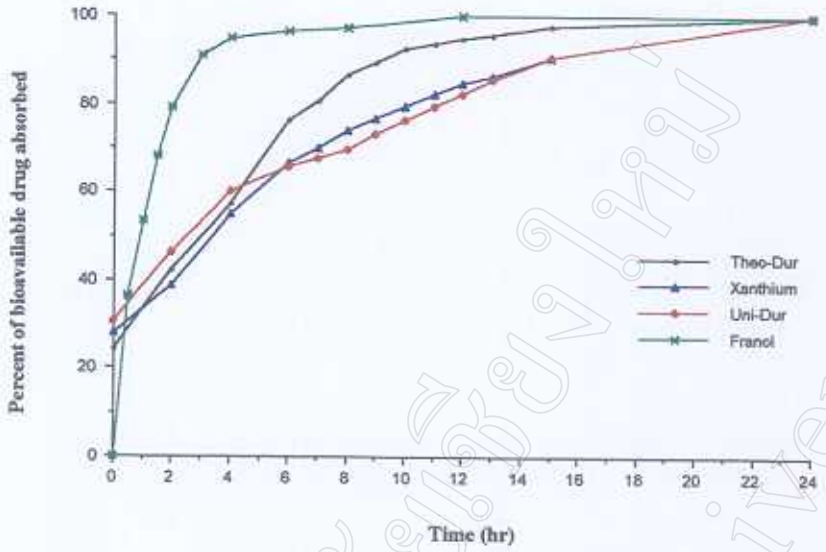

Figure 16. Mean amount (%) of bioavailable drug absorbed with time after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.

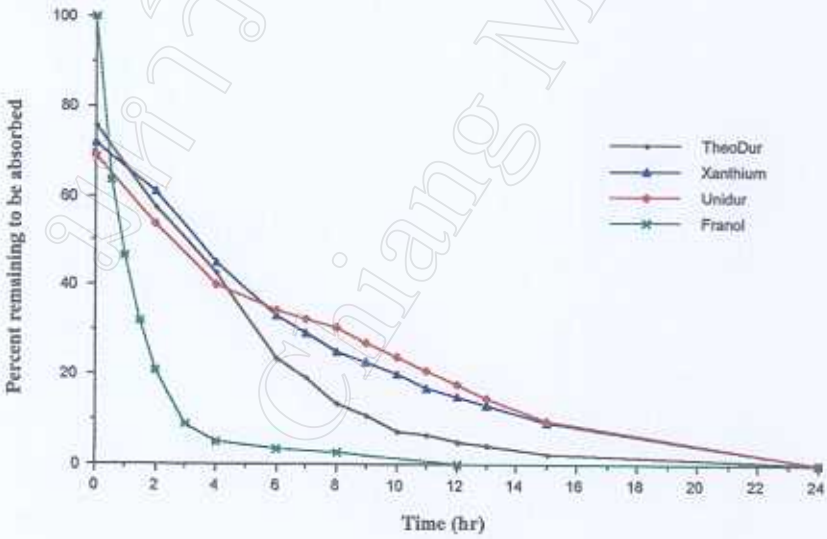

Figure 17. Comparison of mean amount (%) of drug remaining to be absorbed with time after 400 mg oral dose(s) of Uni-Dur®, Theo-Dur®, Xanthium® and Franol®.