RESULTS

Assay Validation Report

Specificity and linearity

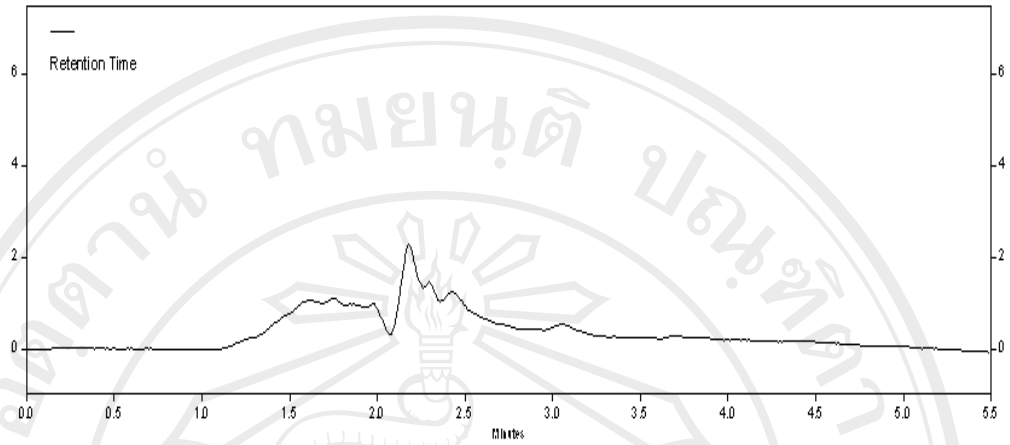
Peak of donepezil and IS (ondansetron**)** were well separated by the HPLC system. Retention times were approximately 3.2 min and 4.5 min for IS and donepezil**,** respectively. There was no significant interference at the retention times of the drug and IS (Figures 1A and 1B).

The calibration curve of donepezil in plasma was linear from 2-100 ng/mL (Table 3). The linear regression of concentrations and peak height ratios of donepezil/IS gave high coefficients of determination (r^2), which was greater than 0.9900 (r^2 = 0.9988, Figure 3).

Precision, accuracy, recovery and stability

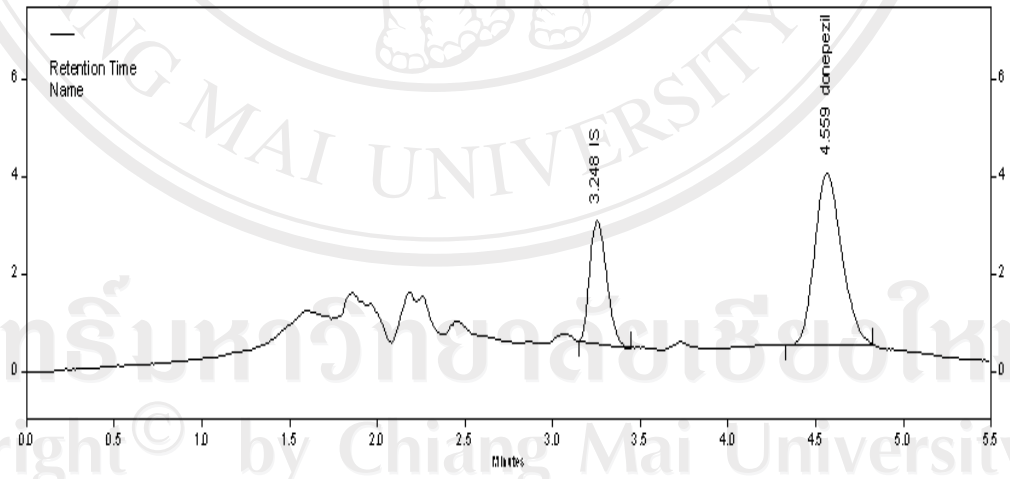
Tables 3 through 6 presented the precision, accuracy, and recovery of donepezil in plasma. Table 3 indicates that the LLOQ of donepezil plasma was 2 ng/mL with the average accuracy of 103.03% (in average) and the average precision of 14.79%. Table 4 shows that the accuracy and average precision of intra-day assay validation were 102.59% and 4.97% and those of inter-day assay validation were 102.69% and 3.69% as displayed in Table 5. Table 6 shows that the mean recoveries of donepezil and the IS were 97.39% and 102.38%, respectively.

Tables 7 through 10 summarize the different stability tests of donepezil in plasma. The average deviations were -2.44, -3.94, -5.59, and +10.54% for freeze-thaw, short-term, long-term, and post-preparative stability of donepezil in plasma, respectively. In addition, Table 11 shows that the average deviations of stock-solution stability for donepezil and IS were -2.12 and +0.97%, respectively.



Time (min)

Figure 1A Chromatograms of blank plasma



Time (min)

Figure 1B Chromatogram of donepezil 100 ng/mL and IS (ondansetron) from human plasma sample.

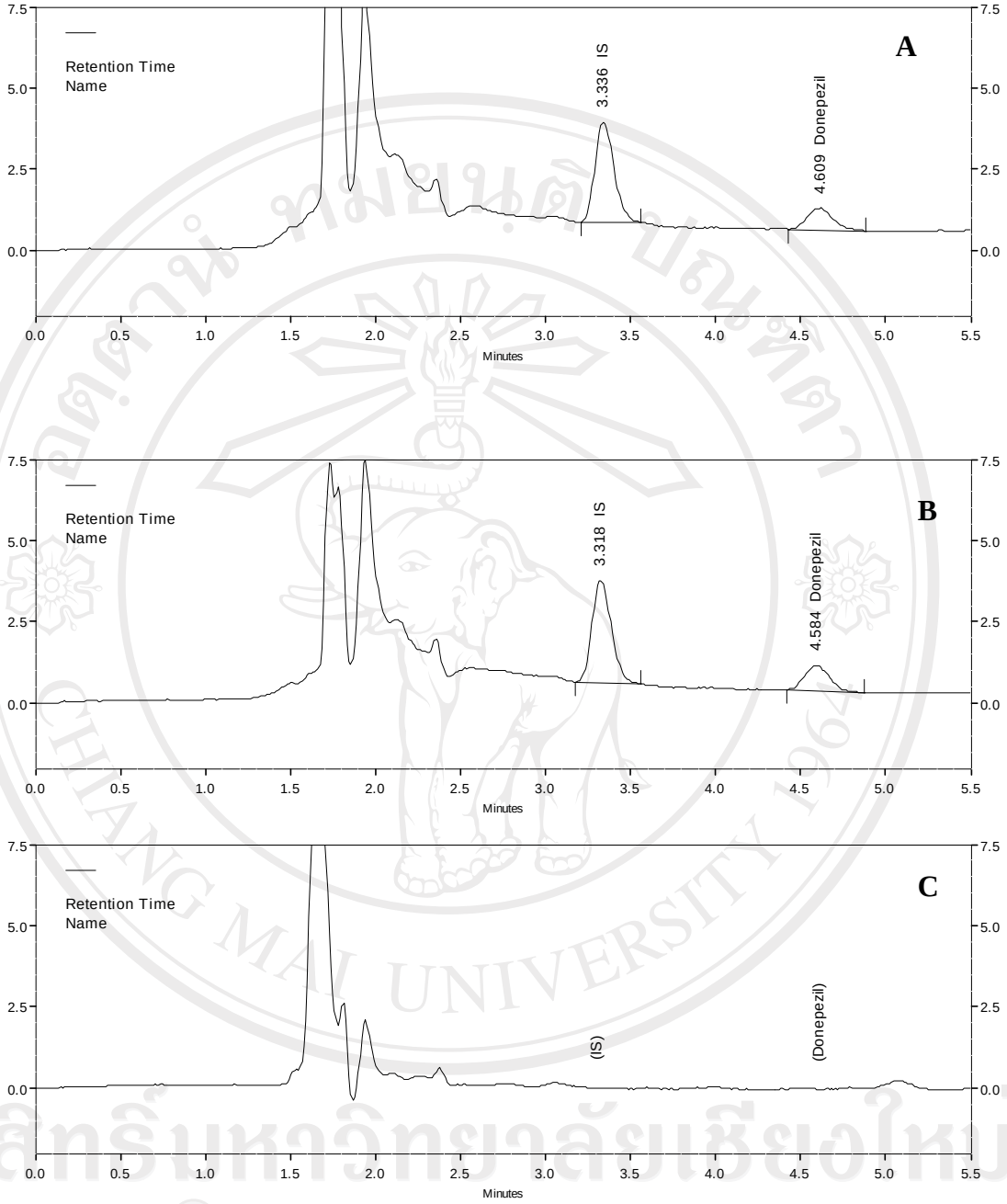


Figure 2 Chromatograms of donepezil and IS from volunteer plasma samples, 2 h after single oral dose administration of test product (A), reference product (B) and blank plasma (C).

Table 3 Various concentration of donepezil in plasma use for construction calibration curve

No.	Spiked concentration (ng/ml)	IS (peak ht)	Donepezil (peak ht)	Donepezil/IS	Calulated concentration (ng/ml)	**Accuracy (%)**
1	2	2322	53	0.0228	2.05	102.50
2	5	2523	191	0.0757	5.70	113.94
3	12.5	2457	358	0.1457	10.52	84.20
4	25	2374	846	0.3564	25.05	100.21
5	50	2319	1726	0.7443	51.81	103.61
6	100	2518	3602	1.4305	99.13	99.13
	2	2670	76	0.0285	2.44	121.95
	2	2616	46	0.0176	1.69	84.43
	2	2747	65	0.0237	2.11	105.39
	2	2758	54	0.0196	1.83	91.31
	2	2656	68	0.0256	2.24	112.08
	Mean	2689.40	61.80	0.02	2.06	**103.03**
	S.D.	61.04	11.84	0.00	0.30	
	Precision (CV, %)				**14.79**	

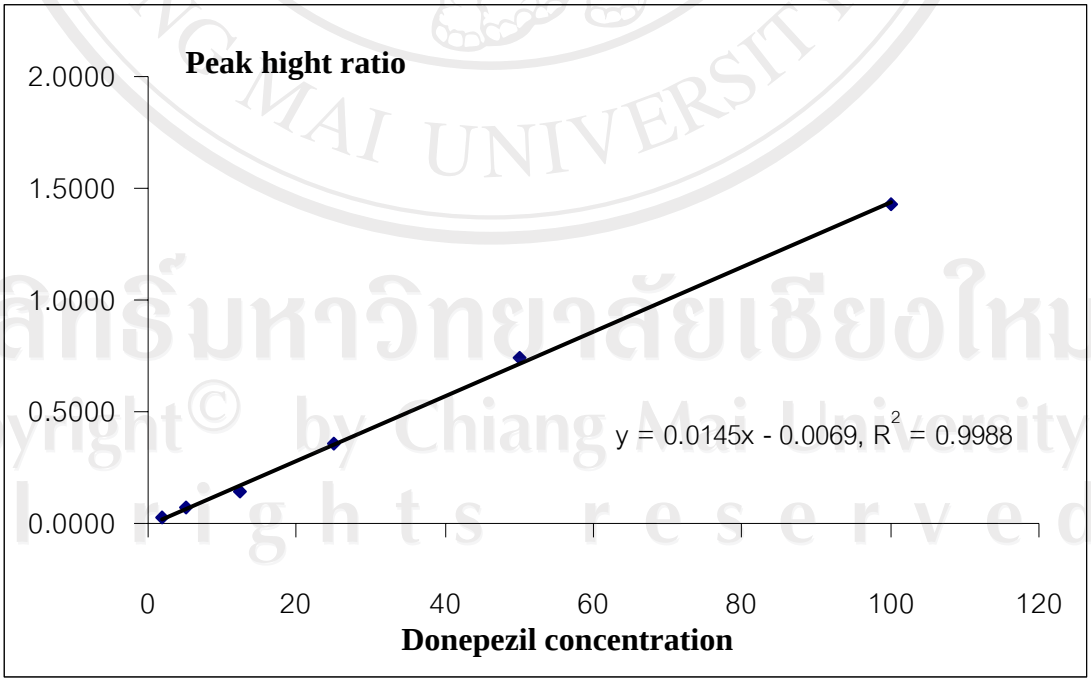


Figure 3 Calibration curve of donepezil in human plasma

Table 4 Intra-day assay validation of donepezil in plasma

QC sample	Spiked concentration (ng/ml)	Donepezil (peak ht)	Internal Standard (peak ht)	Donepezil/IS	Calulated concentration (ng/ml)	**Accuracy (%)**
Low	6	2409	214	0.0888	6.60	110.04
	6	2396	207	0.0864	6.43	107.23
	6	2044	156	0.0763	5.74	95.66
	6	2409	215	0.0892	6.63	110.52
	6	2469	206	0.0834	6.23	103.83
	Mean	2345.40	199.60	0.08	6.33	**105.46**
	S.D.	170.86	24.70	0.01	0.37	
	Precision (CV, %)	**7.28**	**12.38**	**6.25**	**5.78**	
Medium	45	2522	1482	0.5876	41.00	91.12
	45	2350	1405	0.5979	41.71	92.69
	45	2497	1575	0.6308	43.98	97.73
	45	2407	1558	0.6473	45.12	100.26
	45	2550	1723	0.6757	47.07	104.61
	Mean	2465.20	1548.60	0.63	43.78	**97.28**
	S.D.	83.80	118.59	0.04	2.48	
	Precision (CV, %)	**3.40**	**7.66**	**5.74**	**5.68**	
High	90	2442	3138	1.2850	89.10	99.00
	90	2397	3281	1.3688	94.88	105.42
	90	2307	3241	1.4049	97.36	108.18
	90	2237	3123	1.3961	96.76	107.51
	90	2376	3243	1.3649	94.61	105.12
	Mean	2351.80	3205.20	1.36	94.54	**105.04**
	S.D.	80.55	70.23	0.05	3.26	
	Precision (CV, %)	**3.42**	**2.19**	**3.47**	**3.45**	
		Average (%)			**4.97**	**102.59**

Table 5 Inter-day assay validation of donepezil in plasma

Spiked concentration (ng/ml)	**Calculated concentration (ng/ml)**					**Precision (CV, %)**	**Accuracy (%)**
	Day 1	**Day 2**	**Day 3**	**Mean**	**S.D.**		
6	6.33	5.96	6.21	6.17	0.19	3.06	102.8
45	43.78	47.70	44.62	45.37	2.06	4.55	100.8
90	94.54	96.44	90.12	93.70	3.25	3.47	104.1
	Average recovery (%)					**3.69**	**102.6**

Table 6 Recovery of donepezil and IS from plasma

QC Sample	Spiked concentration (ng/ml)	**Donepezil (peak ht)**	
		in mobile phase	after plasma extraction
Low	6	170	214
	6	168	207
	6	180	156
	6	250	215
	6	213	206
	Mean	196.20	199.60
	Recovery (%)		**101.73**
Medium	45	1664	1482
	45	1715	1405
	45	1707	1575
	45	1603	1558
	45	1811	1723
	Mean	1700.00	1548.60
	Recovery (%)		**91.09**
High	90	3054	3138
	90	3024	3281
	90	3336	3241
	90	3333	3123
	90	3385	3243
	Mean	3226.40	3205.20
	Recovery (%)		**99.34**
	Average recovery (%)		**97.39**

Spiked concentration (ng/ml)		**IS (peak ht.)**	
		in mobile phase	after plasma extraction
	30	2302	2409
		2356	2396
		2354	2044
		2245	2409
		2197	2469
	Mean	2290.80	2345.40
	Recovery (%)		**102.38**

Table 7 Freeze-thaw stability of donepezil in plasma

QC Sample	Spiked concentration (ng/ml)	Calculated concentration (ng/ml)	
		before freeze/thaw	after freeze/thaw
Low	6	5.13	5.36
	6	5.41	5.29
	6	5.76	4.75
	Mean	5.43	5.13
	Deviation (%)		**-5.52**
High	90	100.2	99.43
	90	103.3	105.95
	90	99.6	99.56
	Mean	101.01	101.65
	Deviation (%)		**+0.63**
	Average deviation (%) = -2.44		

Table 8 Short-term stability of donepezil in plasma

QC Sample	Spiked concentration (ng/ml)	Donepezil concentration (ng/ml)	
		0 h	8 h
Low	6	7.69	6.57
	6	7.43	6.84
	6	7.32	7.25
	Mean	7.48	6.89
	Deviation (%)		**-7.93**
High	90	87.9	88.28
	90	94.0	95.38
	90	96.0	94.46
	Mean	92.66	92.70
	Deviation (%)		**+0.05**
		Average deviation (%) = -3.94	

Table 9 Long-term stability of donepezil in plasma

QC Sample	Spiked Concentration (ng/ml)	Donepezil concentration (ng/ml)	
		14-Oct-05	16-Dec-05
Low	6	7.69	6.61
	6	7.43	6.33
	6	7.32	7.18
	Mean	7.48	6.71
	Deviation (%)		**-11.50**
High	90	87.9	89.55
	90	94.0	95.48
	90	96.0	93.80
	Mean	92.66	92.95
	Deviation (%)		**0.31**
		Average deviation (%) = -5.59	

Table 10 Post-preparative stability of donepezil determination in plasma

Control Sample	Spiked Concentration (ng/ml)	Donepezil concentration (ng/ml)	
		0 h	3 h
Low	6	6.78	7.94
	6	6.89	7.41
	6	6.59	7.62
	Mean	6.75	7.66
	Deviation (%)		**+13.37**
High	90	94.8	100.90
	90	94.8	103.23
	90	94.6	101.94
	Mean	94.71	102.03
	Deviation (%)		**+7.72**
	Average deviation (%) = +10.54		

Table 11 Stability of donepezil and IS in stock-solution

Control Sample	Spiked Concentration (ng/ml)	Donepezil (peak ht)	
		0 h	8 h
Low	6	250	246
	6	246	246
	6	256	241
	Mean	251	244.33
	Deviation (%)		**-2.53**
High	90	3054	3009
	90	3064	3003
	90	3077	3027
	Mean	3065	3013.00
	Deviation (%)		**-1.70**
		Stock solutions Stability (%) = -2.12	

Spiked concentration (ng/ml)		**IS (peak ht)**	
		0 h	8 h
	30	2235	2267
		2239	2274
		2259	2257
	Mean	2244.33	2266.00
	Deviation (%)		**+0.97**

Study in subjects

. Twenty healthy Thai male volunteers were enrolled into the study. The demographic characteristics of all subjects and the sequence visit with drug administration are listed earlier in Tables 1 and 2. The range of age (mean±S.D.), height, weight and BMI were 20-32 y (24.60±3.55 y), 1.61-1.84 m (1.69±0.06 m), 48.00-77.00 kg (62.38±6.45 kg) and 18.07-24.91 kg/m^2 (21.88±1.97 kg/m^2), respectively (Table 1).

The clinical study was completed within 3 months. The two formulations of donepezil HCl were well tolerated during the clinical trial without any reported serious adverse events. Volunteers No 15 and 16 had sore throat and cough on the third study day of the first visit and volunteer No 20 had mild headache on the second study day of the second visit. During the 3-month study, there was no drop-out; all volunteers continued the study to the end and were discharged in good health.

Pharmacokinetics of donepezil HCl in healthy volunteers

Plasma donepezil HCl concentration-time profiles

The plasma donepezil concentrations at each sampling time following a single oral dose of 5 mg of both generic donepezil HCl and Aricept® are shown in Tables 12 and 13, respectively. In addition, their means, standard deviations (S.D), coefficiens of variation (% C.V.), maximum and minimum values are also respectively shown in Tables 14 and 15. Pair-wise presentation of individual plasma concentration-time profiles of the generic donepezil HCl and Aricept® as well as their mean plasma concentration-time profile are depicted in Figure 1 and Figure 2, respectively. The pair-wise intra-individual concentration-time profiles of the test and the reference (Figure 1) were relatively similar. Likewise, their mean profiles were also comparable although the mean peak donepezil concentration of the test (20.42 ng/mL) was slightly higher than that of the reference (18.93 ng/mL), there was no significant difference ($p>0.05$) between these two values (Tables 16 and 17).

Pharmacokinetics parameters of donepezil HCl and statistical analysis

The pharmacokinetic parameters derived from each subject after receiving 5-mg tablet of donepezil HCl and Aricept® are presented in Tables 16, 17 and 18. Pharmacokinetic parameters including T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{1/2}$, the clearance after oral administration (CL/F) and V_d as well as their means, SD, % CV, maximum and minimum concentrations of the test and the reference, respectively. Furthermore, the intra-individual pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) between the test and the reference were compared and the results are shown in Table 16. The median T_{max} of the test was similar to that of Aricept® (2 h, range 1.0-3.0 h). The calculated mean [90%CI] of the T_{max} difference was 0.05 h [(-0.19)-0.29 hr] which was within the bioequivalence range of ±0.41 h. The mean values (± SD) of the C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ for the test were not significantly different from the reference (20.42 ± 4.5 vs 18.93 ± 3.82 ng/mL, 1051.44 ± 206.87 vs 983.58 ± 199.40 ng.h/mL, and 1375.01 ± 369.01 vs 1277.47 ± 328.51 ng.h/mL, respectively). The average $T_{1/2}$ of donepezil between the test (91.5 h, range 59.1-164 h) and the reference (90.7, range 62.5-148 h) were also similar. The clearance (CL/F) and Vd of the test and the reference were 1.03 $\pm$ 0.22 vs 1.12 $\pm$ 0.29 L/h and 7.88 $\pm$ 1.28 vs 8.48 $\pm$ 1.41 L/kg, respectively(Table 18). The relative bioavailability (F_{rel}) calculated from C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ of the generic Donepezil HCl/Aricept® was 110%, 108%, and 109%, respectively (Table 19).

From the ANOVA table (Table 20-23) the residual inter-subjects variability in the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were significantly high (p=0.0000, 0.0000 and 0.0374 respectively). The intra-subjects % CV estimated from S^2 obtained from the ANOVA after logarithmic transformed for the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were 9%, 10%, and 15%, respectively. Bioequivalence analysis showed that the mean (90% CI) for the ratios $\frac{\text{Test}}{\text{Reference}}$ were 1.07 (1.02-1.13), 1.08 (1.02-1.14), and 1.08 (0.99-1.17), respectively for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. These values were within the bioequivalence range, thus, this study demonstrated the bioequivalence of the generic donepezil HCL and Aricept.

Table 12 Plasma donepezil concentrations (ng/mL) after 5 mg oral administration of the generic donepezil HCl

Volunteer No	P1	P2	Plasma donepezil concentration (ng/ml)																
Time (h)			0	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216
1	X		BLOQ	2.61	8.92	16.79	16.71	14.59	14.06	12.14	10.61	9.67	7.05	4.45	4.60	3.67	2.94	2.24	2.37	2.06
2	X		BLOQ	18.23	19.91	17.90	12.94	12.25	12.49	12.31	9.11	7.08	5.15	4.63	4.68	3.51	3.48	3.67	2.73	BLOQ
3	X		BLOQ	19.67	14.14	10.61	10.24	9.81	9.30	8.38	7.56	6.67	4.73	4.58	4.30	2.57	2.50	2.17	2.06	1.87
4		X	BLOQ	7.26	18.74	19.20	18.28	15.05	12.88	12.70	10.76	9.05	7.61	5.88	4.66	4.51	3.91	3.23	3.09	2.95
5	X		BLOQ	5.92	34.47	26.17	22.08	18.67	18.55	17.26	14.51	12.94	9.40	6.46	5.54	4.45	3.81	2.98	2.94	2.62
6		X	BLOQ	6.64	22.83	17.18	14.47	14.47	14.12	11.77	11.10	9.97	8.45	6.21	6.11	2.73	3.12	2.61	2.56	1.94
7		X	BLOQ	16.41	15.80	11.49	11.71	10.32	9.89	8.11	7.28	6.75	5.26	4.52	4.39	3.50	2.90	2.53	2.39	2.25
8	X		BLOQ	10.46	23.64	16.13	14.86	12.17	11.45	10.62	8.85	7.77	5.48	5.41	3.85	3.80	3.06	2.47	2.63	2.49
9	X		BLOQ	14.52	24.30	19.73	16.23	13.64	12.14	12.07	10.29	9.72	6.31	5.66	5.21	5.18	3.67	3.76	3.20	3.02
10		X	BLOQ	11.15	21.00	20.36	17.29	13.57	13.85	12.82	12.22	7.72	6.61	6.29	5.33	5.63	4.90	4.56	4.35	3.02

P1 = dispense medication on period 1 P2 = dispense medication on period 2 BLOQ= below lower lower limit of quantitation

Table 12 (Cont.) Plasma donepezil concentrations (ng/mL) after 5 mg oral administration of the generic donepezil HCl

Volunteer No	P1	P2	Plasma donepezil concentration (ng/ml)																	
Time (h)			0	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216
11		X	BLOQ	24.68	25.57	20.84	17.72	15.21	12.98	12.93	12.07	9.56	7.16	5.15	4.49	3.90	3.14	2.66	2.34	2.33
12	X		BLOQ	16.52	24.25	16.34	15.02	14.03	11.84	10.26	9.57	8.21	6.23	4.61	4.26	3.73	3.07	2.31	2.12	1.73
13		X	BLOQ	2.44	18.63	13.72	13.52	12.14	13.38	10.39	9.82	9.33	6.44	5.27	3.87	2.44	2.11	2.09	BLOQ	BLOQ
14	X		BLOQ	11.08	17.70	15.49	14.64	12.06	11.21	8.96	7.19	6.50	5.16	3.45	3.00	2.31	2.18	2.34	1.83	1.68
15		X	BLOQ	10.29	18.43	16.82	15.72	13.10	10.73	8.67	8.56	6.64	5.64	4.02	4.20	2.87	2.57	2.51	1.84	1.51
16		X	BLOQ	15.81	16.58	16.48	11.39	9.96	9.20	8.66	7.84	6.90	5.82	3.93	3.16	2.63	2.89	2.39	2.25	2.21
17	X		BLOQ	5.52	15.41	14.81	13.31	10.01	8.85	8.92	7.12	5.82	4.80	4.13	3.46	2.89	2.88	2.82	2.10	1.95
18		X	BLOQ	2.56	10.85	17.16	14.98	12.87	9.87	9.68	8.02	6.44	4.84	4.55	4.02	3.51	3.25	2.35	2.33	1.85
19	X		BLOQ	15.76	16.23	14.85	13.64	12.94	12.44	11.63	9.20	8.73	8.85	8.04	7.47	6.07	5.64	5.35	5.15	4.47
20		X	BLOQ	8.45	18.11	20.16	17.79	16.97	11.60	10.44	8.94	8.20	5.72	4.44	3.91	3.63	2.90	2.72	2.33	1.85

P1 = dispense medication on period 1 P2 = dispense medication on period 2 BLOQ= below lower lower limit of quantitation

Table 13 Plasma donepezil concentrations (ng/mL) after oral administrations of 5 mg Aricept®

Volunteer No	P1	P2	Plasma donepezil concentration (ng/ml)																
Time (h)			0	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216
1		X	BLOQ	12.13	26.10	21.01	18.49	15.95	13.84	12.05	11.32	9.14	7.07	5.80	4.52	2.77	2.62	2.53	1.62	1.41
2		X	BLOQ	21.31	23.66	17.01	15.35	11.79	13.83	12.79	11.20	9.67	5.93	4.23	3.59	3.68	3.18	2.41	2.35	2.05
3		X	BLOQ	14.10	15.37	11.86	10.90	10.03	9.86	8.66	7.30	7.08	4.78	3.76	2.96	2.62	2.43	1.95	1.61	1.34
4	X		BLOQ	17.85	20.77	16.18	14.79	12.08	11.10	12.34	10.36	10.12	7.34	6.76	5.62	4.46	4.14	4.05	4.00	2.83
5		X	BLOQ	9.95	25.88	22.86	19.82	17.18	15.11	14.28	12.29	10.47	7.73	5.82	5.08	4.58	3.60	3.14	3.10	2.76
6	X		BLOQ	4.47	18.26	16.87	14.04	11.40	10.41	9.93	9.52	8.15	7.17	6.39	3.51	3.68	3.44	3.32	2.69	2.25
7	X		BLOQ	6.48	13.48	12.33	11.22	8.27	8.23	8.28	6.19	5.29	4.00	3.01	2.30	2.32	1.88	1.44	1.25	BLOQ
8		X	BLOQ	9.34	16.02	14.11	12.12	12.53	10.09	9.49	8.89	7.54	5.60	5.20	4.47	3.73	3.33	2.82	2.69	2.65
9		X	BLOQ	13.10	21.87	15.29	14.45	12.44	12.97	11.27	10.21	9.58	5.99	5.19	4.22	4.00	3.23	3.01	2.83	2.67
10	X		BLOQ	3.06	18.41	16.05	12.21	11.54	11.02	10.83	9.39	8.61	7.35	4.89	5.02	4.44	4.65	4.10	3.60	2.90

P1 = dispense medication on period 1 P2 = dispense medication on period 2 BLOQ= below lower lower limit of quantitation

Table 13 (Cont.) Plasma donepezil concentrations (ng/mL) after oral administrations of 5 mg Aricept®

Volunteer No	P1	P2	Plasma donepezil concentration (ng/ml)																	
Time (h)			0	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216
11	X		BLOQ	15.80	20.57	15.85	15.54	12.59	11.45	12.15	9.49	9.17	7.25	4.71	4.33	3.68	3.01	3.29	2.56	2.55
12		X	BLOQ	12.86	19.08	14.03	12.89	11.67	10.83	10.16	8.44	6.94	5.37	4.92	3.89	2.70	2.37	2.04	1.96	1.95
13	X		BLOQ	9.45	17.13	14.45	13.15	10.72	10.22	9.43	7.53	6.84	5.08	3.73	2.49	1.96	1.89	1.64	BLOQ	BLOQ
14		X	BLOQ	17.47	15.15	12.88	12.02	11.00	9.90	8.78	7.24	5.59	4.13	3.30	3.01	2.05	2.26	2.10	1.58	BLOQ
15	X		BLOQ	4.74	22.50	17.83	16.15	12.26	12.31	10.29	9.10	7.14	5.60	3.71	2.90	2.73	2.72	2.20	2.25	1.78
16	X		BLOQ	11.76	13.22	12.41	11.44	9.53	9.44	9.04	7.37	6.71	5.40	4.59	4.43	3.62	2.89	2.32	2.03	1.97
17		X	BLOQ	6.71	15.14	18.35	14.86	12.57	11.44	10.62	8.81	7.24	5.38	4.00	4.14	3.57	3.23	2.83	2.32	1.90
18	X		BLOQ	3.67	9.61	12.84	11.33	10.60	11.09	8.04	7.55	6.62	4.88	3.85	3.42	2.65	2.76	2.53	2.30	1.57
19		X	BLOQ	8.10	18.98	16.99	15.35	14.50	10.76	10.26	9.20	8.76	6.23	5.37	4.99	4.93	4.70	4.20	3.99	3.96
20	X		BLOQ	17.77	18.69	17.57	14.54	13.07	12.47	9.55	10.03	8.54	7.26	5.34	5.05	3.10	2.58	2.23	2.06	1.84

P1 = dispense medication on period 1 P2 = dispense medication on period 2 BLOQ= below lower lower limit of quantitation

Table 14 The mean, SD, %CV, maximum and minimum concentration of plasma donepezil after oral administrations of 5 mg generic donepezil HCl

Time after administration (h)	Mean (ng/ml)	S.D.	% CV	Maximum concentration (ng/ml)	Minimum concentration (ng/ml)	Max-Min (ng/ml)
Baseline (T=0)	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
T1=1.0	11.30	6.25	55.30	24.68	2.44	22.24
T2=2.0	19.28	5.66	29.37	34.47	8.92	25.55
T3=3.0	17.11	3.47	20.26	26.17	10.61	15.56
T4=4.0	15.13	2.75	18.19	22.08	10.24	11.84
T5=5.5	13.19	2.31	17.49	18.67	9.81	8.85
T6=6.0	12.04	2.25	18.66	18.55	8.85	9.70
T7=8.0	10.94	2.20	20.13	17.26	8.11	9.16
T8=12.0	9.53	1.94	20.39	14.51	7.12	7.39
T9=24.0	8.18	1.72	20.99	12.94	5.82	7.12
T10=48.0	6.34	1.38	21.75	9.40	4.73	4.67
T11=72.0	5.08	1.09	21.48	8.04	3.45	4.60
T12=96.0	4.53	1.04	22.91	7.47	3.00	4.47
T13=120.0	3.68	1.06	28.72	6.07	2.31	3.77
T14=144.0	3.25	0.85	26.11	5.64	2.11	3.54
T15=168.0	2.89	0.85	29.41	5.35	2.09	3.26
T16=192.0	2.66	0.84	31.39	5.15	1.83	3.31
T17=216.0	2.32	0.71	30.53	4.47	1.51	2.96

Table 15 The mean, standard deviation (SD), %coefficient of variation (%CV), maximum and minimum concentration of plasma donepezil after oral administrations of 5 mg Aricept®.

Time after administration (h)	Mean (ng/ml)	S.D.	% CV	Maximum concentration (ng/ml)	Minimum concentration (ng/ml)	Max-Min (ng/ml)
Baseline (T=0)	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
T1=1.0	11.01	5.31	48.22	21.31	3.06	18.24
T2=2.0	18.49	4.28	23.17	26.10	9.61	16.49
T3=3.0	15.84	2.90	18.29	22.86	11.86	11.00
T4=4.0	14.03	2.41	17.16	19.82	10.90	8.92
T5=5.5	12.09	2.05	16.99	17.18	8.27	8.90
T6=6.0	11.32	1.68	14.84	15.11	8.23	6.88
T7=8.0	10.41	1.65	15.85	14.28	8.04	6.25
T8=12.0	9.07	1.58	17.38	12.29	6.19	6.10
T9=24.0	7.96	1.48	18.53	10.47	5.29	5.18
T10=48.0	5.98	1.15	19.16	7.73	4.00	3.74
T11=72.0	4.73	1.03	21.72	6.76	3.01	3.75
T12=96.0	4.00	0.94	23.63	5.62	2.30	3.32
T13=120.0	3.36	0.87	25.85	4.93	1.96	2.97
T14=144.0	3.05	0.79	25.99	4.70	1.88	2.82
T15=168.0	2.71	0.79	29.25	4.20	1.44	2.76
T16=192.0	2.46	0.78	31.81	4.00	1.25	2.75
T17=216.0	2.26	0.67	29.51	3.96	1.34	2.62

Table 16 Pharmacokinetic parameters after a single oral dose of 5 mg generic donepezil HCl

Volunteer No.	T_{max} (h)	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng.h/ml)	$t_{1/2}$ (h)
1	3.0	16.79	1056.47	1277.23	74.3
2	2.0	19.91	972.86	1336.11	92.2
3	1.0	19.67	856.38	1088.18	85.9
4	3.0	19.20	1209.69	1622.78	97.1
5	2.0	34.47	1420.56	1697.59	73.3
6	2.0	22.83	1186.58	1390.02	72.7
7	1.0	16.41	923.39	1248.25	100.0
8	2.0	23.64	1007.64	1335.34	91.2
9	2.0	24.30	1228.12	1688.19	106.0
10	2.0	21.00	1319.65	1813.62	113.0
11	2.0	25.57	1151.04	1419.03	79.7
12	2.0	24.25	1011.72	1212.44	80.4
13	2.0	18.63	866.39	1044.57	59.1
14	2.0	17.70	795.83	998.02	83.4
15	2.0	18.43	890.19	1069.37	82.3
16	2.0	16.58	877.12	1188.41	97.6
17	2.0	15.41	838.14	1111.86	97.3
18	3.0	17.16	900.95	1154.59	95.0
19	2.0	16.23	1529.03	2587.23	164.0
20	3.0	20.16	987.12	1217.36	86.3
Mean	**2.1**	**20.42**	**1051.44**	**1375.01**	**91.5**
S.D.	**0.6**	**4.50**	**206.87**	**369.01**	**21.3**
% C.V.	**26.3**	**22.03**	**19.67**	**26.84**	**23.3**
Maximum	**3.0**	**34.47**	**1529.03**	**2587.23**	**164.0**
Minimum	**1.0**	**15.41**	**795.83**	**998.02**	**59.1**
Max - Min	**2.0**	**19.06**	**733.20**	**1589.21**	**104.9**
Median	**2.0**				

Table 17 Pharmacokinetic parameters after a single oral dose of 5 mg Aricept®.

Volunteer No.	T_{max} (h)	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng.h/ml)	$t_{1/2}$ (h)
1	2.0	26.10	1068.91	1206.41	67.6
2	2.0	23.66	1045.38	1276.16	78.0
3	2.0	15.37	787.59	944.75	81.3
4	2.0	20.77	1307.22	1745.30	107.0
5	2.0	25.88	1274.30	1616.11	85.8
6	2.0	18.26	1085.11	1390.35	94.0
7	2.0	13.48	607.51	732.50	69.3
8	2.0	16.02	1014.53	1395.79	99.7
9	2.0	21.87	1099.86	1449.09	90.7
10	2.0	18.41	1192.39	1634.84	106.0
11	2.0	20.57	1097.48	1435.40	91.9
12	2.0	19.08	891.10	1147.45	91.1
13	2.0	17.13	675.16	823.09	62.5
14	1.0	17.47	691.61	898.96	91.0
15	2.0	22.50	876.14	1101.44	87.7
16	2.0	13.22	909.74	1187.31	97.7
17	3.0	18.35	951.53	1215.29	96.2
18	3.0	12.84	824.57	1030.17	90.8
19	2.0	18.98	1223.32	2067.30	148.0
20	2.0	18.69	1048.10	1251.74	76.7
Mean	**2.1**	**18.93**	**983.58**	**1277.47**	**90.7**
S.D.	**0.4**	**3.82**	**199.40**	**328.51**	**18.1**
% C.V.	**19.2**	**20.15**	**20.27**	**25.72**	**20.0**
Maximum	**3.0**	**26.10**	**1307.22**	**2067.30**	**148.0**
Minimum	**1.0**	**12.84**	**607.51**	**732.50**	**62.5**
Max - Min	**2.0**	**13.26**	**699.71**	**1334.80**	**85.5**
Median	**2.0**				

Table 18 The clearance (CL/F) and Volume of distribution (Vd/F) of the generic donepezil HCl (test) and Aricept® (reference)

Generic donepezil	BW	CL	Vd	CL/kg	Vd/kg	Aricept®	CL	Vd	CL/kg	Vd/kg
1	58.0	65.2	420	1.12	7.24	**1**	69.1	404	1.19	6.97
2	63.5	62.4	498	0.98	7.84	**2**	65.3	441	1.03	6.94
3	67.0	76.6	570	1.14	8.51	**3**	88.2	621	1.32	9.27
4	62.0	51.4	431	0.83	6.95	**4**	47.7	443	0.77	7.15
5	48.0	49.1	311	1.02	6.48	**5**	51.6	383	1.08	7.98
6	56.0	60.0	377	1.07	6.73	**6**	59.9	488	1.07	8.71
7	63.5	66.8	578	1.05	9.10	**7**	114.0	683	1.80	10.76
8	66.0	62.4	493	0.95	7.47	**8**	59.7	515	0.90	7.80
9	59.0	49.4	451	0.84	7.64	**9**	57.5	451	0.97	7.64
10	69.0	45.9	451	0.67	6.54	**10**	51.0	467	0.74	6.77
11	52.5	58.7	405	1.12	7.71	**11**	58.1	462	1.11	8.80
12	63.0	68.7	478	1.09	7.59	**12**	72.6	573	1.15	9.10
13	68.0	79.8	408	1.17	6.00	**13**	101.0	548	1.49	8.06
14	65.5	83.5	603	1.27	9.21	**14**	92.7	730	1.42	11.15
15	55.0	77.9	555	1.42	10.09	**15**	75.7	575	1.38	10.45
16	67.0	70.1	593	1.05	8.85	**16**	70.2	593	1.05	8.85
17	63.5	74.9	631	1.18	9.94	**17**	68.6	571	1.08	8.99
18	61.0	72.2	594	1.18	9.74	**18**	80.9	636	1.33	10.43
19	77.0	32.2	458	0.42	5.95	**19**	40.3	515	0.52	6.69
20	63.0	68.5	511	1.09	8.11	**20**	66.6	442	1.06	7.02
Mean	**62.4**	**63.8**	**490.8**	**1.03**	**7.88**	**Mean**	**69.5**	**527.1**	**1.12**	**8.48**
SD	**6.5**	**13.1**	**87.1**	**0.22**	**1.28**	**SD**	**18.5**	**94.7**	**0.29**	**1.41**
CV%	**10.3**	**20.5**	**17.8**	**21.17**	**16.25**	**CV%**	**26.6**	**18.0**	**25.42**	**16.65**
Min	**48.0**	**32.2**	**311.0**	**0.42**	**5.95**	**Min**	**40.3**	**383.0**	**0.52**	**6.69**
Max	**77.0**	**83.5**	**631.0**	**1.42**	**10.09**	**Max**	**114.0**	**730.0**	**1.80**	**11.15**

Table 19 Comparison of donepezil pharmacokinetic parameters (C_{max} and AUC) in individual volunteers after single oral administrations of 5 mg donepezil HCl (T) and Aricept® (R)

Volunteer No.	C_{max} (T)	C_{max} (R)	F_{rel} (T/R)	AUC_{0-t} (T)	AUC_{0-t} (R)	F_{rel} (T/R)	AUC_{0-inf} (T)	AUC_{0-inf} (R)	F_{rel} (T/R)
1	16.79	26.10	64.3	1,056.47	1,068.91	98.8	1,277.23	1,206.41	105.9
2	19.91	23.66	84.2	972.86	1,045.38	93.1	1,336.11	1,276.16	104.7
3	19.67	15.37	127.9	856.38	787.59	108.7	1,088.18	944.75	115.2
4	19.20	20.77	92.4	1,209.69	1,307.22	92.5	1,622.78	1,745.30	93.0
5	34.47	25.88	133.2	1,420.56	1,274.30	111.5	1,697.59	1,616.11	105.0
6	22.83	18.26	125.0	1,186.58	1,085.11	109.4	1,390.02	1,390.35	100.0
7	16.41	13.48	121.8	923.39	607.51	152.0	1,248.25	732.50	170.4
8	23.64	16.02	147.5	1,007.64	1,014.53	99.3	1,335.34	1,395.79	95.7
9	24.30	21.87	111.1	1,228.12	1,099.86	111.7	1,688.19	1,449.09	116.5
10	21.00	18.41	114.1	1,319.65	1,192.39	110.7	1,813.62	1,634.84	110.9
11	25.57	20.57	124.3	1,151.04	1,097.48	104.9	1,419.03	1,435.40	98.9
12	24.25	19.08	127.1	1,011.72	891.10	113.5	1,212.44	1,147.45	105.7
13	18.63	17.13	108.8	866.39	675.16	128.3	1,044.57	823.09	126.9
14	17.70	17.47	101.3	795.83	691.61	115.1	998.02	898.96	111.0
15	18.43	22.50	81.9	890.19	876.14	101.6	1,069.37	1,101.44	97.1
16	16.58	13.22	125.4	877.12	909.74	96.4	1,188.41	1,187.31	100.1
17	15.41	18.35	84.0	838.14	951.53	88.1	1,111.86	1,215.29	91.5
18	17.16	12.84	133.6	900.95	824.57	109.3	1,154.59	1,030.17	112.1
19	16.23	18.98	85.5	1,529.03	1,223.32	125.0	2,587.23	2,067.30	125.2
20	20.16	18.69	107.9	987.12	1,048.10	94.2	1,217.36	1,251.74	97.3
Mean	**20.42**	**18.93**	**110.1**	**1051.4**	**983.6**	**108.2**	**1375.0**	**1277.5**	**109.1**
S.D.	**4.50**	**3.80**	**21.9**	**206.9**	**199.4**	**14.8**	**369.0**	**328.5**	**17.5**
% C.V.	**22.0**	**20.2**	**19.9**	**19.7**	**20.3**	**13.7**	**26.8**	**25.7**	**16.0**

Table 20 ANOVA table (logarithmically transformed) and 90% Confidence Interval of the pharmacokinetic parameter [AUC_{0-t}]

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	P-values
Inter-Subjects					
Carry-over	1	0.0166	0.0166	0.2168	0.6471
Residuals	18	1.3741	0.0763	8.8119	0.0000
Intra-Subjects					
Drug	1	0.0499	0.0499	5.7599	0.0274
Period	1	0.0017	0.0017	0.1970	0.6625
Residuals	18	0.1559	0.0087		
Total	39	1.5982			

n= number of volunteer, Significant level $\alpha = 0.05$

	Mean	90 % Confidence Interval
Test / Reference	**1.07**	1.02 – 1.13

Table 21 ANOVA table (logarithmically transformed) and 90% ConfidenceInterval of the pharmacokinetic parameter [$AUC_{0-\infty}$]

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	P-values
Inter-Subjects					
Carry-over	1	0.0462	0.0462	0.4036	0.5332
Residuals	18	2.0590	0.1144	10.9417	0.0000
Intra-Subjects					
Drug	1	0.0597	0.0597	5.7058	0.0281
Period	1	0.0006	0.0006	0.0544	0.8183
Residuals	18	0.1882	0.0105		
Total	39	2.3536			

n= number of volunteer, Significant level $\alpha = 0.05$

	Mean	90 % Confidence Interval
Test / Reference	**1.08**	1.02 – 1.14

Table 22 ANOVA table (logarithmically transformed) and 90% Confidence Interval of the pharmacokinetic parameter [C_{max}]

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	P-values
Inter-Subjects					
Carry-over	1	0.1049	0.1049	1.8881	0.1863
Residuals	18	1.0000	0.0556	2.3740	0.0374
Intra-Subjects					
Drug	1	0.0565	0.0565	2.4134	0.1377
Period	1	0.0173	0.0173	0.7386	0.4014
Residuals	18	0.4212	0.0234		
Total	39	1.5998			

n= number of volunteer, Significant level $\alpha = 0.05$

	Mean	90 % Confidence Interval
Test / Reference	**1.08**	0.99 – 1.17

Table 23 ANOVA table and 90% Confidence Interval of the pharmacokinetic parameter [T_{max}].

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	P-values
Inter-Subjects					
Carry-over	1	0.2250	0.2250	0.8020	0.3823
Residuals	18	5.0500	0.2806	1.4638	0.2134
Intra-Subjects					
Drug	1	0.0250	0.0250	0.1304	0.7222
Period	1	0.0250	0.0250	0.1304	0.7222
Residuals	18	3.4500	0.1917		
Total	39	8.7750			

n= number of volunteer, Significant level $\alpha = 0.05$

	Mean	90 % Confidence Interval
Test-Reference	**0.05**	(-0.19) – 0.29 (acceptable range +0.41)

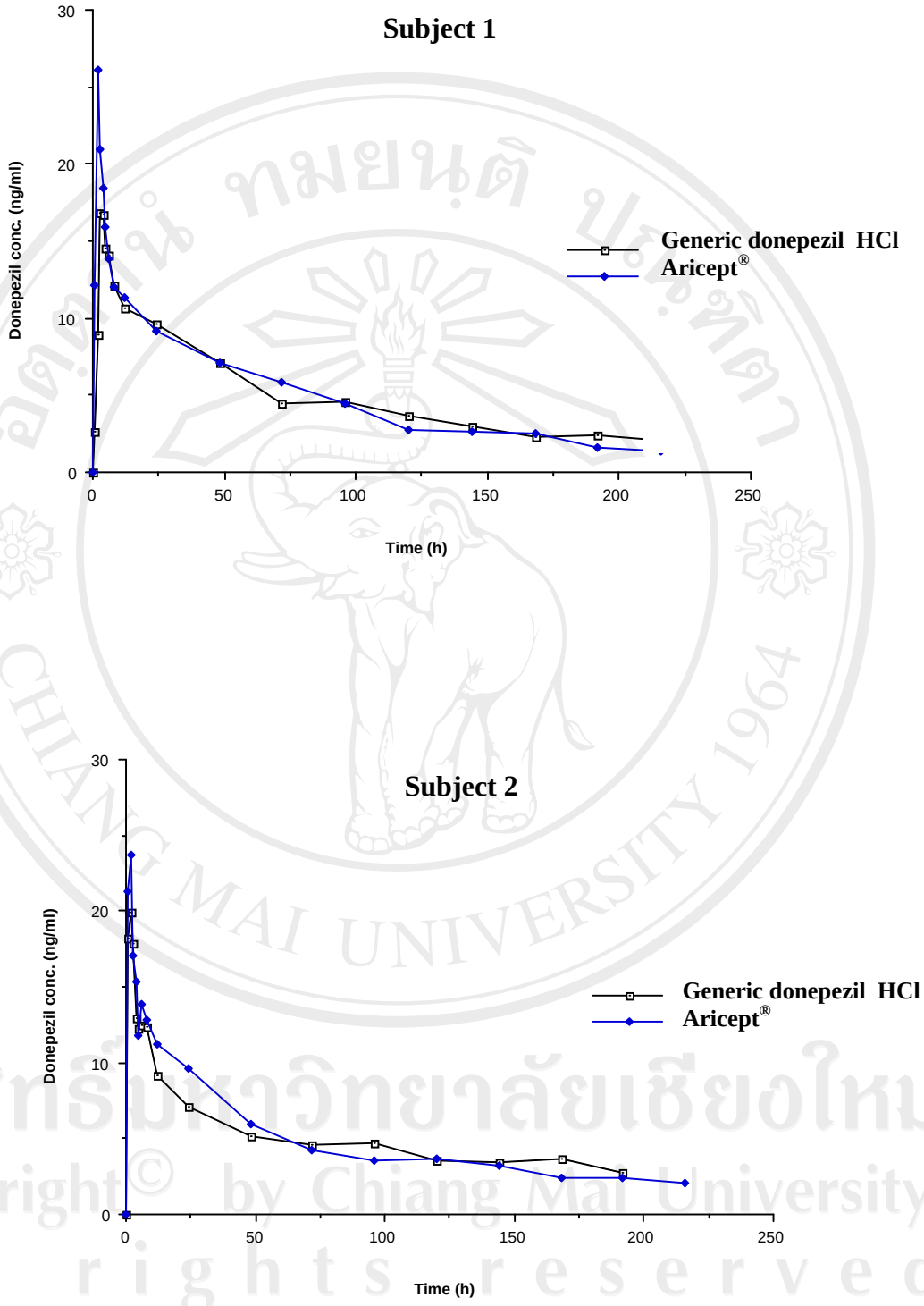
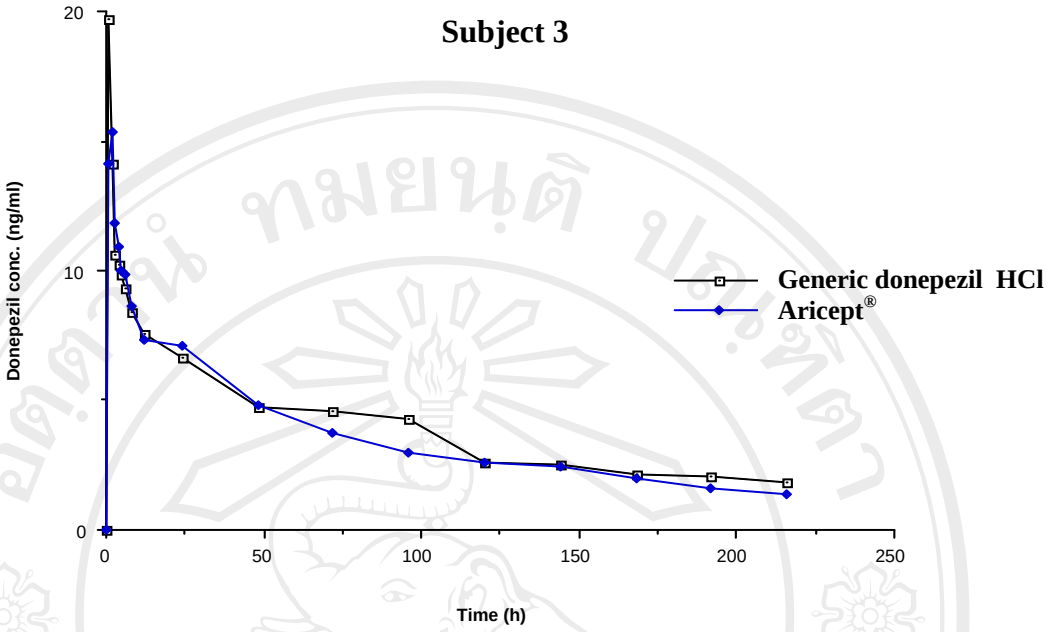


Figure 4 Pair-wise plasma concentration-time profiles (linear-linear plot) after oral administration of 5 mg of the generic donepezil HCl (-□-) and Aricept® (-♦-)



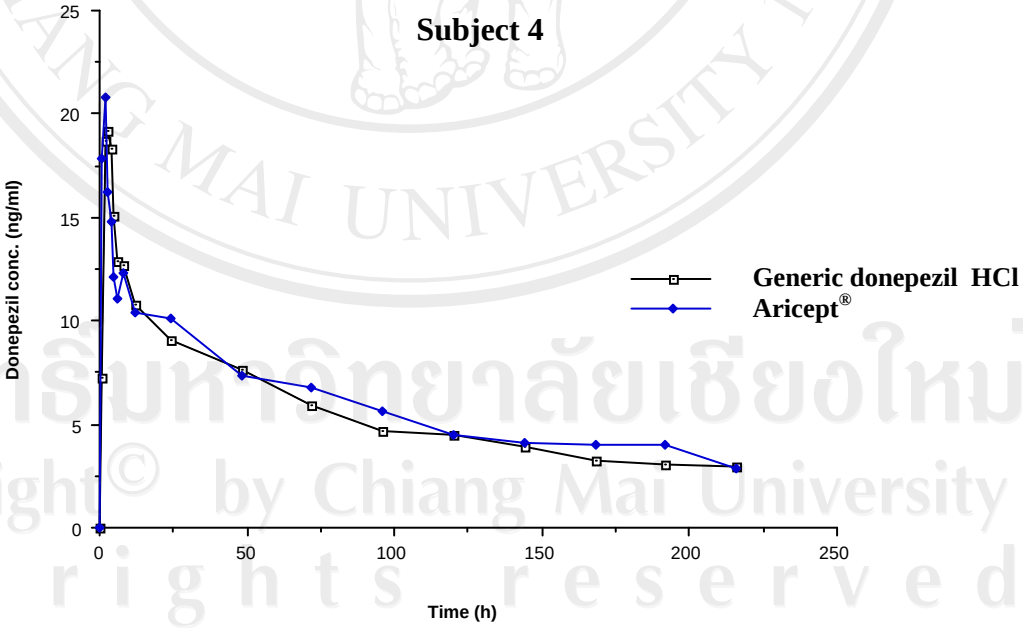
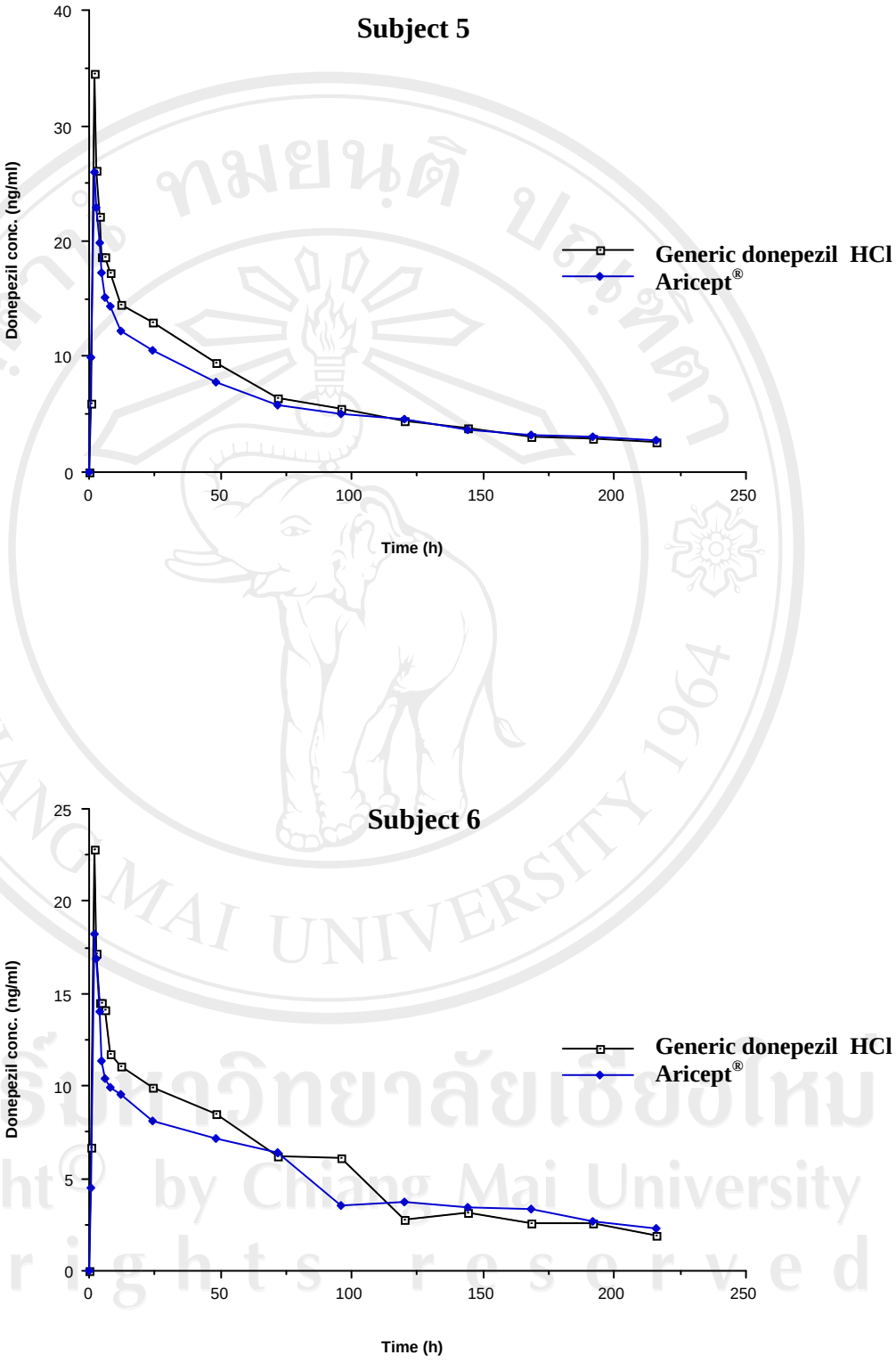


Figure 4 Continued.



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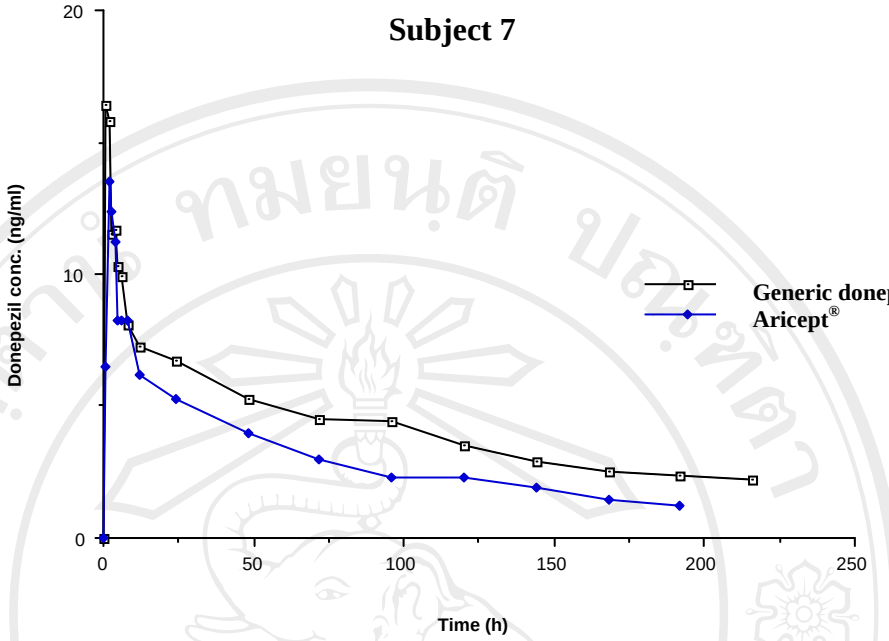

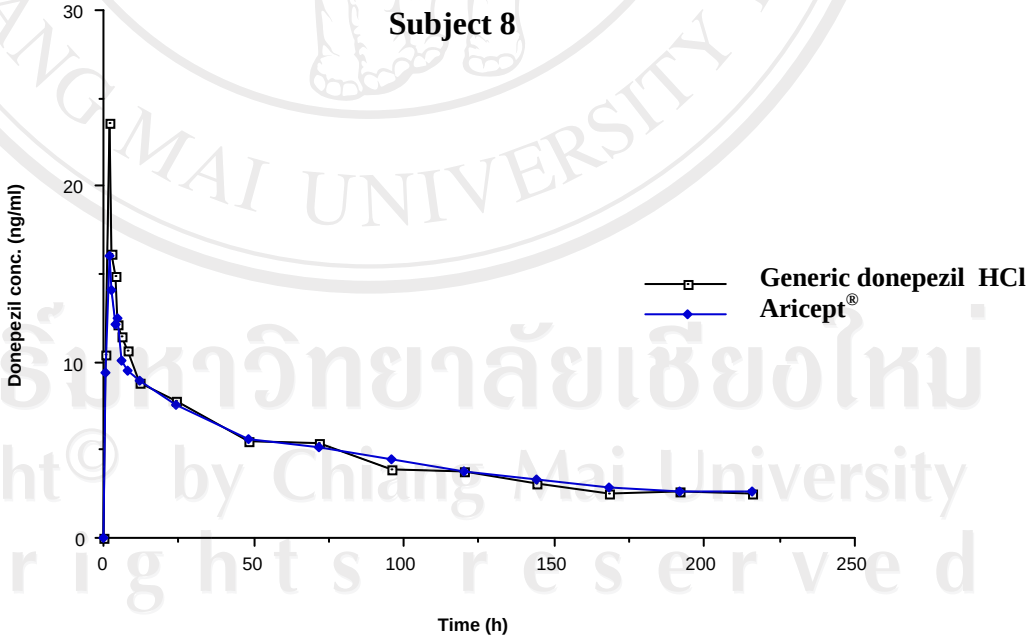

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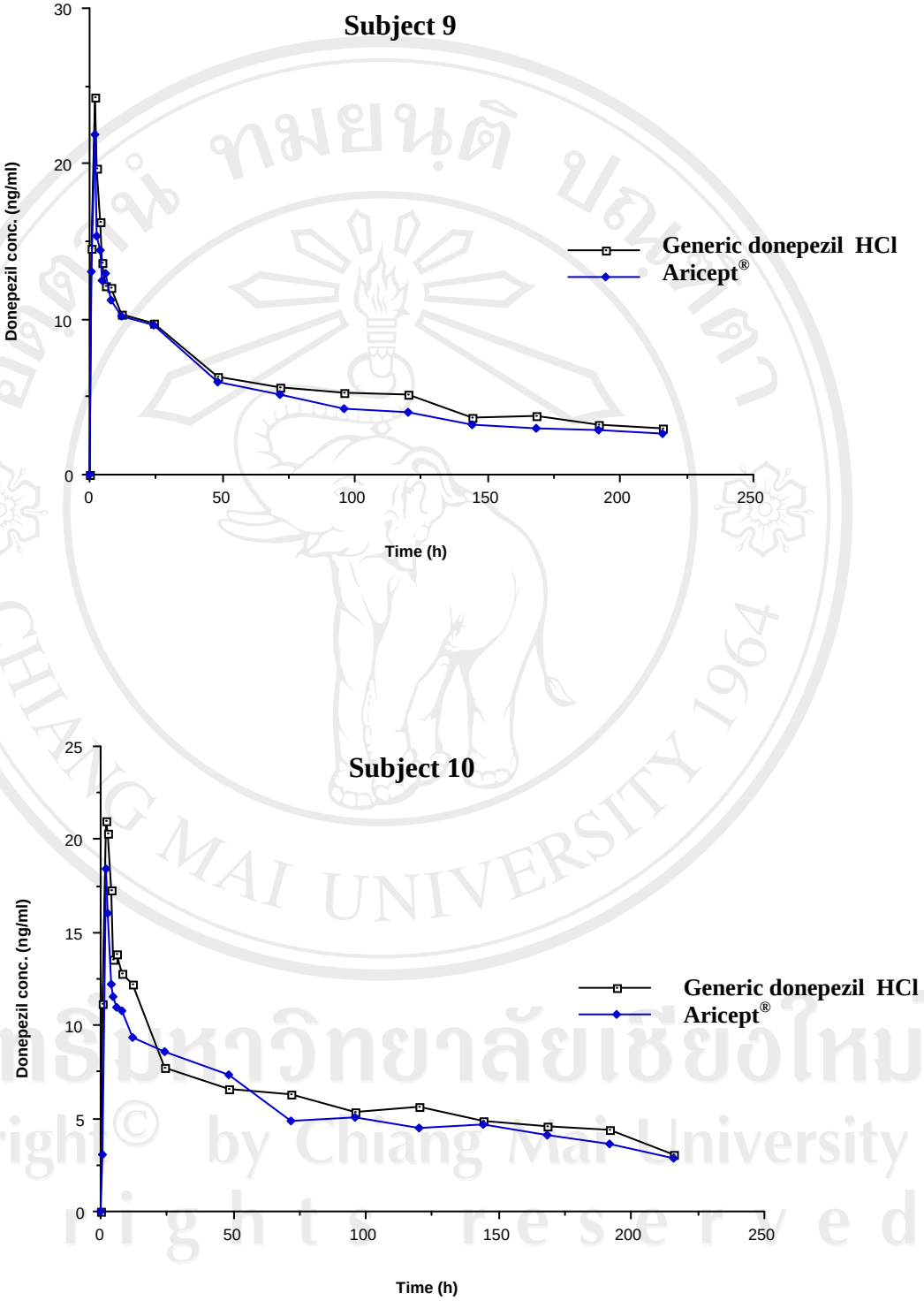

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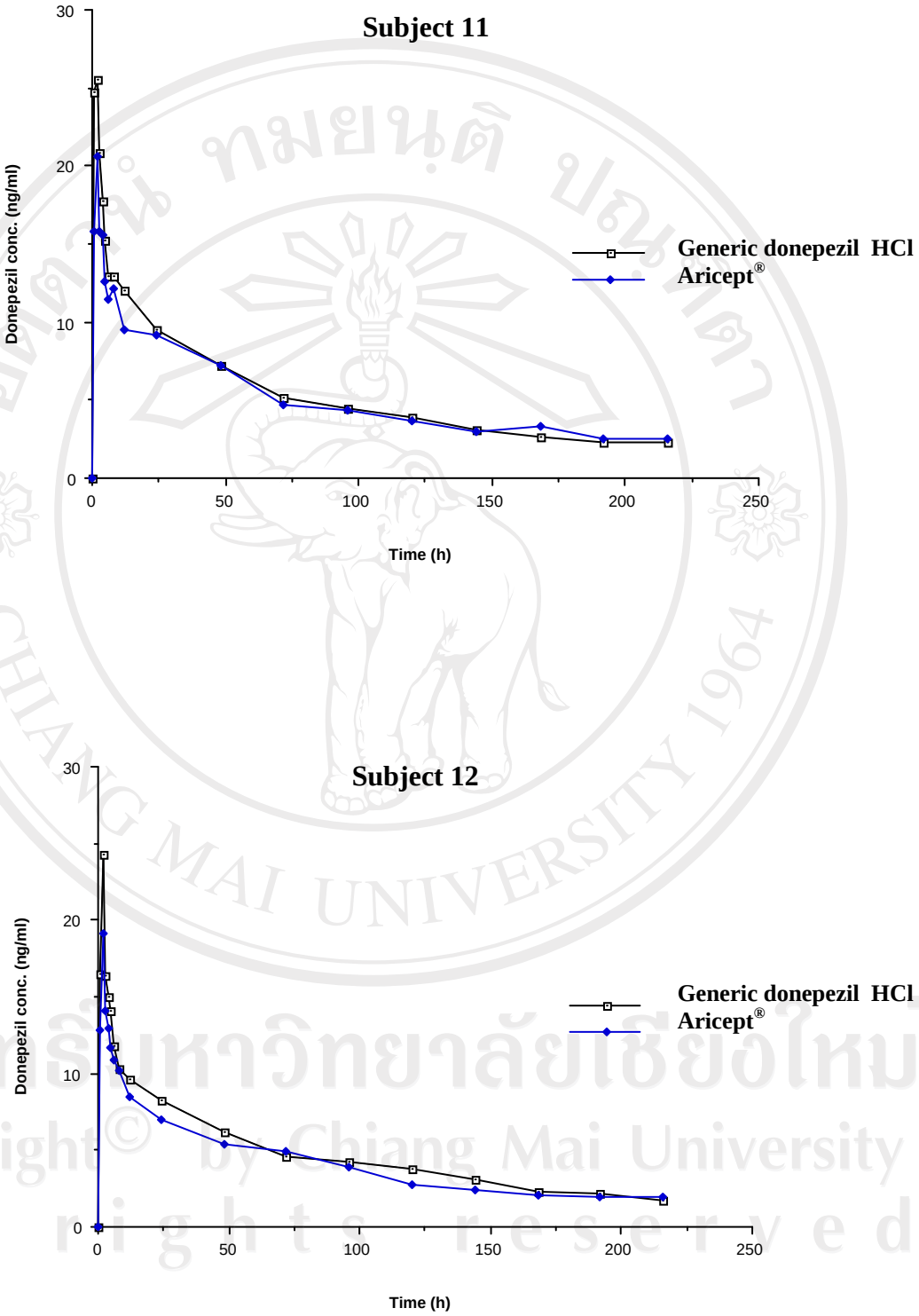

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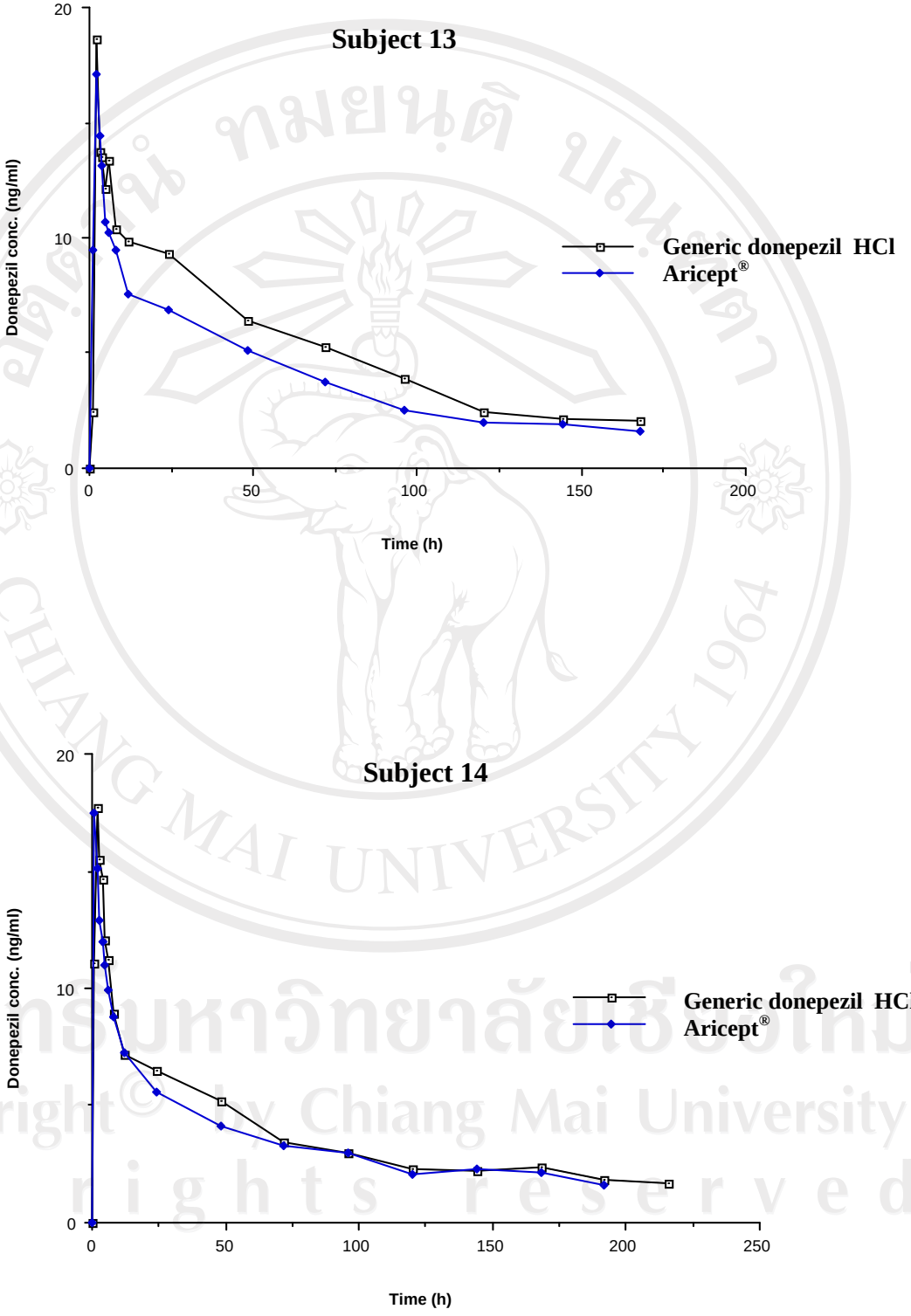

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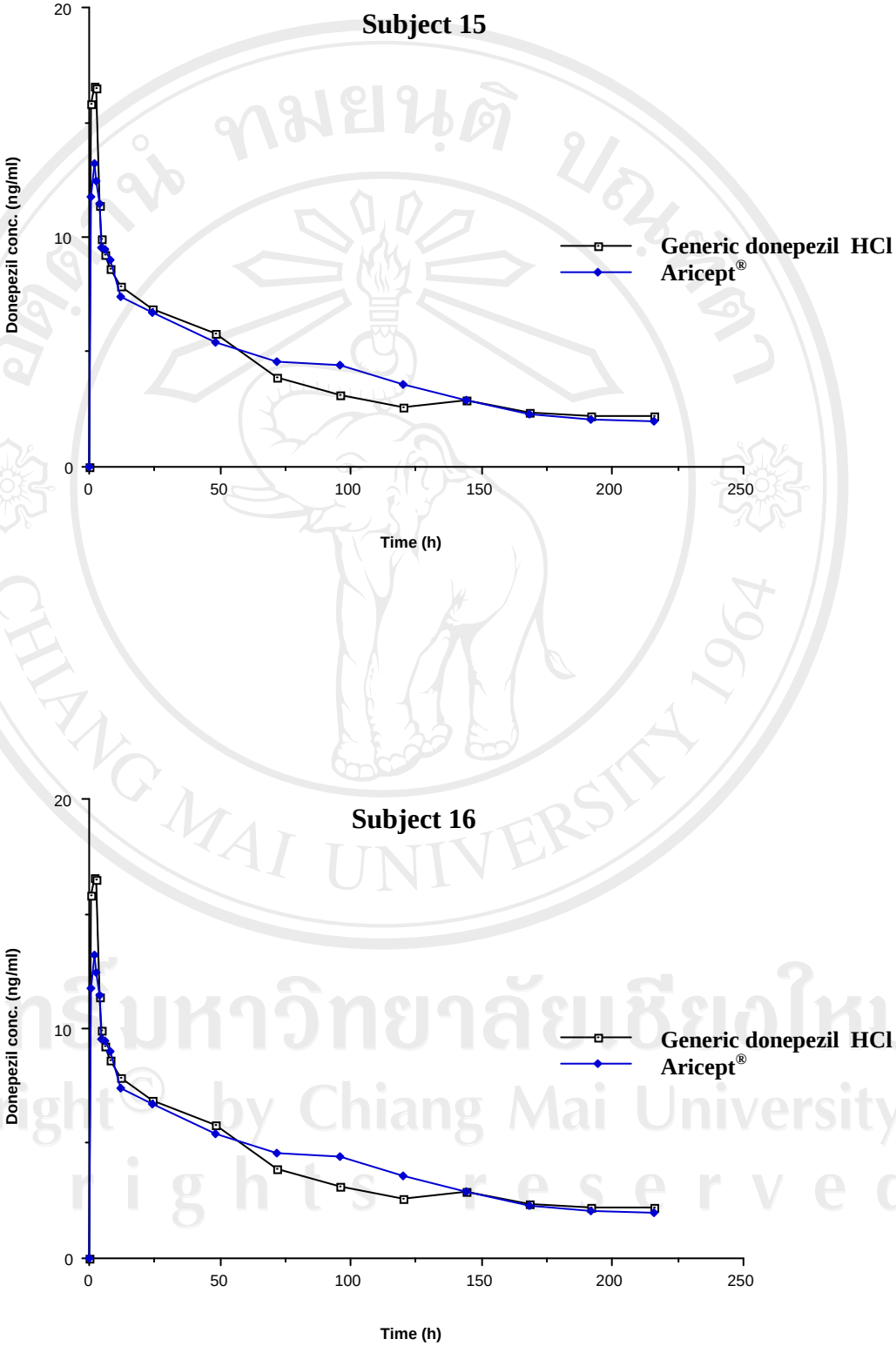
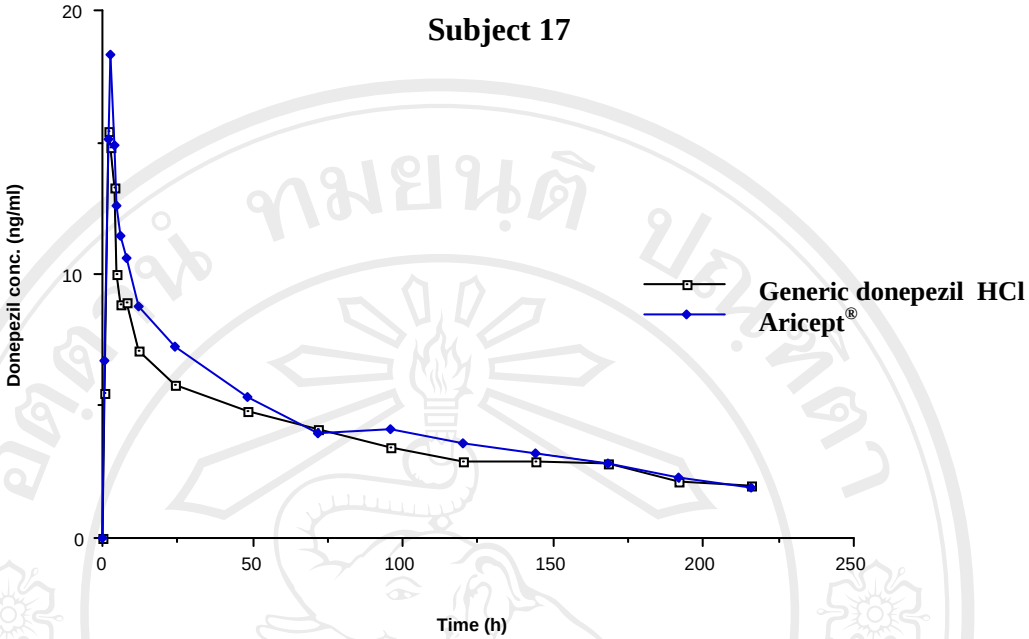


Figure 4 Continued



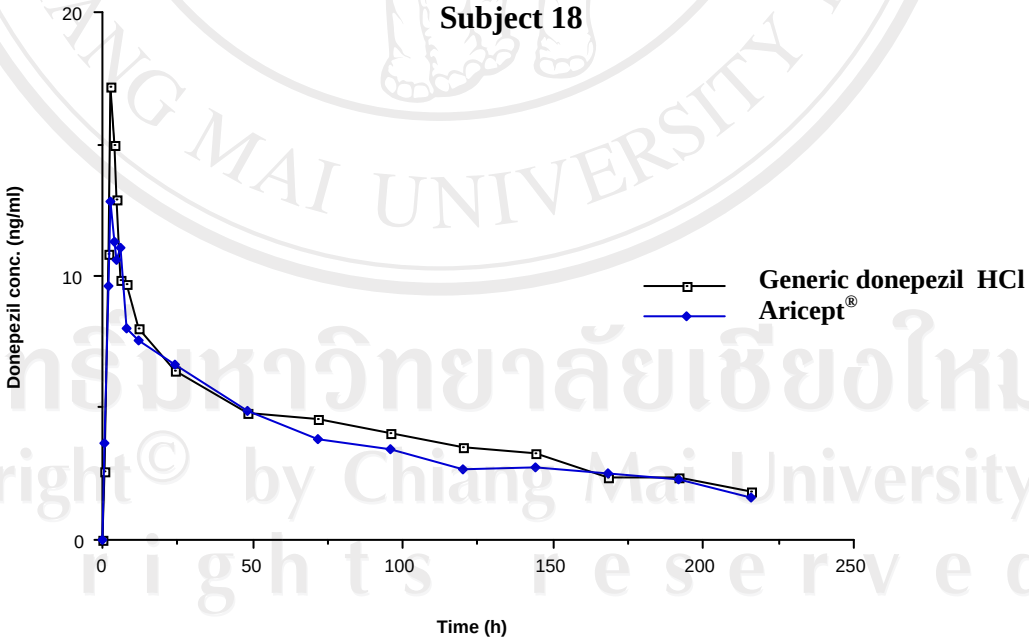


Figure 4 Continued

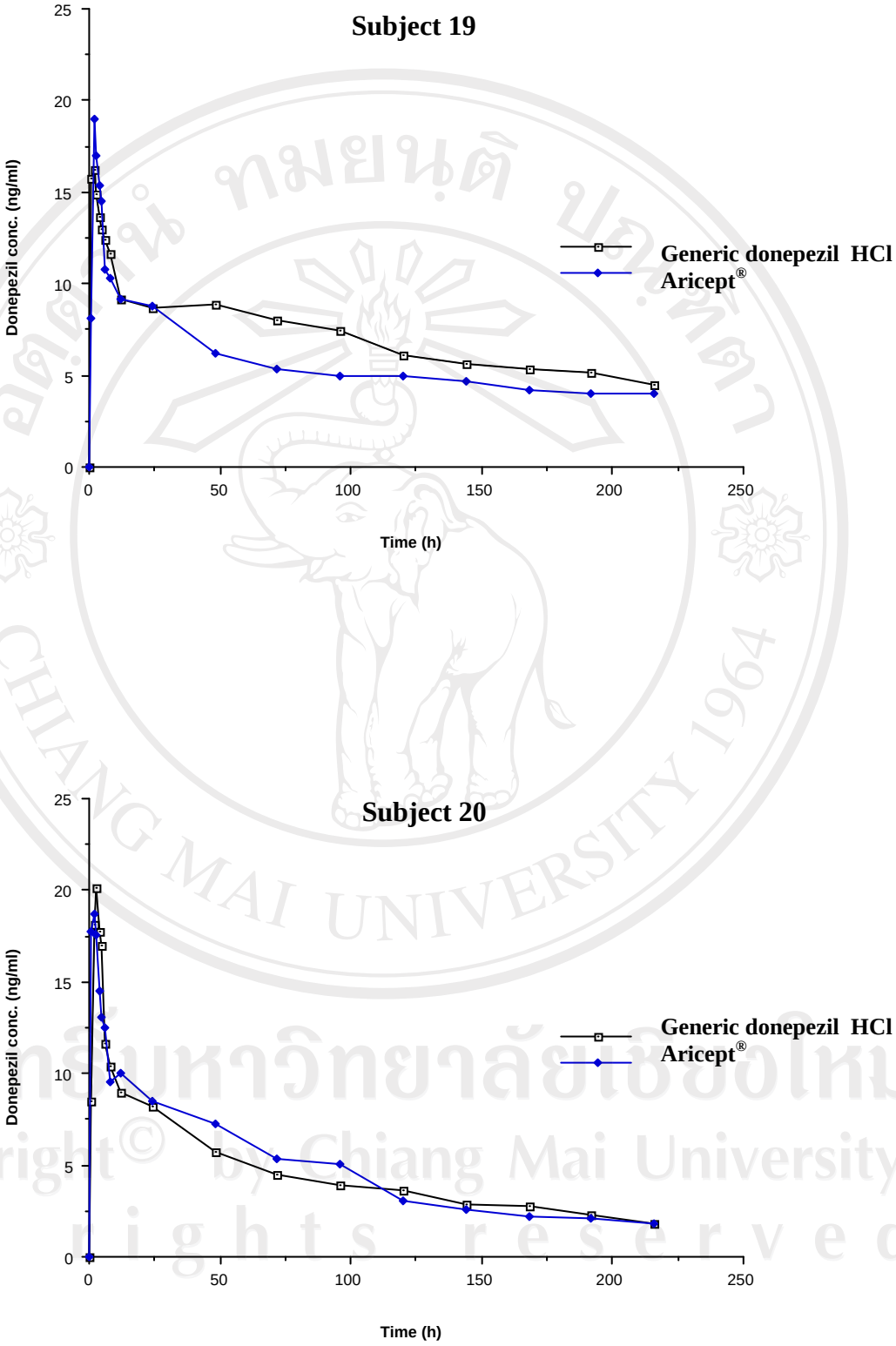


Figure 4 Continued

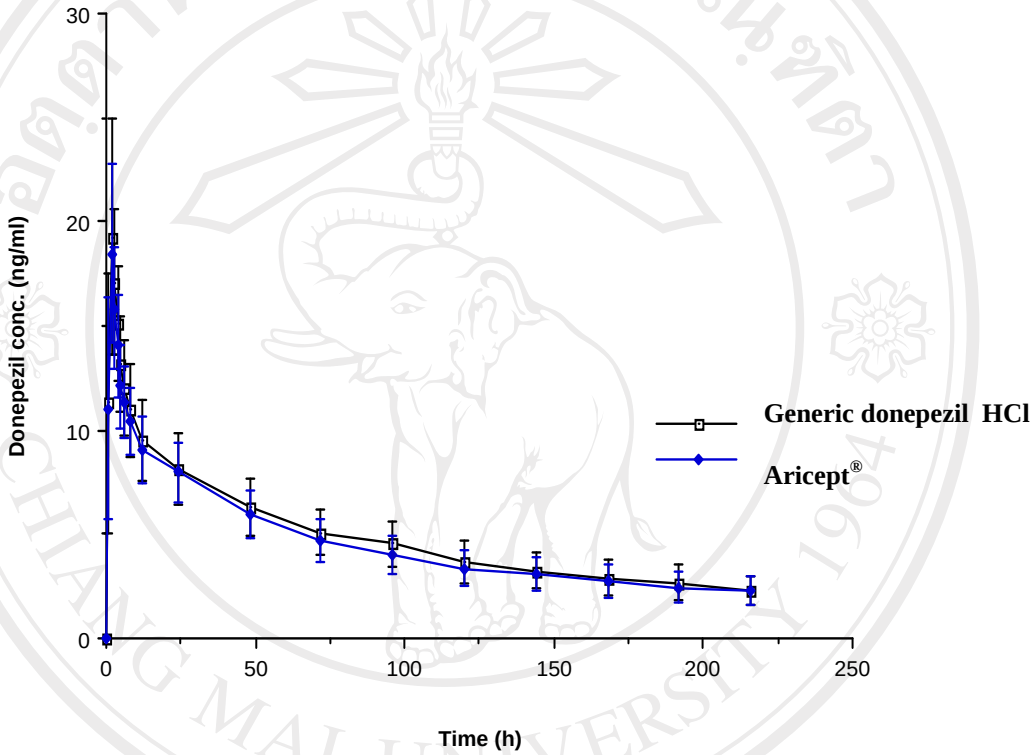


Figure 5 Mean plasma concentration-time profiles (linear-linear plot) after oral administration of 5 mg of the generic donepezil HCl (-□-) and Aricept® (-♦-).

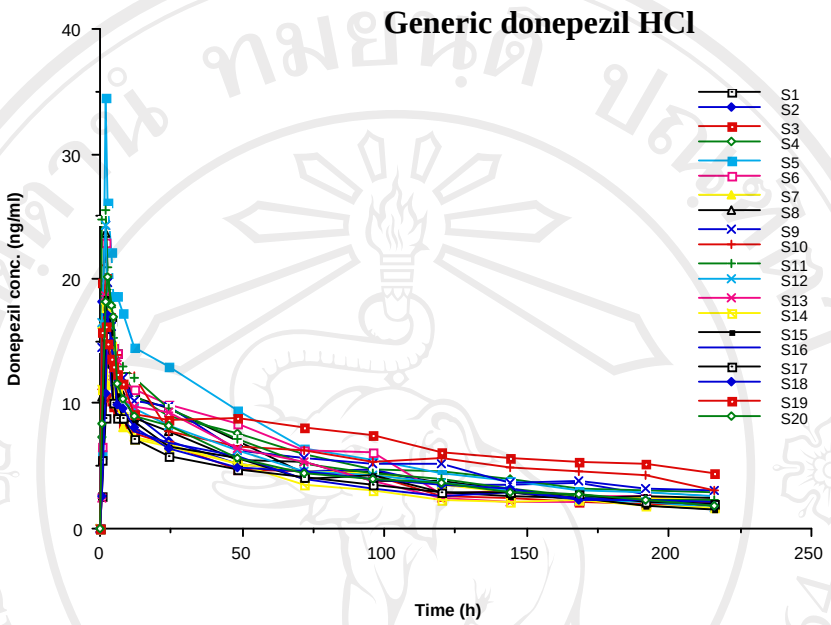


Figure 6 Plasma concentration-time curves of individual subjects (n=20) (linear-linear plot) after oral administration of 5 mg of the generic donepezil HCl

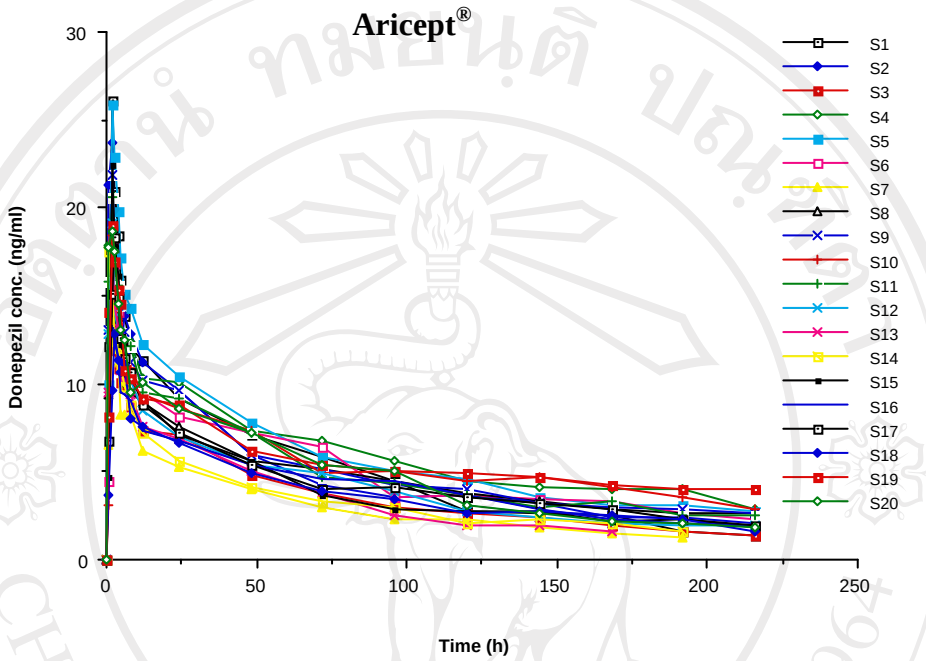


Figure 7 Plasma concentration-time curves of individual subjects(n=20) (linear-linear plot) after oral administration of 5-mg Aricept®