CHAPTER IV

RESULTS AND DISCUSSION

In Vitro Studies

The in vitro tested-data are shown in Table 2. All 5 brands of ranitidine tablets were tested for uniformity of weight, content of active ingredient, disintegration time and dissolution properties. Each of them met the British Pharmacopoeia 1973 requirements (26) for uniformity of weight within the range of limit weight ($\pm$ 5 %). Active ingredient content (ranitidine base) of all assayed products were within 90-110% labelled amount limit. The pH of ranitidine injection was 6.93.

For disintegration test, each of 5 brands of ranitidine tablets met the British Pharmacopoeia 1980 (27) requirements under film-coated tablets. All of them had disintegrated in water at 37 $\pm$ 0.5 C within 60 minutes. After disintegrating, the fragments of undissolved coating materials of brands C and D were remained in the baskets.

Table 2 Characteristics of Five Commercial Brands of Ranitidine Tablets from In Vitro Studies

Brand	Weight [a] (mg)	%Labelled [b] Amount	Disintegration Time [c] (min)	Dissolution Rate Constant [a] (hr^{-1})	
				Simulated Gastric Fluid	Simulated Intestinal Fluid
A	306.69±3.07	95.82±0.21	7.50±3.14	8.34±2.73	9.58±2.51
B	309.73±6.75	91.82±0.69	7.00±0.89	12.99±1.78	9.42±1.64
C	303.93±7.52	92.28±0.40	10.17±0.98	1.31±0.33	7.13±0.73
D	300.71±6.79	90.37±0.89	17.33±3.39	4.31±1.31	5.84±1.70
E	294.48±9.15	101.96±0.52	7.17±0.98	1.46±0.56	8.18±3.16
I	-	100.55±0.28	-	-	-

a = mean ± standard deviation (n = 20)

b = mean ± standard deviation (n = 3)

c = mean ± standard deviation (n = 6)

Figures 2 and 3 illustrate the dissolution profiles of all 5 brands of ranitidine tablets in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), respectively. Only in simulated gastric fluid (pH 1.2), many differences were observed for both rate and extent of dissolution of different brands. The dissolution rate constant and the average percent drug dissolved of brands A and B in both dissolution media were almost the same.

Results of the dissolution profiles in simulated gastric fluid and simulated intestinal fluid are summarized in Tables 3 and 4, respectively. At 30 minutes, almost all 5 brands except brand D were dissolved in simulated intestinal fluid more than 90% as shown in Table 5.

Table 3 Dissolution Profiles of Five Commercial Brands of Ranitidine Tablets in Simulated Gastric Fluid pH 1.2

Time (min)	Average Percent Drug Dissolved [a]				
	Brand A	Brand B	Brand C	Brand D	Brand E
5	3.48±0.55	6.24±1.06	3.62±0.76	6.01±0.76	8.97±0.28
10	31.44±2.50	37.42±3.38	11.00±1.27	15.04±2.14	16.24±0.51
15	60.05±3.85	72.39±3.02	18.24±1.41	26.46±4.52	23.19±0.96
20	74.84±3.52	91.51±1.92	24.31±1.56	38.98±7.49	27.59±1.38
30	100.92±1.21	94.95±2.05	36.57±2.26	66.59±10.58	38.37±1.91
45	100.56±1.73	94.71±1.30	48.85±2.04	84.75±7.52	48.97±2.08
60	101.91±1.48	92.86±1.41	55.10±2.60	87.36±1.86	58.12±1.43
90	100.49±1.35	91.82±1.87	74.17±6.73	87.36±2.42	78.10±8.66
120	100.84±2.50	91.38±2.19	80.27±6.13	85.95±1.96	89.65±7.10

a = mean ± standard deviation (n = 6)

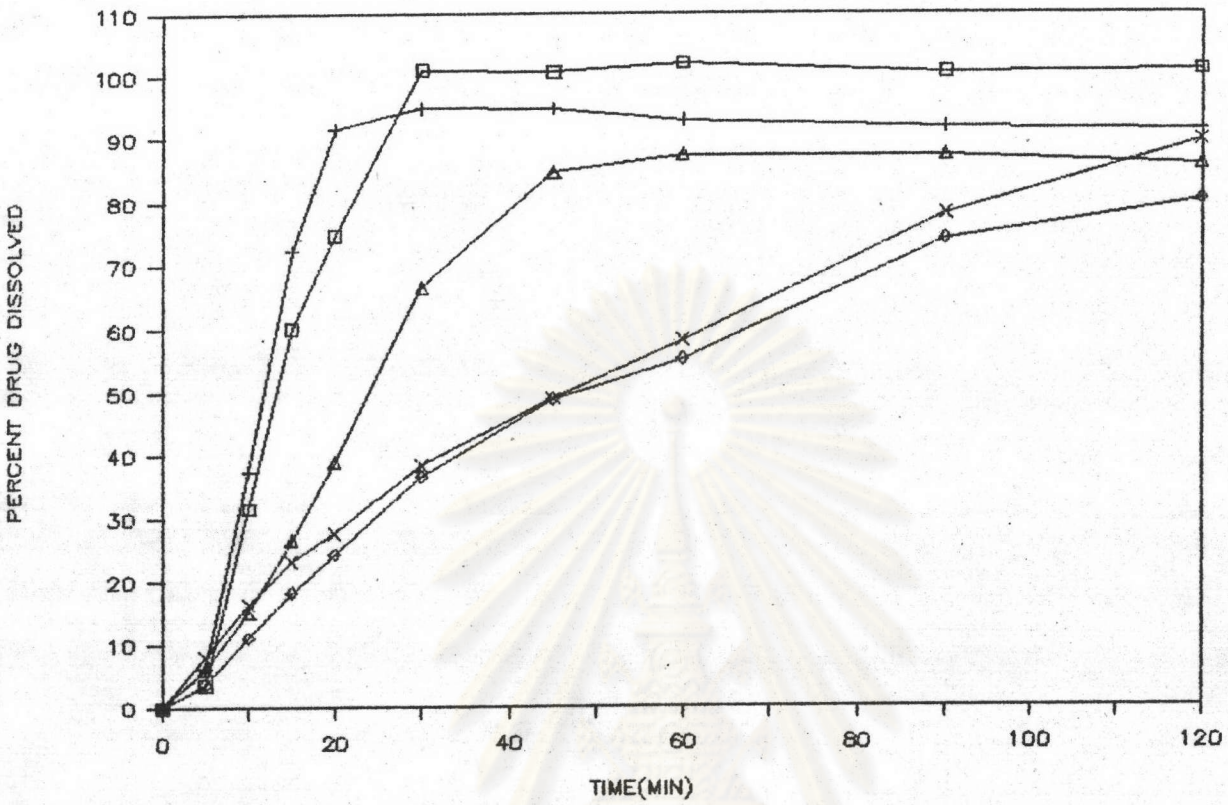


Figure 2 Dissolution Profiles of Five Commercial Brands of Ranitidine Tablets in Simulated Gastric Fluid pH 1.2

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (Δ), Brand E (×)

Table 4 Dissolution Profiles of Five Commercial Brands of Ranitidine Tablets in Simulated Intestinal Fluid pH 7.5

Time (min)	Average Percent Drug Dissolved [a]				
	Brand A	Brand B	Brand C	Brand D	Brand E
5	4.48±1.09	5.52±1.69	2.59±0.83	4.89±0.80	16.32±4.88
10	30.76±1.80	10.94±3.51	22.62±10.33	15.19±2.36	39.85±6.26
15	56.03±3.55	67.14±6.45	52.87±12.02	29.16±4.87	63.11±7.88
20	78.66±4.13	87.84±5.58	76.55±8.91	47.74±4.96	84.55±5.69
30	98.65±3.16	96.70±2.41	92.74±2.99	77.55±6.04	98.57±2.27
45	99.77±0.98	96.67±1.72	97.61±1.38	92.44±2.05	97.26±2.64
60	98.97±0.99	93.81±2.33	95.28±1.81	92.66±2.04	97.82±2.72
90	98.68±1.13	91.59±2.48	95.65±1.36	92.42±2.37	96.94±3.06
120	96.75±3.41	93.08±2.35	93.86±2.03	90.89±2.02	95.65±2.12

a = mean ± standard deviation (n = 6)

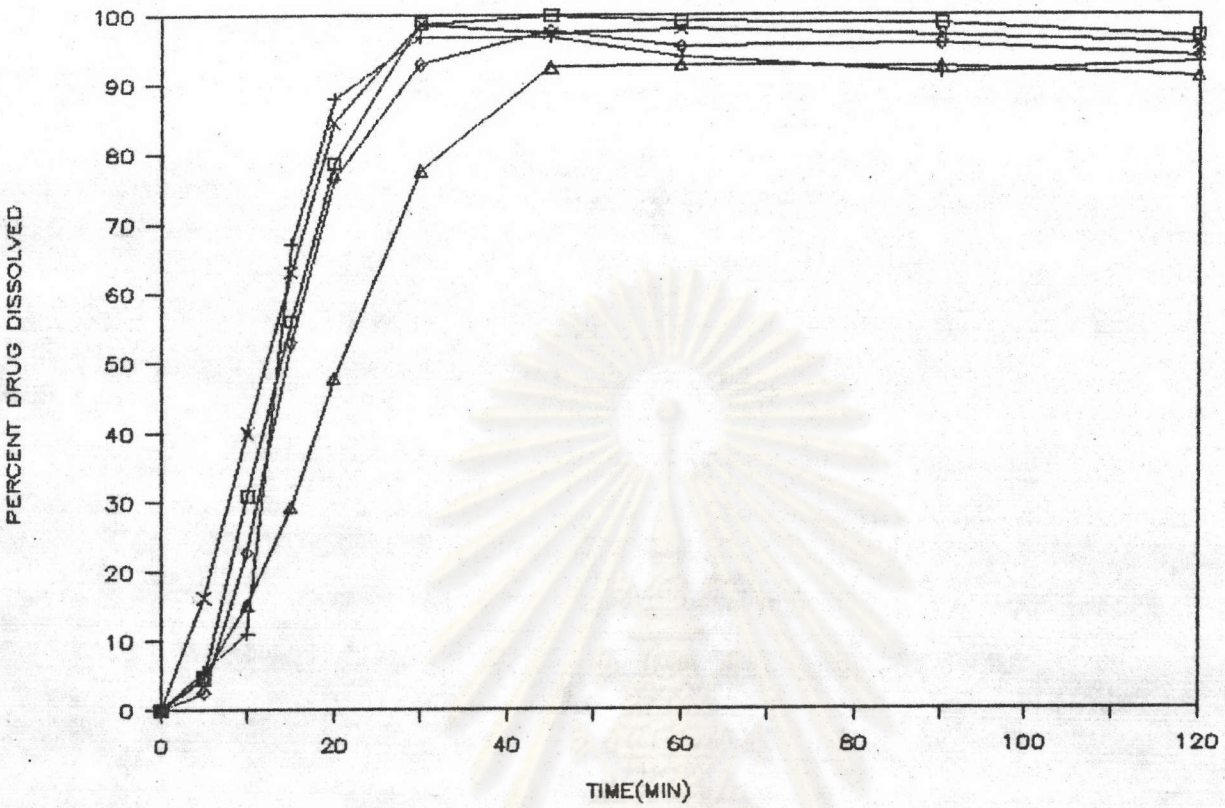


Figure 3 Dissolution Profiles of Five Commercial Brands of Ranitidine Tablets in Simulated Intestinal Fluid pH 7.5

Key : Brand A (◘), Brand B (+), Brand C (◇), Brand D (△), Brand E (×)

Table 5 Average Percent of Drugs Dissolved in Simulated Gastric Fluid and Simulated Intestinal Fluid at 30 minutes

Brand	Average Percent Drug Dissolved [a]	
	Simulated Gastric Fluid	Simulated Intestinal Fluid
A	100.92 ± 1.21	98.65 ± 3.16
B	94.95 ± 2.05	96.70 ± 2.41
C	36.57 ± 2.26	92.74 ± 2.99
D	66.59 ± 10.58	77.55 ± 6.04
E	38.37 ± 1.91	98.57 ± 2.27

a = mean ± standard deviation (n = 6)

The dissolution rate constants assessed by a one way analysis of variance and t-test with 95% confidence limits indicated in Tables 6-9 that there were statistically significant differences among brands A, B, C, D and E in simulated gastric fluid ($p < 0.05$). However, in simulated intestinal fluid there were no statistically significant among brands A, B, C and E. The mean dissolution rate constants of these 4 brands were significantly greater than brand D ($p < 0.05$).

These variations may be due to the solubility of film coating materials in both media. However, most of the film-coated tablets completely dissolved in basic medium. The difference in formulations, sources of raw materials, and/or manufacturing processes might be the important reasons for these differences (34-36).

Table 6 Analysis of Variance for Dissolution Rate Constants (k) of Five Commercial Ranitidine Tablets in Simulated Gastric Fluid pH 1.2

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	596.71	149.18	48.69
Within groups	25	76.60	3.06	
Total	29	673.31	****	

$$F^{e}_{0.05\ (4,\ 25)} = 2.76$$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 7 Comparison of Dissolution Rate Constants of Locally Manufactured Products with Innovator's (Brand A) in Simulated Gastric Fluid Using t-test.

Comparison with	t (Calculate)	Statistical
	Brand A	significance
Brand B	-6.96	S
Brand C	4.60	S
Brand D	-3.99	S
Brand E	-6.81	S

$t^{a}_{(0.05,\ 25)} = 2.06$

S = significant ($p < 0.05$)

a = A t-value from the table

Table 8 Analysis of Variance for Dissolution Rate Constants (k) of Five Commercial Ranitidine Tablet in Simulated Intestinal Fluid pH 7.5

Source of variation	d.f.[a]	S.S.[b]	M.S.[c]	F[d]
Among groups	4	59.68	14.92	2.78
Within groups	25	134.37	5.37	
Total	29	194.05	****	

$$F^{e}_{0.05\ (4,\ 25)} = 2.76$$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 9 Comparison of Dissolution Rate Constants of Locally Manufactured Products with Innovator's (Brand A) in Simulated Intestinal Fluid Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	-1.83	NS
Brand C	-0.12	NS
Brand D	-2.79	S
Brand E	-1.05	NS

$t^{a}_{(0.05,\ 25)} = 2.06$

S = significant ($p < 0.05$)

NS = not significant ($p > 0.05$)

a = A t-value from the table

In Vivo Studies

1. Plasma Ranitidine Concentration Analysis

Chromatograms of ranitidine and internal standard are illustrated in Figure 4. Retention times for ranitidine and internal standard were 4.43 and 2.95 minutes, respectively. Analytical recoveries of ranitidine and internal standard were about 70%. The sensitivity of ranitidine in plasma detected in this study was 20 ng/ml.

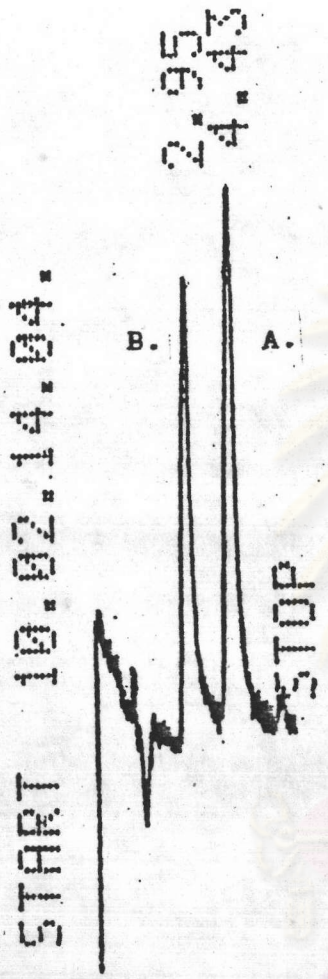
2. Clinical Observations

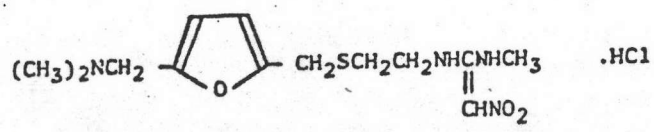
There were no side effects that could be related to ranitidine administration.

3. Plasma Ranitidine Level

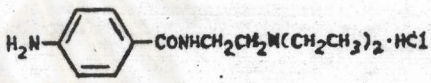
Parenteral Study :

The individual plasma ranitidine concentrations from 12 subjects at appropriate sampling time from 5 min to 7 hours are depicted in Table 10. After IV bolus administration, plasma ranitidine concentration decline rapidly in the first hour and then more slowly as shown in Figure 5. The result indicated that the plasma concentration-time profile was characterized by multicompartment kinetic. Either a bi-or triexponential function has been used to solve for the mathematical model of the drug (17, 20, 22, 37). Base on the





(A)



(B)

Figure 4 High Pressure Liquid Chromatogram[a] of Ranitidine (A) and Internal Standard (B)

a. obtained from HPLC analysis of human plasma containing 0.5 mcg/ml of ranitidine HCl and 80 mcg/ml of procainamide HCl.

Table 10 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Intravenous Administration of 50 mg Ranitidine Injection

Subject No.	Time (min.)										
	5	10	20	30	45	60	90	120	180	300	420
1	2.0227	1.4329	1.3691	0.9821	0.7677	0.3777	0.3579	0.2454	0.2028	0.1097	0.0593
2	1.0669	0.8377	0.7812	0.7073	0.5562	0.4586	0.2482	0.2078	0.1691	0.0785	0.0344
3	1.9115	1.1731	0.8992	0.8685	0.5085	0.3174	0.2550	0.2078	0.0854	0.0739	0.0409
4	2.4477	1.2619	0.9081	0.8573	0.5889	0.4035	0.3081	0.2758	0.1866	0.0887	0.0422
5	1.9318	1.3162	0.7426	0.6044	0.5532	0.2180	0.1389	0.1266	0.0728	0.0261	*
6	2.9262	1.9409	1.7474	1.2056	0.7388	0.6967	0.5128	0.3789	0.2634	0.1115	0.0472
7	2.4446	1.5439	1.0377	0.5762	0.5012	0.4768	0.2581	0.2369	0.1398	0.0361	0.0280
8	2.0889	1.1397	0.9013	0.6255	0.4987	0.2743	0.2544	0.1443	0.1076	0.0582	0.0252
9	1.7635	1.0594	0.9029	0.6257	0.5344	0.2856	0.2555	0.2045	0.1494	0.0797	0.0425
10	1.8954	1.1015	0.7954	0.6612	0.3239	0.2322	0.1990	0.1803	0.1349	0.0652	0.0358
11	2.1500	1.4143	0.8833	0.6848	0.5848	0.3298	0.2494	0.2250	0.1453	0.1155	0.0381
12	2.0060	1.1838	0.9455	0.7517	0.6222	0.4131	0.2616	0.2377	0.1500	0.0876	0.0381
MEAN	2.0546	1.2838	0.9928	0.7625	0.5649	0.3736	0.2749	0.2226	0.1506	0.0775	0.0360
S.D.	0.4283	0.2687	0.2748	0.1783	0.1105	0.1263	0.0875	0.0620	0.0497	0.0270	0.0137

* conc. < 0.020 mcg/ml

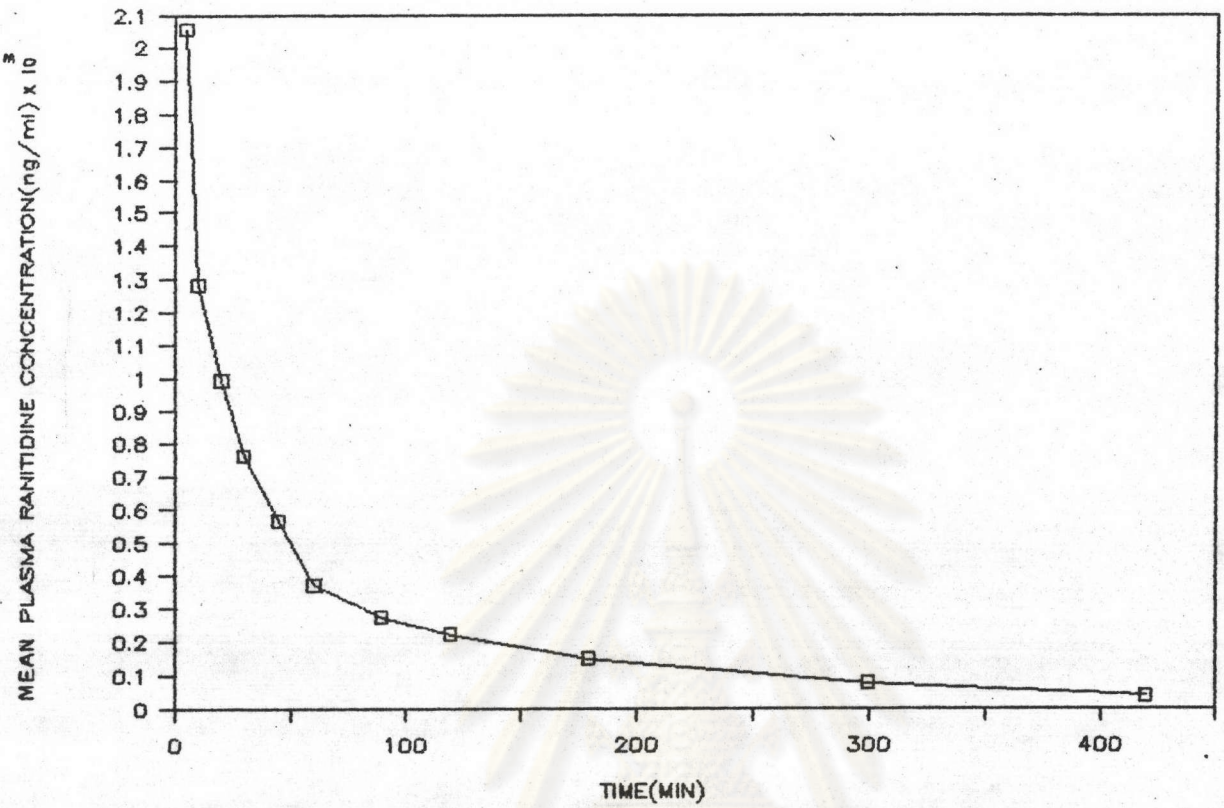


Figure 5 Plasma Ranitidine Concentration (MEAN ± SD) from 12 Subjects Following Intravenous Administration of 50 mg Ranitidine Injection

semilogarithmic plot of individual plasma concentration-time data for 12 subjects, they were best described as biexponential kinetic.

Oral Study :

The individual plasma ranitidine concentration-time profile from 0.5 to 10 hours are depicited in Tables 11-15. Double peaks following oral administration of ranitidine in fasting subjects previously observed (1, 20, 37) were also apparent in some cases of this study (Figures 6-11). The first peak appeared at about 0.5 hours while the second peak was apparent at about 2 to 4 hours after dosing (Table 16). These biphasic characters may be related to food intake (36, 37). Bogues et al. (20) reported that in subject who received food after an oral dose of ranitidine (150 mg), there was no second peak in the plasma concentration-time curve.

The appearance of a second peak following oral ranitidine administration may be due to a mechanism similar to cimetidine which was proposed by Pedersen and Miller (38) It could be : (1) the drug might accumulate in the hepatic parenchymal system or the bile, (2) the rate of accumulation is much higher in the first-pass transfer than from the systemic circulation, (3) the absorbed elements of food

Table 11 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets of Brand A

Subject No.	Time (min.)									
	30	60	90	120	150	180	240	360	480	600
1	0.2793	0.2316	0.2613	0.4430	0.9270	1.1849	0.7681	0.1503	0.1002	0.1073
2	0.0501	0.4770	0.3280	0.4526	0.6736	0.6829	0.4145	0.2457	0.1062	0.0500
3	0.1816	0.3997	0.4850	0.5737	0.7703	1.0173	0.6965	0.3668	0.2584	0.1732
4	0.3964	0.3448	0.5209	0.8888	1.8285	2.1121	1.1352	0.6660	0.3915	0.2187
5	0.2188	0.1573	0.3002	0.8422	0.9090	0.7173	0.5203	0.2073	0.1270	0.0506
6	0.7148	0.9016	0.9935	1.2131	1.6631	1.2647	0.8298	0.5584	0.3587	0.2073
7	0.7489	0.6132	0.9172	0.9819	1.6024	0.8526	0.4641	0.4032	0.2411	0.1181
8	0.1401	0.3014	0.2784	0.2880	0.3569	1.0680	0.5157	0.1414	0.0880	0.0347
9	0.8780	1.0366	0.8340	0.8582	0.9765	1.5475	1.1088	0.5945	0.3125	0.1994
10	0.0645	0.0971	0.2632	0.3502	0.3615	0.9415	0.8324	0.5755	0.3129	0.1654
11	0.2680	0.4015	0.4446	0.5492	0.5895	0.8716	0.6332	0.3083	0.2075	0.1658
12	0.4572	0.5312	0.5344	0.6099	1.1968	1.1027	0.8076	0.4468	0.2948	0.1635
MEAN	0.3665	0.4578	0.5134	0.6709	0.9879	1.1136	0.7272	0.3887	0.2332	0.1378
S.D.	0.2668	0.2704	0.2523	0.2707	0.4734	0.3789	0.2247	0.1744	0.1020	0.0618

Table 12 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets of Brand B

Subject No.	Time (min.)									
	30	60	90	120	150	180	240	360	480	600
1	0.2408	0.1091	0.1543	0.1903	1.1475	0.9680	0.6252	0.3244	0.1764	0.1014
2	0.1716	0.3573	0.3435	0.3816	0.3937	0.6240	0.4240	0.1351	0.1090	0.0506
3	0.1312	0.4854	0.5015	0.4785	0.4049	0.3870	1.0712	0.4371	0.2272	0.1589
4	0.2292	0.4854	0.8176	0.9961	1.0603	1.0368	0.9625	0.4371	0.2980	0.1518
5	0.2738	0.2965	0.3023	0.3999	0.4351	0.5875	0.5287	0.3719	0.1758	0.1309
6	0.5028	0.4044	0.3716	0.4906	0.6240	0.7449	0.9647	0.3073	0.2811	0.0640
7	0.5374	0.5547	0.6242	1.7075	1.4465	0.9955	0.7110	0.4158	0.2075	0.1274
8	0.4462	0.4751	0.4057	0.4307	0.6856	1.3345	0.9895	0.5209	0.2371	0.0935
9	0.2493	0.4680	0.4039	0.4377	0.8531	0.8798	0.3766	0.2579	0.1162	0.0541
10	0.1646	0.1758	0.2187	0.2292	0.4761	0.4988	0.4839	0.4075	0.2856	0.1562
11	0.4371	0.3850	0.3914	1.5147	1.3823	1.0350	0.6829	0.3888	0.2922	0.1802
12	0.3047	0.3695	0.3148	0.4427	0.7879	1.1380	0.6319	0.4024	0.3117	0.1945
MEAN	0.3074	0.3805	0.4041	0.6416	0.8081	0.8525	0.7043	0.3672	0.2265	0.1220
S.D.	0.1330	0.1268	0.1705	0.4742	0.3595	0.2726	0.2287	0.0959	0.0675	0.0470

Table 13 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets of Brand C

Subject No.	Time (min.)									
	30	60	90	120	150	180	240	360	480	600
1	0.3835	0.3726	0.4207	0.3835	1.2460	1.2791	0.7112	0.4164	0.2332	0.1398
2	0.1837	0.1401	0.2261	0.6782	0.5594	0.4680	0.3986	0.1942	0.1532	0.0791
3	0.1973	0.2044	0.2240	0.3057	0.5573	0.8606	0.5440	0.2240	0.1509	0.0823
4	0.5227	0.8274	0.7783	0.6701	0.6543	0.5227	0.3911	0.2157	0.1367	0.0622
5	0.3117	0.3158	0.3658	0.7075	0.9750	0.8087	0.5739	0.4371	0.2003	0.1182
6	0.5943	0.4005	0.4993	0.5281	0.7381	0.8609	0.5014	0.2579	0.1744	0.0871
7	0.3315	0.3573	0.3721	0.8401	1.2347	0.8035	0.5840	0.2670	0.0906	0.0573
8	0.2103	0.2042	0.2301	0.2560	0.4854	0.9202	0.6980	0.3937	0.2197	0.1426
9	0.4682	0.6458	0.6211	0.4750	0.8893	1.6659	1.0168	0.4221	0.2680	0.0725
10	0.0487	0.1569	0.2214	0.2347	0.4204	0.6549	0.5542	0.3304	0.1779	0.0915
11	0.1926	0.4942	0.3573	0.4218	1.0240	1.1573	0.8373	0.5002	0.2906	0.1366
12	0.2353	0.2866	0.3692	0.5952	1.4775	0.9651	0.8456	0.4694	0.2453	0.1312
MEAN	0.3066	0.3672	0.3905	0.5072	0.8551	0.9139	0.6380	0.3440	0.1951	0.1000
S.D.	0.1536	0.1968	0.1653	0.1863	0.3271	0.3174	0.1815	0.1038	0.0561	0.0303

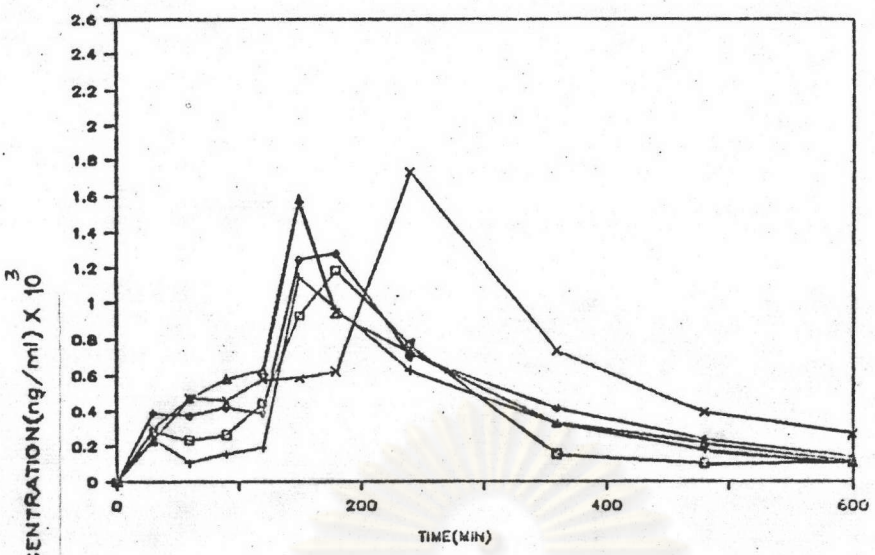
Table 14 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets of Brand D

Subject No.	Time (min.)									
	30	60	90	120	150	180	240	360	480	600
1	0.2251	0.4706	0.5798	0.6282	1.5887	0.9401	0.7256	0.3269	0.2115	0.1086
2	0.1607	0.2902	0.6025	0.7725	1.2822	1.6018	0.8925	0.4629	0.2512	0.1587
3	0.2637	0.2264	0.2219	0.2392	0.2565	1.7444	0.2565	0.1742	0.1355	0.0805
4	0.2823	0.4125	0.7306	0.7840	0.9391	0.6240	0.6008	0.2684	0.1338	0.0573
5	0.1750	0.3190	0.4131	0.4321	0.7387	0.9304	0.5734	0.3871	0.2197	0.1190
6	1.3265	0.9895	0.8010	1.0952	1.3392	1.9453	1.6655	0.7552	0.3485	0.1718
7	0.2425	0.3284	0.2903	0.5280	0.3507	0.2711	0.2214	0.1347	0.0791	0.0569
8	0.2088	0.3430	0.3711	0.4218	0.6773	0.7573	0.5813	0.2536	0.1947	0.0573
9	0.0346	0.2770	0.4467	0.4930	0.5408	0.7670	0.6545	0.3197	0.1778	0.1182
10	0.0539	0.1858	0.1353	0.1313	0.5917	1.2187	0.6076	0.2805	0.1976	0.0970
11	0.3212	0.6392	0.7702	0.7780	0.7091	0.5679	0.4307	0.2555	0.1688	0.0928
12	0.1299	0.2747	0.2885	0.3680	0.9125	0.7637	0.6704	0.3252	0.1709	0.0752
MEAN	0.2854	0.3964	0.4709	0.5559	0.8272	1.0109	0.6567	0.3287	0.1908	0.0995
S.D.	0.3247	0.2128	0.2140	0.2579	0.3877	0.4910	0.3532	0.1533	0.0643	0.0364

Table 15 Plasma Ranitidine Concentrations (mcg/ml) from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets of Brand E

Subject No.	Time (min.)									
	30	60	90	120	150	180	240	360	480	600
1	0.2965	0.4724	0.4573	0.5751	0.5841	0.6210	1.7339	0.7353	0.3911	0.2683
2	0.4715	0.3579	0.3673	0.4241	0.7409	1.3836	0.7353	0.5704	0.3758	0.1653
3	0.3863	0.4724	0.4305	0.9511	1.5560	1.0900	0.7522	0.3906	0.2236	0.1552
4	0.6777	1.0074	1.6139	1.4658	1.3332	1.2929	0.9280	0.6035	0.3619	0.1780
5	0.6671	0.4128	0.8193	0.9842	0.9545	0.9139	0.8976	0.5164	0.3084	0.1951
6	0.7288	0.9923	1.3660	1.2343	1.2473	1.2971	1.0491	0.4800	0.2411	0.2278
7	0.4780	0.7753	2.2045	1.8717	2.0446	1.4731	0.8452	0.4117	0.1664	0.1232
8	0.5100	0.5045	0.8350	1.4905	1.1333	1.0387	1.0323	0.4274	0.2366	0.1891
9	0.2726	0.6067	1.0387	0.8830	1.3522	1.4734	1.0078	0.4745	0.2857	0.1792
10	0.2301	0.2310	0.2613	0.3522	0.7516	1.1318	0.6795	0.5522	0.3522	0.1834
11	0.5685	0.5243	0.7217	1.2431	0.9431	0.7764	0.5757	0.3863	0.2310	0.1704
12	0.1862	0.3405	0.5457	0.5081	0.6136	1.8417	1.6221	0.7117	0.3361	0.2223
MEAN	0.4561	0.5581	0.8884	0.9986	1.1045	1.1945	0.9882	0.5217	0.2925	0.1881
S.D.	0.1761	0.2370	0.5570	0.4584	0.4123	0.3230	0.3393	0.1126	0.0692	0.0360

1



2

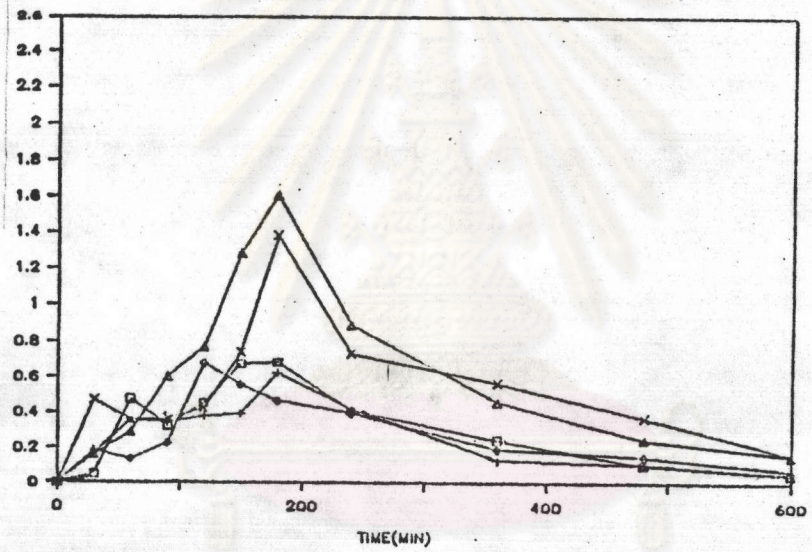
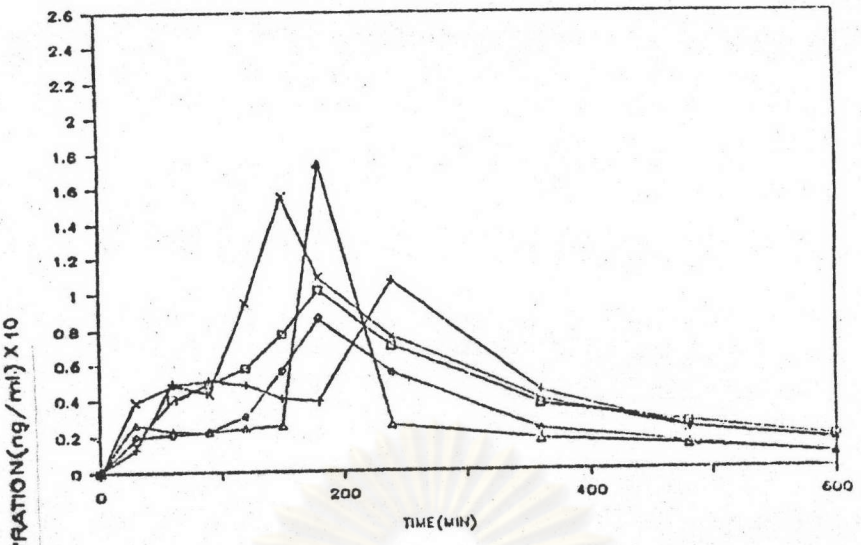


Figure 6 Plasma Ranitidine Concentration-time Profiles of Subjects 1 and 2 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (Δ), Brand E (×),

3



4

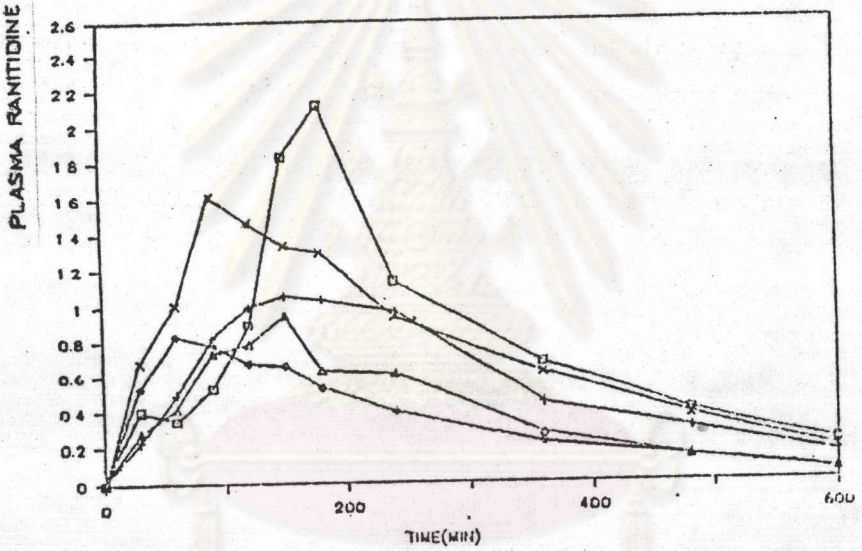


Figure 7 Plasma Ranitidine Concentration-time Profiles of Subjects 3 and 4 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (△), Brand E (×),

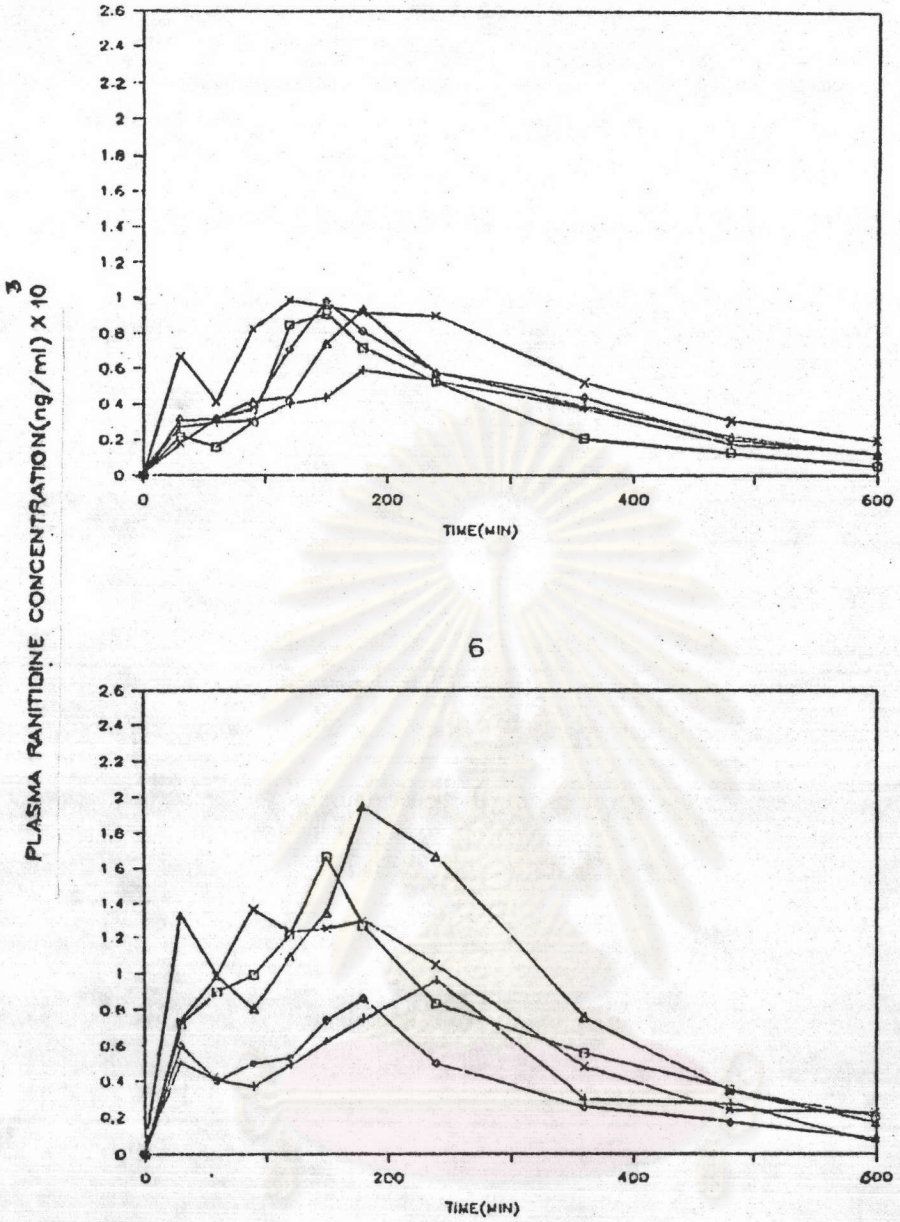


Figure 8 Plasma Ranitidine Concentration-time Profiles of Subjects 5 and 6 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (Δ), Brand E (×),

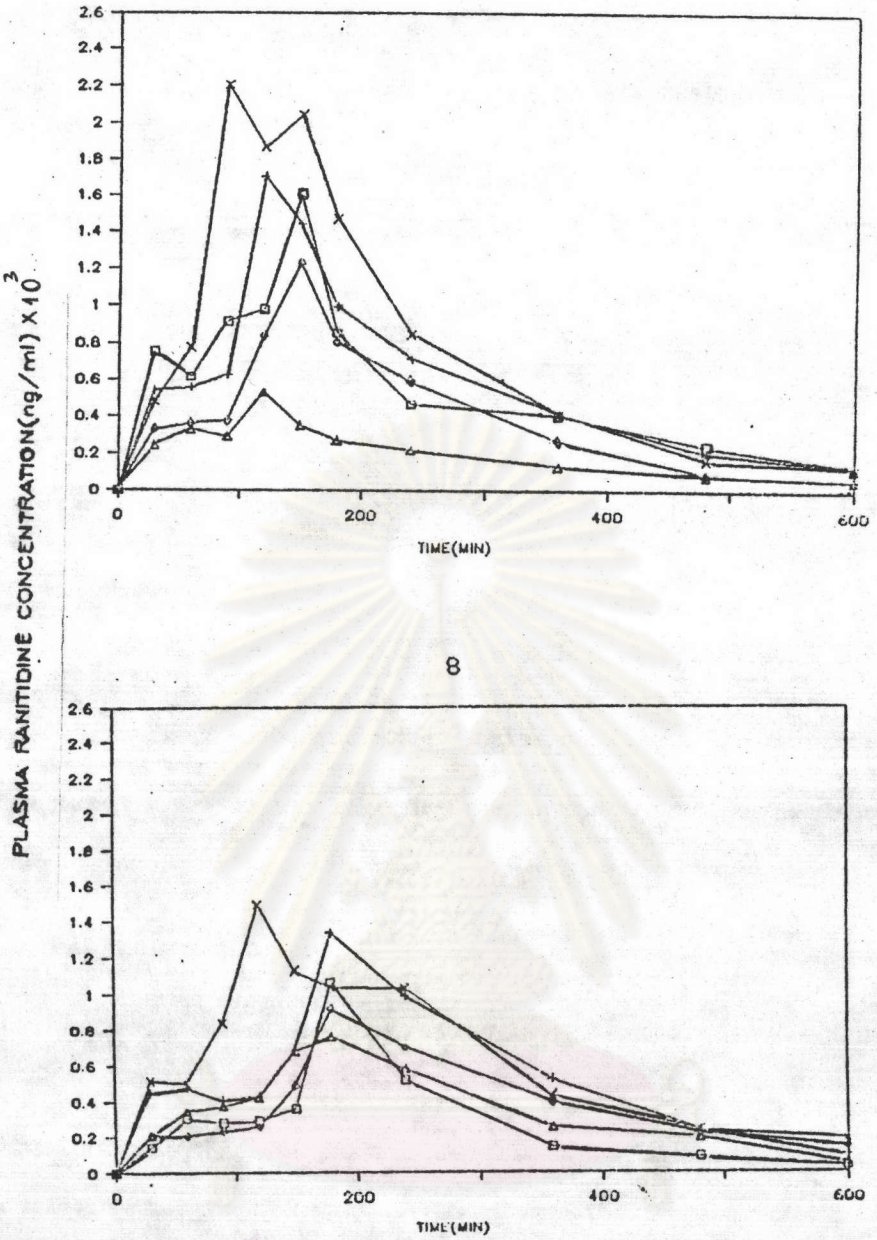
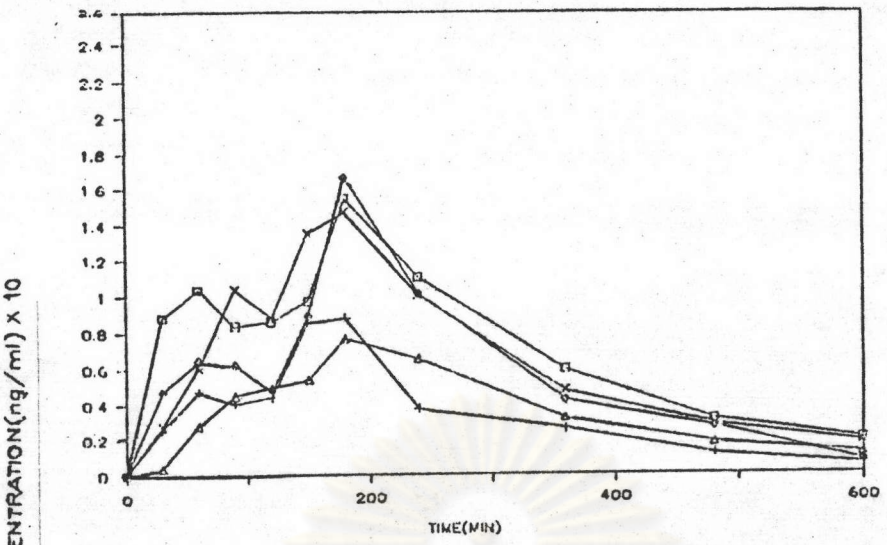


Figure 9 Plasma Ranitidine Concentration-time Profiles of Subjects 7 and 8 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (△), Brand E (×),

9



10

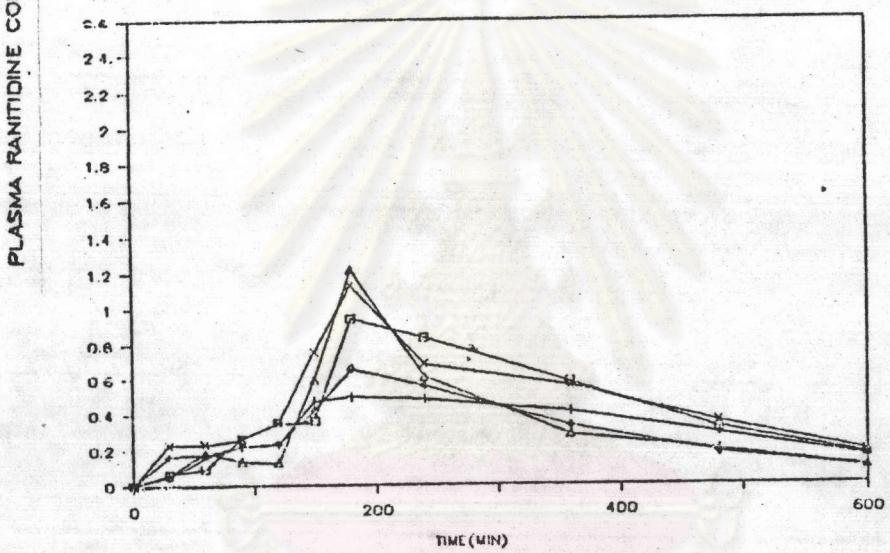
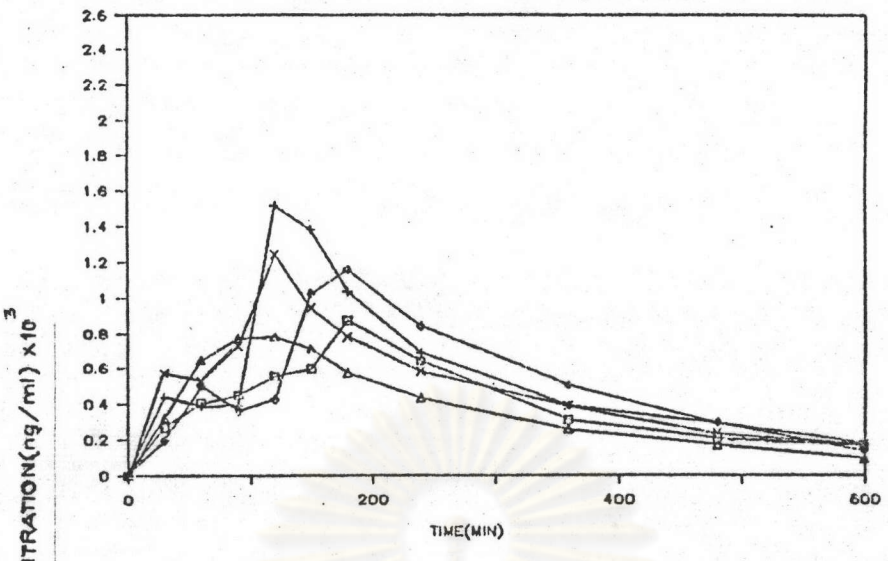


Figure 10 Plasma Ranitidine Concentration-time Profiles of Subjects 9 and 10 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (△), Brand E (×),

11



12

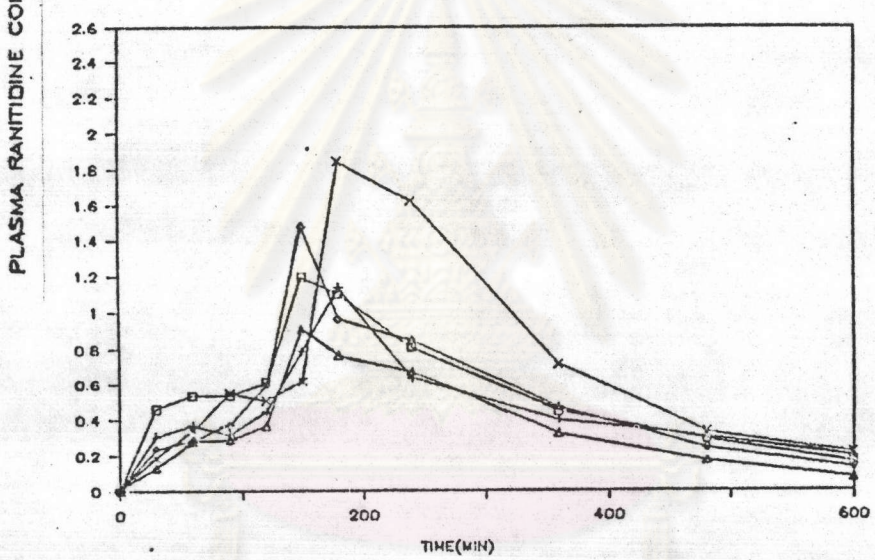


Figure 11 Plasma Ranitidine Concentration-time Profiles of Subjects 11 and 12 Following Oral Administration of Two 150 mg Ranitidine Tablets

Key : Brand A (□), Brand B (+), Brand C (◇), Brand D (Δ), Brand E (X),

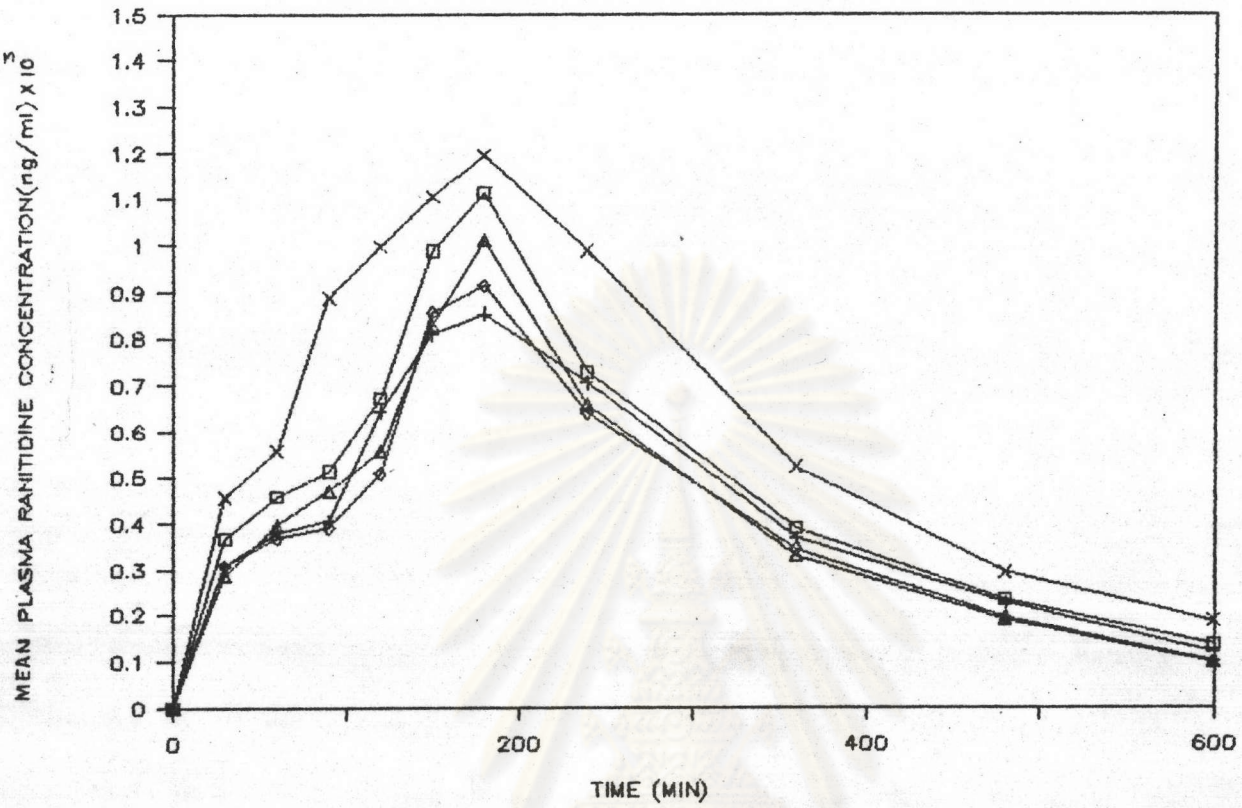


Figure 12 Comparison of Mean Plasma Ranitidine Concentration-time Curve from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets Five Commercial Brands

Key : Brand A (□), Brand B (+), Brand C (◊) Brand D (Δ) and Brand E (X)

Table 16 Peak Plasma Concentration and Time to Peak Concentration Data Following Oral Administration of Two 150 mg Ranitidine Tablets of Five Commercial Brands

Subject	t_{max1} (hrs)					t_{max2} (hrs)					C_{max1} (mcg/ml)					C_{max2} (mcg/ml)				
No.	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
1	0.50	0.50	0.50	-	1.00	3.00	2.50	3.00	2.50	4.00	0.28	0.24	0.38	-	0.47	1.18	1.15	1.28	1.59	1.74
2	1.00	-	0.50	-	0.50	3.00	3.00	2.00	3.00	3.00	0.48	-	0.18	-	0.47	0.68	0.62	0.68	1.68	1.38
3	-	1.50	-	0.50	1.00	3.00	4.00	3.00	3.00	2.50	-	0.50	-	0.26	0.47	1.02	1.07	0.86	1.74	1.56
4	0.50	-	-	-	-	3.00	2.50	1.00	2.50	1.50	0.40	-	-	-	-	2.11	1.06	0.83	0.94	1.61
5	0.50	-	-	-	0.50	2.50	3.00	2.50	3.00	2.00	0.21	-	-	-	0.67	0.91	0.59	0.98	0.93	0.98
6	-	0.50	0.50	0.50	-	2.50	4.00	3.00	3.00	1.50	-	0.50	0.59	1.33	-	1.66	0.96	0.86	1.95	1.37
7	0.50	-	-	1.00	-	2.50	2.00	2.50	2.00	1.50	0.75	-	-	0.33	-	1.60	1.71	1.23	0.53	2.20
8	1.00	1.00	0.50	-	-	3.00	3.00	3.00	3.00	2.00	0.30	0.48	0.21	-	-	1.07	1.33	0.92	0.76	1.49
9	1.00	1.00	1.00	-	1.50	3.00	3.00	3.00	3.00	3.00	1.04	0.47	0.65	-	1.04	1.55	0.88	1.67	0.77	1.47
10	-	-	-	1.00	-	3.00	3.00	3.00	3.00	3.00	-	-	-	0.19	-	0.94	0.50	0.65	1.22	1.13
11	-	0.50	1.00	-	-	3.00	2.00	3.00	2.00	2.00	-	0.44	0.49	-	-	0.87	1.51	1.16	0.78	1.24
12	-	1.00	-	-	-	2.50	3.00	2.50	2.50	3.00	-	0.37	-	-	-	1.20	1.14	1.48	0.91	1.84
MEAN	0.71	0.86	0.67	0.75	0.90	2.83	2.92	2.63	2.71	2.42	0.49	0.43	0.42	0.53	0.62	1.23	1.04	1.05	1.14	1.50
S.D.	0.25	0.35	0.24	0.25	0.37	0.25	0.63	0.61	0.40	0.79	0.28	0.09	0.18	0.47	0.22	0.40	0.35	0.30	0.44	0.31

compete with cimetidine, and (4) when fasted subjects were given food, it may have caused the release of the drug from a storage depot.

However, Robert (16) indicated that according to the limited data available, the effect of food on the pharmacokinetics of ranitidine was insignificant.

4. Bioavailability of Ranitidine

The bioavailability of drug from its dosage form depends on both rate and extent of drug absorption into the general circulation (33, 35). These factors can be evaluated by determining the pharmacokinetic parameters derived from plasma concentration-time profile. The bioequivalence can be assessed by comparing the peak plasma concentration of the drug, Cp_{max}, the time to peak concentrations, t_{max}, and the total area under the plasma concentration-time curves, AUC, after oral administrations of the test formulation and the reference product.

4.1 Time to Peak Plasma Level

As seen in Table 16, the time to peak plasma level determined from the plot were ranged from 0.5-4 hours. The average peak times were 0.71 ± 0.25 ($t\ max_1$), 2.83 ± 0.25 ($t\ max_2$); 0.86 ± 0.35 ($t\ max_1$), 2.92 ± 0.63 ($t\ max_2$);

Table 17 Analysis of Variance for Time to Peak Plasma Concentration (Second) of Five Commercial Ranitidine Tablets.

Source of variation	d.f.[a]	S.S[b]	M.S.[c]	F[d]
Among groups	4	1.81	.45	1.40
Within groups	55	17.79	.32	
Total	59	19.60		****

$$F^{*}_{0.05\ (4,\ 25)} = 2.55$$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 18 Comparison of Time to Peak Plasma Concentration (Second) of 4 Different Brands (B, C, D and E) with the Innovator's (Brand A) Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	0.39	NS
Brand C	0.86	NS
Brand D	0.52	NS
Brand E	1.76	NS

$t^{a}_{(0.05,\ 55)} = 2.00$

NS = not significant ($p > 0.05$)

a = A t-value from the table

0.67 ± 0.24 ($t\ max_1$), 2.63 ± 0.61 ($t\ max_2$); 0.75 ± 0.25 ($t\ max_1$), 2.71 ± 0.40 ($t\ max_2$) and 0.90 ± 0.37 ($t\ max_1$), 2.42 ± 0.79 ($t\ max_2$) for brands A, B, C, D and E, respectively. There were no statistically significant differences among these values (Tables 17, 18).

4.2 Peak Plasma Concentration

Table 16 shows peak plasma levels and the times to peak for each of 5 brands determined from the plot. The average of peak plasma levels from 12 subjects after oral administration of two 150 mg ranitidine tablets were 0.49 ± 0.28 ($C\ max_1$), 1.23 ± 0.40 ($C\ max_2$); 0.43 ± 0.09 ($C\ max_1$), 1.04 ± 0.35 ($C\ max_2$); 0.42 ± 0.18 ($C\ max_1$); 1.05 ± 0.30 ($C\ max_2$); 0.53 ± 0.47 ($C\ max_1$), 1.14 ± 0.40 ($C\ max_2$) and 0.62 ± 0.22 ($C\ max_1$), 1.5 ± 0.31 ($C\ max_2$) mcg/ml for brands A, B, C, D and E respectively. These values were also not statistically significant differences as shown in Tables 19, 20 ($p > 0.05$).

4.3 Area Under Plasma Versus Time Curve

The area under the curve, AUC, and the area under the first moment curve, AUMC, from zero to infinity after intravenous and oral administration are illustrated in Table 21.

Table 19 Analysis of Variance for Peak Plasma Concentration (Second) of Five Commercial Ranitidine Tablets.

Source of variation	d.f.[a]	S.S[b]	M.S.[c]	F[d]
Among groups	4	1.71	.43	2.93
Within groups	55	8.02	.15	
Total	59	9.73		****

$$F^{e}_{0.05\ (4,\ 25)} = 2.55$$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 20 Comparison of Peak Plasma Concentration (Second) of 4 Different Brands (B, C, D and E) with the Innovator's (Brand A) Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	-1.22	NS
Brand C	-1.15	NS
Brand D	-0.58	NS
Brand E	-1.73	NS

$t^{a}_{(0.05,\ 55)} = 2.00$

NS = not significant ($p > 0.05$)

a = A t-value from the table

Table 21 Individual Pharmacokinetic Parameters of Ranitidine from 12 Subjects Following 50 mg Intravenous and 300 mg Oral Administration

Subject	$[AUC]_0^\infty$ (mcg - hr/ml)						$[AUMC]_0^\infty$ (mcg - hr^2 /ml)					
No.	A	B	C	D	E	I	A	B	C	D	E	I
1	4.0087	3.9995	5.3283	5.0500	7.6417	2.2515	17.3964	19.5908	25.9262	22.4223	42.9016	5.5304
2	3.0152	2.6108	2.9230	6.1728	5.9917	1.6032	12.7052	11.0238	14.9281	29.5741	32.3534	3.6431
3	5.1328	4.8833	3.2885	3.2242	5.7408	1.6127	28.6472	25.9457	15.7164	14.3505	27.1630	3.6266
4	8.3237	6.2062	3.6888	3.9653	8.2188	1.9642	41.3049	30.6858	14.4604	15.7758	38.0499	4.2126
5	3.3860	3.8823	4.6283	4.3548	6.7210	1.1458	13.8028	22.6208	23.1951	22.5288	37.3352	1.4363
6	7.7712	4.5988	4.0108	9.5905	7.8333	2.7912	37.9737	20.1011	17.5975	41.0376	36.9726	5.2989
7	5.5737	6.0175	3.9582	2.1077	7.6617	1.6728	24.0910	25.6641	15.1924	9.8093	27.8787	2.7517
8	2.8238	5.5643	4.3260	3.5690	6.7830	1.4287	10.9675	24.9989	24.3222	15.8055	32.8709	2.6306
9	7.8000	3.3793	5.9488	3.9868	6.9868	1.6467	36.6764	13.6942	24.5454	20.8723	33.0493	3.9716
10	5.1248	4.2395	3.2937	3.7155	5.5490	1.4500	30.9728	31.7756	17.8957	18.6945	33.4200	3.3729
11	4.6090	5.3980	5.0808	3.9765	5.5582	1.8132	25.9459	21.4074	25.0670	18.0938	28.6112	4.1769
12	5.9650	5.3797	5.4632	3.8610	7.9155	1.7970	30.3923	32.1741	26.7216	18.0010	40.8990	3.8963
MEAN	5.2945	4.6799	4.3282	4.4645	6.8835	1.7648	25.9063	23.3069	20.4640	20.5805	34.2921	3.7123
S.D.	1.8082	1.0496	0.9284	1.8047	0.9406	0.4083	9.8813	6.4007	4.6638	7.7662	4.8361	1.0720

Table 21 (continued)

Subject No.	MRT (hrs)						MAT (hrs)				
	A	B	C	D	E	I	A	B	C	D	E
1	4.3397	4.8983	4.8657	4.4400	5.6142	2.4562	1.8835	2.4422	2.4095	1.9838	3.1580
2	4.2138	4.2223	5.1072	4.7910	5.3997	2.2725	1.9413	1.9498	2.8347	2.5185	3.1272
3	5.5812	5.3132	4.7792	4.4508	4.7315	2.2488	3.3323	3.0643	2.5303	2.2020	2.4827
4	4.9623	4.9443	3.9200	3.9785	4.6297	2.1447	2.8177	2.7997	1.7753	1.8338	2.4850
5	4.0765	5.8267	5.0115	5.1733	5.5550	1.2535	2.8230	4.5732	3.7580	3.9198	4.3015
6	4.8865	4.3708	4.3875	4.2790	4.7198	1.8985	2.9880	2.4723	2.4890	2.3805	2.8213
7	4.3223	4.2648	3.8382	4.6542	3.6387	1.6450	2.6773	2.6198	2.1932	3.0092	1.9937
8	3.8838	4.4927	5.6223	4.4285	4.8460	1.8413	2.0425	2.6513	3.7815	2.5872	3.0047
9	4.7022	4.0523	4.1260	5.2353	4.7302	2.4118	2.2903	1.6405	1.7142	2.8235	2.3183
10	6.0437	7.4952	5.4333	5.0315	6.0227	2.3260	3.7177	5.1692	3.1073	2.7055	3.6967
11	5.6293	3.9658	4.9337	4.5502	5.1477	2.3035	3.3258	1.6623	2.6302	2.2467	2.8442
12	5.0952	5.9807	4.8912	4.6623	5.1670	2.1682	2.9270	3.8125	2.7230	2.4942	2.9988
MEAN	4.8114	4.9856	4.7430	4.6396	5.0169	2.0808	2.7305	2.9048	2.6622	2.5587	2.9360
S.D.	0.6532	0.9894	0.5425	0.3550	0.5898	0.3418	0.5644	1.0556	0.6260	0.5217	0.5943

Table 21 (continued)

Subject	Kel (hr^{-1})						Ka (hr^{-1})				
No.	A	B	C	D	E	I	A	B	C	D	E
1	0.3720	0.3252	0.3036	0.3342	0.3114	0.3090	0.5319	0.4098	0.4149	0.5051	0.3165
2	0.3654	0.3516	0.2586	0.3228	0.2700	0.3582	0.5155	0.5128	0.3533	0.3968	0.3195
3	0.2490	0.3192	0.3282	0.3540	0.3024	0.3144	0.3003	0.3268	0.3953	0.4545	0.4032
4	0.3066	0.2670	0.2868	0.3576	0.2544	0.3714	0.3546	0.3571	0.5618	0.5464	0.4016
5	0.3762	0.2304	0.2748	0.2796	0.2106	0.5130	0.3546	0.2188	0.2660	0.2551	0.2326
6	0.2610	0.4116	0.3096	0.3594	0.2736	0.4266	0.3344	0.4049	0.4016	0.4202	0.3546
7	0.2958	0.3222	0.4122	0.2616	0.3822	0.4476	0.3731	0.3817	0.4566	0.3322	0.5025
8	0.4728	0.3774	0.2706	0.3492	0.2694	0.3834	0.4902	0.3774	0.2646	0.3861	0.3333
9	0.2970	0.3696	0.4218	0.2808	0.3018	0.3198	0.4367	0.6098	0.5848	0.3546	0.4310
10	0.2508	0.1620	0.2844	0.3372	0.2364	0.3168	0.2688	0.1934	0.3215	0.3690	0.2702
11	0.2430	0.2664	0.3042	0.2622	0.2406	0.3258	0.3003	0.6024	0.3802	0.4444	0.3521
12	0.2658	0.2298	0.3060	0.3294	0.3240	0.3474	0.3413	0.2625	0.3676	0.4016	0.3333
MEAN	0.3130	0.3027	0.3134	0.3190	0.2814	0.3695	0.3835	0.3881	0.3974	0.4055	0.3542
S.D.	0.0672	0.0698	0.0499	0.0359	0.0443	0.0610	0.0850	0.1286	0.0956	0.0743	0.0695

Table 21 (continued)

Subject	% F_{ab}					% F_{rel}				$T_{1/2}$ (hrs)
No.	A	B	C	D	E	B	C	D	E	I
1	29.67	29.61	39.44	37.38	56.57	99.77	132.92	125.98	190.63	1.70
2	31.35	27.14	30.39	64.17	62.29	86.59	96.94	204.73	198.72	1.57
3	53.05	50.47	33.99	33.32	59.33	95.14	64.07	62.81	111.85	1.56
4	70.63	52.66	31.30	33.65	69.74	74.56	44.32	47.64	98.74	1.49
5	49.25	56.47	67.32	63.34	97.76	114.66	136.69	128.61	198.49	0.87
6	46.40	27.46	23.95	57.27	46.77	59.18	51.61	123.41	100.80	1.32
7	55.53	59.95	39.44	21.00	76.33	107.96	71.02	37.81	137.46	1.14
8	32.94	64.91	50.47	41.64	79.13	197.05	153.20	126.39	240.21	1.28
9	78.95	34.20	60.21	40.35	70.72	43.32	76.27	51.11	89.57	1.67
10	58.91	48.73	37.86	42.71	63.78	82.72	64.27	72.50	108.28	1.61
11	42.37	49.62	46.70	36.55	51.09	117.12	110.23	86.28	120.59	1.60
12	55.32	49.89	50.67	35.81	73.41	90.19	91.59	64.73	132.70	1.50
MEAN	50.36	45.93	42.65	42.27	67.24	97.36	91.09	94.33	144.00	1.44
S.D.	14.53	12.48	12.27	12.44	13.24	36.55	34.04	46.45	47.70	0.24

The mean $[AUC]_0^\infty$ after intravenous administration was 1.76 $\pm$ 0.41 mcg - hr/ml while those after oral administration of 5 brands (A, B, C, D and E) were 5.29 $\pm$ 1.81, 4.68 $\pm$ 1.05, 4.33 $\pm$ 0.93, 4.46 $\pm$ 1.80 and 6.88 $\pm$ 0.94 mcg - hr/ml, respectively. Statistical analysis revealed no significant differences among brands A, B, C and D. except those with brand E as reported in Tables 22 and 23 ($p < 0.05$).

4.4 Mean Residence Time and Half-Life

The mean residence time (MRT) represents the time for 63.2% of the administration dose to be eliminated. This value obtained from IV bolus administration is similar to the parameter half-life.

The MRT and half-life are also shown in Table 21. The mean MRT after intravenous administration was 2.08 $\pm$ 0.34 hrs and those after oral administration of brands A, B, C, D and E were 4.81 $\pm$ 0.65, 4.99 $\pm$ 0.99, 4.74 $\pm$ 0.54, 4.64 $\pm$ 0.36 and 5.02 $\pm$ 0.59 hrs, respectively. The average elimination half-life obtained from IV bolus administration was 1.44 $\pm$ 0.24 hours. This value was closed to those previously reports (17, 21, 22, 37, 39, 40, 41).

Table 22 Analysis of Variance for [AUC] of Five Commercial Ranitidine Tablets.

Source of variation	d.f.[a]	S.S[b]	M.S.[c]	F[d]
Among groups	4	52.68	13.17	6.44
Within groups	55	112.50	2.05	
Total	59	165.18		****

$F^{e}_{0.05\,(4,\,25)} = 2.55$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 23 Comparison of [AUC] of 4 Different Brands (B, C, D and E) with the Innovator's (Brand A) Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	-1.04	NS
Brand C	-1.64	NS
Brand D	-1.42	NS
Brand E	2.72	S

$t^{a}_{(0.05,\ 55)} = 2.00$

S = significant ($p < 0.05$)

NS = not significant ($p > 0.05$)

a = A t-value from the table

4.5 Elimination Rate Constant and Absorption Rate Constant.

The Elimination Rate Constant (Kel) and Absorption Rate Constant (Ka) are summarized in Table 21.

The mean Kel of IV bolus data was 0.37 $\pm$ 0.06 hr^{-1} while those obtained from 5 brands after oral administration were 0.31 $\pm$ 0.07, 0.30 $\pm$ 0.07, 0.31 $\pm$ 0.05, 0.32 $\pm$ 0.04 and 0.28 $\pm$ 0.04 for brands A, B, C, D and E, respectively.

The mean Ka for brands A, B, C, D and E were 0.38 $\pm$ 0.09, 0.39 $\pm$ 0.13, 0.40 $\pm$ 0.10, 0.41 $\pm$ 0.07 and 0.35 $\pm$ 0.07, respectively. No statistically significant was observed among these values (Tables 24 and 25).

4.6 Absolute and Relative Bioavailability

The absolute bioavailability or systemic bioavailability of a drug is defined as the fraction or percent of an administered dose that actually reaches the systemic circulation. Absolute bioavailability is determined from blood data after oral administration, with reference to similar data after intravenous administration. The mean absolute bioavailabilities of brands A, B, C, D and E were

Table 24 Analysis of Variance for Absorption Rate Constant (Ka) of Five Commercial Ranitidine Tablets.

Source of variation	d.f.[a]	S.S[b]	M.S.[c]	F[d]
Among groups	4	.02	.01	.49
Within groups	55	.52	.01	
Total	59	.54		****

$$F^{e}_{0.05\ (4,\ 55)} = 2.55$$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 25 Comparison of Absorption Rate Constant (Ka) of 4 Different Brands (B, C, D and E) with the Innovator's (Brand A) Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	0.25	NS
Brand C	0.50	NS
Brand D	0.76	NS
Brand E	-0.76	NS

$t^{a}_{(0.05,\ 55)} = 2.00$

NS = not significant ($p > 0.05$)

a = A t-value from the table

50.36 ± 14.53, 45.93 ± 12.48, 42.65 ± 12.27, 42.27 ± 12.44 and 67.24 ± 13.24 %, respectively as summarized in Table 21, which is in accordance with a value about 50% as reported previously (1, 17, 22, 37, 39).

There were no statistically significant differences among brands A, B, C and D except brand E as shown in Tables 26 and 27.

Table 21 also illustrates the fraction of the oral dose relative to a reference standard, brand A (Frel). The mean relative bioavailabilities of brands B, C, D and E were 97.36 ± 36.55, 91.09 ± 34.04, 94.33 ± 46.45 and 144.00 ± 47.70 %, respectively.

Table 26 Analysis of Variance for Absolute Bioavailability of Five Commercial Ranitidine Tablets.

Source of variation	d.f.[a]	S.S[b]	M.S.[c]	F[d]
Among groups	4	5132.18	1283.04	6.95
Within groups	55	10160.22	184.73	
Total	59	1529.40		****

$F^{e}_{0.05\ (4,\ 55)} = 2.55$

a = degree of freedom

b = sum of square

c = mean square

d = variation ratio

e = F obtained from the table

Table 27 Comparison of Absolute Bioavailability of 4 Different Brands (B, C, D and E) with the Innovator's (Brand A) Using t-test

Comparison with	t (Calculate) Brand A	Statistical significance
Brand B	-0.80	NS
Brand C	-1.39	NS
Brand D	-1.46	NS
Brand E	3.04	S

$t^{a}_{(0.05,\ 55)} = 2.00$

S = significant ($p < 0.05$)

NS = not significant ($p > 0.05$)

a = A t-value from the table

The principal pharmacokinetic parameters of ranitidine following oral administration of five brands were summarized in Table 28. Statistical analysis of these parameters among five brands revealed no significant differences ($p > 0.05$) except only the AUC values. These results indicated that the five brands of ranitidine tablets were all bioequivalent according to the rate of drug absorption. Brands A, B, C and D were completely bioequivalent with respect to both the rate and extent of ranitidine absorption. The AUC of brand E was greater than any others. This may result from the larger content of drug in formular as shown in Table 2. However, this can be concluded that all brands studied could be substituted for each other if the price is not taken into account.

Tables 28 and 29 exhibit the pharmacokinetic parameters estimated from each plasma data of 12 subjects after oral administration of two 150 mg of five brands and 50 mg intravenous administration respectively. These values were slightly different from the previous studies (17, 20, 37, 39-41). As example, Garg. et al. (37) studied with 12 male fasted subjects (19-32 yr.) using a single 100 mg i.v. dose and 100 mg oral dose, they found that the half-lives were 2 hrs. and 2.7 hrs., respectively. The factors possibly affecting these differences were the different methods using to analyze data, as well as the intersubject variability such as the races, ages, weights and normal habits.

Table 28 Estimated Pharmacokinetic Parameters (MEAN ± SD) of Ranitidine from 12 Subjects Following Oral Administration of Two 150 mg Ranitidine Tablets

Parameters	A	B	C	D	E	MEAN ± SD	Statistic
Time to peak concentration, t_{max2} (hr)	2.83 ± 0.25	2.92 ± 0.63	2.63 ± 0.61	2.71 ± 0.40	2.42 ± 0.79	2.70 ± 0.17	NS
Peak plasma concentration, C_{max2} (µg/ml)	1.23 ± 0.40	1.04 ± 0.35	1.05 ± 0.30	1.14 ± 0.44	1.50 ± 0.31	1.19 ± 0.17	NS
Area under the plasma concentration -time curve, $[AUC]_0^\infty$ (ug-hr/ml)	5.29 ± 1.80	4.68 ± 1.00	4.33 ± 0.90	4.46 ± 1.80	6.89 ± 0.90	5.13 ± 0.94	S
First order absorption rate constant, Ka (hr^{-1})	0.38 ± 0.10	0.39 ± 0.13	0.40 ± 0.10	0.41 ± 0.07	0.35 ± 0.07	0.39 ± 0.02	NS

S = significant ($p < 0.05$)

NS = not significant ($p > 0.05$)

Table 29 Estimated Pharmacokinetic Parameters of Ranitidine from 12 Subjects Following 50 mg Intravenous Administration

Parameters	MEAN ± SD
Area under the plasma concentration-time curve, $[AUC]_0^{\infty}$ (μg-hr/ml)	1.76 ± 0.40
Elimination rate constant, Kel (hr^{-1})	0.37 ± 0.06
Mean residence time, MRT (hr)	2.08 ± 0.30
Biological half-life, $t_{1/2}$ (hr)	1.44 ± 0.24

In Vitro-In Vivo Correlations

Table 30 exhibits the relationships among and between various in vitro and in vivo parameters.

There were no correlative significance between disintegration times and dissolution rate constants in both media. This result indicated that disintegration times were not rate limiting step of ranitidine dissolution. Poor correlation was observed between in vitro parameters (disintegration time, dissolution rate constants) and in vivo parameters (Ka, t_{max}), except dissolution rate constants in simulated gastric fluid VS. t_{max} ($p < 0.05$). The correlation between dissolution rate constants in simulated gastric fluid and time to peak concentration may be due to the inconsistently solubility of ranitidine in acid medium, accordingly to different film-forming materials used for coating among brands. In addition, differences in formulation factors and processes for each brand may be taken into account.

This study reveals that all five commercial brands of ranitidine tablet are bioequivalent according to the following parameters : C_{max}, t_{max} and Ka. Base on the absolute bioavailability data the rank of these five brands are, E > A > B > C > D.

Table 30 In Vitro-In Vivo Bioavailability Correlations

Correlation	d.f[a]	CC[b]	t-value	Statistic
Disintegration Times VS. Dissolution Rate Constants	3	0.244(G)	-0.435(G)	NS
	3	-0.778(I)	-2.143(I)	NS
Disintegration Times VS. Ka	3	0.698	1.686	NS
Disintegration Times VS. t_{max}	3	0.066	0.114	NS
Dissolution Rate Constants VS. t_{max}	3	0.892(G)	3.418(G)	S
	3	0.416(I)	0.793(I)	NS

$t_{(0.05,\ 3)}$ from the table = 3.18

G = simulated gastric fluid

I = simulated intestinal fluid

Ka = absorption rate constants

NS = not significant ($p > 0.05$)

S = significant ($p < 0.05$)

t_{max} = time to peak concentration

a = degree of freedom

b = correlation coefficient