CHAPTER IV

RESULTS

In Vitro Studies

The results of the in vitro tests are summarized in table 2. The content of drugs in eight commercial brands of doxycycline capsules were first quantitated by HPLC method. The chromatogram of doxycycline was illustrated in figure 2. Table 3 showed the content uniformity of all eight brands of doxycycline capsules studied, since the contents of two capsules [out of the first ten sampling capsules] of brand A [original brand] were lower than 85 percent according to the requirement of the pharmacopoeia, twenty additional capsules were tested. The final results showed that all eight brands studied met the requirement of the United State Pharmacopoeia, which mean that these eight brands were all chemically equivalent.

The disintegration time of all eight brands of doxycycline capsule were reported in detail in table 4. Rank order of them in term of mean of the disintegration time were brand B < E < F < H < A < D < G < C. Eventhough each capsule of each brand was able to disintegrate within ten minutes. Statistical comparison of the disintegration time among eight brands of doxycycline capsules showed in table 5 indicating that there were statistically significant difference between brands at the significant level of 0.05.

Table 2 Physical Characteristics of Eight Commercial Brands of Doxycycline Capsules [In Vitro Studies]

Brand	Weight[a] (g)	% Labelled[b] Amount	Disintegration[c] Time [min]	Dissolution Rate Constant[c]
A	0.348 ± 0.007	90.75 ± 0.36	5.26 ± 0.381	0.248 ± 0.047
B	0.247 ± 0.011	93.66 ± 2.61	3.50 ± 0.643	0.230 ± 0.062
C	0.284 ± 0.011	90.39 ± 0.33	5.86 ± 0.823	0.157 ± 0.040
D	0.280 ± 0.003	93.58 ± 1.49	5.44 ± 0.666	0.175 ± 0.044
E	0.281 ± 0.008	97.95 ± 0.94	4.12 ± 0.868	0.189 ± 0.043
F	0.260 ± 0.011	98.32 ± 1.57	4.58 ± 1.175	0.179 ± 0.037
G	0.261 ± 0.016	105.55 ± 3.36	5.83 ± 1.365	0.185 ± 0.050
H	0.331 ± 0.007	90.92 ± 0.14	4.94 ± 0.773	0.249 ± 0.086

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

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

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

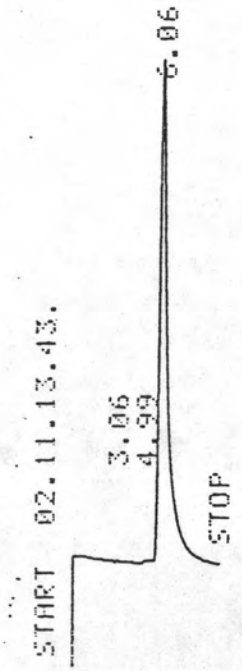

Figure 2 High Performance Liquid Chromatographic Chromatogram of Doxycycline in Capsule Containing 1 mg/ml of Doxycycline.

Table 3 Content Uniformity of Eight Commercial Brands of Doxycycline Capsules

Brand \ Capsule No.	1	2	3	4	5	6	7	8	9	10	% C.V.
A"	86.25	82.06*	86.47	85.94	85.21	86.29	92.14	89.53	81.49*	90.16	
	91.22	95.67	88.47	90.33	91.47	87.80	87.15	84.07*	88.21	89.90	3.77
	94.58	91.36	92.69	90.51	89.83	90.65	92.89	90.56	85.26	88.02	
B	93.51	96.51	96.63	99.93	85.91	98.58	97.41	88.39	94.60	95.20	4.43
C	86.99	99.17	90.37	93.70	89.36	91.95	96.92	91.27	90.51	89.93	3.34
D	100.68	92.39	100.77	91.92	86.11	85.86	88.24	91.36	93.54	85.36	5.82
E	92.15	87.91	88.79	85.33	91.77	88.27	86.06	96.76	85.47	90.16	3.80
F	103.16	101.56	97.32	97.36	102.16	87.35	98.19	99.43	88.98	104.41	5.55
G	97.38	92.58	97.52	95.33	93.38	88.67	90.41	99.32	86.99	99.04	4.42
H	102.99	99.22	100.26	97.83	103.14	101.35	88.76	93.74	89.65	87.33*	5.97

* = out of the range of 85-115%

n = Two capsules were out of the range of 85 - 115%, therefore additional twenty capsules were assayed

Table 4 Disintegration Time of Eight Commercial Brands of Doxycycline Capsules

Brand \ Capsule No.	Disintegration time [min]						Mean	S.D.
	1	2	3	4	5	6		
A	5.35	5.45	5.37	4.50	5.34	5.55	5.26	± 0.381
B	3.10	3.20	4.10	2.55	4.05	4.00	3.50	± 0.643
C	5.05	5.50	6.50	5.00	6.05	7.05	5.86	± 0.823
D	4.50	5.30	5.37	5.05	6.20	6.20	5.44	± 0.666
E	3.05	3.25	4.25	4.00	5.00	5.15	4.12	± 0.868
F	3.05	4.50	5.10	3.45	5.20	6.20	4.58	± 1.175
G	4.50	8.35	5.05	5.30	5.50	6.27	5.83	± 1.365
H	5.00	6.15	5.00	5.15	4.20	4.45	4.94	± 0.733

Table 5 Analysis of Variance and Pairwise Statistical Comparison of Disintegration Time among Eight Brands of Doxycycline Capsules

One way analysis of variance

Source of variance	d.f.	S.S.	MS.	F
Among treatment	7	29.1614	4.1659	5.3647*
Within replication	40	31.0618	0.7765	
Total	47	60.2232		

$F_{0.05\,(7,40)} = 2.25$

Student 's t - statistics

Brand	A	B	C	D	E	F	G	H
A	0.0000							
B	6.3185*	0.0000						
C	2.1531	8.4690*	0.0000					
D	0.6459	6.9618*	1.5072	0.0000				
E	4.0909*	2.2249	6.2441*	4.7369*	0.0000			
F	2.4402*	3.8756*	4.5933*	3.0861*	1.6507	0.0000		
G	2.0455	8.3613*	0.1077	1.3995	6.1364*	4.4857*	0.0000	
H	1.1483	5.1675*	3.3015*	1.7943	2.9426*	1.2919	3.1938*	0.0000

$t_{0.50,\,10} = 2.2281$

* Significant level at $P < 0.05$

The dissolution profiles of all eight brands of doxycycline capsules were illustrated in figure 3. The dissolution data at various times were presented in detail in appendix G.

The dissolution rate constants (K) were calculated from the slope of the first order plot between the amount of doxycycline to be dissolved [$B_\infty - B_t$] versus time in semi-logarithmic scale [appendix H]. The corresponding dissolution rate constant values were reported in table 6. Rank order of eight brands in terms of mean dissolution rate constants were brand H > A > B > E > G > F > D > C. The rate constants were compared by anlysis of variance and Student's t - test with 95% confidence limits as indicated in table 7.

From dissolution profile and the statistical comparison of dissolution rate constants, these eight commercial brands of doxycycline capsules can be classified into three groups as follow:

1. The brands with high dissolution rate included brand A, B, E, G, and H
2. The brands with moderate dissolution rate included brand F and D
3. The brand with low dissolution rate included brand C

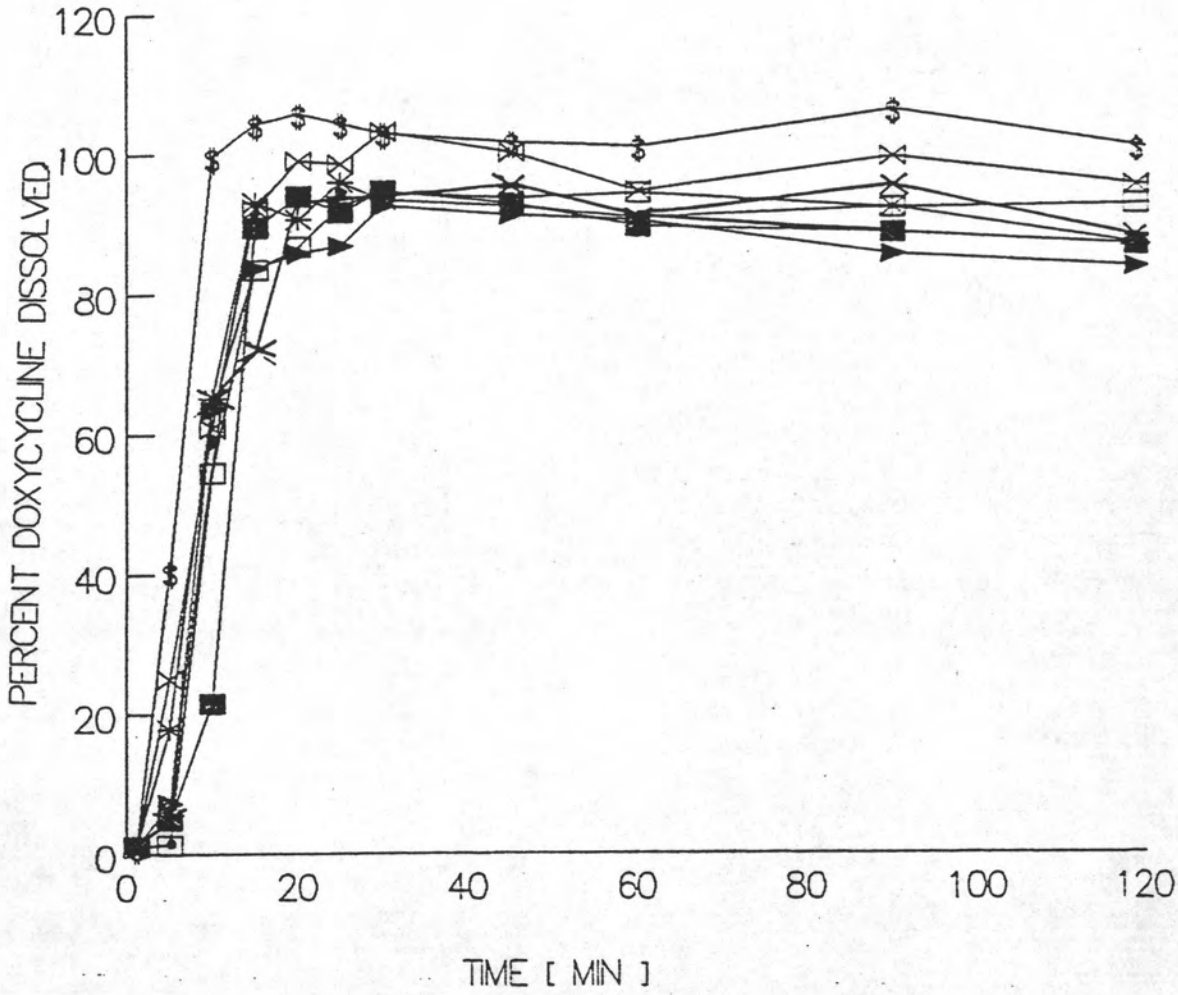

Figure 3 Dissolution Profile of Eight Commercial Brands of Doxycycline Capsules

Brand A [ ], Brand B [ ], Brand C [ ], Brand D [ ]

Brand E [ ], Brand F [ ], Brand G [ ], Brand H [ ]

Table 6 Dissolution Rate Constants of Eight Commercial Brands of Doxycycline Capsules.

Brand \ Capsule No.	Dissolution rate constant						Mean S.D.
	1	2	3	4	5	6	
A	0.178	0.292	0.255	0.305	0.235	0.224	0.248±0.047
B	0.202	0.193	0.145	0.245	0.278	0.317	0.230±0.062
C	0.225	0.153	0.157	0.128	0.108	0.173	0.157±0.040
D	0.223	0.168	0.211	0.103	0.155	0.189	0.175±0.044
E	0.177	0.197	0.261	0.201	0.137	0.159	0.189±0.043
F	0.180	0.127	0.192	0.167	0.240	0.171	0.179±0.037
G	0.249	0.216	0.118	0.136	0.198	0.193	0.185±0.050
H	0.371	0.130	0.311	0.221	0.271	0.192	0.249±0.086

Table 7 Analysis of Variance for Dissolution Rate Constants among Eight Brands of Doxycycline Capsules.

One way analysis of variance

Source of variance	d.f.	S.S.	MS.	F
Among treatment	7	0.0532	0.0076	2.6714*
Within replication	40	0.1137	0.0028	
Total	47			

$F_{0.05\ (7,40)} = 2.25$

Student 's t - statistics

Brand	A	B	C	D	E	F	G	H
A	0.0000							
B	0.5912	0.0000						
C	2.9560*	2.3648*	0.0000					
D	2.3875*	1.7964	0.5685	0.0000				
E	1.9425	1.3513	1.0135	0.4450	0.0000			
F	2.2381*	1.6469	0.7179	0.1494	0.2956	0.0000		
G	2.0529	1.4618	0.9030	0.3346	0.1104	0.1855	0.0000	
H	0.0260	0.6172	2.9819*	2.4136*	1.0685	2.2641*	0.8487	0.0000

$t_{0.05,10} = 2.2281$

* Significant level at $P < 0.05$

One representative from each group classified was selected for bioavailability studies comparing to the original product (brand A). The brands selected were :

1. Brand B [high dissolution rate]
2. Brand D [moderate dissolution rate]
3. Brand C [low dissolution rate]

In Vivo Studies

1. Assay for doxycycline in plasma

A chromatogram from plasma containing both doxycycline and internal standard was illustrated in figure 4. Retention times for internal standard and doxycycline were 3.19 and 4.45 minutes respectively.

Analytical precision and recoveries of doxycycline and internal standard in plasma were shown in appendix I. The within-run precision were obtained by analyzing three series of standard doxycycline solution in plasma within one day. The % C.V. of within-run precision ranged from 3.60% to 14.59 % (n=3). The range of % C.V. of between-run precision was 7.53 to 17.20 % (n=6), which obtained by analyzing six series of standard doxycycline solution in plasma in different days. The % recoveries of doxycycline in plasma were scattered and it is in the range of 77.81 to 103.47% (n=3) while the % recoveries of internal standard (tetracycline) ranged from 37.77 to 50.40 % (n=3).

The % recoveries of doxycycline were obtained by analyzing doxycycline in plasma and aqeous solution. Then the peak heights of doxycycline in plasma were compared with those of doxycycline in

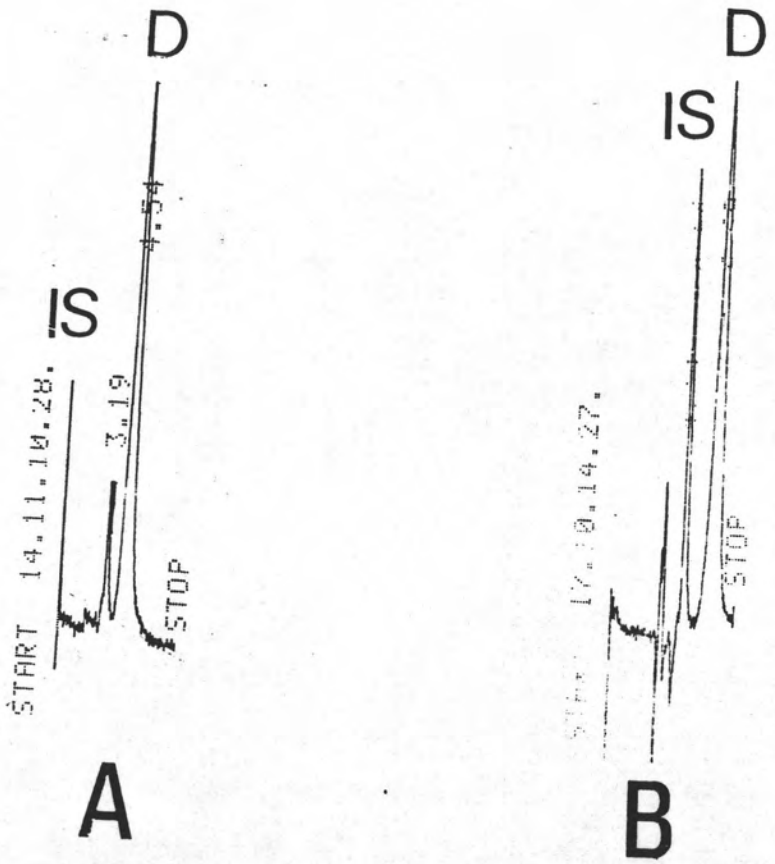

Figure 4 High Performance Liquid Chromatographic Chromatogram of Doxycycline [D] and Internal Standard [IS].

A Obtained from HPLC analysis of human plasma spiking with 1.0 µg/ml of doxycycline and 5 µg/ml of internal standard.

B Obtain from HPLC analysis of aqeous solution containing 1.0 µg/ml of doxycycline and 5 µg/ml of internal standard.

aqeous solution. The % recoveries of the internal standard were also obtained by the same procedure.

2. Plasma Doxycycline Level

The plot of the plasma concentration of doxycycline versus sampling time of each subject for brand A, B, C and D were shown in table 8, 9, 10, and 11 respectively. The mean plasma concentration profiles of the four brands studied were illustrated in figure 5. The difference plasma doxycycline concentration time profiles from time 0 to 33 hours and the expand profiles from time 0 to 9 hours among brands of each subject were graphically illustrated in appendix J.

3. Pharmacokinetics Parameters of Doxycycline Capsules

3.1 Noncompartmental method

The derived pharmacokinetic parameters based on noncompartmental analysis of the plasma concentration-time data obtained after oral administration of doxycycline capsules of brand A, B, C and D were presented in table 12, 13, 14 and 15 respectively.

The peak plasma doxycycline concentration [Cpmax] for brand A, B, C and D showed in table 12, 13, 14 and 15 was reading directly from the plasma concentration - time curve of each individual subject. The mean peak plasma concentrations of brand A, B, C and D were 1.52, 2.16, 2.05 and 1.98 µg/ml, respectively. These peak plasma concentrations showed the statistically significant difference at significant level of 0.05 as shown in table 16. The order ranking from the highest to the lowest peak plasma concentration was brand B, C, D > A.

Table 8 Plasma Doxycycline Concentration at Various Times Following Oral Administeation of 100 mg Doxycycline Capsules, Brand A, to 20 Subjects.

TIME [hr.] / SUBJ. No.	Plasma Doxycycline Concentration [μg/ml]											
	0.00	0.50	1.00	1.50	2.50	3.50	5.00	7.00	9.00	12.00	24.00	33.00
1	0.00	0.00	0.74	1.91	1.69	0.84	0.81	0.71	0.55	1.22	1.27	0.00
2	0.00	0.00	0.00	0.42	1.40	1.12	0.38	0.73	0.51	0.38	0.61	0.00
3	0.00	0.00	0.57	0.18	0.71	0.70	0.51	0.51	0.35	0.57	0.25	0.14
4	0.00	0.75	0.44	1.03	1.27	1.45	0.60	0.51	0.72	0.36	0.25	0.17
5	0.00	0.87	1.33	0.94	0.71	0.97	0.84	0.69	0.60	0.15	0.28	0.13
6	0.00	0.19	0.44	1.52	0.28	1.80	0.91	0.86	0.49	0.71	0.25	0.17
7	0.00	0.00	0.90	2.64	0.61	0.76	0.75	1.05	0.56	0.43	0.18	0.00
8	0.00	0.35	0.91	0.40	0.80	1.07	0.70	0.57	0.33	0.57	0.27	0.00
9	0.00	0.61	1.37	0.31	1.17	0.76	0.41	0.06	0.20	0.11	0.10	0.00
10	0.00	0.30	0.42	1.10	0.78	0.93	0.67	0.31	0.09	0.43	0.25	0.14
11	0.00	0.00	0.65	1.11	1.61	0.76	0.53	0.43	0.39	0.21	0.20	0.06
12	0.00	0.46	1.22	2.11	1.93	1.52	0.51	1.22	1.02	0.84	0.25	0.03
13	0.00	0.05	0.83	0.81	0.99	1.41	0.61	0.71	0.27	0.43	0.31	0.06
14	0.00	0.20	0.63	1.24	1.44	1.41	0.53	0.69	0.73	0.45	0.12	0.15
15	0.00	0.00	0.00	0.20	1.19	1.22	0.74	0.53	0.41	0.64	0.30	0.13
16	0.00	0.54	0.55	1.14	0.99	1.32	0.60	0.49	0.63	0.80	0.24	0.01
17	0.00	0.00	0.16	2.35	0.90	1.04	1.18	0.81	0.91	0.66	0.49	0.33
18	0.00	0.23	0.40	1.30	1.73	0.84	1.11	0.83	0.82	1.85	0.31	0.15
19	0.00	0.52	0.37	0.92	0.60	0.93	0.56	0.29	0.20	0.51	0.08	0.06
20	0.00	1.44	1.14	0.85	0.49	0.22	0.20	0.13	0.03	0.02	0.02	0.00
MEAN	0.00	0.36	0.68	1.13	1.03	1.06	0.68	0.60	0.49	0.54	0.23	0.10
SEM	0.00	0.08	0.09	0.15	0.10	0.08	0.05	0.07	0.06	0.09	0.02	0.02

Table 9 · Plasma Doxycycline Concentration at Various Times Following Oral Administration of 100 mg Doxycycline Capsules, Brand B, to 20 Subjects.

TIME [hr.] / SUBJ. No.	Plasma Doxycycline Concentration [µg/ml]											
	0.00	0.50	1.00	1.50	2.50	3.50	5.00	7.00	9.00	12.00	24.00	33.00
1	0.00	1.09	1.23	1.05	0.76	0.70	0.54	0.59	0.54	0.42	0.40	0.23
2	0.00	0.55	0.50	1.58	2.18	0.83	0.73	0.73	0.54	0.40	0.37	0.23
3	0.00	0.49	2.18	1.69	1.89	1.15	0.67	0.70	1.05	0.61	0.46	0.18
4	0.00	0.46	2.03	1.52	1.69	0.93	0.63	0.68	0.68	0.43	0.54	0.19
5	0.00	0.87	1.07	1.31	1.19	0.94	0.67	0.70	0.45	0.46	0.40	0.27
6	0.00	0.41	1.00	1.11	1.69	0.98	0.70	0.49	1.01	0.89	0.45	0.25
7	0.00	0.50	2.10	1.83	2.08	0.98	1.06	1.03	1.13	0.95	0.49	0.24
8	0.00	0.67	0.75	1.29	3.93	1.82	1.47	1.49	0.76	0.34	1.13	0.35
9	0.00	0.05	0.39	0.57	0.90	1.01	1.07	0.64	0.75	0.55	0.30	0.30
10	0.00	1.39	1.93	1.25	1.12	0.93	0.93	0.54	0.98	0.43	0.31	0.26
11	0.00	1.00	1.39	2.29	2.20	1.26	1.15	1.28	0.75	0.75	0.45	0.40
12	0.00	0.65	2.95	1.24	1.70	0.94	0.69	1.64	0.66	0.49	0.28	0.19
13	0.00	0.61	0.78	1.46	2.79	2.01	1.11	0.99	0.87	1.01	0.70	0.28
14	0.00	0.15	0.55	1.24	2.78	1.85	1.45	1.09	0.96	1.25	0.55	0.42
15	0.00	1.43	1.78	1.12	1.61	1.32	0.99	1.04	0.83	0.87	0.52	0.27
16	0.00	1.25	0.83	1.51	1.88	1.35	1.31	0.89	0.78	0.54	0.31	0.12
17	0.00	1.14	1.72	3.54	1.99	1.65	2.39	1.15	1.47	1.75	0.91	0.35
18	0.00	0.81	1.21	2.16	2.49	2.16	2.21	1.66	1.72	1.22	0.64	0.14
19	0.00	1.08	1.08	1.57	1.25	1.25	0.67	1.05	0.96	1.28	0.44	0.67
20	0.00	0.56	0.64	1.28	1.41	1.36	1.29	1.08	1.03	1.07	0.63	0.36
MEAN	0.00	0.71	1.23	1.46	1.82	1.31	1.22	1.20	1.22	1.26	1.56	1.76
SEM	0.00	0.09	0.16	0.15	0.18	0.15	0.22	0.39	0.39	0.53	1.10	1.52

Table 10 Plasma Doxycycline Concentration at Various Times Following Oral Adminstration of 100 mg Doxycycline Capsules, Brand C, to 20 Subjects

TIME [hr.] / SUBJ. No.	Plasma Doxycycline Concentration [µg/ml]											
	0.00	0.50	1.00	1.50	2.50	3.50	5.00	7.00	9.00	12.00	24.00	33.00
1	0.00	1.14	0.67	0.70	1.79	1.38	1.17	0.78	0.37	0.99	0.21	0.31
2	0.00	0.51	0.82	2.00	1.85	1.39	0.54	0.78	0.85	0.37	0.40	0.35
3	0.00	0.00	1.31	2.04	2.28	2.12	1.58	1.00	0.78	1.08	0.55	0.47
4	0.00	0.56	1.45	2.27	1.85	1.08	1.38	1.42	0.75	1.27	0.60	0.14
5	0.00	1.39	1.22	2.57	2.19	1.94	1.78	0.99	0.91	1.14	0.82	0.35
6	0.00	0.33	1.18	0.06	2.72	1.42	2.12	1.72	1.12	1.97	1.21	0.45
7	0.00	0.47	0.50	1.32	0.98	0.81	0.57	0.59	0.39	0.56	0.23	0.18
8	0.00	0.74	0.52	0.75	1.03	0.80	0.74	0.52	0.60	0.64	0.19	0.12
9	0.00	0.24	1.11	1.57	1.36	0.71	0.48	0.53	0.14	0.38	0.23	0.17
10	0.00	0.79	0.86	1.21	0.87	0.80	0.55	0.55	0.40	0.36	0.19	0.27
11	0.00	0.83	0.90	1.58	0.92	0.89	0.63	0.73	0.53	0.54	0.23	0.21
12	0.00	0.58	1.42	2.11	1.65	1.37	0.59	0.55	0.67	0.33	0.34	0.58
13	0.00	1.04	2.18	1.22	1.27	1.08	0.82	0.74	0.60	0.38	0.23	0.27
14	0.00	1.05	1.94	0.60	1.08	0.98	0.73	0.62	0.52	0.36	0.28	0.19
15	0.00	1.22	2.87	1.25	1.35	0.93	0.91	0.92	0.63	0.84	0.29	0.25
16	0.00	0.78	1.50	2.33	1.08	0.98	0.73	0.70	0.44	0.62	0.25	0.26
17	0.00	0.35	1.72	1.19	0.96	0.98	1.05	0.55	0.44	0.42	0.36	0.27
18	0.00	1.50	2.39	1.20	0.83	1.22	0.64	0.89	0.52	0.62	0.27	0.28
19	0.00	0.42	2.55	1.27	1.38	1.15	0.92	0.63	0.53	0.54	0.39	0.28
20	0.00	1.24	2.23	2.51	1.53	2.30	1.55	1.05	0.81	0.94	0.44	0.00
MEAN	0.00	0.76	1.47	1.49	1.45	1.22	0.97	0.81	0.60	0.72	0.38	0.27
SEM	0.00	0.09	0.15	0.15	0.12	0.10	0.10	0.07	0.05	0.09	0.05	0.03

Table 11 Plasma Doxycycline Concentration at Various Times Following Oral Administration of 100 mg Doxycycline Capsules, Brand D, tO 20 Subjects.

TIME [hr.] / SUBJ. No.	Plasma Doxycycline Concentration [µg/ml]											
	0.00	0.50	1.00	1.50	2.50	3.50	5.00	7.00	9.00	12.00	24.00	33.00
1	0.00	0.51	0.66	1.37	1.17	0.88	0.85	0.97	0.46	0.54	0.24	0.38
2	0.00	1.31	0.94	0.66	1.83	0.79	0.69	0.77	0.46	0.68	0.59	0.31
3	0.00	0.73	1.85	0.99	1.60	0.88	0.71	1.79	1.04	0.70	0.28	0.42
4	0.00	0.33	1.75	1.06	0.96	1.55	0.66	0.69	0.92	0.54	0.31	0.23
5	0.00	1.57	2.32	1.60	1.73	1.41	1.21	0.96	0.80	0.67	0.30	0.19
6	0.00	1.01	1.82	0.96	1.55	1.22	0.87	1.07	0.83	0.71	0.54	0.36
7	0.00	0.59	1.85	2.57	2.51	1.31	1.31	1.31	1.70	0.65	0.56	0.13
8	0.00	0.67	1.69	1.82	2.57	2.22	1.19	0.76	1.36	0.82	0.42	0.14
9	0.00	1.35	1.25	1.72	1.34	1.25	1.11	0.66	0.66	0.78	0.06	0.06
10	0.00	0.37	0.89	1.62	1.79	1.37	0.90	1.47	0.91	0.84	0.24	0.08
11	0.00	1.14	1.93	2.30	2.56	1.55	1.85	0.87	1.22	0.56	0.36	0.28
12	0.00	0.37	3.66	3.97	2.33	2.15	2.28	2.03	1.62	1.28	1.08	0.64
13	0.00	0.38	0.78	0.90	1.89	0.83	0.57	0.65	0.58	0.63	0.30	0.19
14	0.00	0.82	1.04	1.38	1.04	1.64	1.01	0.73	0.53	0.59	0.32	0.23
15	0.00	0.57	0.79	1.10	1.34	1.38	0.79	0.90	0.78	0.63	0.49	0.27
16	0.00	0.27	0.74	0.46	0.91	1.10	0.50	0.67	0.66	0.87	0.31	0.23
17	0.00	0.31	0.60	1.02	1.27	1.00	0.78	0.48	0.57	0.63	0.41	0.27
18	0.00	0.28	0.43	1.37	2.02	0.89	0.83	0.65	0.74	0.60	0.28	0.14
19	0.00	1.56	1.43	1.69	1.87	1.21	0.93	0.97	0.76	0.89	0.87	0.38
20	0.00	1.55	2.29	0.84	1.25	0.78	0.60	0.52	0.58	0.38	0.32	0.21
MEAN	0.00	0.78	1.44	1.47	1.68	1.27	0.98	0.94	0.86	0.70	0.42	0.25
SEM	0.00	0.10	0.17	0.17	0.12	0.09	0.10	0.09	0.08	0.04	0.05	0.03

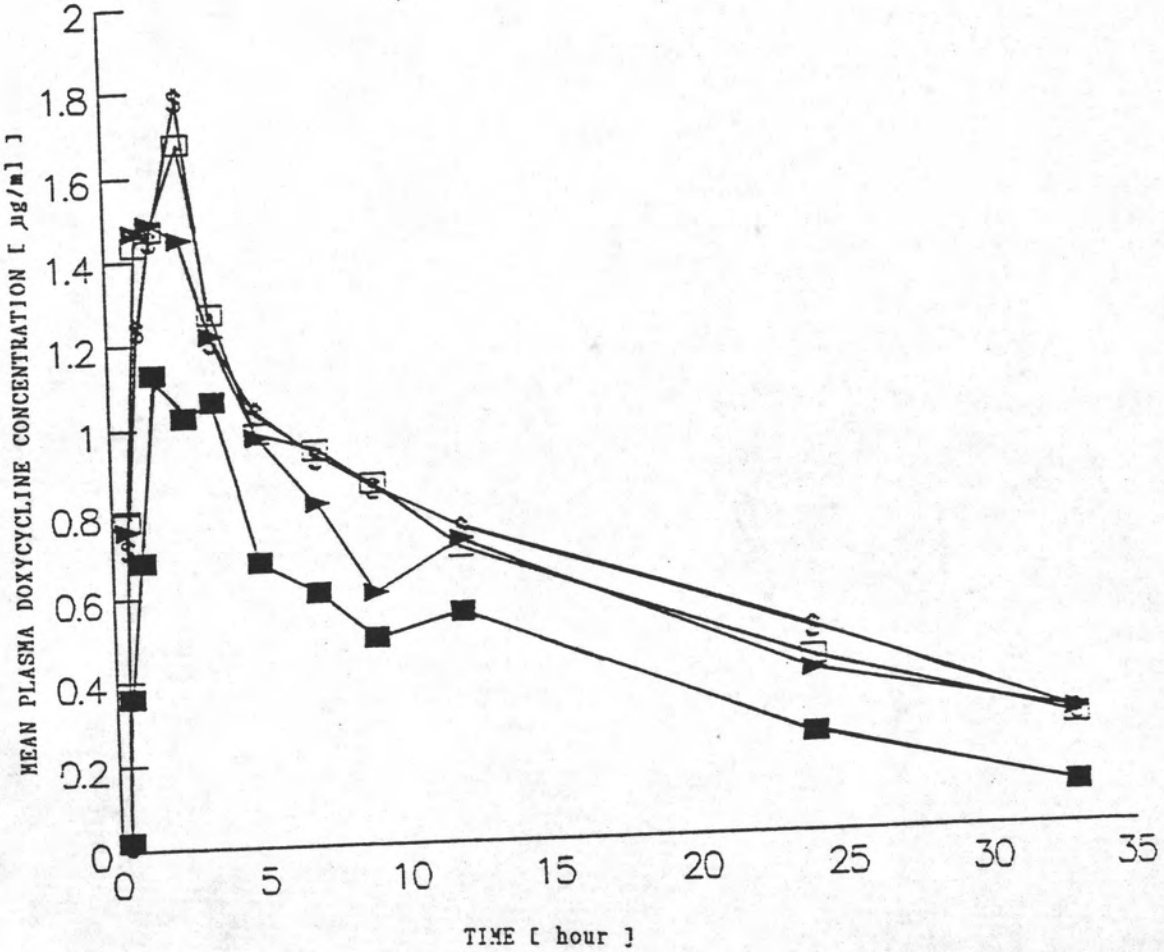

Figure 5 Comparison of the Mean Plasma Doxycycline Concentration Profile of Four Different Brands Following Oral Administration of 100 mg Doxycycline Capsules to 20 Subjects.

Key Brand A [—■—], Brand B [—$—],
Brand C [—▶—], Brand D [—□—]

Table 12 Pharmacokinetic Parameters of Doxycycline Calculated by Noncompartmental Method, Following the Administration of 100 mg Doxycycline Capsules, Brand A, to 20 Subjects

Subject No.	Cpmax[a] [µg/ml]	Tmax[b] [hour]	AUC 0 to 33 [µg.hr/ml]	AUC total [µg.hr/ml]	Ke [hour^{-1}]	half life [hour]
1	1.91	1.50	31.55	31.55	0.03	21.39
2	1.40	2.50	15.98	15.98	0.02	30.53
3	0.78	2.50	12.48	15.17	0.05	13.56
4	1.40	3.50	14.41	17.70	0.05	13.43
5	1.33	1.00	12.78	15.10	0.06	12.33
6	1.80	3.50	17.88	20.62	0.06	11.23
7	2.64	1.50	14.00	14.00	0.05	13.25
8	1.07	3.50	13.38	13.38	0.04	15.61
9	1.37	1.00	6.55	6.55	0.03	24.23
10	1.10	1.50	11.47	14.41	0.05	13.08
11	1.68	2.50	10.62	11.41	0.07	9.48
12	2.18	1.50	21.25	21.47	0.14	5.10
13	1.41	3.50	14.74	15.46	0.09	7.96
14	1.44	2.50	14.02	16.08	0.07	9.79
15	1.22	3.50	14.93	16.58	0.08	9.07
16	1.32	3.50	16.20	16.26	0.19	3.57
17	2.35	1.50	21.75	29.94	0.04	17.24
18	1.73	2.50	27.49	28.69	0.12	5.67
19	0.92	1.50	9.84	10.60	0.08	9.07
20	1.44	0.50	3.67	3.6663	0.06	12.01
MEAN	1.52	2.25	15.25	16.55	0.07	12.88
SEM	0.10	0.22	1.41	1.63	0.01	1.43

a,b Obtained by reading directly from plasma concentration time profile

Table 13 Pharmacokinetic Parameters of Doxycycline Calculated by Noncompartmental Method, Following the Administration of 100 mg Doxycycline Capsules, Brand B, to 20 Subjects

Subject No.	Cpmax [a] [µg/ml]	Tmax [b] [hour]	AUC 0 to 33 [µg.hr/ml]	AUC 0 to ∞ [µg.hr/ml]	Ke [hour^{-1}]	half life [hour]
1	1.23	1.00	15.36	22.72	0.03	22.21
2	2.18	2.50	16.94	23.03	0.04	18.38
3	2.18	1.00	21.31	24.07	0.03	20.26
4	2.03	1.00	19.12	23.65	0.04	16.99
5	1.31	1.50	16.86	26.52	0.03	24.84
6	1.69	2.50	21.69	25.89	0.06	11.79
7	2.10	1.00	20.09	29.67	0.07	10.52
8	3.93	2.50	31.34	38.12	0.05	13.48
9	1.07	5.00	16.48	24.18	0.04	17.95
10	1.93	1.00	17.64	23.24	0.05	15.00
11	2.29	1.50	25.28	38.56	0.03	24.75
12	2.95	1.00	19.33	23.16	0.05	13.56
13	2.79	2.50	29.36	33.97	0.06	11.53
14	2.78	2.50	30.56	38.41	0.05	13.00
15	1.78	1.00	24.80	30.49	0.05	14.50
16	1.88	2.50	19.53	21.15	0.07	9.48
17	3.54	1.50	42.50	49.35	0.05	13.72
18	2.49	2.50	35.81	37.22	0.10	7.11
19	1.57	1.50	27.92	51.46	0.03	24.40
20	1.41	2.50	27.88	34.98	0.05	13.59
MEAN	2.16	1.90	23.99	30.99	0.05	15.85
SEM	0.16	0.22	1.59	1.96	0.00	1.14

a,b Obtained by reading directly from plasma concentration time profile

Table 14 Pharmacokinetic Parameters of Doxycycline Calculated by Noncompartmental Program, Following the Administration of 100 mg Doxycycline Capsules, Brand C, to 20 Subjects.

Subject No.	Cpmax[a] [µg/ml]	Tmax[b] [hour]	AUC 0 to 33 [µg.hr/ml]	AUC total [µg.hr/ml]	Ke [hour^{-1}]	half life [hour]
1	1.79	2.50	20.46	25.54	0.06	11.53
2	2.00	1.50	18.92	32.60	0.03	27.39
3	2.28	2.50	29.74	41.33	0.05	15.37
4	2.27	1.50	29.45	30.77	0.10	6.69
5	2.57	1.50	33.91	40.20	0.06	12.60
6	2.72	2.50	44.75	51.38	0.07	10.13
7	1.32	1.50	14.06	17.64	0.05	13.67
8	1.03	2.50	14.39	16.25	0.07	10.37
9	1.57	1.50	12.37	17.16	0.04	19.04
10	1.21	1.50	12.64	19.01	0.04	16.66
11	1.58	1.50	15.43	20.08	0.04	15.43
12	2.11	1.50	18.38	32.72	0.02	30.29
13	2.18	1.00	16.09	22.51	0.04	16.23
14	1.94	1.00	14.06	18.14	0.05	13.61
15	2.87	1.00	21.00	25.97	0.05	15.23
16	2.33	1.50	17.40	23.55	0.04	16.27
17	1.72	1.00	16.35	28.14	0.02	30.39
18	2.39	1.00	18.17	25.54	0.04	17.95
19	2.55	1.00	18.85	27.18	0.03	20.26
20	2.51	1.50	26.53	26.53	0.05	14.20
MEAN	2.05	1.55	20.65	27.11	0.05	16.67
SEM	0.11	0.12	1.81	1.99	0.00	1.42

a,b Obtained by reading directly from plasma concentration time profile

Table 15 Pharmacokinetic Parameters of Doxycycline Calculated by Noncompartmental Program, Following the Administration of 100 mg Doxycycline Capsules, Brand D, to 20 Subjects.

Subject No.	Cpmax [a] [µg/ml]	Tmax [b] [hour]	AUC 0 to 33 [ug.hr/ml]	AUC 0 to∞ [ug.hr/ml]	Ke [hour^{-1}]	half life [hour]
1	1.38	1.50	16.76	36.77	0.02	38.08
2	1.83	2.50	21.11	29.82	0.04	19.30
3	1.85	1.00	22.32	32.73	0.04	17.07
4	1.75	1.00	17.73	22.06	0.05	13.08
5	2.32	1.00	21.75	24.56	0.07	10.36
6	1.82	1.00	23.61	34.73	0.03	21.39
7	2.57	1.50	27.83	29.32	0.09	7.89
8	2.57	2.50	26.03	27.58	0.09	7.87
9	1.72	1.50	17.11	17.57	0.13	5.42
10	1.79	2.50	21.32	22.15	0.10	6.81
11	2.56	2.50	25.06	30.15	0.05	12.98
12	3.97	1.50	45.95	62.90	0.04	18.28
13	1.89	2.50	16.59	20.04	0.06	12.31
14	1.64	3.50	18.37	23.90	0.04	16.70
15	1.38	3.50	20.78	27.31	0.04	17.07
16	1.10	3.50	17.78	21.34	0.06	10.76
17	1.27	2.50	17.78	24.51	0.04	17.24
18	2.02	2.50	17.19	19.14	0.07	9.93
19	1.87	2.50	29.14	38.98	0.04	17.95
20	2.29	1.00	15.40	21.07	0.04	19.04
MEAN	1.98	2.08	21.98	28.33	0.06	14.98
SEM	0.14	0.19	1.50	2.20	0.01	1.57

a,b Obtained by reading directly from plasma concentration time profile

Table 16 Analysis of Variance and Pairwise Statistical Comparison of the Cpmax Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules to 20 subjects. (using data from table 12,13,14, and 15)

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	4.6382	1.9534	4.2474*
Within subjects	76	27.6639	0.3640	
Total	79	32.3021		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	3.3545*	0.0000		
C	2.7780*	0.5766	0.0000	
D	2.4111*	0.9435	0.3669	0.0000

$t_{0.05,\ 38} = 2.0247$

* significant level at $p < 0.05$

The time to peak plasma level [Tmax] of brand A, B, C and D presented in table 12, 13, 14 and 15 respectively, was also reading directly from the plasma concentration - time curve of each individual subject. The mean Tmax for brand A, B, C and D were 2.25, 1.90, 1.55 and 2.08 hours, respectively. Statistical result illustrated in table 17 showed no significant difference among brands.

The area under the entire plasma concentration - time curve [AUC_o^{∞}] and the area under the plasma concentration - time curve during the thirty - three hours of sample collection [AUC_o^{33}] showed the statistically significant difference among four commercial brands as illustrated in table 18 and table 19, respectively. Both AUC_o^{33} and AUC_o^{∞} of the original brand [A] were significantly lower than those of the local-made brands [B, C, D]. The mean area under the plasma concentration - time curve [AUC_o^{∞}] of brand A, B, C, D were 16.55, 30.99, 27.11 and 28.33 $\mu g.hr.ml^{-1}$ respectively.

The mean elimination rate constants obtained from noncampartmental computer program for brand A, B, C and D were 0.069, 0.049, 0.047 and 0.057 $hour^{-1}$ respectively. These values showed no statistically significant difference among brands ($p > 0.05$) as indicated in table 20.

The plasma half-life of the drug after administration of these four different brands also showed no statistical significant difference ($p > 0.05$) as presented in table 21. The mean plasma half-life of brand A, B, C and D were12.88 , 15.85, 16.67 and 14.98 hours respectively.

Table 17 Analysis of Variance of Tmax Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 12, 13, 14 and 15),

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	5.3594	1.7835	2.3353
Within subjects	76	58.1375	0.7650	
Total	79	63.4970		

$F_{0.05\ (3,76)} = 2.7387$

Table 18 Analysis of Variance and Pairwise Statistical Comparison of AUC_0^∞ Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules to 20 subjects. (using data from table 12, 13, 14, and 15).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	2346.844	782.2813	9.9050*
Within subjects	76	6002.348	78.9783	
Total	79	8349.191		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	5.0742*	0.0000		
C	3.6935*	1.3806	0.0000	
D	4.1277*	0.9465	0.4342	0.0000

$t_{0.05,\ 38} = 2.0247$

* significant level at $p < 0.05$

Table 19 Analysis of Variance and Pairwise Statistical Comparison of AUC_{∞}^{33} Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules. to 20 Subjects. (using data from table 12, 13, 14, and 15).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	835.9844	278.6615	5.2801*
Within subjects	76	4010.996	52.7763	
Total	79	4846.980		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	3.8001*	0.0000		
C	2.3462*	1.4534	0.0000	
D	2.9252*	0.8749	0.5789	0.0000

$t_{0.05,\ 38} = 2.0247$

* significant level at $p < 0.05$

Table 20 Analysis of Variance of Elimination Rate Constants Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 12, 13, 14 and 15).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.0332	0.0111	2.4550
Within subjects	76	0.3423	0.0045	
Total	79	0.3754		

$F_{0.05\ (3,76)} = 2.7387$

Table 21 Analysis of Variance of Half - Life Obtained by Noncompartmental Analysis after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects. (using data from 12, 13, 14 and 15).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	158.8711	52.9570	1.3046
Within subjects	76	3085.064	40.5930	
Total	79	3243.936		

$F_{0.05\ (3,76)} = 2.7387$

3.2 Compartmental Method

3.2.1 CSTRIP computer program

The plasma - concentration time data was first analyzing by CSTRIP computer program. The results showed that most of the data were fitted to a one compartmental model with or without a lag time. Hence, individual plasma doxycycline profile from each treatment was analyzed according to one compartment open model with first - order absorption and elimination rates with or without a lag time. The following pharmacokinetic parameters were estimated from CSTRIP program: the absorption rate constant (Ka), the elimination rate constant (Ke), the plasma half-life ($t_{1/2}$) , and the lag time. Other parameters such as peak plasma concentration (Cpmax), time to peak plasma concentration (Tmax), area under the plasma concentration-time curve (AUC) and the apparent volume of distribution volume (Vd) were obtained by calculating from the equations mentioned in chapter 3. All parameters of brand A, B, C and D were reported in tables 22, 23, 24 and 25, respectively.

The absorption rate constants did not show significant differences among brands [P > 0.05] as presented in table 26.

Analysis of variance and statistical comparison of the Cpmax were reported in table 27. They were statistically significant difference from each other according to the t-test. The mean Cpmax of brands A, B, C and D were 0.965, 1.274, 1.135 and 1.281 µg/ml respectively.

The mean Tmax for brand A, B, C, and D were 3.72, 2,87, 2,67 and 2.15 hour respectively. They were also statistically significantly

Table 22 Pharmacokinetic Parameters of Doxycycline Calculated by CSTRIP Program, Following the Administration of 100 mg Doxycycline Capsules, Brand A, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	lag time [hour]	AUC total [µg.hr.ml^{-1}]	Tmax [hour]	Cpmax [µg/ml]	Vd [L/Kg]
1	1.13	0.00*	159.74*	0.17	251.64*	5.10	1.07	1.41
2	0.46	0.03	26.43	0.35	30.11	7.00	0.66	2.18
3	0.58	0.05	13.56	0.00	14.04	4.62	0.56	2.66
4	0.97	0.06	11.13	0.00	16.83	3.02	0.86	1.87
5	4.56	0.07	10.58	0.00	15.15	0.94	0.93	2.10
6	0.56	0.06	12.05	0.00	17.53	4.54	0.77	2.11
7	1.30	0.09	7.81	0.00	14.43	2.22	1.04	1.37
8	1.24	0.04	15.48	0.00	16.98	2.78	0.67	2.53
9	0.33	0.03	24.23	0.00	61.19	8.09	1.37	6.94
10	1.05	0.05	12.96	0.00	12.85	2.99	0.58	2.35
11	1.17	0.09	7.95	0.00	11.08	2.39	0.78	1.62
12	0.91	0.12	5.95	0.00	17.64	2.59	1.50	1.06
13	1.45	0.08	8.90	0.15	14.09	2.28	0.92	1.52
14	0.73	0.08	8.82	0.00	14.91	3.43	0.88	1.55
15	0.27	0.08	9.07	0.00	15.71	6.53	0.72	1.63
16	0.95	0.13	5.46	0.00	12.58	2.45	1.16	1.12
17	0.95	0.04	17.07	0.44	28.98	3.89	1.01	1.70
18	1.23	0.07	10.04	0.25	22.83	2.73	1.32	1.27
19	2.85	0.08	8.57	0.00	8.71	1.29	0.63	2.73
20	0.42	0.06	12.01	0.00	44.97	5.45	1.87	0.65
MEAN	1.16	0.06	11.40	0.07	19.53	3.72	0.96	1.60
SEM	0.21	0.01	1.32	0.03	2.92	0.42	0.07	0.17

* These values were excluded when calculated the mean and SEM.

Table 23 Pharmacokinetic Parameters of Doxycycline Calculated by CSTRIP Program, Following the Administration of 100 mg Doxycycline Capsules, Brand B, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	lag time [hour]	AUC total [µg.hr.ml^{-1}]	Tmax [hour]	Cpmax [µg/ml]	Vd [L/Kg]
1	0.31	0.03	23.44	0.00	18.30	8.44	0.42	2.84
2	1.68	0.05	14.53	0.00	22.43	2.18	0.96	1.61
3	0.82	0.07	10.64	0.00	22.80	3.36	1.18	1.28
4	0.92	0.06	11.91	0.00	21.58	3.20	1.03	1.56
5	4.04	0.04	15.57	0.00	22.85	1.13	0.96	2.05
6	1.87	0.05	15.26	0.00	25.85	2.04	1.06	1.81
7	0.74	0.16	4.33	0.00	8.91	2.63	0.92	1.23
8	0.79	0.05	13.49	0.00	35.85	3.70	1.51	1.04
9	1.19	0.04	15.62	0.35	22.90	3.23	0.89	1.28
10	0.81	0.05	14.60	0.00	21.14	3.71	0.83	1.61
11	1.83	0.05	13.22	0.00	32.51	2.00	1.52	0.92
12	2.22	0.06	10.78	0.00	21.30	1.64	1.22	1.59
13	0.95	0.06	12.19	0.00	32.90	3.16	1.55	0.89
14	0.73	0.05	13.29	0.21	36.43	4.11	1.54	0.96
15	7.04	0.05	13.84	0.00	29.93	0.71	1.44	1.31
16	1.68	0.08	8.45	0.00	21.04	1.89	1.47	1.03
17	1.24	0.06	12.46	0.00	45.01	2.63	2.15	0.80
18	0.68	0.09	7.65	0.00	34.93	3.42	2.29	0.63
19	4.30	0.03	27.05	0.00	47.92	1.20	1.19	1.57
20	1.25	0.04	16.39	0.13	35.90	2.93	1.34	1.12
MEAN	1.75	0.06	13.73	0.03	28.02	2.87	1.27	1.36
SEM	0.35	0.01	1.08	0.02	2.08	0.35	0.10	0.11

Table 24 Pharmacokinetic Parameters of Doxycycline Calculated by CSTRIP Program, Following the Administration of 100 mg Doxycycline Capsules, Brand C, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	lag time [hour]	AUC total [µg.hr.ml^{-1}]	Tmax [hour]	Cpmax [µg/ml]	Vd [L/Kg]
1	1.93	0.05	13.11	0.00	22.59	1.92	1.07	1.29
2	1.11	0.05	14.01	0.00	25.39	2.94	1.08	1.37
3	1.28	0.05	14.00	0.17	37.65	2.82	1.62	1.02
4	1.30	0.07	9.66	0.00	27.51	2.36	1.65	0.99
5	2.65	0.05	14.25	0.00	39.53	1.54	1.77	1.08
6	0.46	0.04	15.88	0.27	50.37	5.89	1.70	0.97
7	1.67	0.05	13.75	0.00	17.13	2.16	0.79	2.03
8	1.26	0.06	10.79	0.00	15.00	2.50	0.81	2.00
9	0.72	0.06	11.53	0.00	13.67	3.78	0.65	1.58
10	6.31	0.05	14.47	0.00	17.52	0.78	0.81	1.92
11	3.31	0.06	12.51	0.00	18.78	1.26	0.97	1.50
12	1.43	0.04	17.20	0.00	28.34	2.56	1.02	1.90
13	3.61	0.06	11.44	0.00	20.93	1.15	1.18	1.32
14	0.46	0.05	13.77	0.00	15.90	5.37	0.60	2.27
15	3.76	0.06	11.45	0.00	24.35	1.12	1.37	1.33
16	2.08	0.06	11.85	0.00	21.03	1.77	1.10	1.45
17	0.85	0.05	14.01	0.00	20.97	3.56	0.86	1.93
18	0.63	0.04	15.44	0.00	21.11	4.54	0.77	2.11
19	0.82	0.05	12.75	0.00	23.19	3.53	1.03	1.53
20	1.80	0.07	9.41	0.00	28.97	1.85	1.85	0.79
MEAN	1.87	0.05	13.06	0.02	24.50	2.67	1.14	1.52
SEM	0.32	0.00	0.44	0.02	1.99	0.31	0.09	0.09

Table 25 Pharmacokinetic Parameters of Doxycycline Calculated by CSTRIP Program, Following the Administration of 100 mg Doxycycline Capsules, Brand D, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	lag time [hour]	AUC total [µg.hr.ml^{-1}]	Tmax [hour]	Cpmax [µg/ml]	Vd [L/Kg]
1	1.49	0.04	16.83	0.00	23.84	2.47	0.88	1.57
2	2.95	0.03	23.08	0.00	30.85	1.57	0.88	1.86
3	1.58	0.05	15.12	0.00	29.40	2.31	1.20	1.41
4	1.65	0.05	13.37	0.00	21.62	2.17	0.99	1.75
5	4.37	0.07	9.44	0.00	24.65	0.95	1.68	1.15
6	2.93	0.04	16.86	0.00	32.41	1.48	1.25	1.60
7	1.56	0.08	8.54	0.00	28.68	2.00	1.96	0.75
8	1.53	0.08	8.43	0.00	26.68	2.02	1.84	0.88
9	3.29	0.11	6.10	0.00	15.22	1.06	1.52	0.75
10	1.44	0.09	7.36	0.21	20.70	2.23	1.60	0.83
11	3.21	0.07	9.94	0.00	29.90	1.22	1.90	0.75
12	1.20	0.04	17.17	0.00	60.16	2.93	2.14	0.90
13	1.40	0.06	12.53	0.00	19.41	2.40	0.93	1.56
14	2.09	0.06	12.27	0.00	21.88	1.78	1.11	1.47
15	1.49	0.05	14.73	0.00	26.61	2.40	1.11	1.57
16	0.82	0.04	15.75	0.00	21.29	3.78	0.79	1.91
17	0.98	0.04	16.94	0.00	23.54	3.39	0.83	2.08
18	0.87	0.06	10.98	0.16	17.17	3.41	0.87	1.85
19	3.80	0.04	18.93	0.00	39.14	1.23	1.36	1.35
20	1.65	0.05	14.92	0.00	18.54	2.23	0.77	1.97
MEAN	2.02	0.06	13.47	0.02	26.59	2.15	1.23	1.40
SEM	0.22	0.00	0.95	0.01	2.14	0.17	0.10	0.10

Table 26 Analysis of Variance of the Absorption Rate Constants [Ka] Obtained by Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24 and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	8.5656	2.8552	1.6927
Within subjects	76	128.1962	1.6870	
Total	79	136.7617		

$F_{0.05\ (3,76)} = 2.7387$

Table 27 Analysis of Variance and Pairwise Statistical Comparison of the Cpmax Obtained from Compartmental Method using CSTRIP Program after Administration of four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	1.3316	0.4439	2.7498 *
Within subjects	76	12.4486	0.1638	
Total	79	13.7802		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	2.4222*	0.0000		
C	1.3283	1.0939	0.0000	
D	2.5004*	0.0781	1.1721	0.0000

$t_{0.05,\ 38} = 2.0248$

* significant level at $p < 0.05$

different from each other as seen in table 28.

The analysis of variance of AUC_o^∞ of the four commercial products was shown in table 29. No statistical significant differences among these values at the significant level of 0.05% were observed.

The elimination rate constant, plasma half-life, lag time and the apparent volume of distribution were reported in table 30, 31, 32 and 33 respectively. Neither value showed significant difference among brands.

3.2.2 PCNONLIN computer program

Not only the CSTRIP program was used to analyze the pharmacokinetic parameters, but the PCNONLIN program was also ultilized to estimate and calculate these parameters by iteration method. All data were assumed to follow the one compartment model with or without lag time in PCNONLIN program.

The pharmacokinetic parameters of brand A, B, C, and D calculated by PCNONLIN program were described in table 34, 35, 36 and 37 respectively.

Analysis of variance of absorption rate constant [Ka] of doxycycline capsule were reported in table 38. No significant difference among these values were observed [$P > 0.05$].

There were significant differences of the peak plasma concentration [Cpmax] among the four commercial brands as shown in table 39 [$P < 0.05$]. The mean Cpmax of brand A, B, C and D were 1.02,

Table 28 Analysis of Variance and Pairwise Statistical Comparison of Tmax Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25) .

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	25.4507	8.4836	3.8018*
Within subjects	76	169.5922	2.2315	
Total	79	195.0429		

$F_{0.05\,(3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	1.7994	0.0000		
C	2.2228*	0.4234	0.0000	
D	3.3235*	1.5242	1.1008	0.0000

$t_{0.05,\,38} = 2.0247$

* Significant level at $P < 0.05$

Table 29 Analysis of Variance of AUC_0^{∞} Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	671.418	223.806	2.0022
Within subjects	72	8048.348	111.7826	
Total	75	8719.766		

$F_{0.05\ (3,72)} = 2.7444$

Table 30 Analysis of Variance of Elimination Rate Constants [Ke] Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects. (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.0011	0.0004	0.6786
Within subjects	76	0.0416	0.0005	
Total	79			

$F_{0.05\ (3,76)} = 2.7387$

Table 31 Analysis of Variance of Half-life Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	538.4766	179.4922	0.6144
Within subjects	76	22201.17	292.1207	
Total	79	22739.65		

$F_{0.05\ (3,76)} = 2.7387$

Table 32 Analysis of Variance of Lag - Time Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.0031	0.0010	0.1735
Within subjects	76	0.4529	0.0060	
Total	79	0.4560		

$F_{0.05\ (3,76)} = 2.7387$

Table 33 Analysis of Variance of Apparent Volume of Distribution Obtained from Compartmental Method using CSTRIP Program after Administration of Four Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 22, 23, 24, and 25).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	1.7207	0.5736	2.3238
Within subjects	76	17.7715	0.2468	
Total	79	19.4922		

$F_{0.05\ (3,72)} = 2.7444$

Table 34 Pharmacokinetic Parameters of Doxycycline Calculated by PCNONLIN Program, Following the Administration of 100 mg Doxycycline Capsules, Brand A, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	Vd [L/Kg]	lag time [hour]	AUC total [ug.hr/ml]	Tmax [hour]	Cpmax [ug/ml]
1	4.28	0.02	31.46	1.40	0.68	49.98	1.91	1.07
2	0.92	0.10	7.12	1.40	0.00	12.64	1.96	1.17
3	0.65	0.05	12.98	2.48	0.00	14.39	4.21	0.61
4	0.86	0.13	5.31	1.26	0.00	11.96	2.59	1.11
5	3.49	0.09	7.55	1.76	0.00	12.93	1.07	1.08
6	0.70	0.08	8.64	1.48	0.00	17.91	3.49	1.09
7	1.31	0.12	5.75	1.12	0.00	13.00	2.00	1.23
8	1.10	0.07	9.34	1.95	0.00	13.28	2.64	0.81
9	3.90	0.13	5.19	1.51	0.00	6.46	0.90	0.77
10	0.71	0.20	3.49	1.14	0.00	7.10	2.48	0.86
11	0.75	0.22	3.19	0.90	0.00	7.96	2.35	1.04
12	1.23	0.10	6.81	1.06	0.00	20.21	2.21	1.64
13	1.44	0.12	5.85	1.21	0.46	11.66	2.36	1.10
14	0.70	0.15	4.69	1.01	0.00	12.12	2.81	1.18
15	0.43	0.08	8.45	1.63	0.00	14.64	4.79	0.81
16	1.12	0.08	8.83	1.45	0.00	15.68	2.55	1.01
17	1.77	0.08	8.79	1.24	0.00	20.50	1.30	1.58
18	1.37	0.05	15.12	1.36	0.44	32.02	3.01	1.30
19	1.16	0.12	5.77	1.98	0.00	8.09	2.18	0.75
20	6.20*	0.04	17.26	8.01*	0.00	5.27	0.82	0.20
MEAN	1.39	0.10	9.08	1.34	0.08	15.39	2.38	1.02
SEM	0.25	0.01	1.40	0.11	0.04	2.21	0.22	0.07

* These values were excluded when calculated the mean and SEM.

Table 35 Pharmacokinetic Parameters of Doxycycline Calculated by PCNONLIN Program, Following the Administration of 100 mg Doxycycline Capsules, Brand B, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	Vd [L/Kg]	lag time [hour]	AUC total [µg.hr/ml]	Tmax [hour]	Cpmax [µg/ml]
1	15.44*	0.08	8.92	1.42	0.00	13.96	0.34	1.06
2	1.01	0.14	5.08	0.98	0.00	12.83	2.29	1.28
3	1.70	0.12	5.75	0.95	0.00	16.72	1.67	1.65
4	2.71	0.07	10.60	1.52	0.00	19.75	1.41	1.18
5	2.54	0.09	8.09	1.63	0.00	14.89	1.38	1.13
6	1.44	0.05	13.70	1.67	0.00	25.24	2.41	1.12
7	1.79	0.07	9.51	0.92	0.00	26.13	1.86	1.66
8	0.57	0.19	3.71	0.52	0.00	19.82	2.92	2.15
9	0.86	0.06	11.91	1.14	0.48	19.54	3.84	0.93
10	6.27*	0.10	7.08	1.03	0.00	16.02	0.67	1.47
11	1.51	0.10	6.74	0.70	0.00	21.73	1.91	1.84
12	3.52	0.07	10.26	1.54	0.00	20.86	1.14	1.30
13	0.85	0.09	7.47	0.72	0.00	25.10	2.92	1.78
14	1.91	0.08	8.57	0.80	0.88	28.25	2.60	1.99
15	6.17*	0.06	12.46	1.26	0.00	28.03	0.77	1.49
16	1.19	0.11	6.15	0.93	0.00	17.09	2.19	1.57
17	1.77	0.05	12.73	0.79	0.00	46.79	2.03	2.28
18	0.75	0.08	8.46	0.66	0.00	36.79	3.31	2.30
19	3.49	0.03	25.39	1.49	0.00	47.18	1.40	1.24
20	1.05	0.04	16.28	1.10	0.15	36.21	3.33	1.35
MEAN	1.43	0.08	9.94	1.09	0.08	24.65	2.02	1.54
SEM	0.23	0.01	1.09	0.08	0.05	2.21	0.21	0.09

* These values were excluded when calculated the mean and SEM.

Table 36 Pharmacokinetic Parameters of Doxycycline Calculated by PCNONLIN Program, Following the Administration of 100 mg Doxycycline Capsules, Brand C, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	Vd [L/Kg]	lag time [hour]	AUC total [µg.hr/ml]	Tmax [hour]	Cpmax [µg/ml]
1	1.80	0.05	13.71	1.23	0.00	24.77	2.04	1.83
2	0.95	0.17	4.16	0.78	0.00	13.26	2.22	1.53
3	4.30	0.06	11.35	0.97	0.74	32.11	1.74	1.84
4	1.50	0.06	10.94	1.01	0.00	30.53	2.20	1.68
5	1.52	0.08	8.91	0.87	0.00	30.95	2.06	2.05
6	0.65	0.04	18.28	0.95	0.30	59.40	4.94	1.89
7	1.42	0.08	8.28	1.62	0.00	12.92	2.12	0.91
8	1.64	0.06	11.93	2.00	0.00	16.44	2.11	0.85
9	0.87	0.31	2.24	0.60	0.00	7.02	1.34	1.23
10	2.63	0.10	6.81	1.45	0.00	10.91	1.29	0.97
11	2.41	0.09	7.97	1.25	0.00	14.41	1.43	1.11
12	2.03	0.10	7.27	1.40	0.00	16.24	1.58	1.33
13	2.81	0.14	4.99	0.93	0.00	12.95	1.13	1.54
14	7.88*	0.10	6.83	1.38	0.00	13.00	0.56	1.25
15	3.57	0.12	5.75	1.00	0.00	16.18	0.98	1.73
16	1.79	0.17	3.96	0.89	0.00	11.50	1.44	1.56
17	1.76	0.11	6.34	1.40	0.00	13.10	1.68	1.99
18	25.11*	0.12	5.61	1.14	0.00	14.23	0.21	1.71
19	1.80	0.15	4.49	0.97	0.00	12.90	1.49	1.58
20	1.76	0.11	6.05	0.64	0.00	23.04	1.66	2.18
MEAN	1.76	0.11	7.79	1.12	0.05	19.29	1.74	1.54
SEM	0.23	0.01	0.84	0.02	0.04	2.59	0.20	0.08

* These values were excluded when calculated the mean and SEM.

Table 37 Pharmacokinetic Parameters of Doxycycline Calculated by PCNONLIN Program, Following the Administration of 100 mg Doxycycline Capsules, Brand D, to 20 Subjects.

Subject No.	Ka [hour^{-1}]	Ke [hour^{-1}]	half life [hour]	Vd [L/Kg]	lag time [hour]	AUC total [µg.hr/ml]	Tmax [hour]	Cpmax [µg/ml]
1	1.31	0.07	9.81	1.22	0.00	17.79	2.35	1.06
2	15.54*	0.04	16.09	1.55	0.00	25.90	0.38	1.10
3	2.45	0.04	15.43	1.34	0.00	31.72	1.66	1.32
4	1.72	0.08	9.01	1.41	0.00	18.13	1.89	1.21
5	3.51	0.11	6.42	1.16	0.00	16.64	1.02	1.90
6	3.40	0.05	13.69	1.49	0.00	28.28	1.26	1.34
7	1.36	0.09	7.67	0.70	0.00	27.63	2.13	2.06
8	0.96	0.13	5.30	0.68	0.00	21.61	2.40	2.07
9	2.96	0.10	6.90	0.76	0.00	16.90	1.18	1.51
10	1.57	0.08	8.49	0.88	0.38	22.55	2.36	1.57
11	3.10	0.07	9.60	0.75	0.00	28.89	1.24	1.91
12	2.30	0.04	17.47	0.86	0.00	63.75	1.80	2.35
13	1.09	0.09	7.50	1.23	0.00	14.69	2.48	1.08
14	1.38	0.10	7.18	1.14	0.00	16.54	2.07	1.31
15	1.17	0.06	11.81	1.44	0.00	23.22	2.70	1.16
16	0.94	0.04	17.13	1.88	0.00	23.48	3.49	0.82
17	1.15	0.06	11.86	1.80	0.00	19.03	2.73	0.95
18	3.43	0.13	5.40	1.16	0.92	13.40	1.91	1.51
19	10.93*	0.05	14.96	1.22	0.00	33.93	0.50	1.54
20	10.79*	0.08	8.23	1.38	0.00	14.62	0.45	1.19
MEAN	1.69	0.08	10.50	1.20	0.06	23.93	1.80	1.45
SEM	0.25	0.01	0.87	0.08	0.05	2.42	0.18	0.09

* These values were excluded when calculated the mean and SEM.

Table 38 Analysis of Variance of Absorption Rate Constant [Ka] Obtained from Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	42.3846	14.1282	0.9658
Within subjects	76	1111.788	14.6288	
Total	79	1154.173		

$F_{0.05\ (3,76)} = 2.7387$

Table 39 Analysis of Variance and Pairwise Statistical Comparison of Cpmax Obtained from Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	3.6648	1.2216	8.1646*
Within subjects	76	11.3713	0.1496	
Total	79	15.0362		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	4.2515*	0.0000		
C	4.2515*	0.0000	0.0000	
D	3.5156*	0.7358	0.8861	0.0000

$t_{0.05,\ 38} = 2.0247$

* Significant level at $P < 0.05$

1.54, 1.54, and 1.45 μg/ml respectively .

The statistical result of time to peak plasma concentration [Tmax] was shown in talbe 40. There were no significant diffrence among the four commercial brands at the significant level of 0.05 .

The statistical comparison of the area under the curve was presented in table 41. The area under the curve of brand A was significantly less than that of brand B and D while there were no statistically significant differences between brand B and C, B and D, C and D, A and C.

The statistical comparison of the elimination rate constant, half-life and the lag time were reported in table 42, 43 and 44, respectively. They all showed no statistically significant differences among the four commercial products.

The last pharmacokinetic parameter anlyzed was the apparent volume of distribution [V_d]. As shown in table 45, the Vd [data from table 34, 35, 36 and 37] were significantly different among brands. The statistical rank order of the apparent volume of distribution was $A > D \sim C \sim B$ [$P < 0.05$].

4. Comparison among Different Methods Used for Pharmacokinetic Analysis

The mean values of all pharmacokinetic parameters [and their statistical results] calculated by noncompartmental method, CSTRIP and PCNONLIN programs, were summarized in table 46, 47 and 48, respectively. Statistical comparison of the parameters, calculated by different methods and programs, described a few dissimilar results.

Table 40 Analysis of Variance of Tmax Obtained by Compartmental Method, using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	5.0704	1.6901	1.9449
Within subjects	76	66.0432	0.8690	
Total	79	71.1137		

$F_{0.05\ (3,76)} = 2.7387$

Table 41 Analysis of Variance and Pairwise Statistical Comparison of AUC Obtained by Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 32, 33, 34, and 35).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	1126.086	375.362	3.1978*
Within subjects	76	8912.09	17.3828	
Total	79	10047.18		

$F_{0.05\ (3,76)} = 2.7387$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	2.7057*	0.0000		
C	1.1412	1.5645	0.0000	
D	2.4985*	0.2072	1.3572	0.0000

$t_{0.05\ (38)} = 2.0247$

* Significant level at $P < 0.05$

Table 42 Analysis of Variance of Elimination Rate Constant [Ke] Obtained by Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.0161	0.0054	2.6279
Within subjects	76	0.1555	0.0020	
Total	79	0.1716		

$F_{0.05\ (3,76)} = 2.7387$

Table 43 Analysis of Variance of Half - Life Obtained by Compartmental Method, using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	84.7568	28.2523	1.1933
Within subjects	76	1799.3710	23.6759	
Total	79	1884.1270		

$F_{0.05\ (3,76)} = 2.7387$

Table 44 Analysis of Variance of Lag Time Obtained by Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.0087	0.0029	0.0701
Within subjects	76	3.1214	0.0412	
Total	79	3.1400		

$F_{0.05\ (3,76)} = 2.7387$

Table 45 Analysis of Variance and Pairwise Statistical Comparison of Apparent Volume of Distribution [Vd] Obtained by Compartmental Method using PCNONLIN Program after Oral Administration of Different Brands of Doxycycline Capsules to 20 Subjects (using data from table 34, 35, 36, and 37).

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	1.3934	0.4645	3.7079*
Within subjects	72	9.0190	0.1253	
Total	75	10.4124		

$F_{0.05\,(3,72)} = 2.7444$

Student's t-statistics

Brand	A	B	C	D
A	0.0000			
B	3.0478*	0.0000		
C	2.5251*	0.5224	0.0000	
D	2.4381*	0.6095	0.0871	0.0000

$t_{0.05,36} = 2.0283$

* Significant level at $P < 0.05$

Table 46 The Mean and SEM Values of Pharmacokinetic Parameters for Doxycycline Obtained from Noncompartmental Method. Following Oral Administration of 100 mg Capsules of Four Different Brands to 20 Subjects.

Parameters	Brand				Statistical Significant
	A	B	C	D	
Peak plasma concentration [μg/ml]	1.525±0.103	2.154±0.164	2.048±0.113	1.980±0.138	A < D~C~B
Time to peak plasma concentration (hr.)	2.250±0.219	1.900±1.586	1.550±0.117	2.075±0.191	NS
Area under the plasma concentration time curve, AUC_0^{33} [μg.hr.ml^{-1}]	15.249±1.413	23.989±1.586	20.647±1.806	21.980±1.504	A< C~D~B
Area under the plasma concentration time curve, AUC_0 [μg.hr.ml^{-1}]	16.547±1.625	30.992±1.955	27.112±1.988	28.331±2.205	A < C~D~B
Elimination rate constant [hr^{-1}]	0.069±0.009	0.049±0.004	0.046±0.004	0.057±0.006	NS
Half life [hr]	12.880±1.429	15.853±1.137	16.672±1.423	14.976±1.570	NS

a = Significant level at $p < 0.05$

NS = no significant level at $p > 0.05$

Table 47 The Mean and SEM Values of Pharmacokinetic Parameters for Doxycycline Obtained from Compartmental Method, CSTRIP program Following Oral Administration of 100 mg Capsules of Four Different Brands to 20 Subjects.

Parameters	Brand				Statistical Significant
	A	B	C	D	
Absorption rate constant [hr^{-1}]	1.155±0.213	1.753±0.354	1.871±0.316	2.015±0.225	NS
Peak plasma concentration [µg/ml]	0.965±0.075	1.274±0.096	1.135±0.085	1.281±0.096	A < D~B,A~C
Time to peak plasma concentration (hr.)	3.715±0.417	2.867±0.353	2.669±0.308	2.151±0.173	A >C~D,A~B
Area under the plasma concentration time curve, AUC_o^∞ [$\mu g.hr.ml^{-1}$]	19.539±2.924	28.024±2.081	24.496±1.990	26.585±2.136	NS
Elimination rate constant [hr^{-1}]	0.065±0.006	0.058±0.006	0.054±0.002	0.058±0.005	NS
Half life [hr]	11.403±1.319	13.735±1.082	13.064±0.439	13.474±0.951	NS
Lag time [hr]	0.067 ±0.029	0.035±0.020	0.022±0.015	0.018±0.012	NS
Apparent volume of distribution [L/kg]	1.601±0.169	1.357±0.110	1.520±0.095	1.397±0.099	NS

a = Significant level at $p < 0.05$

NS = no significant level at $p > 0.05$

Table 48 The Mean and SEM Values of Pharmacokinetic Parameters for Doxycycline Obtained from Compartmental Method, PCNONLIN program Following Oral Administration of 100 mg Capsules of Four Different Brands to 20 Subjects.

Parameters	Brand				Statistical Significant
	A	B	C	D	
Absorption rate constant [hr^{-1}]	1.394±0.251	1.433±0.226	1.761±0.230	1.690±0.249	NS
Peak plasma concentration [μg/ml]	1.021±0.070	1.538±0.089	1.538±0.085	1.448±0.091	A <D~C~B
Time to peak plasma concentration (hr.)	2.380±0.219	2.021±0.207	1.736±0.202	1.801±0.182	NS
Area under the plasma concentration time curve, AUC_0^∞ [$\mu g.hr.ml^{-1}$]	15.391±2.208	24.646±2.206	19.293±2.585	23.935±2.424	A <D~B,A~C
Elimination rate constant [hr^{-1}]	0.120±0.019	0.084±0.008	0.112±0.013	0.076±0.006	NS
Half life [hr]	9.079±1.395	9.943±1.048	7.788±0.836	10.496±0.874	NS
Lag time [hr]	0.079±0.043	0.075±0.048	0.052±0.038	0.065±0.047	NS
Apparent volume of distribution [Vd]	1.367±0.108	1.088±0.077	1.123±0.017	1.202±0.076	A >D~C~B

a = Significant level at $p < 0.05$

NS = no significant level at $p > 0.05$

For example the area under the concentration - time curve from noncompartmental program were significantly different among brands while those values calculated by CSTRIP program were not at significant level = 0.05.

But AUC_o^{∞} obtained from different programs [noncompartmental, CSTRIP, and PCNONLIN program] of brand A, B, C, and D showed no statistically significant differences among programs [P > 0.05] as shown in table 49, 50, 51, and 52 respectively.

5. In Vitro - In Vivo Correlation

The bioavailability of drug depends on both the rate and the extent of drug absorption into the systemic circulation. Hence, parameters describing the bioavailability of drug are Ka, Cpmax, Tmax and AUC. Since the absorption rate constants calculated from both CSTRIP and PCNONLIN programs and time to peak plasma level obtained from reading directly and PCNONLIN program showed no significant diffenence while the other three in vivo parameters [Cpmax, AUC_o^t, and AUC_o^{∞}] were significantly different among brands, these three parameters were selected to test for their correlation with the in vitro parameters [disintegration time and dissolution rate constant]. In addition, the values chosen were those obtained from the noncompartmental method.

The relationships among and between various in vitro and in vivo parameters are presented in table 53. Neither in vivo parameters [Cpmax, AUC_o^t and AUC_o^{∞}] showed any significant correlation with the in vitro parameters. At the same time, the disintegration times were not significantly correlated to the dissolution rate constants indicating that the disintegration of the

Table 49 Analysis of Variance of AUC_0^{∞} Obtained from Noncompartmental, CSTRIP, and PCNONLIN Program after Oral Administration of Doxycycline Capsules, Brand A, to 20 Subjects [Using Data from table 12, 22, and 34].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among programs	2	469.6738	234.8369	2.840
Within brand	54	4464.543	82.6767	
Total	56	4934.217		

$F_{0.05\ (2,56)} = 3.174$

Table 50 Analysis of Variance of AUC_0^{∞} Obtained from Noncompartmental, CSTRIP, and PCNONLIN Program after Oral Administration of Doxycycline Capsules, Brand B, to 20 Subjects [Using Data from table 13, 23, and 35].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among programs	2	403.3477	201.6738	2.207
Within brand	57	5207.59	91.3612	
Total	59	5610.938		

$F_{0.05\ (2,57)} = 3.162$

Table 51 Analysis of Variance of AUC_0^{∞} Obtained from Noncompartmental, CSTRIP, and PCNONLIN Program after Oral Administration of Doxycycline Capsules, Brand C, to 20 Subjects [Using Data from table 14, 24, and 36].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among programs	2	633.6836	316.8418	3.093
Within brand	57	5838.293	102.4262	
Total	59	6471.977		

$F_{0.05\ (2,57)} = 3.162$

Table 52 Analysis of Variance of AUC_0^{∞} Obtained from Noncompartmental, CSTRIP, and PCNONLIN Program after Oral Administration of Doxycycline Capsules, Brand D, to 20 Subjects [Using Data from table 15, 25, and 37]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among programs	2	196.0078	98.0039	0.913
Within brand	57	6119.27	107.3556	
Total	59	6315.277		

$F_{0.05\ (2,57)} = 3.162$

Table 53 In Vitro - In Vivo Correlation

Correlation	Degree of freedom[a]	Correlation coefficient	t-value	Statistical significant
Disintegration times vs Dissolution rate constants	6	-0.1703	-0.4234	NS[b]
Disintegration times vs				
Cpmax	2	-0.5504	-0.9411	NS
AUC_o^t	2	-0.4064	-0.6290	NS
AUC_o^∞	2	-0.4971	-0.8102	NS
Dissolution rate constants vs				
Cpmax	2	-0.3360	-0.5045	NS
AUC_o^t	2	-0.4983	-0.8127	NS
AUC_o^∞	2	-0.4093	-0.6344	NS

$t_{0.05, 6} = 2.4469$

$t_{0.05, 2} = 4.3027$

a degree of freedom = number of pairs - 2

b not significant level at $P > 0.05$

doxycycline capsule was not the rate determining step of its dissolution rate.