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APPENDICES

APPENDIX A

TEST PRODUCTS

Brand name	Manufacturer/ Distributor	Mfd. date	Batch no.
Cifran 250	Ranbaxy	0-1-90	000190
Cilab	Biolab	4-6-90	005236
Cifroxin	Siam Pharmaceutical Co. Ltd.	20-6-90	T22 TF 16
Ciprobay	Bayer	30-5-90	477 F

APPENDIX B

SUBJECTS

Table 37 Demographic Data

Subject no.	Sex	Age (yr.)	Weight (kg.)	Height (cm.)
1	M	34	60.0	169
2	M	58	52.0	170
3	M	24	55.0	171
4	M	30	70.0	177
5	M	33	50.0	171
6	M	26	58.0	178
7	M	30	57.0	161
8	M	28	50.5	153
9	M	38	62.0	171
10	M	36	62.0	170
11	M	37	63.0	165
12	M	27	54.0	163
Mean	-	33.42	57.79	168.25
SD	-	8.96	5.93	6.90

APPENDIX C

CALIBRATION CURVE

Table 38 Calibration Curve Data of Ciprofloxacin in Carbondioxide Free Water

No.	Concentration (mcg/ml)	Absorbance at 276 nm	Inversely Estimated[b] Concentration (mcg/ml)	%Theory[c]
1	0.4941	0.060	0.5142	104.07
2	0.7905	0.084	0.7922	100.22
3	0.9881	0.102	1.0006	101.27
4	1.4822	0.140	1.4407	97.20
5	1.9762	0.186	1.9734	99.86
6	2.9643	0.268	2.9231	98.61
7	3.9524	0.365	4.0465	102.38
8	4.9405	0.438	4.8919	99.02
9	5.9286	0.528	5.9342	100.09
			Mean	100.30
			SD	2.06
			C.V.[d]	2.05%

a. $r^2 = 0.999$, $y = 0.0156 + 0.0863x$

b. $\text{Inversely estimated concentration} = \dfrac{\text{Absorbance} - 0.0156}{0.0863}$

c. $\%\ \text{Theory} = \dfrac{\text{Inversely estimated concentration}}{\text{Known concentration}} \times 100$

d. $\%\ \text{C.V.} = \dfrac{\text{SD}}{\text{Mean}} \times 100$

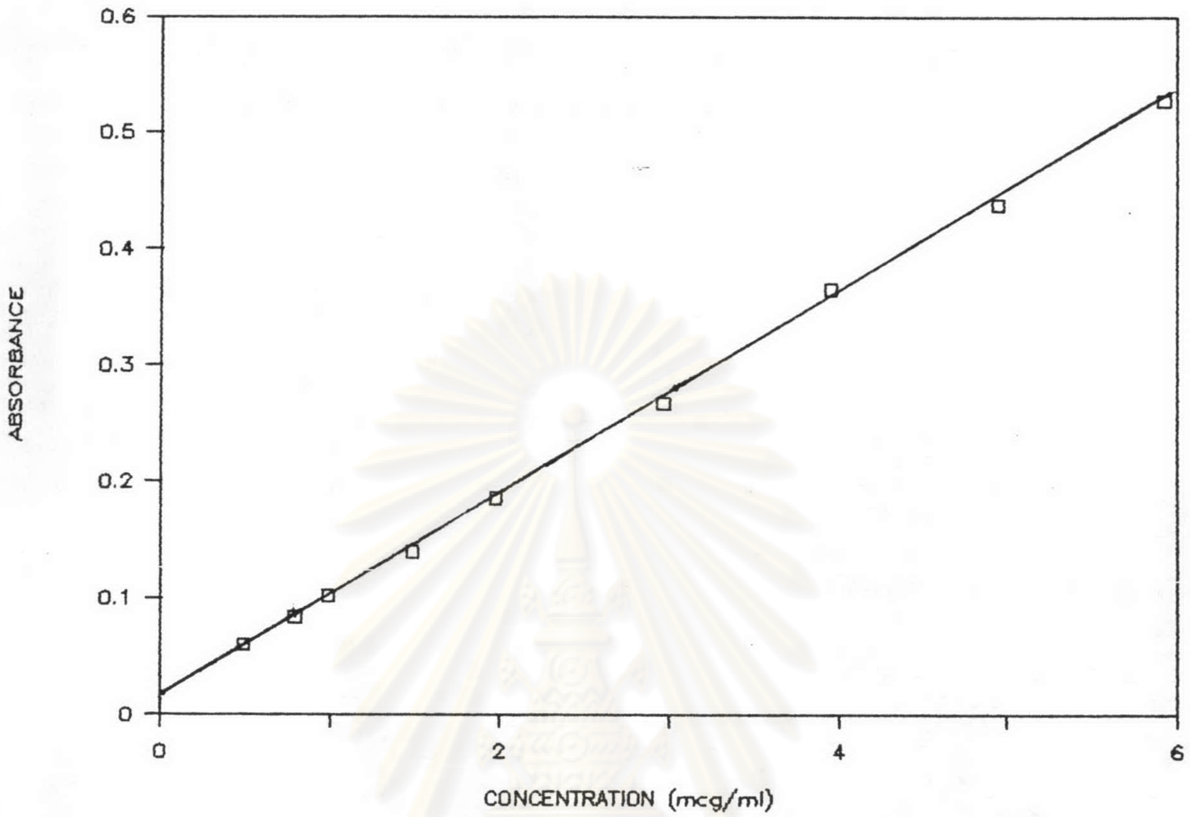


Figure 17 Calibration curve of ciprofloxacin in carbondioxide-free water

Table 39 Calibration Curve Data of Ciprofloxacin Spiked in Drug Free Plasma

No.	Concentration (mcg/ml)	Peak Height Ratio	Inversely Estimated[b] Concentration (mcg/ml)	%Theory[c]
1	0.15	0.14	0.1514	100.93
2	0.20	0.17	0.1976	98.80
3	0.40	0.28	0.3670	91.75
4	0.60	0.44	0.6133	102.22
5	0.80	0.57	0.8134	101.68
6	1.00	0.74	1.0716	107.16
7	1.40	1.01	1.4908	106.49
8	1.80	1.21	1.7988	99.93
9	2.20	1.41	2.1067	95.76
			Mean	100.52
			SD	4.83
			C.V.[d]	4.81%

a. $r^2 = 0.994$, $y = 0.0416 + 0.6495x$

b. Inversely estimated concentration $= \dfrac{\text{Peak height ratio} - 0.0416}{0.6495}$

c. % Theory $= \dfrac{\text{Inversely estimated concentration}}{\text{Known concentration}} \times 100$

d. % C.V. $= \dfrac{\text{SD}}{\text{Mean}} \times 100$

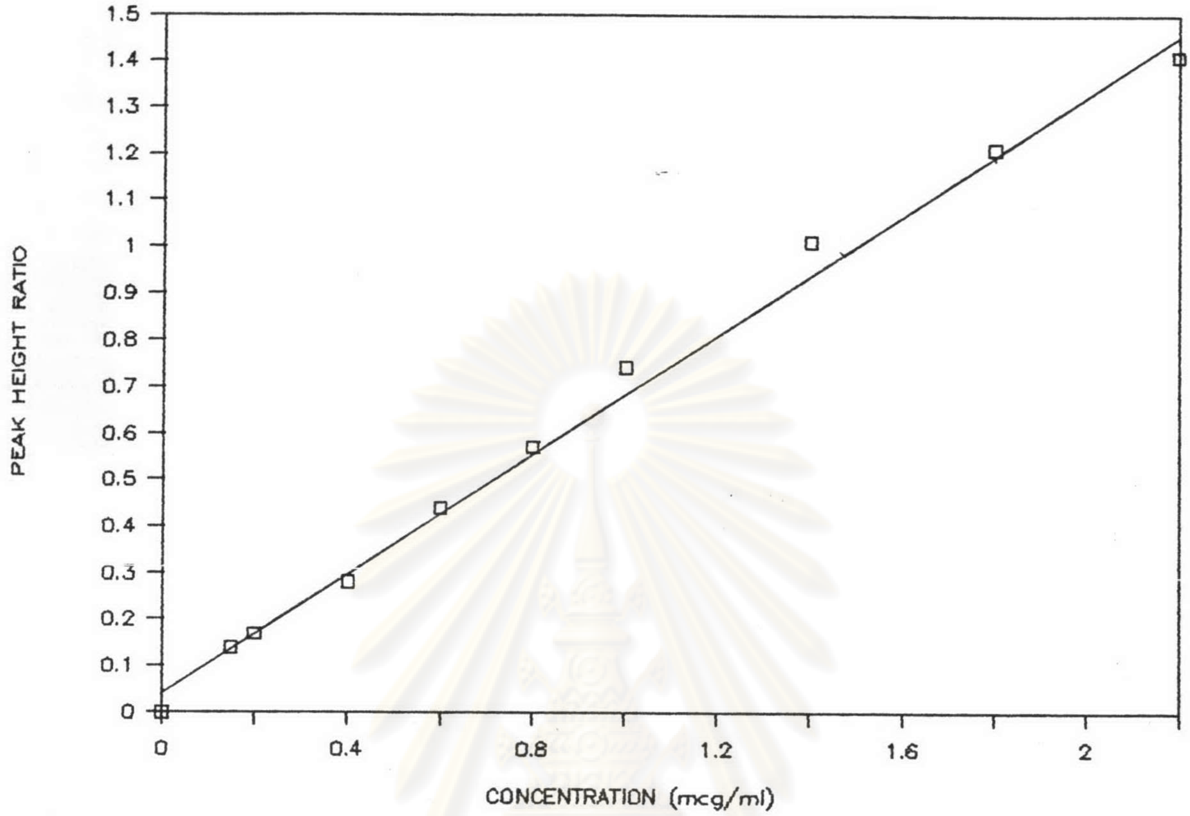


Figure 18 Calibration curve of ciprofloxacin in drug-free plasma

APPENDIX D

COMPARTMENTAL ANALYSIS

The pharmacokinetic analysis of individual plasma ciprofloxacin levels from each treatment was performed using the CSTRIP, a fortran IV computer program for obtaining polyexponential parameter estimates (Sedmen and Wagner, 1976).

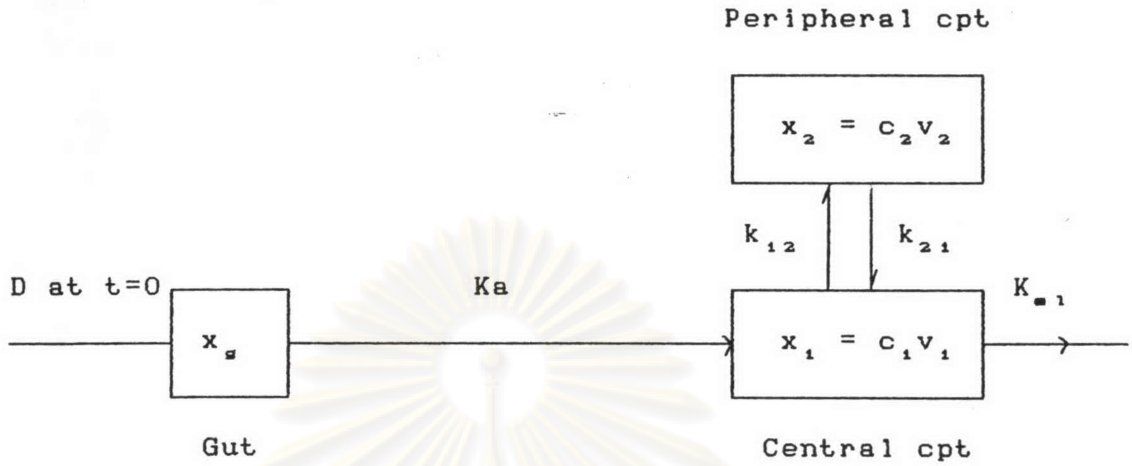
The analysis indicated that a triexponential equation:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ie^{-Kat}$$

Where C_t is the plasma concentration at time t
A, B and I are the coefficients

with no lag time well described the concentration-time curve for ciprofloxacin.

Thus, the pharmacokinetic model of these data was the two compartment open model with first order absorption and elimination as shown in Figure 19.



where D is the amount of drug administration

x_g, x_1, x_2	are the amount of drug in gut, central and peripheral compartment, respectively.
c_1, c_2	are the concentration of drug in central and in peripheral compartment, respectively.
$v_1 v_2$	are the volume of ditribution of drug in central and in peripheral compartment, respectively.
K_a	is the absorption rate constant
k_{12}, k_{21}	are distribution rate constant for transfer of drug from central to peripheral and peripheral to central compartment, respectively.
K_{el}	is the elimination rate constant of drug from central compartment.

Figure 19 Diagram of two compartment open model with first order absorption and elimination

The parameter estimates were directly obtained from the CSTRIP program as seen from the output in Figure 20 were

$$A = 2.2059$$
$$B = 0.7999$$
$$I = -3.0059$$
$$\alpha = 1.0245 \text{ hour}^{-1}$$
$$\beta = 0.1433 \text{ hour}^{-1}$$
$$K_a = 3.6980 \text{ hour}^{-1}$$

Hence, an equation to describe the model was

$$C_t = 2.2059e^{-1.0245t} + 0.7999e^{-0.1433t} - 3.0059e^{-3.6980t}$$

..........CURVE STRIPPING..........

****

DATA SET NUMBER 1

THE NUMBER OF EXPONENTIALS = 2
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST)
L1= 6
L2= 4

THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
A1= 0.113563E+01 B1= 0.180006E+00
A2=-0.113563E+01 B2= 0.130127E+01
F= 0.246748E+01

NO LAG TIME WAS NEEDED TO DESCRIBE THESE DATA
THEREFORE, THE SUM OF THE EXPONENTIAL TERMS WAS FORCED THROUGH ZERO

R SQUARE(2) = 0.15281

NO.	TIME	C(OBS)	C(EST)	/ DEV
1	0.0000	0.0000	0.0000	0.00
2	0.5000	1.5932	0.4454	72.04
3	1.0000	1.6449	0.6395	61.13
4	1.5000	0.9628	0.7056	26.71
5	2.0000	0.9507	0.7082	25.51
6	2.5000	0.7384	0.6802	7.88
7	3.0000	0.6182	0.6385	-3.34
8	5.0000	0.3609	0.4600	-27.46
9	8.0000	0.2921	0.2690	7.90
10	12.0000	0.1350	0.1310	2.99

THE NUMBER OF EXPONENTIALS = 3
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST)
L1= 3
L2= 5
L3= 2

THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
A1= 0.799977E+00 B1= 0.143311E+00
A2= 0.220594E+01 B2= 0.102456E+01
A3=-0.300591E+01 B3= 0.369807E+01
F= 0.839819E-01

NO LAG TIME WAS NEEDED TO DESCRIBE THESE DATA
THEREFORE, THE SUM OF THE EXPONENTIAL TERMS WAS FORCED THROUGH ZERO

R SQUARE(3) = - 0.97117

NO.	TIME	C(OBS)	C(EST)	/ DEV
1	0.0000	0.0000	0.0000	0.00
2	0.5000	1.5932	1.5932	0.00
3	1.0000	1.6449	1.4105	14.25
4	1.5000	0.9628	1.1079	-15.07
5	2.0000	0.9507	0.8830	7.12
6	2.5000	0.7384	0.7291	1.26
7	3.0000	0.6182	0.6224	-0.68
8	5.0000	0.3609	0.4035	-11.91
9	8.0000	0.2921	0.2548	12.77
10	12.0000	0.1350	0.1433	-6.15

THE NUMBER OF EXPONENTIALS = 4
SUMMARY OF EXPONENTIAL STRIPPING

THIS SET OF DATA CAN NOT BE DESCRIBED BY THE SUM OF 4 EXPONENTIALS

Figure 20 The output of CSTRIP computer program for analysis of ciprofloxacin concentration-time data

APPENDIX E

STATISTICS

1. Mean (x)

$$\overline{x} = \frac{\Sigma X}{N}$$

2. Standard deviation (SD.)

$$S.D. = \sqrt{\frac{\Sigma(x - x)^2}{N-1}}$$

3. Standard error of the mean (SEM)

$$SEM = \frac{S.D.}{\sqrt{N}}$$

4. Testing the difference of the two mean by Student's t-test

Let μ_1, μ_2 = Population means

X_1, X_2 = Sample means

σ_1, σ_2 = Population variances

N_1, N_2 = Sample size

The null hypothesis Ho = $\mu_1 = \mu_2$

The alternative hypothesis Ha = $\mu_1 \neq \mu_2$

The statistic t is given as t = $\dfrac{(\overline{x}_1 - \overline{x}_2) - (\mu_1 - \mu_2)}{S_p}$

4.1 If $\sigma_1^2 \neq \sigma_2^2$, the statistic is given as

$$= \frac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{S_p}$$

Where S_p^2 is the pooled variance : $S_p^2 = \frac{(S_1)^2}{N_1} + \frac{(S_2)^2}{N_2}$

with degree of freedom; d.f. $= \dfrac{\left(\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}\right)^2}{\dfrac{\left(\frac{S_1^2}{N_1}\right)^2}{N_1} + \dfrac{\left(\frac{S_2^2}{N_2}\right)^2}{N_2}}$

4.2 If $\sigma_1^2 = \sigma_2^2$ the statisitic t for this case is

$$t = \frac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{S_p}$$

Where the pooled variance is ;

$$S_p^2 = \frac{1}{N_1} + \frac{1}{N_2} \quad \frac{(N_1-1)S_1^2 + (N_2-1)S_2^2}{N_1 + N_2 - 2}$$

with degree of freedom; df = $N_1 + N_2 - 2$

This t value is compared with $t_{(tab)}$ which is obtained from the table for $\alpha/2$

If $t > t_{(tab)}$, the null hypothesis that $\mu_1 = \mu_2$ is rejected and the alternative hypothesis is accepted. If t is not significant, the null hypothesis stands.

5. <u>Analysis of variance</u> (ANOVA)

Analysis of Variance for completely Randomized Design

Source of Variation	Sum of Squares	d.f.	Mean Square	Variation Ratio
Among groups (Treatment)	$\sum_{j=1}^{k} n_j (\bar{X}_{.j} - \bar{X}_{..})^2$	k-1	$\frac{SS_{among}}{k-1}$	V.R. = $\frac{MS_{among}}{MS_{within}}$
Within groups (Error)	$\sum_{j=1}^{k} \sum_{i=1}^{k} (X_{ij} - \bar{X}_{.j})^2$	N-k	$\frac{SS_{within}}{N-k}$	
Total	$\sum_{j=1}^{k} \sum_{i=1}^{k} (X_{ij} - \bar{X}_{..})^2$	N-1		

Where X_{ij} = observed value i at Treatment j

$i = 1, 2, \ldots, n$

$j = 1, 2, \ldots, k$

$T_{.j} = \sum_{i=1}^{n_j} X_{ij}$

$\bar{X}_{.j} = \frac{T_{.j}}{n_j}$

$T_{..} = \sum_{j=1}^{k} T_{.j}$

$$\bar{X} = \frac{T..}{N}$$

$$N = \sum_{j=1}^{k} n_j$$

The V.R. value is compared with the critical value, F, which is obtained from table at degree of freedom (k-1) and (N-k)

In this study "k" represents number of brands studied

"N" represents total number of samples

If $F > F_{(tab)}$, the null hypothesis that $\mu_1 = \mu_2 = \mu_3 = \ldots \mu_k$ is rejected and the alternative hypothesis is accepted. If F is not signifiant, the null hypothesis stands.

6. Correlation coefficient test

The correlation coefficient is a quantitative measure of the relationship of correlation between two variable, x and y

$$r = \frac{N\Sigma xy - \Sigma x\Sigma y}{\sqrt{[N\Sigma x^2 - (\Sigma x)^2][N\Sigma y^2 - (\Sigma y)^2]}}$$

where r = the correlation coefficient

N = the number of x and y pairs

Test of zero Correlation

Let ρ = the true correlation coefficient, estimated by r

The null hypothesis Ho : $\rho = 0$

The alternative hypothesis Ha : $\rho \neq 0$

$$t_{N-2} = \left| \frac{r\sqrt{N-2}}{\sqrt{1-r^2}} \right|$$

The value of t is refered to a t distribution with (N-2) degree of freedom. If $t > t_{tab)}$, we reject the null hypothesis and accept the alternative hypothesis. If t is not significant, the null hypothesis stands.

VITAE

Miss Srisutha Peemanee was born on June 13^{th} 1966, in Bangkok. She received a Bachelor of Science in Pharmacy in 1989 from the Faculty of Pharmacy, Chiang Mai University.