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APPENDICES

APPENDIX A

TEST PRODUCTS

Brand name	Manufacturer	Mfd. date	Batch no.
Foxinon	M & H Manufacturing Co. Ltd.	13-12-88	62111
Janacin	Biolab	8-3-89	903100
Lexinor	Astra	7-11-88	B 281146
Norbactin	Ranbaxy	9-88	N 00788 E
Norfloxin	T.O. Chemical	23-11-88	121701
Norxacin	Siam Pharmaceutical Co. Ltd.	16-8-89	T 225H 14

APPENDIX B

DISSOLUTION MEDIUM & MOBILE PHASE

Dissolution Medium

buffer pH 4.0 - To 900 ml of water in a 1000- ml volumetric flask add 2.86 ml of glacial acetic acid and 1.0 ml of a 50% (w/w) solution of sodium hydroxide, dilute with water to volume, and mix. If necessary, adjust with glacial acetic acid or the sodium-hydroxide solution to a pH of 4.0 .

Mobile Phase : Assay for content of active ingredient

Prepare a filtered and degassed mixture of phosphoric acid solution (1 in 1000) and acetonitrile (850:150). Make adjustment if necessary.

APPENDIX C

SUBJECTS

Table 30 Demographic Data

Subject No.	Sex.	Age. (yr)	Weight (kg)	Height (cm)
1	M	22	77	177
2	M	30	70	170
3	M	22	58	164
4	M	20	67	171
5	M	25	56	180
6	M	19	54	174
7	M	23	54	168
8	M	29	65	168
9	M	21	60	167
10	M	22	64	163
11	M	21	53	165
12	M	36	61	167
	MEAN	24.17	61.58	169.50
	SD	5.02	7.33	5.21

APPENDIX D

CALIBRATION CURVE DETERMINATION

The typical calibration curves data for norfloxacin concentration in buffer pH 4.0 and in human plasma are presented in Tables 31, 32 and Figures 18, 19 respectively.

Table 31 Typical Calibration Curve Data for Norfloxacin Concentrations in buffer pH 4.0 Estimated Using Linear Regression[a]

Standard No.	Conc. (µg/ml)	Absorbance at 313 nm	Inversely[b] estimated Conc. (µg/ml)	% Theory[c]
1	4.9890	0.208	4.9778	99.78
2	5.9968	0.249	6.1154	102.15
3	6.9846	0.276	6.8646	98.28
4	7.9824	0.317	8.0022	100.25
5	8.9802	0.349	8.8901	98.99
6	9.9780	0.392	10.0832	101.05
7	11.9736	0.461	11.9145	99.51
8	13.9692	0.533	13.9123	99.59
9	15.9648	0.605	16.0488	100.53
10	17.9604	0.677	18.0466	100.48
11	19.9560	0.749	19.8779	99.61
			MEAN	100.02
			S.D.	0.99
			C.V.[d]	0.99%

a. $r^2 = 0.999$, $y = 0.0361 x + 0.0282$

b. Inversely estimated concentration $= \dfrac{\text{Absorbance} - 2.82 \times 10^{-2}}{3.6 \times 10^{-2}}$

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

d. % C.V. $= \dfrac{\text{S.D.}}{\text{MEAN}} \times 100$

Table 32 Typical Calibration Curve Data for Norfloxacin Concentrations in Human Plasma Estimated Using Linear Regression[a]

Standard No.	Conc. (µg/ml)	Height Ratio NOR*/IS**	Inversely estimated[b] Conc. (µg/ml)	%Theory[c]
1	0.0998	0.082	0.1017	101.85
2	0.1997	0.151	0.1965	98.43
3	0.4993	0.379	0.5123	102.61
4	0.6990	0.536	0.7289	104.27
5	0.9986	0.712	0.9735	97.49
6	1.4979	1.068	1.4649	97.81
7	1.9972	1.486	2.0424	102.26
8	2.4965	1.802	2.4793	99.31
			MEAN	100.50
			SD	2.39
			C.V.[d]	2.38%

a. $r^2 = 0.999$, $y = 0.7233\ x + 0.0084$

b. Inversely estimated concentration $= \dfrac{\text{Height ratio} - 8.4 \times 10^{-3}}{7.23 \times 10^{-1}}$

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

d. % C.V. $= \dfrac{\text{S.D.}}{\text{MEAN}} \times 100$

Nor* = Norfloxacin

IS** = Internal Standard

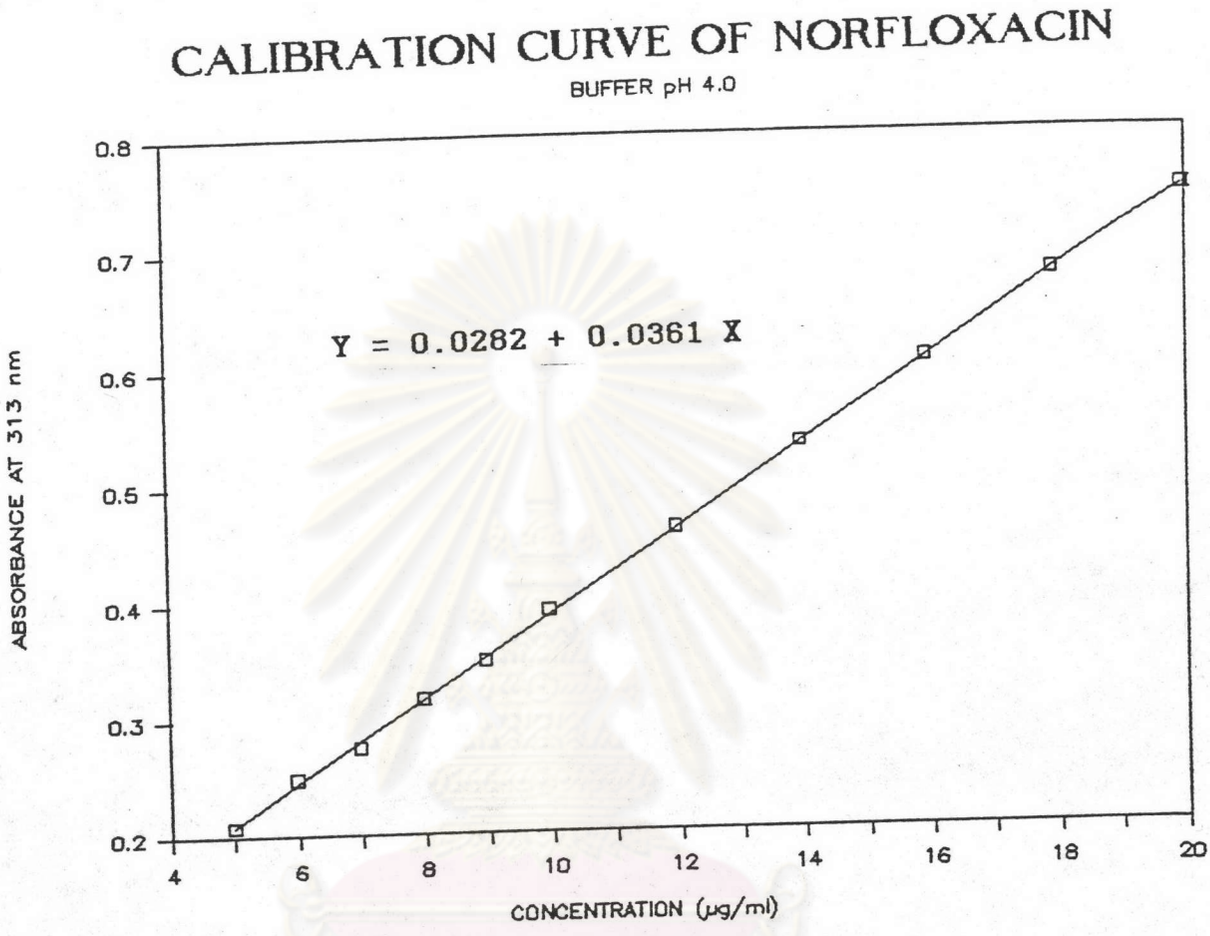

Figure 18 Typical Calibration Curve for Norfloxacin Concentration in Dissolution Medium

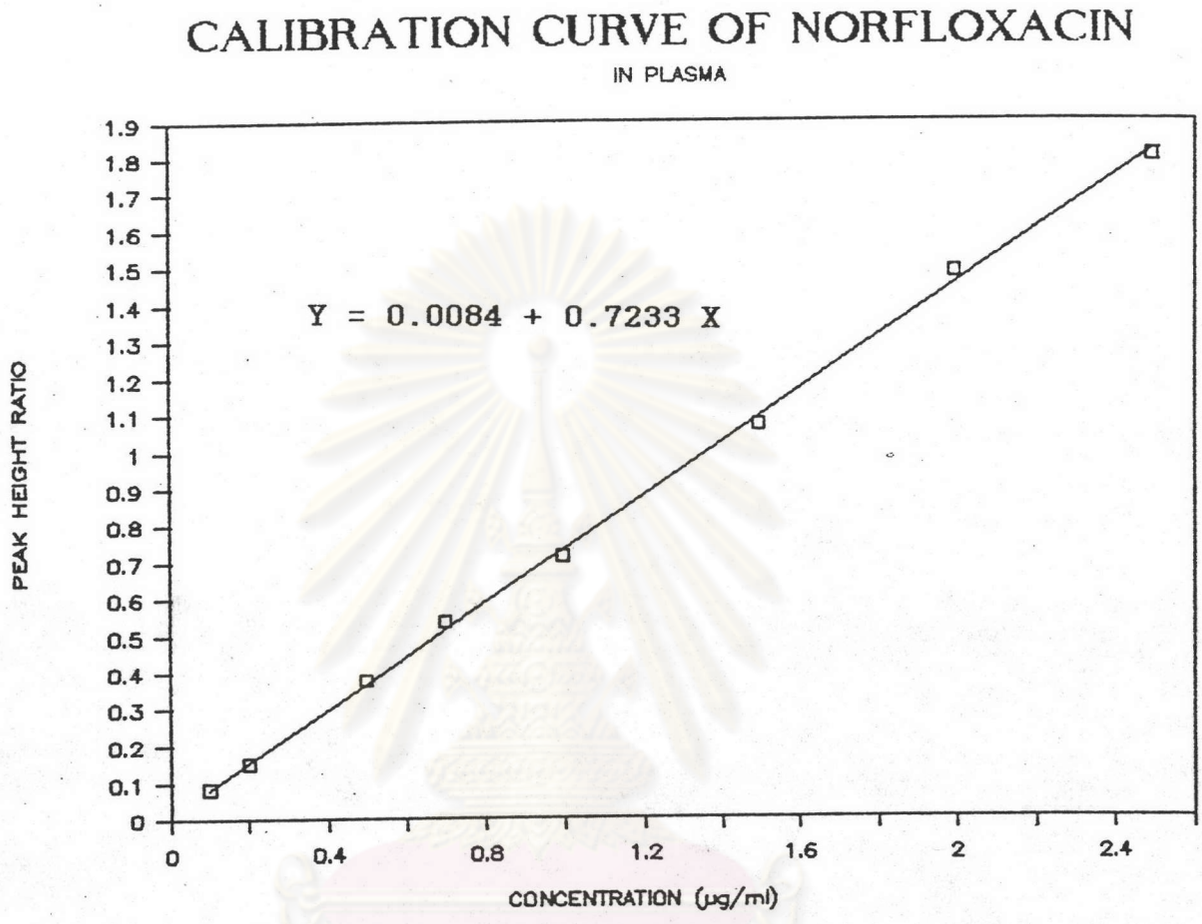

Figure 19 Typical Calibration Curve for Norfloxacin Concentration in Human Plasma

APPENDIX E

COMPARTMENTAL ANALYSIS

The most commonly employed approach for characterizing the pharmacokinetic of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiological or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first - order linear kinetics.

Kinetic linearity (Wagner, 1975) may be defined as direct proportionally of transfer rates to concentrations or concentration differences. An important consequence of a linear system in pharmacokinetics is that the total area under blood (plasma or serum) concentration - time curve, following intravenous administration, is a linear function of the dose administered.

A compartmentalized system is only an approximation of a biological system, because variation in physical distribution, nonhomogeneity of the media and diffusion processes are all interrelated with chemical changes. Thus, a "compartment" is really an "average" rather than an exact state, and is really a reflected characteristic of a system rather than an absolute one.

It is essential to remember that pharmacokinetic models are not the system itself, but rather an abstraction of it that emphasizes those aspects which the investigators feel to be important. The major contribution of a suitable model is that it allows the investigator to apply mathematical techniques.

The model is actually the equation, or sets of equations, which describe the proposed system. The solution of the differential equations of linear compartmental systems all turn out to be polyexponential in form. That is, the integrated equations can be generalized as follows :-

$$C = \sum_{i=1}^{n} C_i e^{-\lambda t} \qquad \text{.....(4)}$$

In this equation, C, may represent the blood concentration at time t, C_i is the ith coefficient, which may be positive or negative, and λ_i is the exponent of the ith exponential term.

In order to determine whether a given set of data may be described by such a polyexponential equation the usual procedure is to perform an operation called by "stripping" or "method of residuals". This method, (a) determines whether the data may be adequately described by a polyexponential equation; and (b) provides estimates of the coefficients (C_i values) and exponents (λ_i values).

In this study, the CSTRIP, a Fortran IV computer program (Sedman and Wagner, 1976), was used to estimate the polyexponential parameters by stripping method. This program overcomes the problems associated with the use of previously published techniques (Standard Residual Method, The Theory of Difference Equations) and it also provide rapidly economical calculation of all polyexponential parameters.

An example of calculation from data sets of the fifth subject receiving norfloxacin tablet brand A was illustrated in Figure 21.

The analysis indicated that a triexponential equation with no lag time was needed to describe this data.

$$C = Ae^{-t} + Be^{-t} + Ie^{-K_a t} \qquad (5)$$

where; C is the concentration at time t

A, B and I are the coefficient

This program also calculated the coefficient of determination of the estimated equation fitting to the data. For example the coefficient of determination of the three exponentials for this subject is larger than that of the two exponentials (0.8728 > 0.7812). Consequently, this data was well described to follow the two compartment open model with first order absorption and first order elimination as shown in Figure 20.

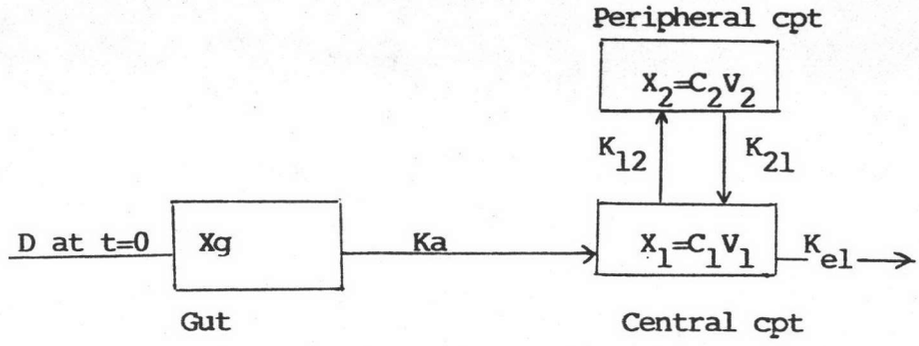

Figure 20. Diagram of two Compartment open model with first order absorption and first order elimination

The essential parameters (A, B, I, α, β and K_a) were directly obtained from the CSTRIP program.

As seen from the output of CSTRIP program in Figure 21..

A = 3.2701

B = 0.7329

I = -4.0030

α = 1.1977 $hour^{-1}$

β = 0.0968 $hour^{-1}$

K_a = 2.0289 $hour^{-1}$

```
1.........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=    9
     L2=    2

THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
 A1=  .109869E+01      B1=  .144652E+00
 A2= -.109869E+01      B2=  .269646E+01
 F=  .316787E+00


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

R SQUARE(2) =     .78127

 NO.          TIME          C(OBS)          C(EST)          / DEV
   1          .0000          .0000          .0000            .00
   2          .5000          .7367          .7367            .00
   3         1.0000         1.3868          .8766          36.79
   4         1.5000          .8939          .8651           3.22
   5         2.0000          .9019          .8177           9.34
   6         2.5000          .7391          .7640          -3.37
   7         3.0000          .5594          .7115         -27.20
   8         4.0000          .4743          .6160         -29.87
   9         6.0000          .4020          .4613         -14.74
  10         8.0000          .3660          .3454           5.63
  11        12.0000          .2220          .1936          12.77


THE NUMBER OF EXPONENTIALS = 3
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST)
     L1=    5
     L2=    2
     L3=    4

THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
 A1=  .732974E+00      B1=  .968208E-01
 A2=  .327024E+01      B2=  .119782E+01
 A3= -.400321E+01      B3=  .202905E+01
 F=  .184101E+00


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

R SQUARE(3) =     .87288

 NO.          TIME          C(OBS)          C(EST)          / DEV
   1          .0000          .0000          .0000            .00
   2          .5000          .7367         1.0436         -41.66
   3         1.0000         1.3868         1.1262          18.79
   4         1.5000          .8939          .9854         -10.24
   5         2.0000          .9019          .8327           7.67
   6         2.5000          .7391          .7140           3.39
   7         3.0000          .5594          .6291         -12.45
   8         4.0000          .4743          .5236         -10.39
   9         6.0000          .4020          .4125          -2.60
  10         8.0000          .3660          .3381           7.64
  11        12.0000          .2220          .2294          -3.31
```

Figure 21 The output of CSTRIP analysis of norfloxacin concentration-time data

APPENDIX F

STATISTICS

1. Mean ($\bar{x}$)

$$\bar{X} = \frac{\Sigma X}{N}$$

2. Standard deviation (S.D.)

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

3. Standard error of the mean (SEM)

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

4. Testing the difference of two means, 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 $t = \frac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{S_p}$

First homogeneity of variance is tested using the F test , which is defined as follow :

$$F = \frac{(S_1)^2}{(S_2)^2}$$

Where $(S_1)^2$ = the larger of the two sample variances

$(S_2)^2$ = the smaller of the two sample variances

With this test , the null hypothesis of no difference between the two population variances is evaluated. If the F is not significant the null hypothesis stands.

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

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

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. :

$$d.f. = \frac{\left(\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}\right)^2}{\frac{\left(\frac{S_1^2}{N_1}\right)^2}{N_1 - 1} + \frac{\left(\frac{S_2^2}{N_2}\right)^2}{N_2 - 1}}$$

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

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

where the pooled variance is

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

with degree of freedom

$$d.f. = N_1 + N_2 - 2$$

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

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. Analysis of variance (ANOVA)

Analysis of Variance for Completely Randomized Design

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

where X_{ij} = Observed value i at Treatment j

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

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

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

$\bar{X}.j = \frac{T.j}{nj}$

$T.. = \sum_{j=i}^{k} T.j$

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

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

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 significant, the null hypothesis stands.

6. Correlation coefficient test

The correlation coefficient is a quantitative measure of the relationship of correlation between two variables, 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 = 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 : $\rho \neq 0$

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

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 Anong Taechanukulchai was born on September 9th 1964, in Bangkok. She received a Bachelor of Science in Pharmacy (second class honors) in 1987 from the Faculty of Pharmacy, Mahidol University.