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Appendix A

Drug Information

Local manufactured product

Trade name	:	Hidil
Active ingredient	:	gemfibrozil 300 mg
Manufacturer	:	Berlin pharmaceutical industry CO., LTD (Thailand)
Appearance	:	Hard gelatin capsule consisted of two section, one slips over the other, color of the one section was reddish-brown, the other was white. The capsules were marked by symbol " ∝ " on the outer shell
Mfg date	:	14/8/96
Lot No.	:	964038

Original product

Trade name	:	Lopid
Active ingredient	:	gemfibrozil 300 mg
Manufacturer	:	Parke-Davis division of Warner-Lambert CO. (USA)
Appearance	:	Hard gelatin capsule consisted of two section, one slips over the other, color of the one section was reddish-brown, the other was white. The capsules were marked by symbol " *lopid* " on the outer shell
Mfg date	:	24/8/96
Lot No.	:	559086

Appendix B

Physical Examination And Laboratory Reports

Table 21 Physical characteristics of the 12 volunteers in bioavailability study

subject No.	sex	age (year)	weight (kg)	height (cm)
01	M	23	55	172
02	M	35	57	172
03	M	39	59	164
04	M	33	68	168
05	M	21	54.5	174
06	M	19	57	168
07	M	23	53	168
08	M	27	46	155
09	M	36	64	168
10	M	18	49	165
11	M	25	60	168
12	M	18	54	167
ranged		**18-39**	**46-68**	**155-174**

Table 22 Physical examination

subject No.	vital signs				diagnosis
	temperature*	pulse	respiration	blood pressure	
1	-	76	20	120/80	healthy
2	-	80	18	120/80	healthy
3	-	72	20	120/80	healthy
4	-	86	22	140/80	healthy
5	-	72	20	110/70	healthy
6	-	84	18	110/80	healthy
7	-	82	20	100/60	healthy
8	-	84	20	100/60	healthy
9	-	74	20	120/70	healthy
10	-	80	20	110/70	healthy
11	-	78	20	100/60	healthy
12	-	78	18	110/70	healthy

* not determine

Table 23 Chemical laboratory results

Test	normal value	subject No.					
		01	02	03	04	05	06
FBS (mg/ml)	70-110	81	89	83	96	77	82
urea nitrogen (mg/ml)	10-20	15	11	11	16	10	12
creatinine (mg/ml)	0.5-2.0	1.1	1.1	1.0	1.1	0.9	1.0
SGOT (U/L)	0-38	25	22	31	20	10	18
SGPT (U/L)	0-38	29	13	28	23	4	10
alkaline phosphatase (U/L)	98-279	131	131	183	102	169	158
cholesterol (mg/ml)	150-250	183	156	225	209	163	158
triglyceride (mg/ml)	40-155	59	127	120	74	39	62

Table 23 (cont.) Chemical laboratory results

Test	normal value	subject No.					
		07	08	09	10	11	12
FBS (mg/ml)	70-110	78	92	91	87	77	94
urea nitrogen (mg/ml)	10-20	9	9	13	9	11	8
creatinine (mg/ml)	0.5-2.0	0.8	1.2	0.9	0.9	1.1	0.9
SGOT (U/L)	0-38	23	18	24	21	18	29
SGPT (U/L)	0-38	9	7	35	11	16	13
alkaline phosphatase(U/L)	98-279	121	171	191	242	141	263
cholesterol (mg/ml)	150-250	168	130	201	138	131	180
triglyceride (mg/ml)	40-155	84	61	129	76	109	119

Table 24 Hematological laboratory results

Test	subject No.					
	01	02	03	04	05	06
hematocrit (%)	47.4	46.4	47.4	41.3	43.2	46.5
hemoglobin (%)	15.1	15.2	15.3	13.7	14.9	15.2
white blood cell (x $10^3/\mu l$)	7.12	6.01	9.95	10.85	7.34	6.83
platelets count (x $10^3/\mu l$)	223	196	230	327	316	216
Differentiate :						
neutrophil (%)	42.2	49.9	53.3	58.7	61.4	50.6
lymphocytes (%)	36.7	38.4	26.2	21.4	24.3	37.1
monocytes (%)	4.9	6.0	6.6	5.0	4.3	6.8
eosinophil (%)	12.5	1.9	8.7	11.2	5.6	1.8
basophil (%)	0.2	0.5	1.3	0.7	0.5	0.6

Table 24 (cont.) Hematological laboratory results

Test	subject No.					
	07	08	09	10	11	12
hematocrit (%)	52.1	48.4	43.5	50.3	48.0	53.1
hemoglobin (%)	16.8	15.4	14.8	15.8	15.1	17.4
white blood cell (x $10^3/\mu l$)	6.23	8.72	10.62	8.24	6.09	8.14
platelets count (x $10^3/\mu l$)	216	218	253	323	294	258
Differentiate :-						
neutrophil (%)	52.3	48.5	82.5	50.2	36.2	49.4
lymphocytes (%)	32.0	37.6	11.2	29.5	47.7	38.6
monocytes (%)	7.6	4.5	3.4	7.2	6.1	6.5
eosinophil (%)	3.7	5.7	0.9	9.3	5.8	2.2
basophil (%)	0.9	1.1	0.6	0.5	1.1	0.4

Table 25 Urinalysis results

Test	subject No.					
	01	02	03	04	05	06
Monoscopic :						
red blood cell (/HPF)	-	10-20	-	-	-	-
white blood cell (/HPF)	0-1	-	0-1	0-1	0-1	0-1
casts	-	-	-	-	-	-
organism	-	few	-	-	-	-
crystal	-	-	-	-	-	-
epith.	0-1	-	0-1	1-2	0-1	0-1
Chemistry :						
specific gravity	1.020	1.010	1.020	1.010	1.020	1.015
pH	5	6	6	6.5	6	5
nitrogen	Neg	Neg	Neg	Neg	Neg	Neg
protein	Neg	Neg	Neg	Neg	Neg	Neg
glucose	Neg	Neg	Neg	Neg	Neg	Neg
ketone	Neg	Neg	Neg	Neg	Neg	Neg

Table 25 (cont.) Urinalysis results

Test	subject No.					
	07	08	09	10	11	12
Monoscopic :						
red blood cell (/HPF)	-	-	-	-	-	-
white blood cell (/HPF)	-	-	0-1	1-2	1-2	1-2
casts	-	-	-	-	-	-
organism	-	-	-	-	-	-
crystal	-	calcium oxalate	0-1	-	-	-
epith.	1-2	-	-	1-2	1-2	-
Chemistry :						
specific gravity	1.020	1.025	1.015	1.025	1.025	1.020
pH	6	6	6	6	6	6
nitrogen	Neg	Neg	Neg	Neg	Neg	Neg
protein	Neg	Neg	Neg	Neg	Neg	Neg
glucose	Neg	Neg	Neg	Neg	Neg	Neg
ketone	Neg	Neg	Neg	Neg	Neg	Neg

Appendix C

Serum Concentration Time Data

Table 26 Serum gemfibrozil concentration-time data for subject 01P-04P following single oral dose of 600 mg gemfibrozil in pilot study

Time (hour)	concentration (μg/ml)			
	subject 01P	subject 02P	subject 03P	subject 04P
	A	A	B	B
0.16	0.2388	0.4295	0.1211	0.2540
0.5	12.49	4.238	2.298	19.17
0.75	12.60	3.275	10.46	39.21
1.0	13.62	2.601	20.92	43.66
1.25	19.97	2.553	36.19	42.46
1.5	31.86	12.94	32.78	44.34
1.75	46.44	45.68	23.67	46.18
2.0	39.37	48.99	23.71	42.69
2.5	19.49	31.72	18.52	36.55
3.0	15.30	22.21	16.44	30.84
4.0	9.258	13.21	12.32	18.43
6.0	2.395	3.090	4.111	5.134
8.0	0.6904	1.742	1.320	2.337
12.0	0.8915	0.5280	1.269	0.7975

Table 24 Serum concentration* time data from 12 subjects following 600 mg single oral administration of brand A gemfibrozil capsule

Subject	Time (hour)											
No.	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.5	5.0	7.0	9.0	12.0
01	1.281	6.565	9.958	14.30	38.30	43.36	35.85	32.69	10.16	3.215	1.827	0.6909
02	2.689	13.49	13.57	12.39	23.42	38.87	43.70	31.51	14.40	4.037	2.073	0.5833
03	11.16	38.94	35.53	44.86	43.45	38.74	24.63	11.98	4.193	2.163	0.7714	0.3171
04	11.09	11.02	20.33	42.25	40.03	36.80	23.94	13.81	5.799	4.649	1.725	0.6538
05	17.89	23.55	27.24	27.17	27.93	32.47	27.49	13.73	5.011	0.9377	0.6377	0.3004
06	2.956	2.91	4.411	10.50	26.14	50.97	46.89	25.95	6.894	0.9694	0.8075	0.3503
07	4.457	15.69	14.44	18.82	25.07	30.02	30.13	13.23	3.841	0.9877	0.4189	0.3986
08	6.718	14.35	17.19	26.55	35.76	41.90	44.60	21.56	6.364	3.424	1.514	0.3657
09	2.215	9.439	13.65	15.94	16.16	20.93	17.49	14.05	8.590	2.404	1.937	1.126
10	3.185	14.87	22.54	21.35	19.79	17.90	29.01	28.24	7.535	2.043	1.380	1.153
11	15.36	26.72	32.10	43.45	51.72	43.90	34.48	18.20	6.481	2.300	1.246	0.1349
12	23.92	35.33	33.68	34.84	40.77	41.77	28.66	16.14	7.403	2.957	1.326	0.6387
mean	8.644	17.67	20.39	26.03	32.38	36.47	32.31	20.09	7.223	2.505	1.305	0.5594
SD	7.356	11.14	9.982	12.58	10.81	9.654	9.102	7.630	2.878	1.209	0.5439	0.3190
SEM	2.124	3.215	2.881	3.631	3.121	2.787	2.625	2.203	0.8309	0.3490	0.1570	0.0921

Before administration , serum gemfibrozil concentration = 0 for every subjects , serum concentration* = μg/ml

SD = standard deviation , SEM = standard error of mean

Table 25 Serum concentration* time data from 12 subjects following 600 mg single oral administration of brand B gemfibrozil capsule

Subject No.	Time (hour)											
	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.5	5.0	7.0	9.0	12.0
01	6.415	18.05	32.59	36.51	36.30	37.97	31.68	16.76	9.516	1.540	0.6389	0.0000
02	13.38	47.80	50.47	43.07	49.20	44.71	33.17	21.43	8.917	1.783	1.505	0.7684
03	3.388	5.957	15.57	27.81	32.64	47.49	35.72	15.72	5.162	1.190	0.8386	0.7992
04	3.109	3.618	6.082	22.93	47.62	48.22	33.71	15.07	3.706	0.7163	0.3876	0.2038
05	2.276	7.691	16.16	32.75	38.47	40.69	32.33	15.58	5.155	1.156	1.236	0.7152
06	3.878	10.50	32.97	44.32	48.02	35.59	26.60	12.76	4.214	0.7686	0.2098	0.1351
07	0.5419	10.03	14.39	26.93	32.67	36.20	31.63	14.27	7.930	1.894	1.296	0.9637
08	8.044	9.437	13.72	18.41	18.56	30.35	28.69	25.85	14.24	3.868	2.133	1.074
09	1.389	9.422	18.75	12.28	11.82	10.48	26.75	12.31	6.592	1.838	0.6568	0.0000
10	5.240	6.949	10.09	9.310	10.46	11.56	16.80	6.436	4.637	3.253	1.229	0.3391
11	8.627	29.47	38.93	39.27	38.88	35.87	23.32	13.66	5.526	1.137	0.7368	0.4929
12	14.88	46.14	33.97	46.47	40.66	37.88	22.80	15.36	13.88	3.730	1.497	0.9674
mean	5.930	17.09	23.64	30.01	33.78	34.75	28.60	15.439	7.456	1.906	1.035	0.5383
SD	4.569	15.52	13.65	12.52	13.46	12.24	5.545	4.755	3.586	1.109	0.5452	0.3932
SEM	1.319	4.480	3.939	3.614	3.887	3.534	1.601	1.373	1.035	0.3200	0.1574	0.1135

Before administration , serum gemfibrozil concentration = 0 for every subjects , serum concentration* = μg/ml

SD = standard deviation , SEM = standard error of mean

Appendix D

Chromatograms

Example of chromatograms of serum gemfibrozil at each sampling time point following 600 mg single oral administration of two brands gemfibrozil and example of chromatograms series for calibration curve were shown as follows :

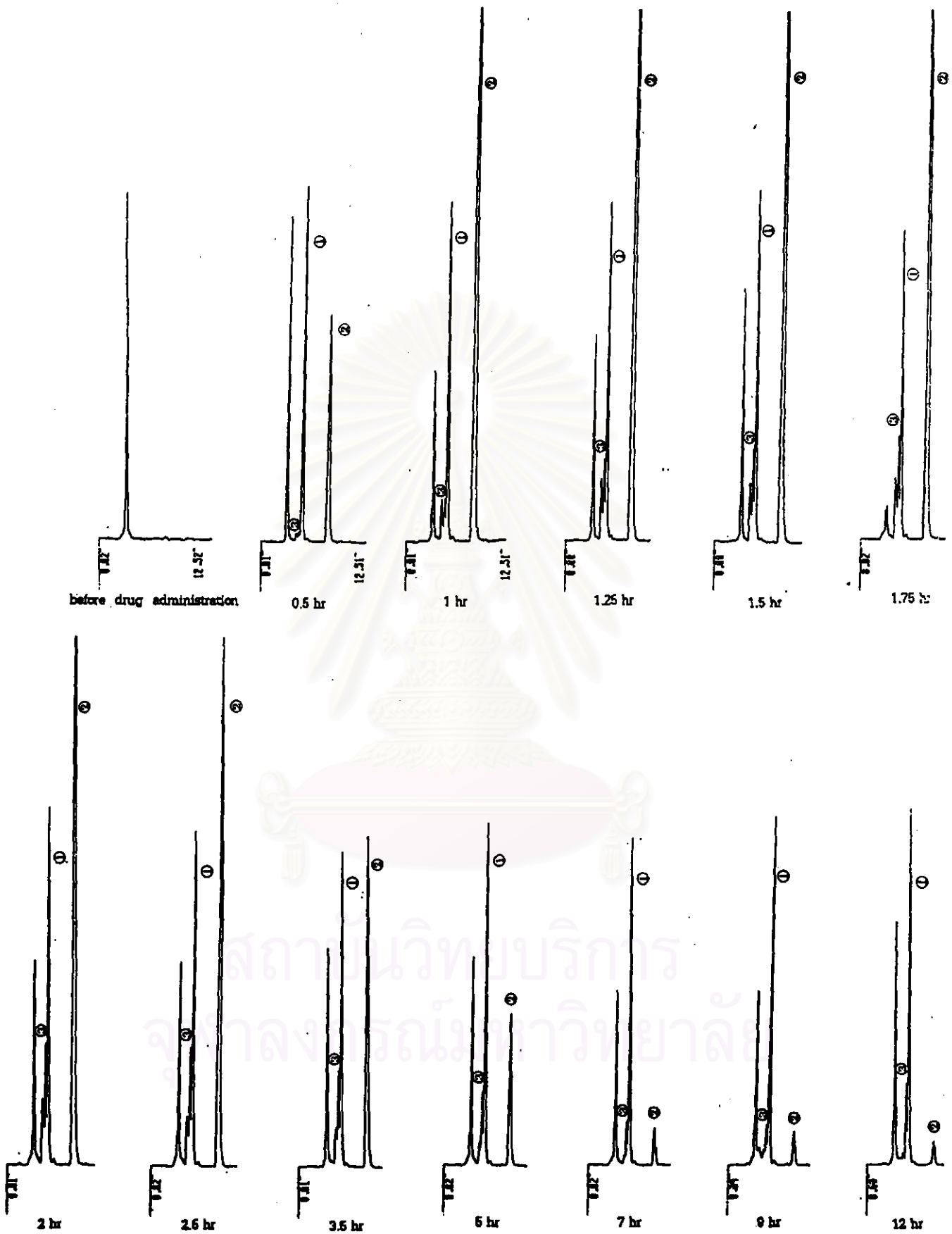

Figure 25 Chromatograms of serum gemfibrozil at each sampling time point for brand A [① = flurbiprofen ② = gemfibrozil ③ = unidentified metabolites]

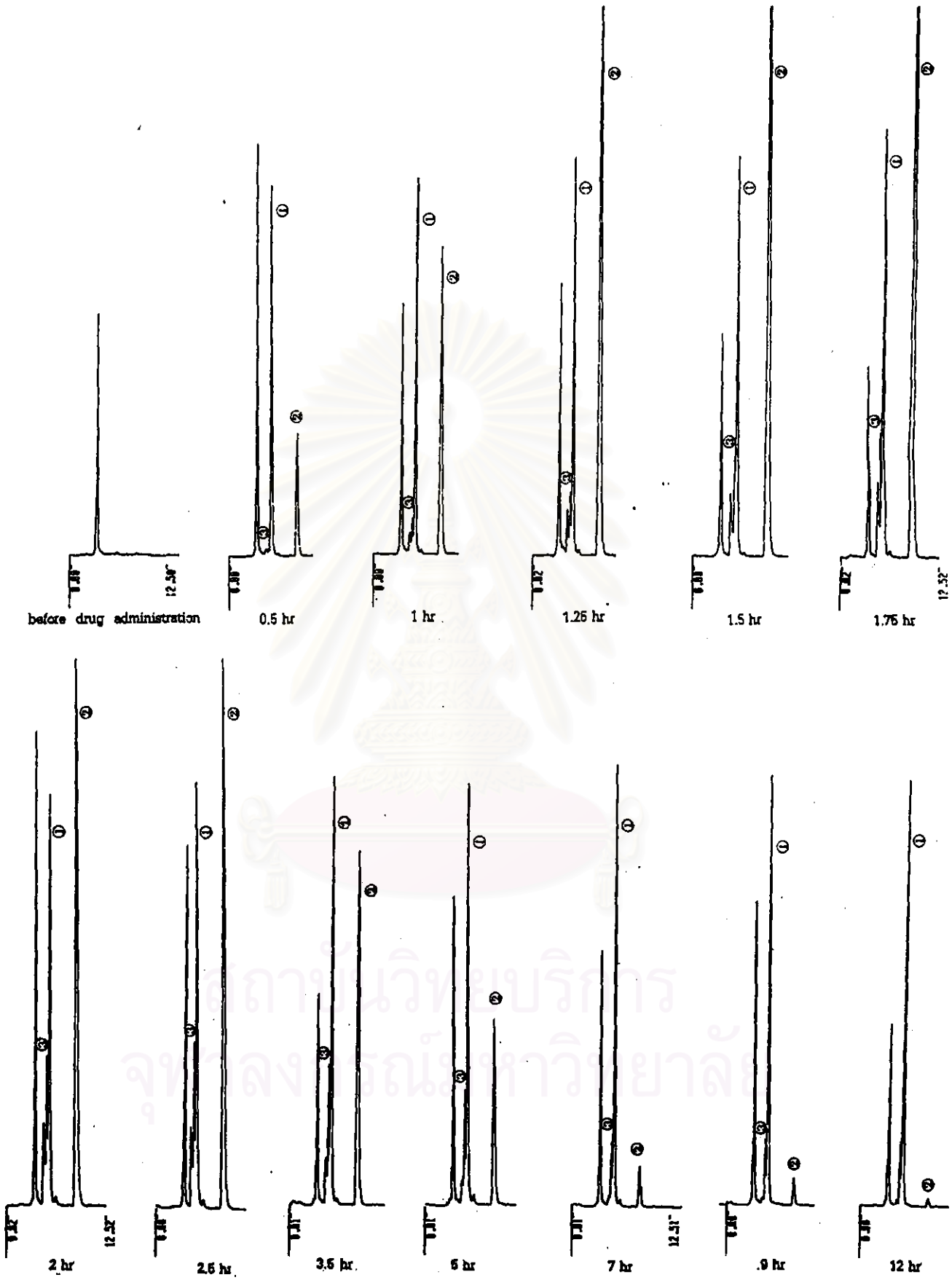

Figure 26 Chromatograms of serum gemfibrozil at each sampling time point for brand B [① = flurbiprofen ② = gemfibrozil ③ = unidentified metabolites]

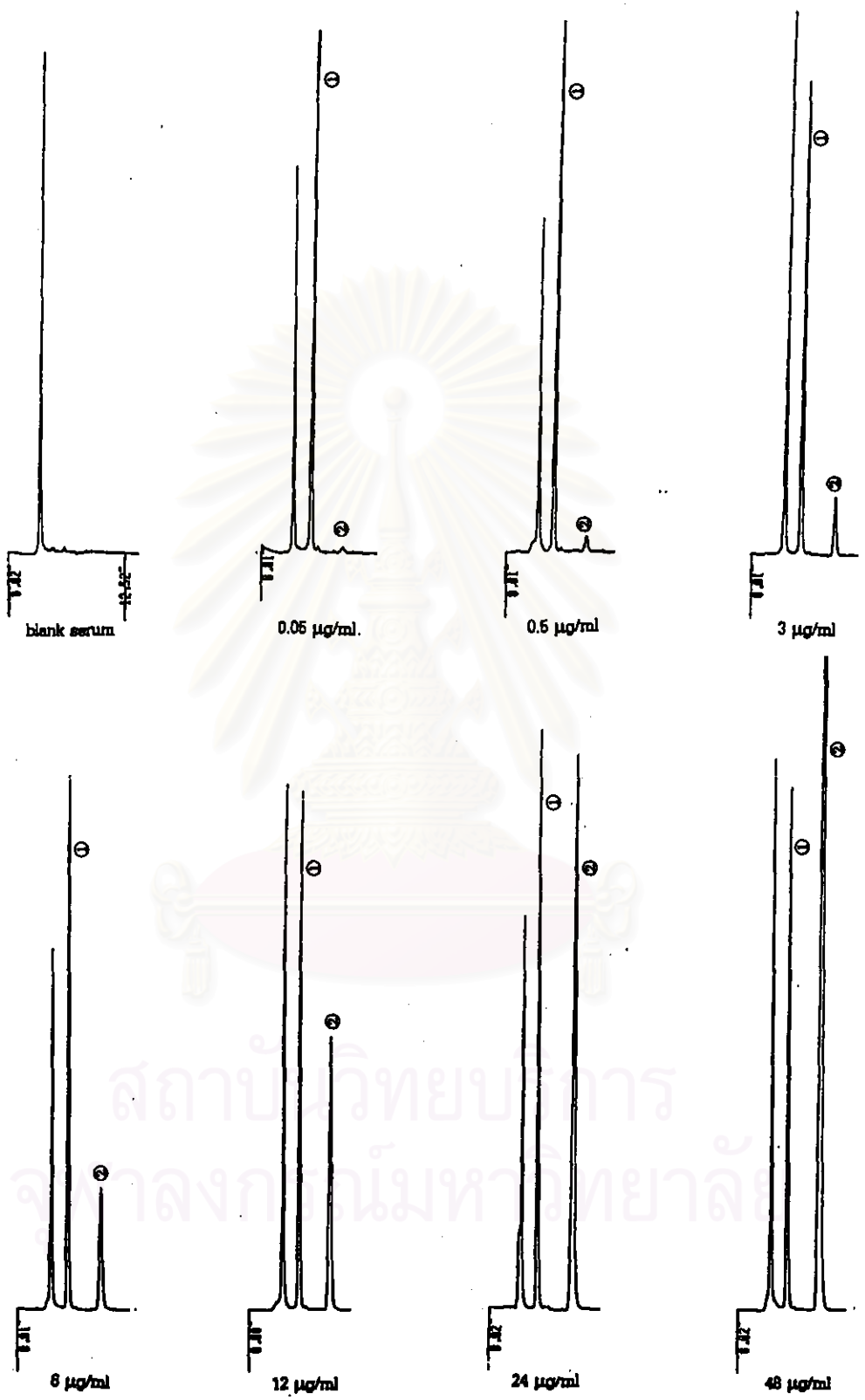

Figure 27 Chromatograms series of calibration curve

[① = flurbiprofen ② = gemfibrozil]

Appendix E

RSTRIP program

Table 29 Example of stripping by RSTRIP program ; data from subject 5 following single oral dose of 600 mg brand A gemfibrozil

Time	C-obs	Ct	Ct-Cobs		Cest	Cest / Cobs x 100
0	0	113.1	113.1		0	0
0.50	20.20	85.00	64.80		21.92	108.5
1.00	27.36	63.89	36.53		28.70	104.9
1.25	28.17	55.39	27.22		29.11	103.3
1.50	27.86	48.02	20.17	②	28.39	101.9
1.75	26.80	41.64	14.84		26.97	100.6
2.00	25.26	36.10	10.84		25.34	100.3
2.50	21.52	27.13	5.615		20.99	97.52
3.50	14.07	15.33	1.258		13.42	95.39
5.00	6.510	6.510			6.175	94.86
7.00	2.078				2.045	98.39
9.00	0.6251				0.6596	105.5
12.0	0.0984				0.1194	121.3
					mean	102.7
					SD	6.862
					%CV	6.682

① $\ln Ct = \ln 113.1 - 0.5711t$

② $\ln Ct = \ln 113.1 - 1.1676t$

$Cest = 113.1\, e^{-0.5711t} - 113.1\, e^{-1.1676t}$

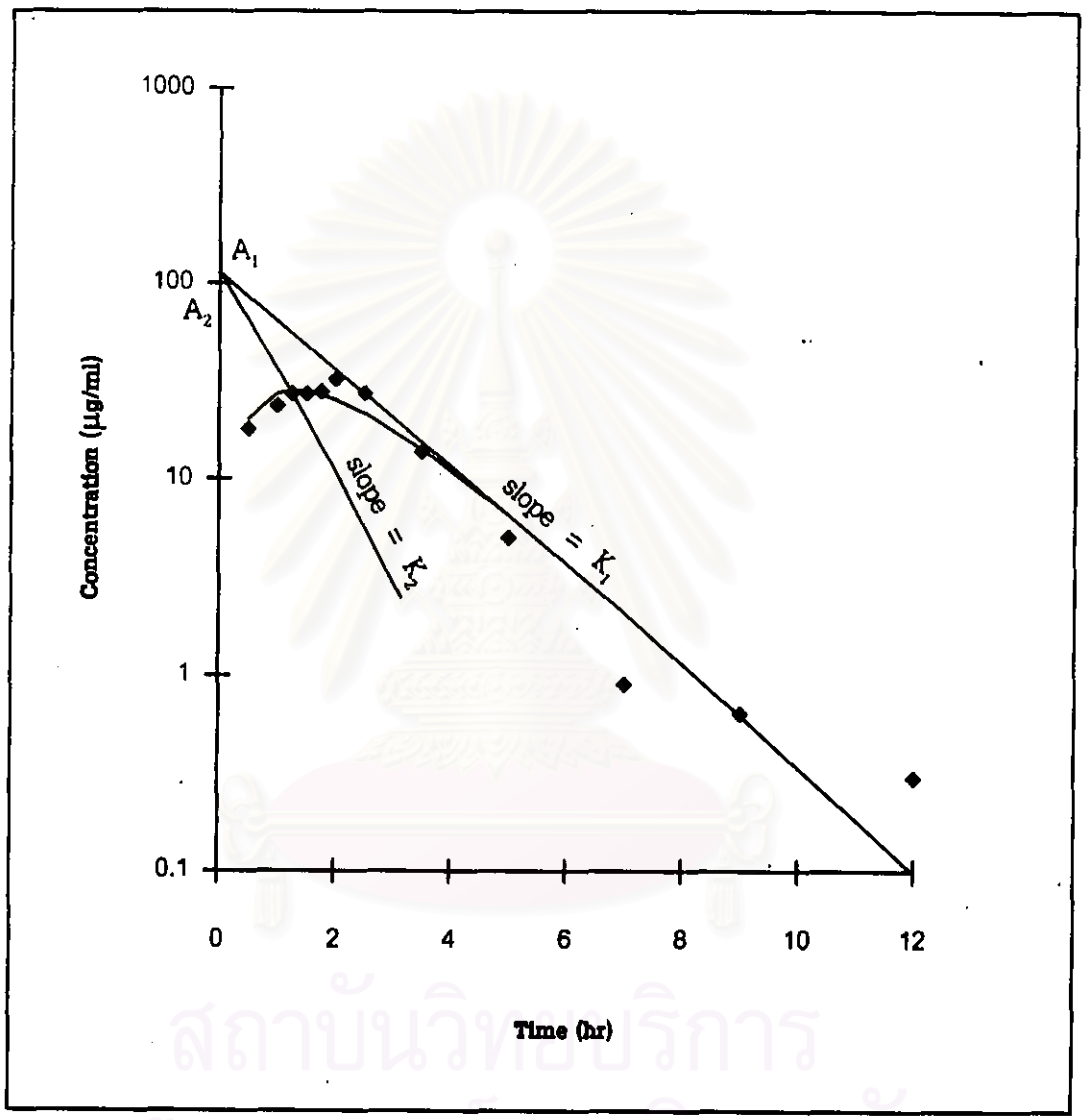

Figure 28 Example of pharmacokinetic parameters calculating by Residual method via RSTRIP program ; data from subject 5 following single oral dose of 600 mg brand A gemfibrozil

```
                Summary of Stripping for dataset:  GEM5A

 No parameters for 1 exponentials.

 2-term:   A[1]=  117.10      k[1]=  0.62848        Lag time=  0.14826
           A[2]= -116.98      k[2]=  1.1956              MSC=  3.2783

 3-term:   A[1]=  52.861      k[1]=  0.49513        Lag time=  0.11432
           A[2]=  44.099      k[2]=  0.64161             MSC=  2.9168
           A[3]= -96.905      k[3]=  1.2080

 4-term:   A[1]=  48.787      k[1]=  0.48513        Lag time=  0.27630
           A[2]=  21.174      k[2]=  0.51989             MSC=  2.4542
           A[3]= -89.960      k[3]=  1.5381
           A[4]=  0.00000     k[4]=  1.6150

 No parameters for 5 exponentials.


                          press any key to continue
```

```
              Least Squares Optimization for data set GEM5A
 after 35 function calls...          A[1]=  191.45      k[1]=  0.62913
 current sum of squares:   9.3100     A[2]= -191.45      k[2]=  0.94129
                lag time:  0.00000

                     Iterations...

                       sumsq[31] =  9.3314
                       sumsq[32] =  9.3255
                       sumsq[33] =  9.3178
                       sumsq[34] =  335.00
                       sumsq[35] =  9.3100   <-----
                       sumsq[26] =  9.4320
                       sumsq[27] =  9.3896
                       sumsq[28] =  9.3343
                       sumsq[29] =  272.32
                       sumsq[30] =  9.3367

                     Minimum successfully found
                      press any key to continue
```

Figure 29 The output of RSTRIP program

Summary of Least Squares for dataset GEM5A

computation time:	1.15 secs	A[1]= 191.45	k[1]=	0.62913
calculated lag time:	0.00000	A[2]= -191.45	k[2]=	0.94129
sum of squared residuals:	9.3100			
Model Selection Criterion:	3.5358			
Weighting Factor:	0.82000			

time	y-obs	y-calc	resid	wt*res-sq
0.00000	0.00000	0.00000	0.00000	0.00000
0.50000	17.887	20.199	-2.3122	0.50231
1.0000	23.554	27.364	-3.8100	1.0883
1.2500	27.241	28.173	-0.93158	0.057750
1.5000	27.173	27.859	-0.68587	0.031368
1.7500	27.926	26.797	1.1291	0.083132
2.0000	32.475	25.262	7.2131	2.9976
2.5000	27.485	21.518	5.9668	2.3519
3.5000	13.727	14.072	-0.34470	0.013870
5.0000	5.0107	6.5097	-1.4990	0.59937

press any key to continue

Summary of Least Squares for dataset GEM5A

time	y-obs	y-calc	resid	wt*res-sq
7.0000	0.90980	2.0780	-1.1682	1.4747
9.0000	0.63770	0.62521	0.012489	0.00022555
12.000	0.30040	0.098390	0.20201	0.10940

press any key to continue

Figure 29 (cont.) The output of RSTRIP program

```
Statistical Analysis for data set GEM5A

Maximum concentration is  28.187 at time  1.2907

                                integrals to     integrals to
                              last time point      infinity
-------------------------------------------------------------
  Area Under Curve:              100.76             100.92
1st Moment Integral:             265.48             267.62
    Residence time:              2.6347             2.6519
-------------------------------------------------------------

                Half-life[1]:    1.1018
                Half-life[2]:    0.73638

                    Lag time:    0.00000

                press any key to continue
```

```
Statistical Analysis for data set GEM5A

Goodness-of-fit statistics:

                Weighted sum of squared obs:   362.20
                  Sum of squared deviations:   9.3100
                Standard deviation of data:    0.96488
                                 r-squared:    0.97430
                    Coeff of determination:    0.98163
                               Correlation:    0.99092
                Model Selection Criterion:     3.3358
                          Weighting Factor:    0.82000

                press any key to continue
```

Figure 29 (cont.) The output of RSTRIP program

Appendix F

Noncompartmental Analysis

Noncompartmental methods for calculating absorption, disposition and elimination parameters are based on the theory of statistical moment. The statistical moments offer the advantage of clearly showing the overall properties of time course because these moments can be calculated by simple numerical integration of experimental data without a pharmacokinetic model.

Statistical moments

The application of statistical moments as a method for pharmacokinetic analysis of drug disposition was reported in 1978 by Yamaoka et al.

The time course of plasma concentration (C_p) following a single dose of drug can usually be regarded as a statistical distribution curve. The zero and first moment for the curve are defined as follow :

$$AUC = \int_0^\infty C_p \, dt$$

$$MRT = \frac{\int_0^\infty tC_p \, dt}{\int_0^\infty C_p \, dt}$$

where t is time, and the area under plasma concentration-time curve (AUC), the mean residence time of a drug in body (MRT) are zero and first moment, respectively

Estimation of areas

The zero moment of drug concentration in plasma versus time course is the total area under the curve from time zero to infinity ($AUC_{0-\infty}$). This total area can be calculated by numerical integration using trapezoidal method from the time course data of plasma concentration. Because drug concentration (C^*) is usually observed in a limited period of time (t^*), the extrapolation from t^* to infinity which is usually estimated as follow

$$\int_{t^*}^{\infty} C\,dt = \frac{C^*}{k}$$

where k, the apparent first order elimination rate constant. This area must be added to the area calculated from time zero to t^* to obtain the total area under the curve.

The first moment of a plasma concentration-time curve is the total area under the curve resulting from a plot of drug concentration and the time versus time. The area under the C.t versus t plot from t = 0 to the last sampling time, t^*, can be calculated by means of the trapezoidal rule. The area from t^* to infinity may be estimate from the following equation.

$$\int_{t^*}^{\infty} tC\,dt = \frac{t^* C^*}{\beta} + \frac{C^*}{\beta^2}$$

C^* is drug concentration at the last sampling time , t^*, and β is the terminal first order elimination rate constant. This area is added to the area from $t = 0$ to $t = t^*$. The total area under the C.t versus t plot is termed the AUMC or area under the first moment curve.

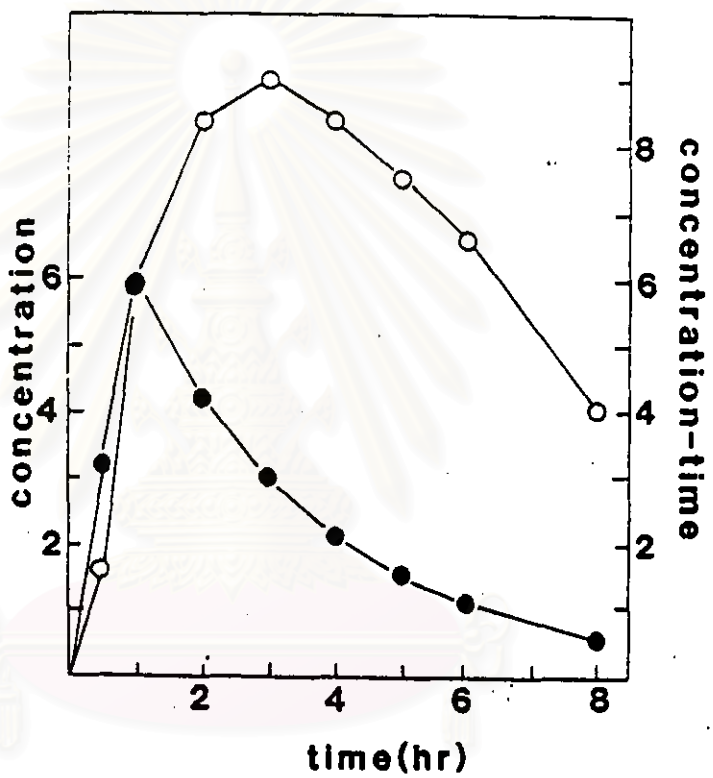

Figure 30 Plots of drug concentration (μg/ml) (●) and drug concentration-time (μg-hr/ml) (O) versus time. The area under the drug concentration versus time plot is AUC ; the area under the drug concentration-time versus time plot is AUMC.

Mean residence time (MRT)

The mean residence time of drug after administration provides a useful estimate of the persistence time in the in the body and in this sense is close relative of the parameter termed half-life whereas half-life represents the time required to eliminate 50% of the dose, MRT represents the time required to eliminate 63.2 % of the dose.

Appendix G

MKMODEL

MKMODEL - a mathematical modelling tool for the PROPHET system was developed in 1982 by N. Holford.

The models supplied in drug library are representative of those commonly used in pharmacology. This program consisted pharmacokinetic, pharmacodynamic , binding and variance model. Only the partial pharmacokinetic model is presented in this article.

Pharmacokinetic model

The time course of drug concentration after a single dose can be described by a combination of an input model defining the rate and duration of drug input and disposition model defining the distribution and elimination of drug. The pharmacokinetic parameter was calculated from this program as follow :

1. Absorption rate constant (KA)

First order drug input assumes the rate of drug entry proportional to amount of remaining to be absorbed. The proportionality factor is the absorption rate constant. For instance, absorption from the gut may be defined by :

$$\text{Rate in} = KA \times G(t)$$

where G(t) is the amount of the dose remaining in the gut at time t. KA is the absorption rate constant. From this program KA was calculated by equation

$$KA = 2/ Tmax$$

2. Volume of distribution (V)

The distribution of a drug can be described by apparent volume of distribution. The steady state volume is the same as the central compartment volume for a one compartment model. For two compartment model the central compartment volume is used as the model volume parameter. The steady state volume can be readily calculated using the VSS function in the WORKSHEET module that calculated VSS by equation.

$$VSS = dose\ (AUMC)/(AUC)^2 - CL\ (Tmax)/2$$

3. Clearance (CL)

All the process of drug elimination whether by metabolism or excretion of unchanged drug can be described by clearance. Clearance is redily estimated from observed concentration using the CL function in the WORKSHEET that calculated by equation

$$CL = dose/AUC$$

4. Hybrid rate constant (L1 , LZ)

The hybrid rate constant known as the distribution and elimination rate constants are used in the drug two compartment model. The distribution or rapid disposition constant (L1) is also known as alpha. The elimination or slow disposition constant (LZ) is also known as beta or the terminal rate constant. The L1 and LZ were calculated from slope of the terminal line in one and two-compartment model , respectively.

5. AUC and AUMC

This program calculated area under the concentration versus time curve ($AUC_{0-\infty}$) and area under the first moment curve ($AUMC_{0-\infty}$) from zero time to infinity. The area of AUC and AUMC from zero time to last sampling time calculated by means of trapezoidal rule and added the area from last sampling time to infinity that calculated from monoexponential equation as described in Appendix F.

Trapezoidal method

The area under plasma concentration-time curve for pharmacokinetic analysis are estimated by trapezoidal method. This method calculated AUC from the area divided into number of trapezoidals under the plasma concentration curve.

After a single dose of drug was administered, the blood sample was collected from zero time (t_0) to last sampling time (t_n).

If $C(t_0)$, $C(t_1)$, $C(t_{n-1})$ and $C(t_n)$ is concentration at t_0, t_1, t_{n-1} and t_n, respectively.

$$\text{Total area} = \Delta t \frac{|C(t_0) + C(t_1)|}{2} + \Delta t \frac{|C(t_1) + C(t_2)|}{2} + \ldots\ldots$$

$$\Delta t \frac{|C+(t_{n-2}) + C(t_{n-1})|}{2} + \Delta t \frac{|C+(t_{n-1}) + C(t_n)|}{2}$$

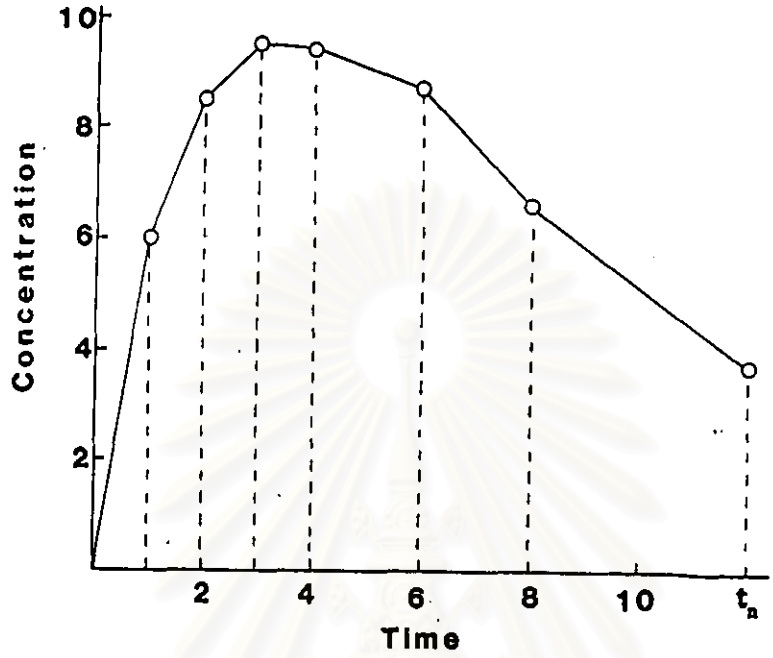

Figure 31 Area under the concentration-time cuve calculating by trapezoidal rule.

Calculation for pharmacokinetic model

The first thing , the time and concentration value must be entered in specific column and then enter the dose of drug administered in specific cell.

Set points for LZ, the data where the terminal log-linear phase starts should be known to enter a number indicating the number of observations in log-linear phase. Suppose 4 was entered. The calculator table will use the last four concentration-time points to estimate LZ. After entering the number of points for LZ . This program will estimate the parameter and display them in the calibrator table. The output of calculation was shown in Figure 32.

ONE COMPARTMENT FIRST ORDER

NAME	TYPE	VALUE	SD	LOWER	UPPER	TIME	CONC
DOSE	C	600				0	0
V	?	8.554				.5	15.357
CL	?	4.6142				1	26.721
KA	?	1.1429				1.25	32.096
TLAG	C	0				1.5	43.449
PWR	?	2				1.75	51.716
VO	C	0				2	43.897
						2.5	34.183
						3.5	18.204
	5 <-----POINTS FOR LZ					5	6.4807
^LZ	.54946					7	2.3002
TMAX	1.75	CMAX	51.716			9	1.2457
^CL	4.6142	AUC	130.03			12	.1349
^VSS	8.554	AUMC	354.85				

TWO COMPARTMENT FIRST ORDER

NAME	TYPE	VALUE	SD	LOWER	UPPER	TIME	CONC
DOSE	C	600				0	0
V	?	11.602				.5	15.357
CL	?	4.6142				1	26.721
L1	?	8.1449				1.25	32.096
LZ	?	.54946				1.5	43.449
KA	?	1.1429				1.75	51.716
TLAG	C	0				2	43.897
PWR	?	2				2.5	34.183
VO	C	0				3.5	18.204
	5 <-----POINTS FOR LZ					5	6.4807
^LZ	.54946					7	2.3002
TMAX	1.75	CMAX	51.716			9	1.2457
^CL	4.6142	AUC	130.03			12	.1349
^VSS	8.554	AUMC	354.85				
^V1	11.602						
^L1	8.1449						

Figure 32 The output of MKMODEL

Appendix H

Statistics

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

$$\bar{X} = \frac{\sum x}{N}$$

2. Standard deviation (SD)

$$SD = \sqrt{\frac{\sum (x - \bar{x})^2}{N - 1}}$$

3. Standard error of mean (SEM)

$$SEM = \frac{SD}{\sqrt{N}}$$

4. Test 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

$$t = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1, \mu_2)}{Sp}$$

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

$$t = \frac{(\bar{x}_1 - \bar{x}_2)}{Sp}$$

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.

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

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

$$t = \frac{(\bar{x}_1 - \bar{x}_2)}{Sp}$$

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 , d.f.

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

This t value is compare 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 stand.

5. Correlation coefficient test

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

$$r = \frac{N \sum XY - \sum X \sum Y}{\sqrt{[N \sum X^2 - (\sum X)^2][N \sum Y^2 - (\sum Y)^2]}}$$

where, r = correlation coefficient

N = the number of x and y pairs

Vitae

Miss Chonticha Rodragkwan was born 4th July , 1969 in Bangkok. She had graduated with Bachelor Degree in Nursing of Science from Faculty of Medicine , Ramathibodi Hospital , Mahidol University in 1991, After graduation , She was experianced in nursing of Medicine Ward at Ramathibodi Hospital. She had studied in Inter-Department of Pharmacology, Chulalongkorn University, since 1995.