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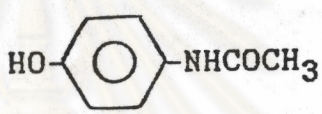
APPENDICES

APPENDIX A

Paracetamol

Names	:	Acetaminophen, paracetamol, p-acetaminophenol
Description	:	White , odorless , slightly bitter crystalline powder
Empirical formula	:	$C_8H_9NO_2$
Structural Formula	:	
Molecular Weight	:	151.16
Melting Point	:	169-170.5°C
Solubility	:	1 in 70 of water,1 in 20 of boiling water,1 in 7 of alcohol, 1 in 40 of glycerol,1 in 9 of propylene glycol, soluble in solutions of alkali hydroxides.A saturated solution has a pH of about 6.
Stability	:	Paracetamol is very stable in aqueous solution. Its pH-rate profile reveals specific acid and specific base catalysis with the maximum stability in the pH range 5 to 7.

Pharmacological Effects :

Paracetamol has analgesic and antipyretic actions that do not differ significantly from those of aspirin. However , it has only weak anti-inflammatory effect. Single or repeated therapeutic doses of paracetamol has no effect on cardiovascular and respiratory systems. It does not produce the gastric irritation , erosion , or bleeding that may occur likewise salicylates.

Pharmacokinetic and Metabolism :

Paracetamol is rapidly absorbed after oral administration with peak levels obtained within 40 to 60 minutes.Variations in the amount of paracetamol absorbed occur depending on the vehicle used and route of administration.

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable . Following therapeutic doses , 90 to 100 % of the drug may be recovered in urine within the first day.

Following usual doses , approximately 25 % of the drug is reported to be metabolized on the first pass through the liver.In therapeutic doses the drug is excreated largely in the urine as various conjugates : 44-45 % as glucuronide conjugates ,20-30 % as sulfate and 15-55 % as cysteine and mercapturic acid conjugates. The small amount of

hydroxylated and deacetylated metabolites have been detected. The unchanged drug comprises approximately 2 % of the dose.

When high doses are ingested , paracetamol undergoes N-hydroxylation to form N-acetyl-benzoquinoneimine, a highly reactive intermediate. This metabolite reacts with sulhydryl groups in proteins and glutathione . When hepatic glutathione is depleted (e.g. after the ingestion of large doses of paracetamol) , reaction with hepatic proteins is increased and hepatic necrosis is the result.

Paracetamol half-life ranges from 2-4 hours in normal people .Both half-life and volume of distribution in children are comparable to those in adults.

Preparations , Routes of Administration , and Dosage:

Paracetamol preparations include tablets,capsules suppositories , chewable tablets , elixirs and suspensions. The conventional oral and rectal dose is 500 to 1,000 mg, the total daily dose should not exceed 4,000 mg. For children, the single dose is 40 to 480 mg , depending upon age and weight ; no more than five doses should be administered in 24 hours .Paracetamol should not be administered more than 10 days or to young children except upon advice of a physician (1,23,24).

APPENDIX B

Sartorius Absorption Simulator

Principle (12,13)

The SM 16750 Sartorius Absorption Simulator is a model, in which is simulated the in vivo passive transport of the drugs by diffusion through special artificial lipoid barriers. It was included that the apparatus provided a suitable adaptation to each drug (lipophily , ionisation) and is used mainly for the study of the absorption of new drug, and for the formulatory development of pharmaceutical preparations .

The apparatus consists principally of two containers for the artificial gastro-intestinal fluid (phase I) and artificial plasma (phase II) .(Figure 6)

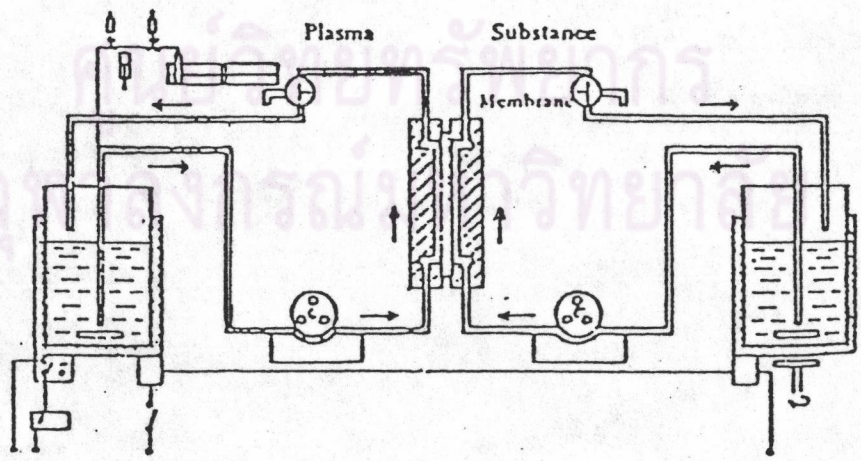


Figure 6 Schematic diagram of the SM 16750 Sartorius Absorption Model.

Since it was only that the portion of a drug which was dissolved in phase I could be diffused , the model was applied by using a small filter attached the end of the tube connection . When the time began , the aqueous phases were circulated by a peristaltic pump . The temperature and flow rate should be checked during the experiment, 39°C ± 1°C and 10-15 $ml.min^{-1}$,respectively. Samples taken from each container at equal time intervals, were determined for the concentration of the drug .The rate of absorption of a drug from the gastro-intestinal tract can be expressed by the absorption rate constant , Ka or Ki. Similarly , the specific diffusion of a drug in the Absorption Simulator can be expressed as the diffusion rate constant ,Kd . Because of these two quantities are found to be directly proportional to each other , the in vitro absorption rate constant , Ki , can be calculated directly from the diffusion rate constant, Kd.

Evaluation of Results

The diffusion of a drug through the lipid barrier was a first order reaction . At the first period, the movement of the substance was predominately from phase I to phase II . Then back diffusion happened from phase II to phase I and finally the diffusion rates should be equal in both directions. The diffusion rate constant ,Kd , was most easily determined during the first period because the increase in concentration of the drug in phase II usually had a linear relationship with the time .

Determination of the Starting Concentration , Ci_o.

The sum of drug concentrations in phase I and II were plotted against times , which should give a straight line paralleled to the abscissa. The starting concentration in phase I was obtained by extrapolation of the graph (Figure 7).

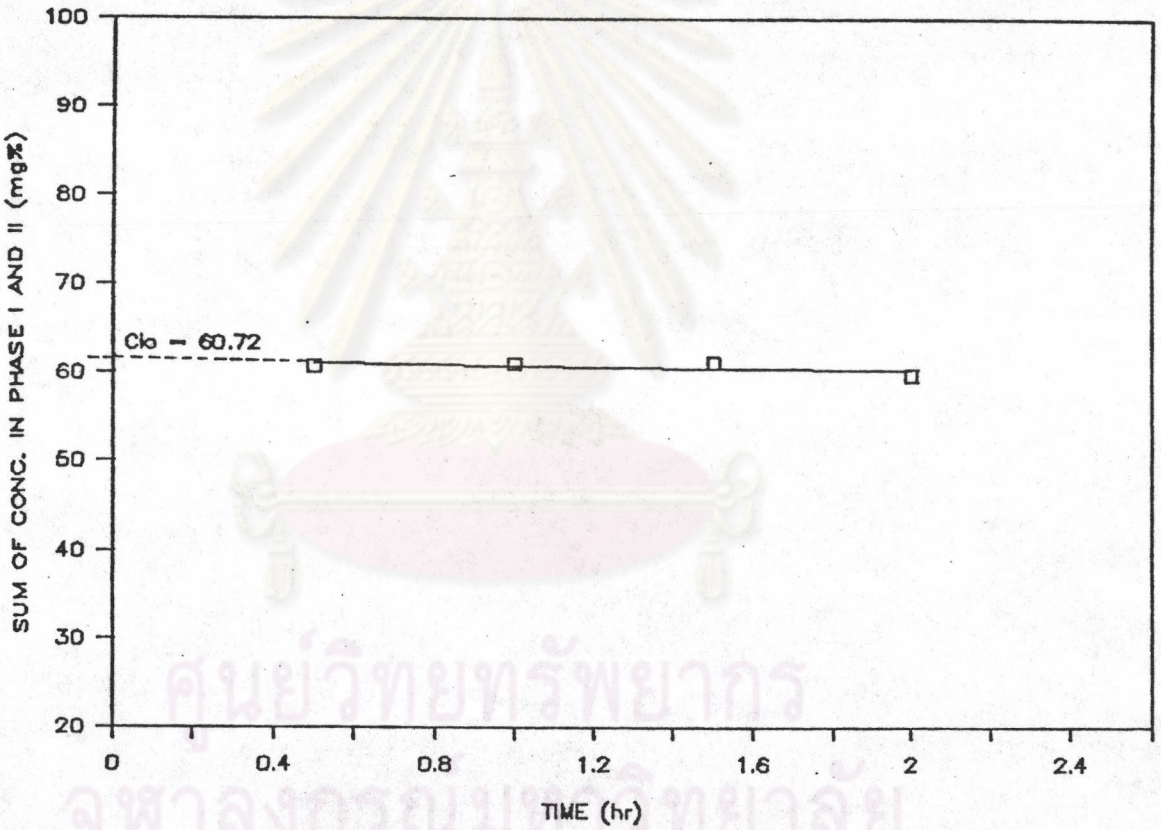


Figure 7 Determination of the starting concentration , data set from the simulated intestinal absorption experiment 1 of paracetamol elixir, Brand E.

Calculation of the Diffusion Rate Constant,Kd.

A simple plot of the drug concentration in phase II or Cii against time at first period showed a straight line (Figure 8).

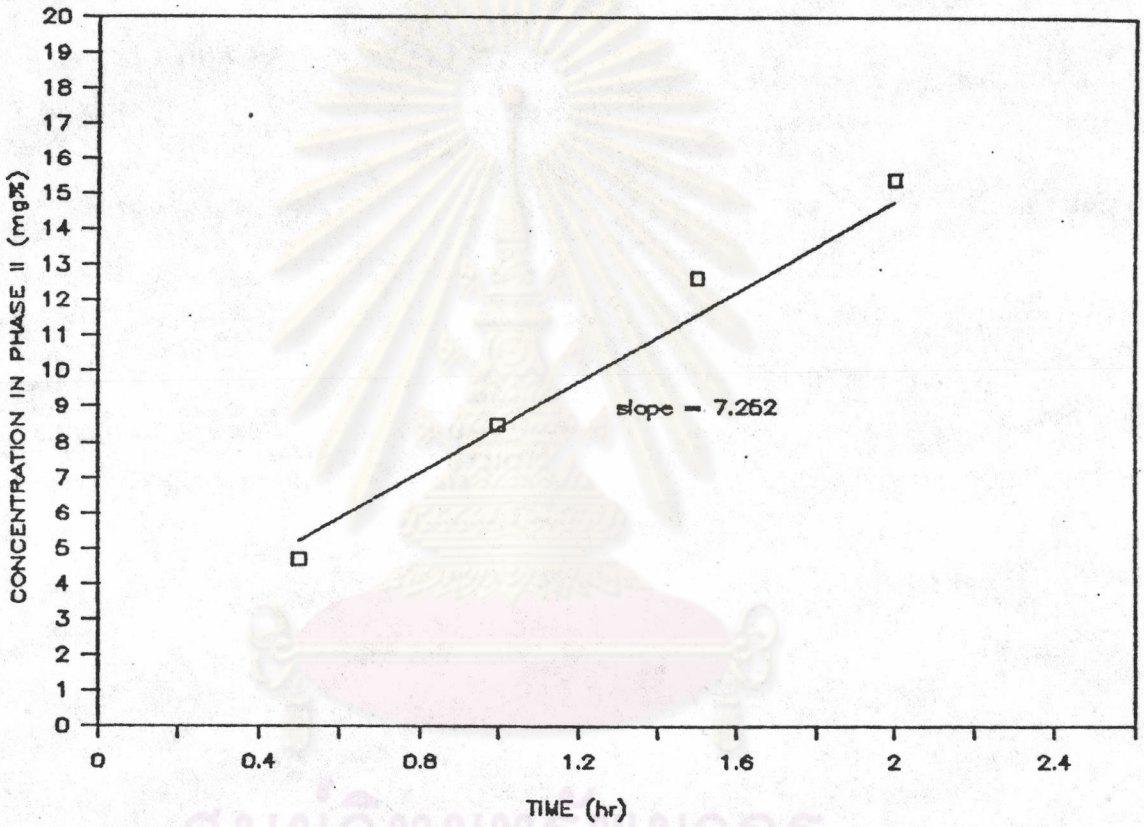


Figure 8 Paracetamol concentration in Phase II against time curve, data set from the simulated intestinal absorption experiment 1 of paracetamol elixir, Brand E.

The diffusion rate constant was calculated from the slope of this line according to Equation 3.

$$Kd = \frac{Cii_2 - Cii_1}{T_2 - T_1} \cdot \frac{1}{Ci_o} \cdot \frac{Vii_o}{F} \quad (cm.hr^{-1}) \quad Eq...3$$

Ci_x = Drug concentration in phase II at time T_x $(mg.ml^{-1})$

Vii_o = Volume of the aqueous phase II at time T_o = 100 ml

F = Effective barrier area (cm^2) = 80 cm^2

T_x = Time (hr)

Ci_o = Starting concentration $(mcg.ml^{-1})$

Calculation of the In Vitro Absorption Rate Constant, Ki.

The in vitro absorption rate constants were calculated according to the Equation 4.

Absorption in	G-factor (cm^{-1})	Kd_o ($cm.hr^{-1}$)
Stomach	4.3	0.0042
Small intestine	10.0	0.0108

$$Ki = G \cdot (Kd - Kd_o) \quad (hr^{-1}) \quad Eq...4$$

Ki = In vitro absorption rate constant (hr^{-1})

Kd = Diffusion rate constant $(cm.hr^{-1})$

Kd_o = Diffusion rate constant through the pores of the barriers with unfilled lipid phase $(cm.hr^{-1})$

For example, the data set from Table 3 for the study of absorption from stomach and intestine of Brand E in experiment 1 was chosen.

Absorption from stomach :

According to the Equations 3 and 4 , where the slope was 2.950 $mg\%.hr^{-1}$ (r^2=0.9), Vii_o was 100 ml, Ci_o was 61.88 mg%,F was 80 cm^2, G was 4.3 cm^{-1} and Kd_o was 0.0042 $cm.hr^{-1}$,therefore

$$Kd = 2.950 \times \frac{1}{61.88} \times \frac{100}{80} = 0.0596 \quad cm.hr^{-1}$$

$$Ki = 4.3 \times (0.0596-0.0042) = 0.2382 \quad hr^{-1}$$

Absorption from intestine :

According to the Equations 3 and 4, where the slope was 7.252 $mg\%.hr^{-1}$ (r^2=0.9) , Vii_o was 100 ml, Ci_o was 60.72 mg%,F was 80 cm^2, G was 10.0 cm^{-1} and Kd_o was 0.0108 $cm.hr^{-1}$,therefore

$$Kd = 7.252 \times \frac{1}{60.72} \times \frac{100}{80} = 0.1493 \quad cm.hr^{-1}$$

$$Ki = 10 \times (0.1493-0.0108) = 1.3849 \quad hr^{-1}$$

APPENDIX C

Test Products

Code	Brand name	Manufacturer	Mft.date	Batch no.
E[a]	Tempra Elixir	Bristol Myers	4-3-1987	00708
S1[b]	Calpol Suspension	Glaxo-Vidhyasom Ltd.	3-10-1985	CLS 04105
S2[b]	Lotemp Suspension	Biolab Co.,Ltd.	14-3-1987	703107
S3[b]	Medamol Suspension	Medical Supply Co.,Ltd.	27-8-1987	27080
S4[c]	Acetasil S	Silom Medicol	14-5-1986	8610304

[a] Green and clear solution with burning taste .

[b] Red with medium viscous suspension .

[c] Yellow, lemon taste with high viscous suspension.

APPENDIX D

STANDARD CURVE DETERMINATION

The typical standard curves and data for paracetamol concentrations in artificial gastric fluid pH 3 , artificial plasma pH 7.5 , artificial intestinal fluid pH 6 , artificial plasma pH 7.8 and pooled urine are presented in Tables 27-31 and Figures 8-13, respectively.

Table 27 Typical Standard Curve Data for Paracetamol Concentrations in Artificial Gastric Fluid pH 3.0 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 245 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	3.00	0.199	2.99	99.49
2	4.00	0.262	3.95	98.84
3	5.00	0.331	5.02	100.30
4	6.00	0.399	6.06	101.01
5	7.00	0.461	7.01	100.20
6	8.00	0.524	7.98	99.79
7	9.00	0.591	9.01	100.15
8	10.00	0.655	10.00	99.98
9	11.00	0.720	11.00	99.98
10	12.00	0.784	11.98	99.85
11	13.00	0.850	13.00	99.98
			Mean	99.96
			S.D.	0.53
			C.V.[4]	0.53 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0049}{0.0650}$

3. %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

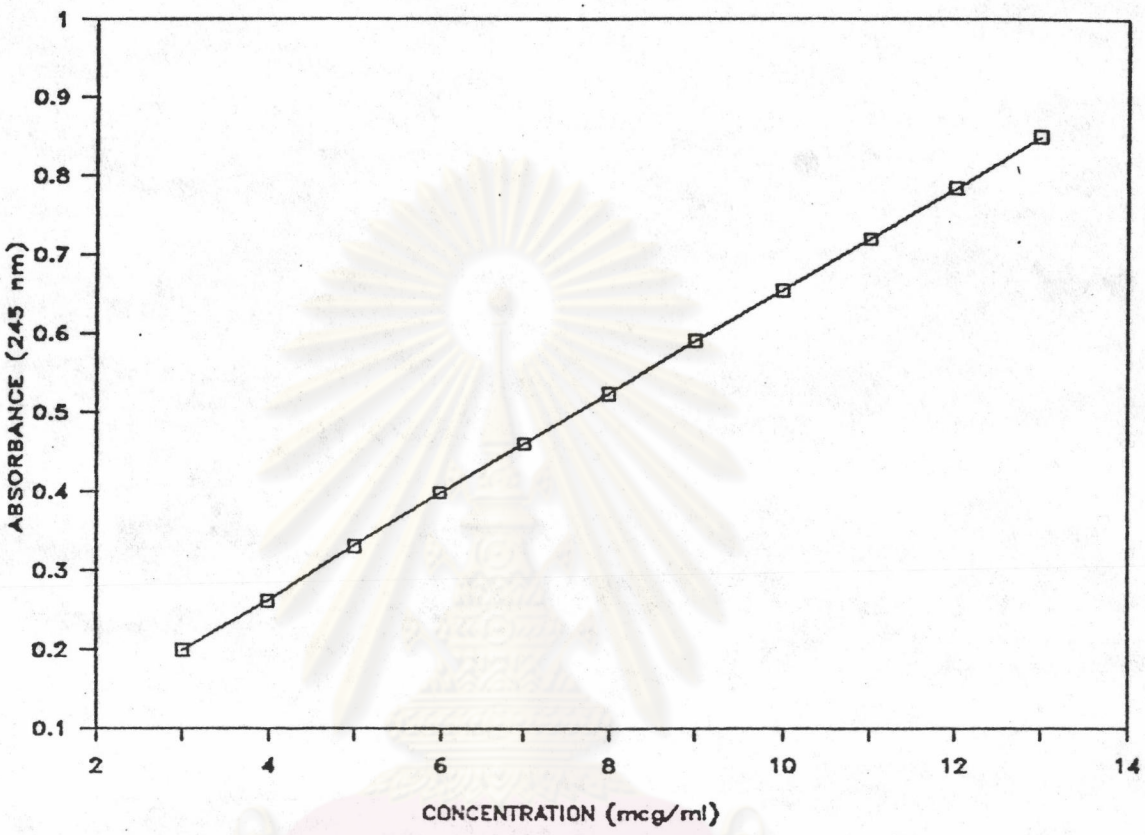


Figure 9 Typical standard curve for paracetamol concentrations in artificial gastric fluid pH 3 .

Table 28 Typical Standard Curve Data for Paracetamol Concentrations in Artificial Plasma pH7.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 245 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	3.00	0.214	2.97	98.90
2	4.00	0.279	3.98	99.61
3	5.00	0.346	5.03	100.66
4	6.00	0.407	5.99	99.79
5	7.00	0.473	7.02	100.29
6	8.00	0.536	8.01	100.08
7	9.00	0.602	9.04	100.43
8	10.00	0.666	10.04	100.41
9	11.00	0.722	10.92	99.25
10	12.00	0.791	12.00	99.97
11	13.00	0.855	13.00	100.00
			Mean	99.94
			S.D.	0.53
			C.V.[4]	0.53 %

1. r^2 = 0.9998

2. Inversely estimated concentration = $\frac{\text{Absorbance} - 0.0244}{0.0639}$

3 %Theory = $\frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

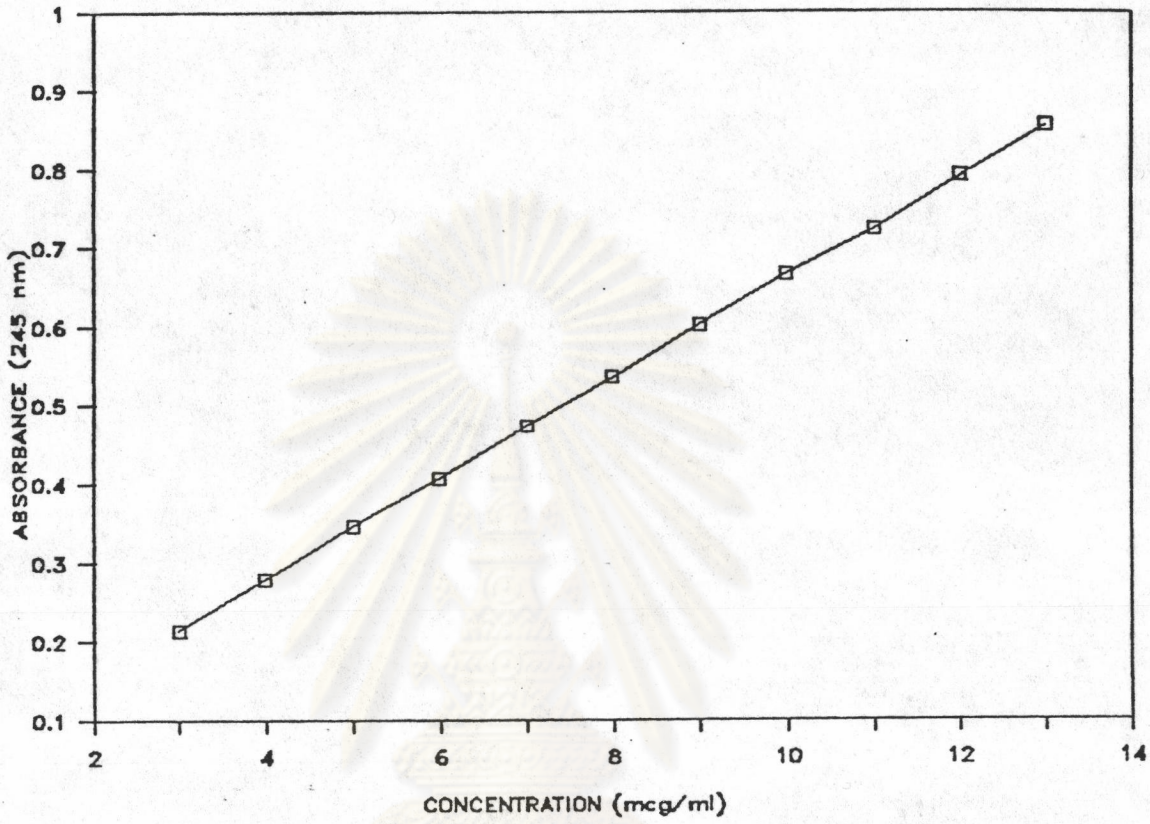


Figure 10 Typical standard curve for paracetamol concentrations in artificial plasma pH 7.5 .

Table 28 Typical Standard Curve Data for Paracetamol Concentrations in Artificial Intestinal Fluid pH 6.0 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 245 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
3	5.00	0.338	5.12	102.45
4	6.00	0.405	6.15	102.55
5	7.00	0.470	7.15	102.18
6	8.00	0.526	8.01	100.18
7	9.00	0.595	9.08	100.84
8	10.00	0.662	10.11	101.06
9	11.00	0.726	11.09	100.82
10	10.02	0.793	12.12	101.00
11	1.003	0.852	13.03	100.22
			Mean	101.21
			S.D.	0.85
			C.V.[4]	0.84 %

1. $r^2 = 0.9997$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0103}{0.0650}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

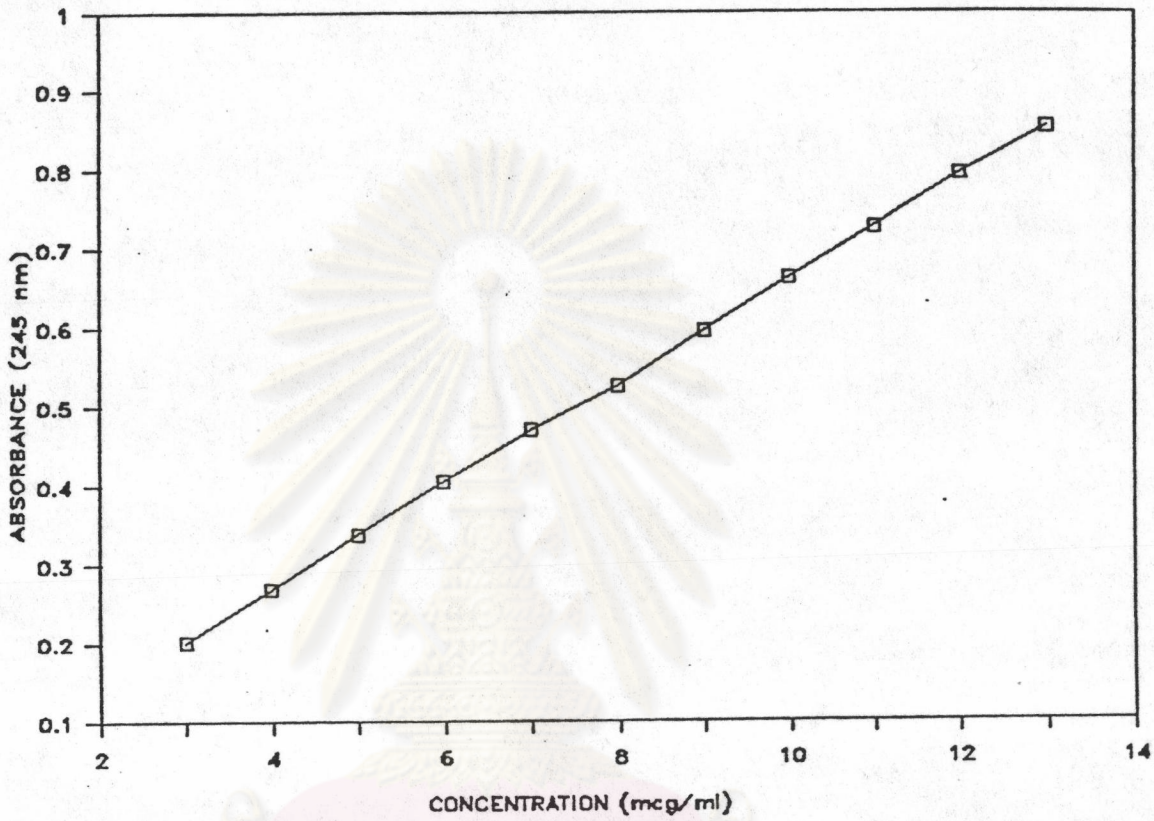


Figure 11 Typical standard curve for paracetamol concentrations in artificial intestinal fluid pH 6.

Table 30 Typical Standard Curve Data for Paracetamol Concentrations in Artificial Plasma pH7.8 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 245 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	3.00	0.203	2.99	99.80
2	4.00	0.271	4.02	100.46
3	5.00	0.335	4.98	99.65
4	6.00	0.402	5.99	99.87
5	7.00	0.469	7.00	100.02
6	8.00	0.535	8.00	99.85
7	9.00	0.600	8.98	99.73
8	10.00	0.671	10.05	100.45
9	11.00	0.736	11.02	100.22
10	12.00	0.802	12.02	100.16
11	13.00	0.864	12.95	99.64
			Mean	99.99
			S.D.	0.30
			C.V.	0.30 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0043}{0.0664}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

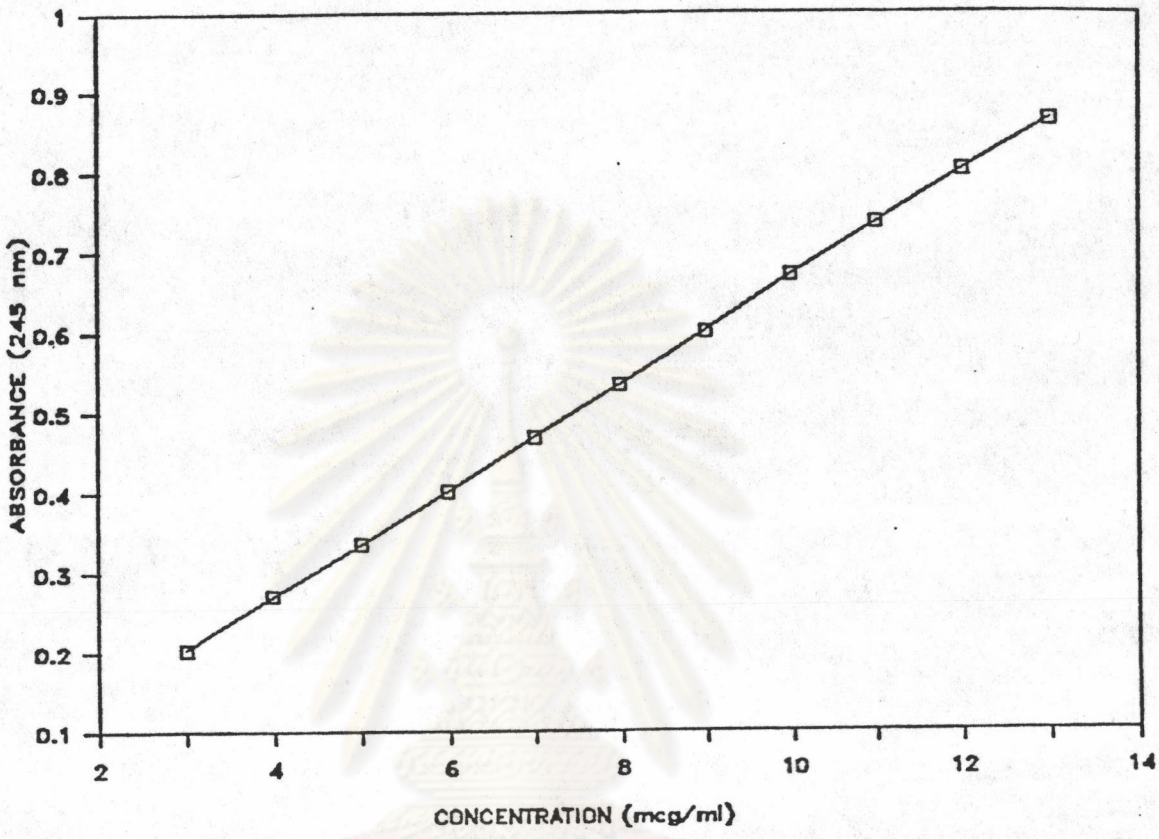


Figure 12 Typical standard curve for paracetamol concentrations in artificial plasma pH 7.8 .

Table 31 Typical Standard Curve Data for Paracetamol Concentrations in pooled urine Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 630 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	20.00	0.081	21.58	107.90
2	40.00	0.185	39.90	99.75
3	60.00	0.299	59.95	99.91
4	80.00	0.409	79.27	99.08
5	100.00	0.522	99.11	99.11
6	120.00	0.631	118.28	98.57
7	140.00	0.760	141.00	100.71
8	160.00	0.870	160.37	100.23
9	180.00	0.976	179.07	99.48
10	200.00	1.104	201.53	100.76
			Mean	100.55
			S.D.	2.68
			C.V.[4]	2.66 %

1. $r^2 = 0.9997$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0419}{0.0057}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

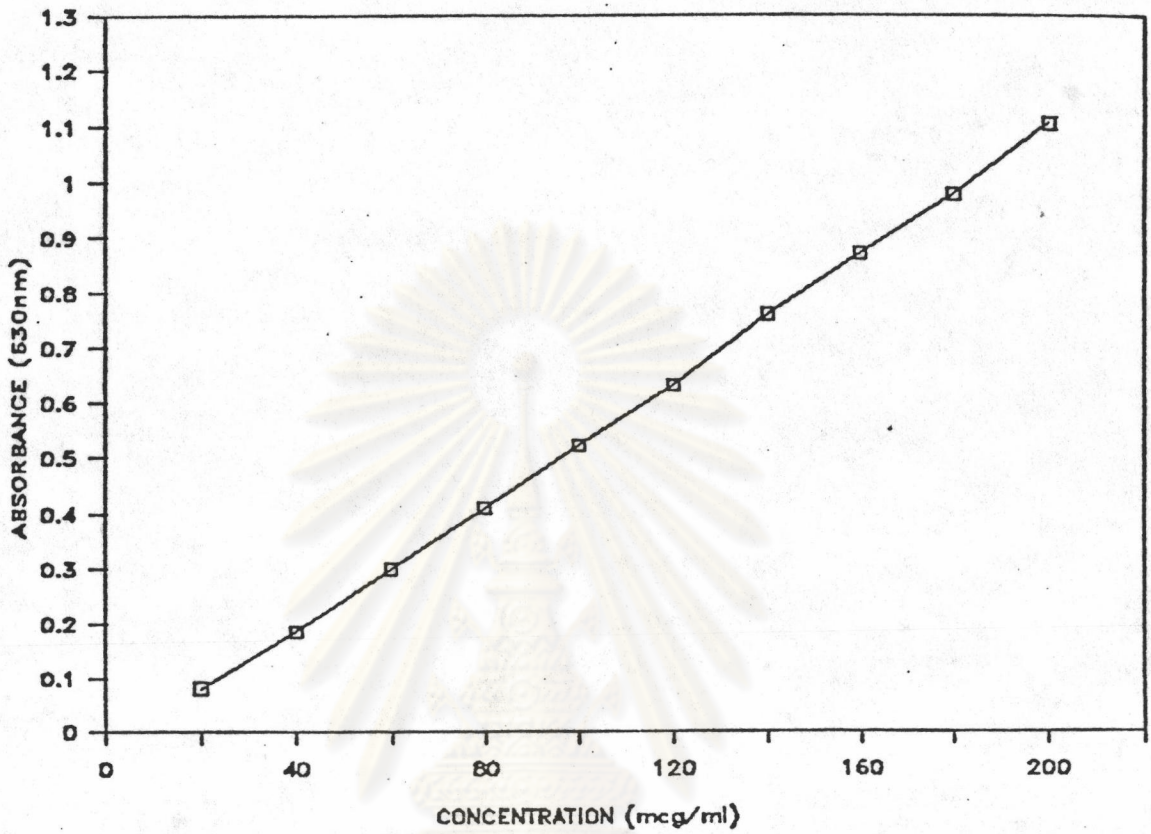


Figure 13 Typical standard curve for paracetamol concentrations in pooled urine .

APPENDIX E

Subjects

Table 33 Physical Characteristics of the Subjects.

Subject No.	Sex	Age(yr)	Weight(kg)	Height(cm)
1	F	30	45	157
2	F	24	45	161
3	F	26	48	152
4	F	25	56	164
5	M	19	63	164
6	M	20	50	162
7	M	21	65	175
8	M	20	48	166
Mean		23.13	52.50	162.63
S.D.		3.80	7.91	6.72

APPENDIX F

Calculation of K and Ka from the Urinary Excretion Data (14,25,26,27)

It was found that the paracetamol excretion data could be well described by a one compartment open model with first order drug absorption and first order drug elimination.(Figure 14)

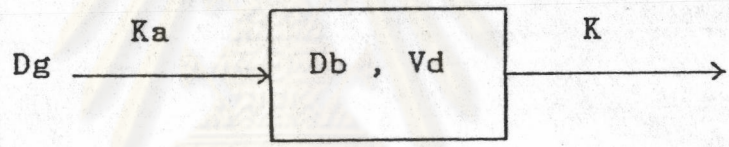


Figure 14 One-compartment open model with first order absorption and first order elimination.

The differential equation that described the rate of drug change in the body was as follow

$$\frac{dDb}{dt} = F.Ka.Dg - K.Db \qquad \text{Eq...5}$$

Where Db is the amount of drug in the body, F is the fraction of dose(Do) to be absorbed, Dg is the amount of drug in the gut.

Since the drug in the gastrointestinal tract also followed a first order decline process, Dg was equal to $Do.e^{-Kat}$.Therefore

$$\frac{dDb}{dt} = F.Ka.Do.e^{-Kat} - K.Db \qquad \text{Eq...6}$$

Using Laplace and Anti-Laplace Transformation, the Equation 6 could also be expressed as

$$Db = \frac{Ka.F.Do}{Ka-K} . (e^{-Kt} - e^{-Kat}) \qquad \text{Eq...7}$$

As a rate of elimination of drug in the body was a first order process, the elimination rate expression was

$$\frac{dDu}{dt} = Ke.Db \qquad \text{Eq...8}$$

Where Du is the amount of drug in urine and Ke is the renal excretion rate constant.From the Equations 6 and 7 the new expression was

$$\frac{dDu}{dt} = \frac{Ke.Ka.F.Do}{Ka-K} . (e^{-Kt} - e^{-Kat}) \qquad \text{Eq...9}$$

After drug absorption was virtually complete, e^{-Kat} approched zero,and the Equation 9 reduced to the expression:

$$\frac{dDu}{dt} = \frac{Ke.Ka.F.Do}{Ka-K} . e^{-Kt} \qquad \text{Eq...10}$$

Taking the natural logarithm of both sides of this expression, the Equation 10 became :

$$\ln\left(\frac{dDu}{dt}\right) = \ln \frac{Ke.Ka.F.Do}{Ka-K} - Kt \qquad \text{Eq...11}$$

When ln(dDu/dt) was plotted against time at the midpoint of collection period, a straight line was obtained with a slope of K.

The value of Ka was obtained by using the method of residuals or a feathering technique which was easily explained by the Equation 12, (Eq.9)-(Eq.10).

$$\left(\frac{dDu}{dt}\right)res = \frac{Ke.Ka.F.Do}{Ka-K} \cdot e^{-Kat} \qquad \text{Eq...12}$$

Where (dDu/dt)res was the residual rate of urinary drug excretion .Taking the national logarithm of both sides of this expression, the Equation 12 became :

$$\ln\left(\frac{dDu}{dt}\right)res = \ln \frac{Ke.Ka.F.Do}{Ka-K} - Ka.t \qquad \text{Eq...13}$$

When ln(dDu/dt)res was plotted against time at midpoint of the collection period, a straight line was obtained with a slope of Ka.

For example, the data set from Table 22 for Brand E in subject No.8 was chosen. The rate of drug excretion

versus the midpoint of the collection period was plotted on the semilog paper. (Table 29 and Figure 13)

The slope of the terminal phase (K) and the residual line (Ka) were 0.155 and 1.910 hr^{-1}, respectively. The lag time, Tlag, the time at the point of intersection of these two straight lines on the x-axis, was calculated by the Equation 14.

$$Tlag = \frac{\ln B - \ln A}{Ka - K} \qquad \text{Eq...14}$$

Where A and B were respective intercepts on the y-axis after extrapolation of the terminal and residual line. According to this data, therefore

$$Tlag = \frac{\ln 78.34 - \ln 105.11}{1.910 - 0.155}$$

$$Tlag = \frac{4.665 - 4.361}{1.910 - 0.155} = 0.17 \text{ hr}$$

Also, parameters from the other data sets were calculated and confirmed by the CSTRIP computer program.

Table 33 Striping Biexponentials from Set of the Amount of Paracetamol Excreted into the Urine in Subject No.8 Following a Single Oral dose of 600 mg Paracetamol from Paracetamol Elixir, Brand E.

Time (hr)	Du (mg)	T(interval) (hr)	Tm (hr)	dDu/dt (mg/hr)	(dDu/dt)' (mg/hr)	(dDu/dt)res (mg/hr)	(dDu/dt)" (mg/hr)	(dDu/dt)×100 (dDu/dt)"
0.5	5.68	0.5	0.25	11.37	75.36	63.99	10.16	89.35
1.0	21.84	0.5	0.75	43.69	69.74	26.05	44.65	102.19
1.5	27.53	0.5	1.25	55.06	64.54	9.48	54.88	99.68
2.0	29.85	0.5	1.75	59.70	59.72	0.02	56.01	93.82
3.0	53.31	1.0	2.50	53.31	53.17		52.28	98.07
4.0	55.61	1.0	3.50	55.61	45.54		45.40	81.64
6.0	87.17	2.0	5.00	43.59	36.09		36.08	82.78
8.0	57.66	2.0	7.00	28.83	26.47		26.47	91.82
12.0	55.73	4.0	10.00	13.93	16.63		16.63	119.34
16.0	25.59	4.0	14.00	6.40	8.94		8.94	139.80
24.0	18.95	8.0	20.00	2.37	3.53		3.53	148.94
32.0	12.65	8.0	28.00	1.58	1.02		1.02	64.60
							Mean	101.00
							SD	25.99
							CV	25.65 %

$(dDu/dt)' = 78.34.e^{-0.155t}$

$(dDu/dt)res = dDu/dt - (dDu/dt)'$

$(dDu/dt)" = 78.34.e^{-0.155t} - 105.11.e^{-1.910t}$

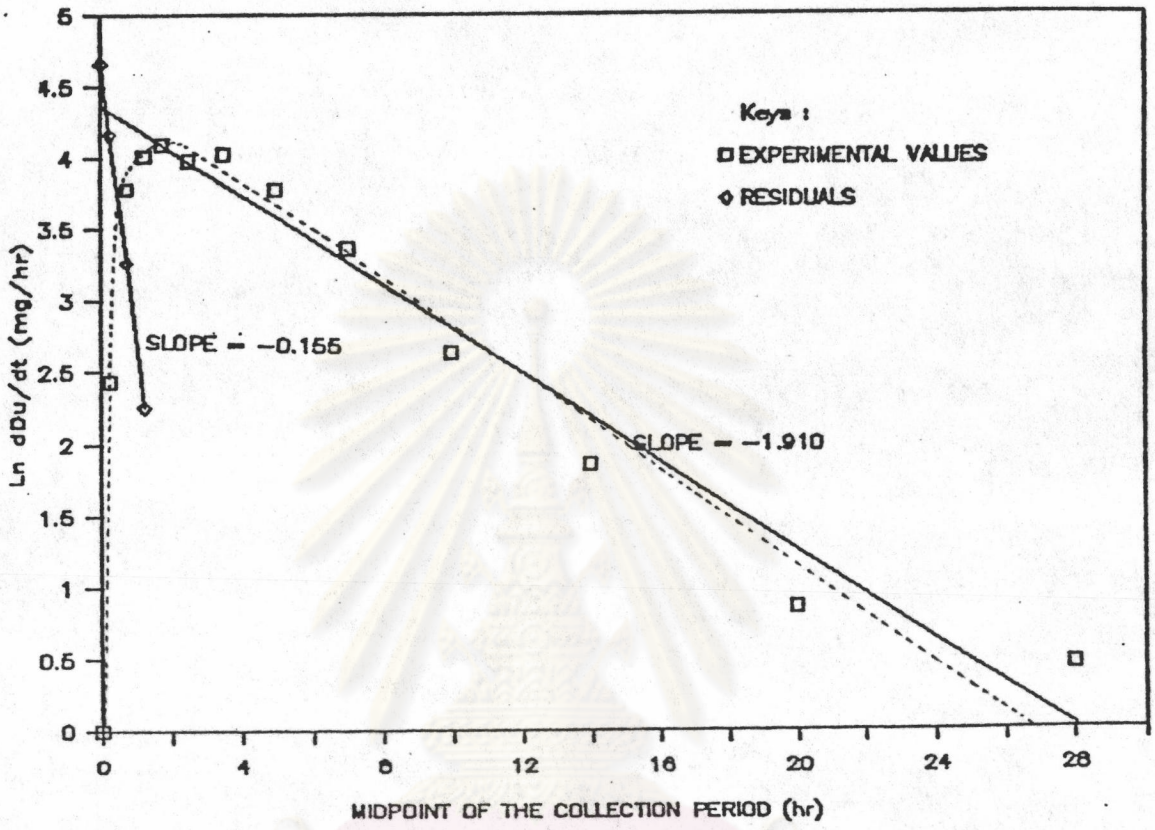


Figure 15 Experimental values and calculated curve in subject No.8 after oral single dose of 600 mg paracetamol from paracetamol elixir, Brand E.

APPENDIX G

STATISTICS

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

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

2. Standard Deviation (S.D.)

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

3. Standard Error (S.E.)

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

4. Testing the Difference of Two Means.

(by T - test)

Let μ_1 , μ_2 = Population means

X_1 , X_2 = Sample means

σ_1 , σ_2 = Population variances

s_1 , s_2 = Sample standard deviation

N_1 , N_2 = Sample size

The null hypothesis $H_o : \mu_1 = \mu_2$

The alternative hypothesis $H_a : \mu_1 \neq \mu_2$

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

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

$$F = \frac{(s_1)^2}{(s_2)^2}$$

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

$$S_p^2 = \left[\frac{1}{N_1} + \frac{1}{N_2}\right]\left[\frac{(N_1 - 1)\, S_1^2 + (N_2 - 1)\, S_2^2}{N_1 + N_2 - 2}\right]$$

with degree of freedom , d.f. :

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

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. Correlation Coefficient Test

The correlation coefficient is a quantitative measure of the relation ship 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 = Corelation coefficient

N = the number of X, Y paris

Test of Zero Correlation

Let ρ = the true correlation coeffient, estimated by r

The null hypothesis $H_o : \rho = 0$

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

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

The value of t is refered to a t distribution with (n-2) degree of freedom. If the t is not significant, the null hypothesis stands.

6. Analysis of Variance (ANOVA)

Analysis of Variance for Completely Randomized Design

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

where X_{ij} = Observed value 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 the table at degree of freedom (k-1) and (N-k).

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 (28).

VITAE

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