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APPENDICES

APPENDIX A

TEST PRODUCTS

Code	Brand Name	Manufacturers	Mfd. Date	Batch No.
A	Naprosyn®	Syntex Laboratories Limited	2-9-85	E8891
B	Naproxen®	Standard Pharmaceutical Co., Ltd.	5-7-86	2902
C	Napsen®	Sriprasit Pharma Co., Ltd.	10-2-87	T87031
D	Ultrazyn®	Trusty Drugs Co., Ltd.	3-85	53639
E	Naproxen®	The Government Pharmaceutical Organization	9-86	F909636
F	Napxen®	Berlin Pharmaceutical Industry Ltd., Part.	3-11-86	860095
G	Naproxen®	Utopian Co., Ltd.,	8-8-86	814397
H	Nasin®	The Medicpharma Co., Ltd.	30-5-86	0-53701
I	Vinsen®	Chew Brothers & Co., Ltd., Part.	25-4-85	T503801

APPENDIX B

PREPARATION OF DISSOLUTION MEDIA (34)

a. Simulated Gastric Fluid (pH 1.2 ± 0.1)

2.0 g. of sodium chloride was dissolved in 7.0 ml. of hydrochloric acid and sufficient water to make 1,000 ml. The solution was adjusted to a pH of 1.2 ± 0.1

b. Simulated Intestinal Fluid (pH 7.5 ± 0.1)

6.8 g. of monobasic potassium phosphate was dissolved in 250 ml. of water, mixed, and 190 ml. of 0.2 N. sodium hydroxide and 400 ml. of water were added. The solution was adjusted with 0.2 N. sodium hydroxide to a pH of 7.5 ± 0.1, and diluted with water to 1,000 ml.

APPENDIX C

STANDARD CURVE DETERMINATION

The typical standard curves and data for naproxen concentrations in simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 7.5), and human plasma were presented in Tables 56-58 and Figures 29-31, respectively.

Table 56 Typical Standard Curve Data for Naproxen Concentrations in Simulated Gastric Fluid (pH 1.2) Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Absorbance at λ 331 nm	Inversely estimated concentration[2] (µg/ml)	% Theory[3]
1	2.01	0.016	2.24	111.60
2	4.03	0.027	3.62	89.80
3	8.06	0.063	8.12	100.77
4	10.07	0.091	11.62	115.43
5	12.08	0.092	11.75	97.26
6	16.11	0.122	15.50	96.22
7	18.13	0.141	17.88	98.61
8	22.15	0.174	22.01	99.35
9	26.18	0.206	26.01	99.34
10	30.21	0.238	30.01	99.34
11	34.24	0.271	34.14	99.70
12	38.27	0.302	38.02	99.34
13	44.31	0.354	44.52	100.47
14	50.35	0.404	50.77	100.84
			MEAN	100.58
			S.D.	6.21
			C.V.[4]	6.16 %

1. $R^2 = 0.999$, $Y = 0.0079X - 0.0019$
2. Inversely estimated concentration = (Absorbance + 0.0019)/0.0079
3. $\%\ \text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{Known concentration}} \times 100$
4. $\%\ \text{C.V.} = \frac{\text{S.D.}}{\text{MEAN}} \times 100$

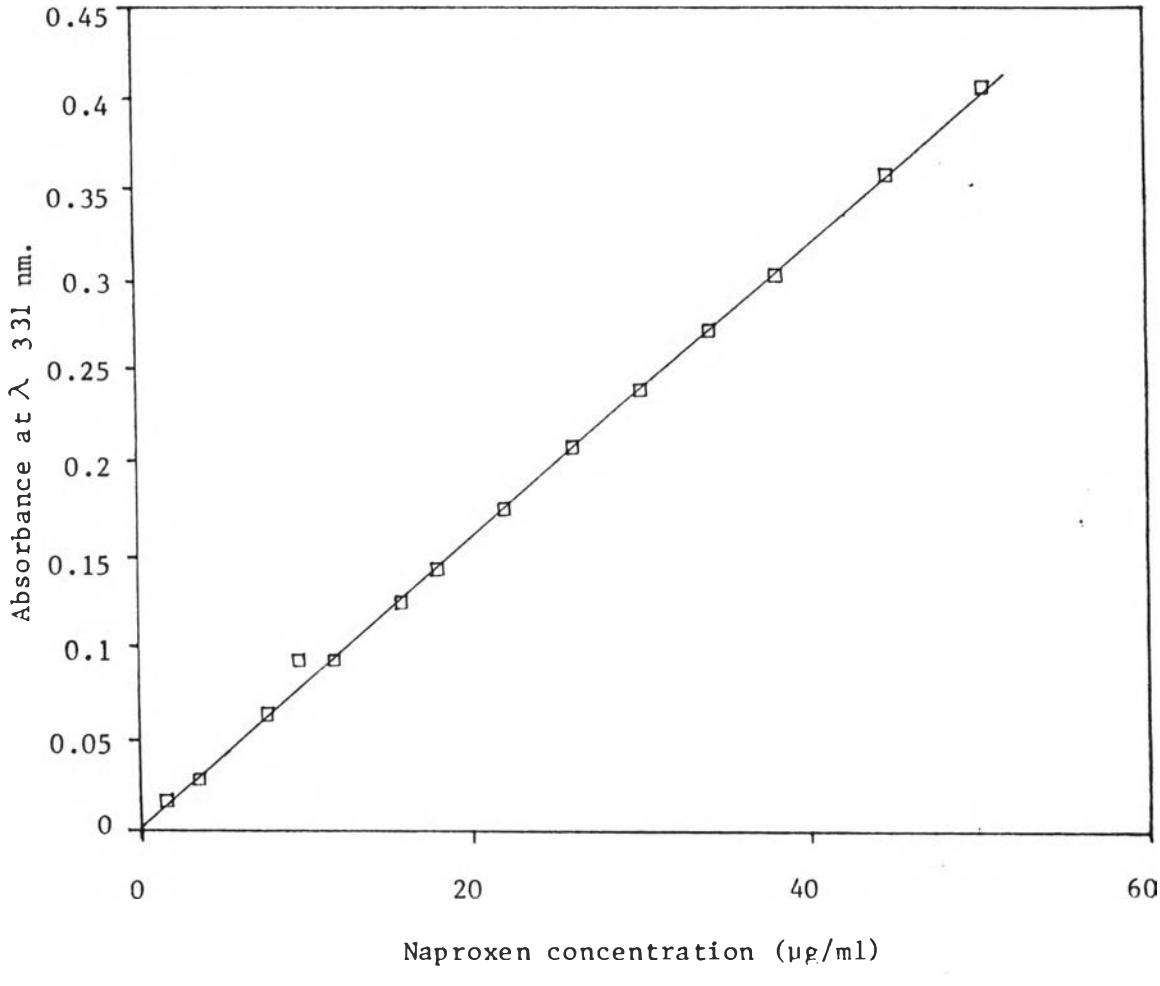

Figure 29 Typical standard curve for naproxen concentrations in simulated gastric fluid pH 1.2

Table 57 Typical Standard Curve Data for Naproxen Concentrations in Simulated Intestinal Fluid (pH 7.5) Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Absorbance at λ 331 nm	Inversely estimated concentration (µg/ml)[2]		% Theory[3]
1	20.00	0.147	20.10		100.48
2	36.00	0.259	36.05		100.14
3	50.00	0.349	48.87		97.74
4	60.00	0.429	60.27		100.44
5	70.00	0.501	70.52		100.75
6	80.00	0.571	80.49		100.62
7	90.00	0.640	90.32		100.36
8	100.00	0.704	99.44		99.44
9	106.00	0.751	106.14		100.13
10	110.00	0.780	110.27		100.24
11	120.00	0.845	119.53		99.61
				MEAN	100.00
				S.D.	0.85
				C.V.[4]	0.85 %

1. $R^2 = 0.999$, $Y = 0.0059 + 0.007X$

2. Inversely estimated concentration = (Absorbance - 0.0059)/0.007

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

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

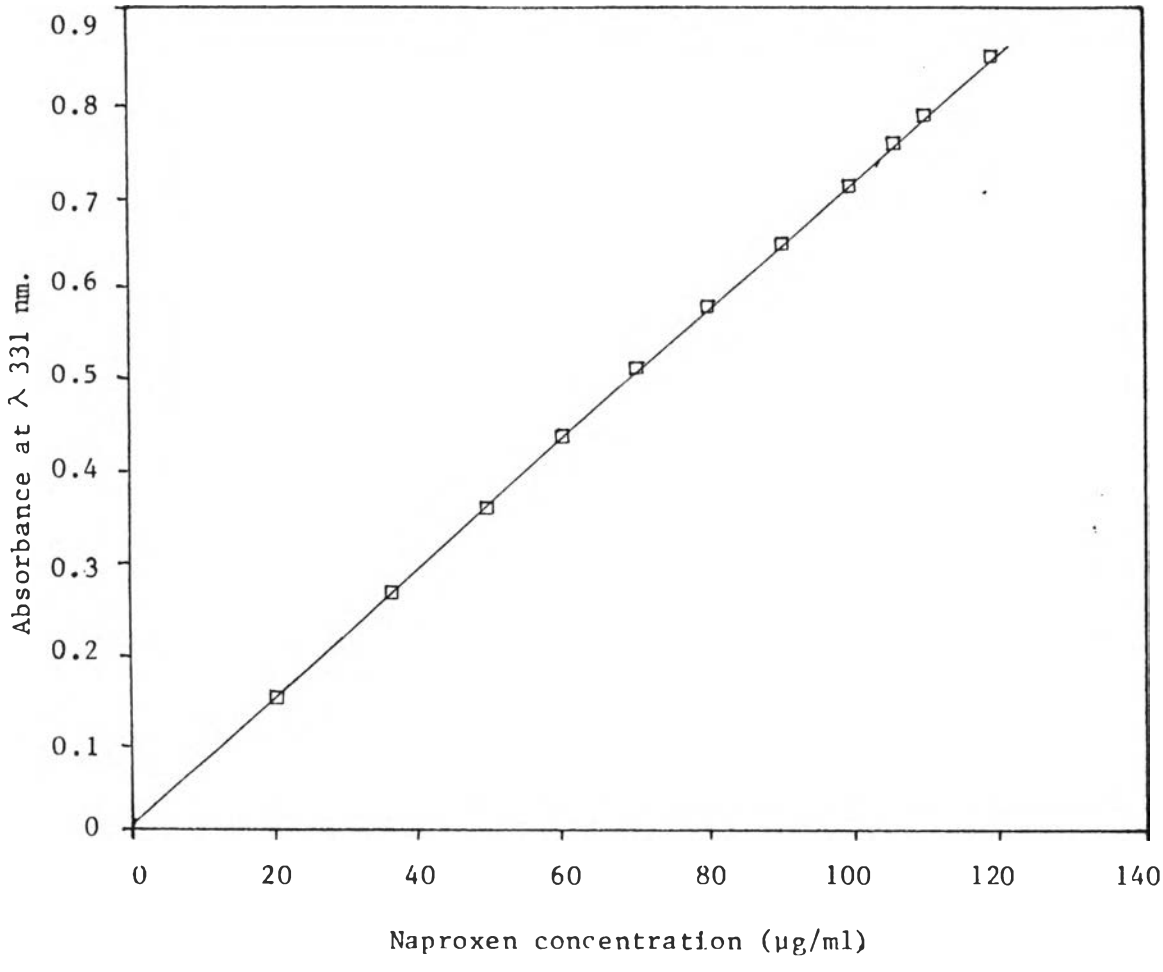

Figure 30 Typical standard curve for naproxen concentrations simulated intestinal fluid pH 7.5

Table 58 Typical Standard Curve Data for Naproxen Concentrations in Human Plasma Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Peak height ratio[a]	Inversely[2] estimated concentration (µg/ml)	% Theory[3]
1	5	0.216	5.07	101.44
2	10	0.417	10.10	100.99
3	20	0.739	18.59	92.96
4	30	1.182	32.19	107.32
5	40	1.565	39.11	97.77
6	50	2.087	52.82	105.64
7	60	2.280	56.83	94.71
8	70	2.826	69.47	99.25
9	80	3.043	81.42	101.78
			MEAN	100.21
			S.D.	4.67
			C.V.[4]	4.66 %

1. $R^2 = 0.995$, $Y = 0.0388X + 0.0192$

2. Inversely estimated concentration

   = (Peak height ratio - 0.0192)/0.0388

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

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

a. = Naproxen/Phenylbutazone

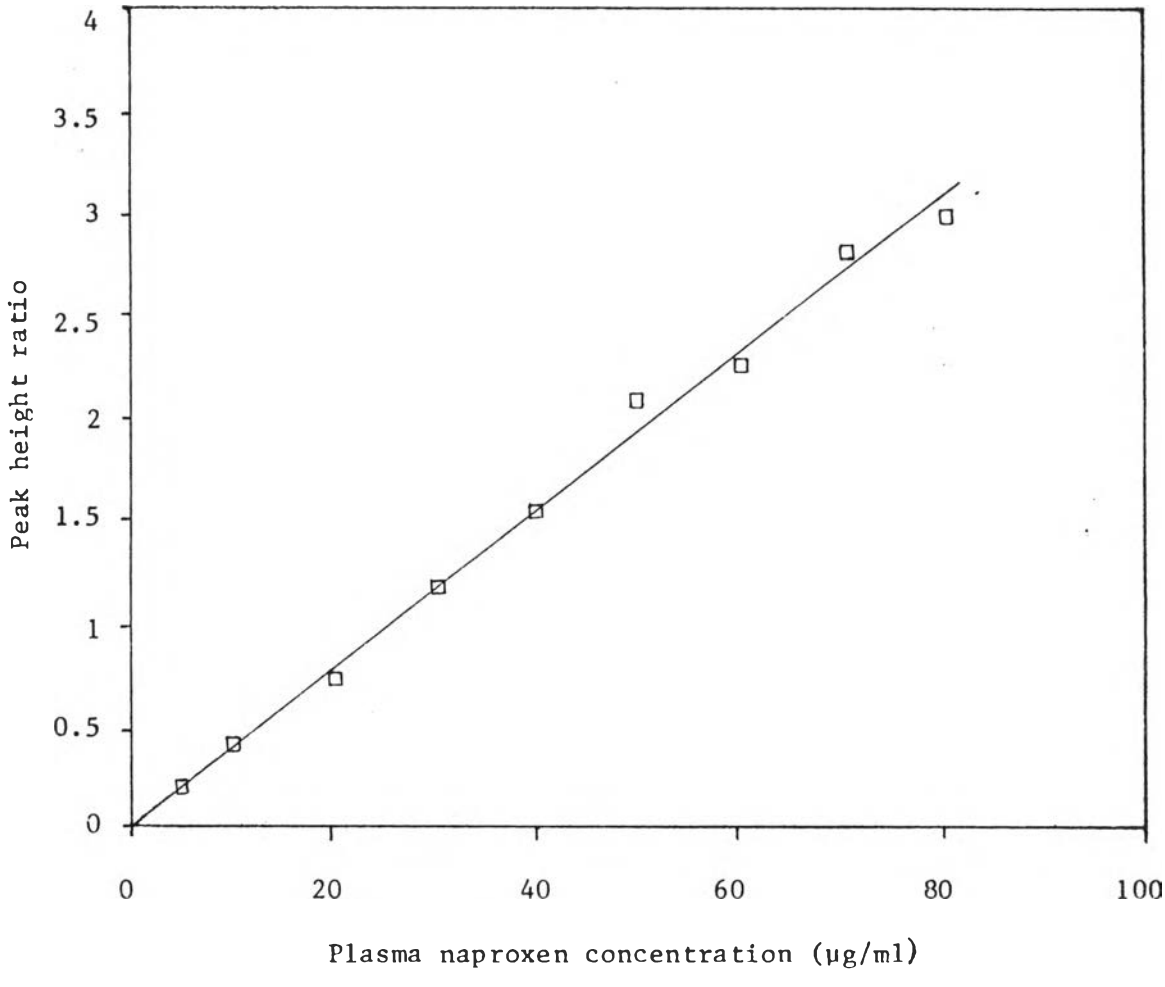

Figure 31 Typical standard curve for naproxen concentrations in human plasma.

APPENDIX D

Table 59 Physiological Characteristics of the Subjects

Subject No.	Sex	Age (yr)	Height (cm)	Weight (kg)
1	M	21	167	61
2	M	23	170	51.2
3	M	19	164	63
4	M	21	174	65
5	M	20	162	48
6	M	20	170	61
7	M	21	175	65
8	M	21	173	62
	Mean	20.75	169.37	59.52
	S.D.	1.16	4.72	6.38

APPENDIX E

NONCOMPARTMENTAL ANALYSIS (35)

Noncompartmental methods for the estimation of certain pharmacokinetic parameters are usually based on the estimation of the area under a plot of drug concentration versus time. Noncompartmental methods have been used to estimate bioavailability, clearance, apparent volume of distribution, and the fraction of dose of a drug that is converted to a specific metabolite, based on data following single dose of drug and metabolite. These methods do not require the assumption of a specific compartmental model for either drug or metabolite. In fact, these methods can be applied to virtually any compartmental model, provided that we can assume linear pharmacokinetics.

Statistical Moments

The application of statistical methods to pharmacokinetics was reported in 1979 by Yamaoka et al. (36) and cutler (37). In 1980, Rigelman and Collier (38) applied statistical moment theory to the evaluation of drug absorption.

The time course of drug in plasma can usually be regarded as a statistical distribution curve. Irrespective of the route of administration, the zero and the first moments are defined as follows:

$$AUC = \int_0^\infty C\,dt \qquad (1)$$

$$MRT = \frac{\int_0^\infty t.C\,dt}{\int_0^\infty C\,dt} = \frac{AUMC}{AUC} \qquad (2)$$

Where MRT is the mean residence time of a drug in the body. AUC and MRT are termed the zero and first moment, respectively, of the drug concentration-time curve.

In the usual single-dose pharmacokinetic study, blood sampling is stopped at some time t* when drug concentration, C*, is measurable. Hence, estimation of the area under the blood level-time curve from zero time to infinity, AUC_0^∞, must be carried out in two steps. The area under the curve from zero time to t* is calculated by means of the linear trapezoidal method. To this partial area we must add area under the curve from t* to infinity which is usually estimated as follows :

$$\int_{t^*}^{\infty} C\,dt = \frac{C^*}{\lambda_n} \qquad (3)$$

Where λn is 2.303 times the slope of the terminal region of a plot of log drug concentration versus time. The sum of the two partial areas is AUC_0^∞.

The same approach must be used to estimate total AUMC. The area under the first moment curve from t* to infinity is estimated as follow :

$$\int_{t^*}^{\infty} t.C\,dt = \frac{t^*C^*}{\lambda_n} + \frac{C^*}{\lambda^2_n} \qquad (4)$$

Estimation of Areas

The areas under blood concentration-time curve for phamacokinetic analysis are estimated by the trapezoidal rule. The zero moment (AUC) is calculated from the areas divided into a

number of trapezoids under the plasma concentration-time curve and the first moment (AUMC) is also calculated from the areas divided into a number of trapezoids under the plasma concentration-time versus time curve which are given by equations 5, 6, respecitvely

$$AUC \Big|_{t_1}^{t_2} = \frac{(t_2 - t_1)(C_1 + C_2)}{2} \qquad (5)$$

$$AUMC \Big|_{t_1}^{t_2} = \frac{(t_2 - t_1)(t_1C_1 + t_2C_2)}{2} \qquad (6)$$

The summation of each area yields the true estimated AUC and AUMC.

Absorption Rate Constant

In the statistical moment theory, mean residence time (MRT) represents the time for 63.2% of the administered dose to be eliminated. MRT_{oral} is calculated from equation 2 as described before and MRT_{iv} is estimated as follow :

$$MRT_{iv} = \frac{1}{\lambda_n} \sim \frac{1}{Kel} \qquad (7)$$

(Kel is the elimination rate constant estimated from the terminal slope of the semilogarithmic plasma concentration-time curve)

The product of the difference of MRT_{oral} and MRT_{iv} represents mean absorption time (MAT). If the absorption of drug is the first order process, the absorption rate constant (Ka) is calculated from the reciprocal of MAT.

$$MAT = MRT_{oral} - MRT_{iv} \quad (8)$$

$$Ka = \frac{1}{MAT} \quad (9)$$

Half-life

The half-life calculated by noncompartmental method is given by a following equation.

$$t_{1/2} = 0.693\ MRT_{iv} \quad (10)$$

APPENDIX F

STATISTICS

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

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

2. Standard deviation (S.D.)

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

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

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

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

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

$$\text{d.f.} = N_1 + N_2 - 2$$

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	$\frac{SS\ among}{k-1}$	V.R. = $\frac{MS\ among}{MS\ within}$
Within groups (Error)	$\sum_{j=1}^{k} \sum_{j=1}^{n_j} (X_{ij} - X_{.j})^2$	N-k	$\frac{SS\ within}{N-k}$	
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,..., n

j = 1, 2,..., 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.

6. Correlation coefficient test

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

$$r = \frac{N\Sigma XY - \Sigma X\Sigma Y}{\sqrt{\left[N\Sigma x^2 - (\Sigma x)^2\right]\left[N\Sigma y^2 - (\Sigma y)^2\right]}}$$

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 : $\rho \neq 0$

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

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 Usa Amornsiripanish was born on February 25th, 1964, in Nakhonpathom. She obtained her degree in Bachelor of Science in Pharmacy, Mahidol University in the year 1986.