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APPENDIX A

TEST PRODUCTS

Code	Brand name	Manufacturer	Mft. date	Batch no.
A	Zantac tablet	Glaxo UK. Ltd.	06-08-87	B19127HA
B	Ranidine tablet	Biolab Co. Ltd.	20-12-87	711392
C	Radine tablet	Pond's Chemical	13-08-87	308-394
D	Histac tablet	Ranbaxy India	00-06-87	HST35-87E
E	Zantidon tablet	Siam Bhaesaj	13-10-88	22RJ105
I	Zantac injection	Glaxo UK. Ltd.	01-06-88	B2678HB

APPENDIX B

STANDARD CURVES DETERMINATION

The typical standard curves and data for ranitidine hydrochloride concentrations in carbondioxide free water, simulated gastric fluid pH 1.2, simulated intestinal fluid pH 7.5 and pooled plasma are presented in Tables 31-34 and Figures 14-17, respectively.

Table 31 Typical Standard Curve Data for Ranitidine Hydrochloride Concentrations in Carbondioxide Free Water. Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 313 nm.	Inversely estimated[2] conc.	% Theory[3] (mcg/ml)
1	1.00	0.048	1.02	101.75
2	2.00	0.091	1.97	98.46
3	3.00	0.136	2.97	98.83
4	4.00	0.188	4.12	102.90
5	6.00	0.272	5.97	99.58
6	8.00	0.362	7.97	99.58
7	10.00	0.458	10.09	100.91
8	15.00	0.669	14.76	98.41
9	20.00	0.912	20.14	100.69
			MEAN	100.12
			S.D.	1.46
			C.V.[4]	1.46%

1. $r^2 = 0.9997$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0020}{0.0452}$

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

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

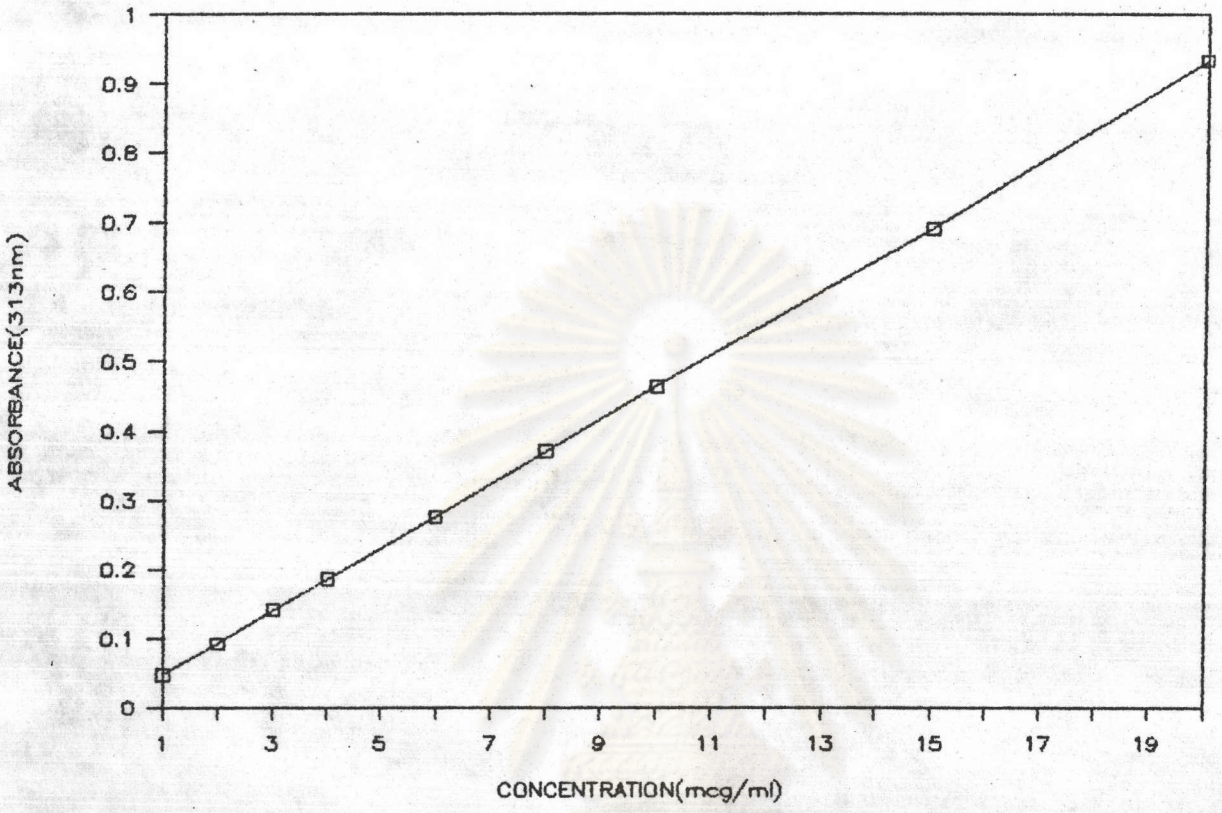

Figure 13 Typical Standard Curve for Ranitidine Hydrochloride Concentration in Carbondioxide Free Water

Table 32 Typical Standard Curve Data for Ranitidine Hydrochloride Concentrations in Simulated Gastric Fluid pH 1.2. Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 228 nm.	Inversely estimated[2] conc.	% Theory[3] (mcg/ml)
1	1.00	0.068	0.98	97.64
2	2.00	0.122	1.96	97.91
3	3.00	0.178	2.98	99.21
4	4.00	0.237	4.05	101.23
5	6.00	0.351	6.12	102.03
6	8.00	0.460	8.10	101.30
7	10.00	0.572	10.14	101.40
8	15.00	0.825	14.74	98.27
9	20.00	1.118	20.07	100.34
			MEAN	99.92
			S.D.	1.60
			C.V.[4]	1.60%

1. $r^2 = 0.9996$

2. Inversely estimated concentration $= \frac{\text{Absorbance}-0.0143}{0.0550}$

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

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

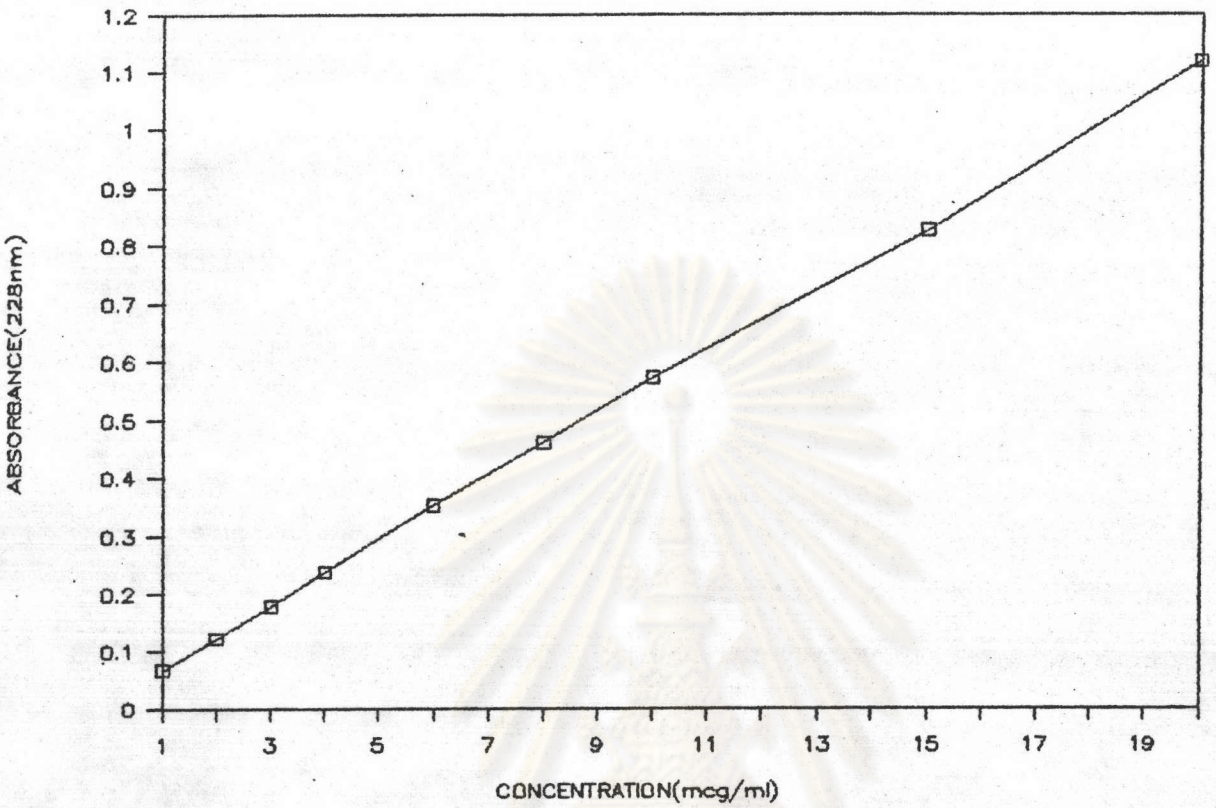

Figure 14 Typical Standard Curve for Ranitidine Hydrochloride Concentration in Simulated Gastric Fluid pH 1.2

Table 33 Typical Standard Curve Data for Ranitidine Hydrochloride Concentrations in Simulated Intestinal Fluid pH 7.5. Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 228 nm.	Inversely estimated[2] conc.	% Theory[3] (mcg/ml)
1	1.00	0.047	0.98	98.66
2	2.00	0.092	1.99	99.66
3	3.00	0.135	2.96	98.51
4	4.00	0.182	4.01	100.17
5	6.00	0.275	6.09	101.45
6	8.00	0.362	8.03	100.42
7	10.00	0.455	10.11	101.14
8	15.00	0.662	14.74	98.30
9	20.00	0.903	20.14	100.68
			MEAN	99.89
			S.D.	1.11
			C.V.[4]	1.11%

1. $r^2 = 0.9997$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0029}{0.0447}$

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

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

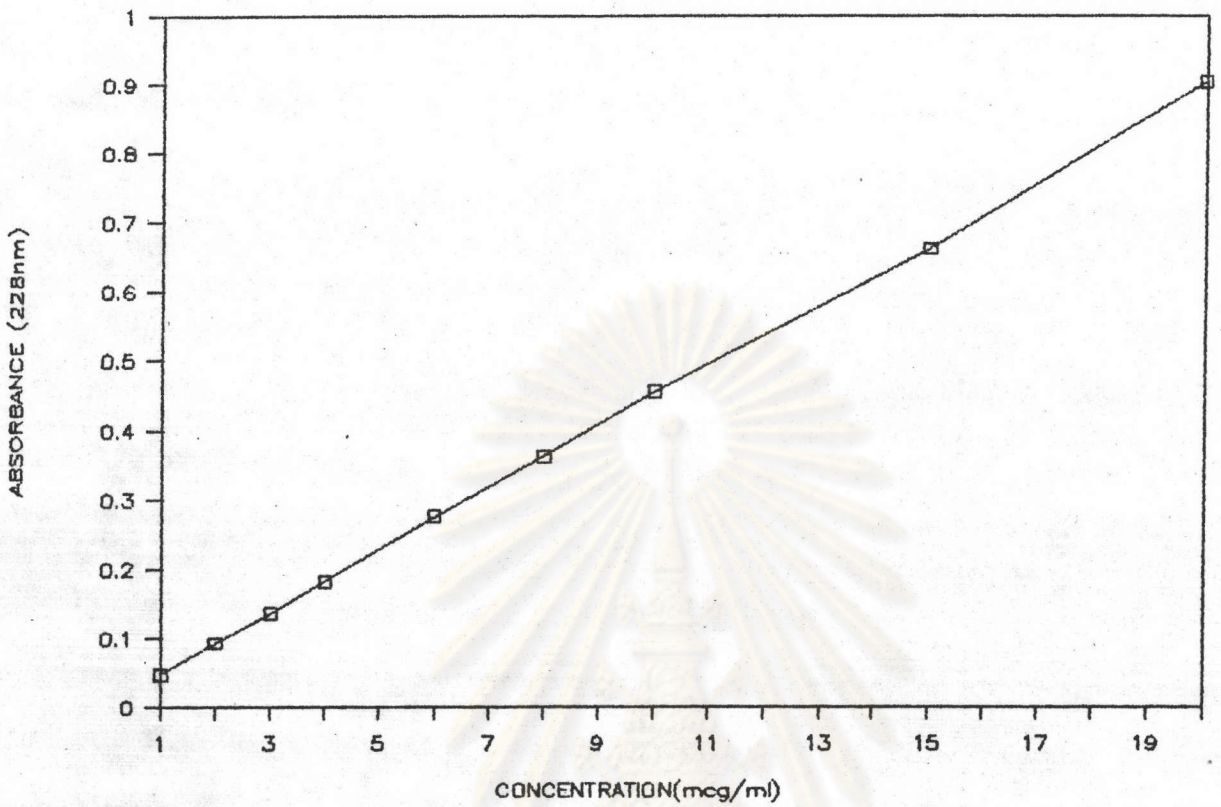

Figure 15 Typical Standard Curve for Ranitidine Hydrochloride Concentration in Simulated Intestinal Fluid pH 7.5

Table 34 Typical Standard Curve Data for Ranitidine Hydrochloride Concentrations in Pooled Human Plasma. Estimated Using Linear Regression[1]

Standard No.	Conc. (ng/ml)	Peak Height R^a/IS^b ratio	Inversely estimated[2] conc. (ng/ml)	% Theory[3]
1	50.00	0.2325	50.72	101.44
2	100.00	0.3600	101.72	101.72
3	200.00	0.6316	210.36	105.18
4	300.00	0.8600	301.72	100.57
5	500.00	1.3556	499.96	99.99
6	800.00	2.1418	814.44	101.81
7	1000.00	2.6591	1021.36	102.14
8	2000.00	5.1875	2032.72	101.64
			MEAN	101.81
			S.D.	1.44
			C.V.[4]	1.41%

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Peak Height Ratio} - 0.1057}{0.0025}$

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

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

a = Ranitidine HCl b = Procainamide HCl

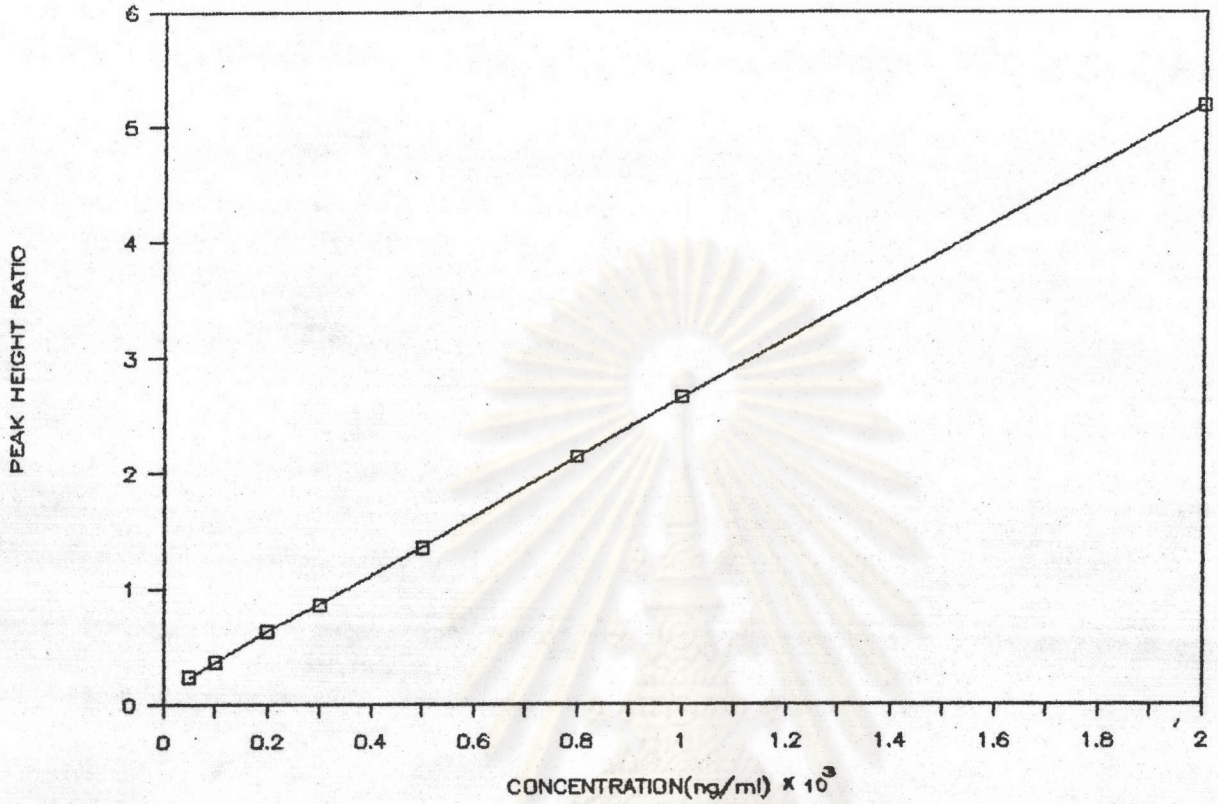

Figure 16 Typical Standard Curve for Ranitidine Hydrochloride Concentration in Pooled Human Plasma

APPENDIX C

DISSOLUTION MEDIA

Composition of two dissolution media

1. Simulated gastric fluid pH 1.2

Sodium chloride	2	gm.
Pepsin *	3.2	gm.
Hydrochloric Acid (37%)	7	ml.
Water q.s. to	1000	ml.

2. Simulated intestinal fluid pH 7.5

Monobasic Potassium Phosphate	6.8	gm.
0.2 N NaOH	190	ml.
Pancreatin *	10	gm.
Water q.s. to	1000	ml.

* Both dissolution media used in this study had no enzymes.

APPENDIX D

SUBJECTS

Table 35 Subject Demographic Data

Subject No.	Sex	Age (yr.)	Weight (kg.)	Height (cm.)
1	M	20	61	170
2	M	23	52	170
3	M	20	63	164
4	M	22	60	173
5	M	21	62	167
6	M	22	50	163
7	M	22	64	175
8	M	22	65	174
9	M	23	70	173
10	M	20	77	179
11	M	24	69	170
12	M	23	59	170
MEAN		21.8	62.7	170.7
SD.		1.3	7.1	4.4

APPENDIX E

NONCOMPARTMENT MODEL

Noncompartmental method of analysis has been used to determine certain pharmacokinetic parameters from the plasma concentration data without fitting them to any specific compartment model. These methods are usually based on the determination of the area under the drug concentration-time curves, and/or the area under the moment curves. The method can also be applied to virtually any compartment model that follows linear pharmacokinetics.

Statistical Moments :

The application of the statistical concept of moments to pharmacokinetics was reported in 1979 by Yamaoka et al. (42) and Cutler (43). In 1980, Riegelman and Collier (34) applied statistical moment theory to the evaluation of drug absorption.

Not all of the drug transitted through the body be metabolized or excreted at the same time. The individual molecules of drug will move through a body compartment, therefore the residence time of the drug in the body can be conceived as a frequency distribution with the mean and variance about the mean. Analysis of the distribution function can be made by the use of statistical moment method.

In pharmacokinetics, we have regularly measured the area under the concentration-time curve from zero time to infinity $[AUC]_0^\infty$. The area under the first moment of the curve is defined as the area under the curve of the product of time, t, and plasma concentration, Cp, from zero time to infinity $[AUMC]_0^\infty$ versus time; thus

$$[AUC]_0^\infty = \int_0^\infty C_p dt \qquad \text{Eq ....4}$$

and

$$[AUMC]_0^\infty = \int_0^\infty tC_p dt \qquad \text{Eq ....5}$$

Since it is very inconvenient to collect blood sample until there is no drug concentration be measured (at infinity time), the blood sampling is usually collected until some appropriate of time, t^*. Thus, for the determination of the area under the drug concentration curve from zero time to the last sampling time can be calculated using the trapezoidal rule, and the residual area of the curve from t^* to infinity can be determined by integrating the drug concentration from last sampling time point, t^*, to infinity. The result is as the equation 6

$$\int_{t^*}^\infty C_p dt = \frac{C^*}{Kel} \qquad \text{Eq .... 6}$$

Where C^* is the last sampling time concentration, Kel or the elimination rate constant calculated from the slope of the terminal log-linear portion of the plasma concentration-time curves. The sum of the two partial area is $[AUC]_0^\infty$.

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

$$\int_{t^*}^{\infty} tC_p dt = \frac{t^*C^*}{Kel} + \frac{C^*}{K^2el} \qquad \text{Eq .... 7}$$

Therefore:

$$[AUC]_0^\infty = \int_0^{t^*} C_p dt + \frac{C^*}{Kel} \qquad \text{Eq .... 8}$$

$$[AUMC]_0^\infty = \int_0^{t^*} tC_p dt + \frac{t^*C^*}{Kel} + \frac{C^*}{K^2el} \qquad \text{Eq .... 9}$$

The mean residence time (MRT) can be defined as the mean time for the intact drug molecules to transit through the body and involves a composite of all kinetic processes, including in vivo release from the dosage form, absorption into the body, and all disposition processes. Thus, the MRT represents the time for 63.2% of the administered dose to be eliminated by all processes.

Thus, $$MRT = \frac{[AUMC]_0^{\infty}}{[AUC]_0^{\infty}} \qquad \text{Eq ... 10}$$

The MRT of a drug after IV bolus administration provides a useful estimate of the persistent time in the body that is a close relative to the parameter termed half-life. It can be shown that

$$t_{1/2} = 0.693\ MRT_{i.v.} \qquad \text{Eq .... 11}$$

The MRT for the noninstantaneous input (n.i.v.) involves a mean absorption time (MAT), and can be defined as follows :

$$MRT_{n.i.v.} = MAT + MRT_{i.v.} \qquad \text{Eq .... 12}$$

The term MAT is used to refer to the mean time involved in the in vivo release and absorption processes as they occur in the input compartment. When the absorption is first order process MAT can be defined as follows :

$$MAT = \frac{1}{Ka} \qquad \text{Eq .... 13}$$

Where Ka is the apparent first order absorption rate constant.

Therefore, Moment analysis and the concept of MRT are much useful for comparing the absorption characteristics of a drug from different formulations.

Bioavailability :

Bioavailability is usually referred to as the fraction (F) of an oral dose that actually reaches the systemic circulation. F can be calculated as follows :

$$F = \frac{[AUC_{oral}]_0^{\infty}}{[AUC_{intravenous}]_0^{\infty}} \times \frac{Dose_{intravenous}}{Dose_{oral}} \quad \text{Eq .... 14}$$

Equation 14 assumes equal clearances in the oral and intravenous studies. The fraction of the oral dose available relatively to a standard other than an intravenous injection (Frel) may be estimated by means of a similar equation

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. Testing the Difference of Two Means

(by T - test)

Let μ_1 , μ_2 = Population means

X_1 , X_2 = Sample means

$_1 , _2$ = Population means

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 sive 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 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.

3.1 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. :

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

3.2 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

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

with degree of freedom, d.f. :

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

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

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.

4. Correlation Coefficient Test

The correlation coefficient is a quantitative measure of the relationship of correlation between two variable (X and Y)

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

where r = Correlation coefficient

N = the number of X, Y pairs

Test of Zero Correlation

Let ρ = the true correlation coefficient, estimated by r

The null hypothesis $H_o : \rho = 0$

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

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

The value of t is refered to a t distribution with (n-2) degree of freedom. If the 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-group (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-group (Error)	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - X_{.j})^2$	N-k	$\frac{SS_{within}}{N-k}$	
Total	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - X_{..})^2$	N-1		

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

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

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

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

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

$$T.. = \sum_{j=1}^{k} T._{j}$$

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

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

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 (39).

VITAE

Miss Suhoung Thitisatthayakorn was born on January 15 th, 1957, in Bangkok. She obtained her degree in Bachelor of Science in Pharmacy (Second Class Honour), Chulalongkorn University, in the year 1980.

She is now working as senior food and drug specialist at Food and Drug Administration, Ministry of Public Health, Bangkok Thailand.