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APPENDICES

APPENDIX A

Solubility of Hydrochlorothiazide in Various Solvents

Table 31 Solubility of Hydrochlorothiazide in Aqueous Solutions (14).

Solvent	Temperature (° C)	pH of the solution	Solubility g in 100 ml solution
water	25	7.2	60.9x10 ⁻³
water	37	7.2	108 x10 ⁻³
0.9% NaCl	25	6.1	59.4x10 ⁻³
0.1N NaCl	25	1.0	60.8x10 ⁻³
0.1N acetic acid	25	2.9	63.6x10 ⁻³
0.1N acetic buffer pH 4.4	25	4.5	62.3x10 ⁻³
0.067 M phosphate buffer pH 7.4	25	7.4	61.6x10 ⁻³
0.05 M borate buffer pH 9.0	25	8.9	103 x10 ⁻³
1 M ammonia		11.6	2.2
0.1 N NaOH	25	10.2	1.79
simulated gastric fluid pH 1.1	37	1.1	108 x10 ⁻³
simulated intestinal fluid pH 7.4	37	7.5	109 x10 ⁻³

Table 32 Solubility of Hydrochlorothiazide in Non Aqueous Solvents
(14).

Solvent	Temperature (°C)	Solubility g in 100 ml solution
acetone	25	13.7
acetic acid	25	0.15
acetonitrile	25	2.0
ethylacetate	25	0.59
chloroform	23	0.1
ethanol (96%)	23	1.3-1.4
methanol	23	3.9-4.1
dichloromethane	23	<0.02

APPENDIX B

Statistics

1. Mean (\bar{X})

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

2. Standard Deviation (S.D.)

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

3. Analysis of Variance (ANOVA)

Source of Variation	d.f.	SS	MS	VR
Among groups (Treatment)	k-1	SS _{among}	MS _{among} = SS _{among} / (k-1)	VR = $\frac{\text{MS}_{\text{among}}}{\text{MS}_{\text{within}}}$
Within groups (Error)	N-k	SS _{within}	MS _{within} = SS _{within} / (N-k)	
Total	N-1	SS _{total}		

d.f. = degree of freedom

SS = Sum of Squares

$$SS_{\text{among}} = \sum_{j=1}^k n_j (x_{.j} - x_{..})^2$$

$$SS_{\text{within}} = \sum_{j=1}^k \sum_{i=1}^k (x_{ij} - x_{.j})^2$$

$$SS_{\text{total}} = \sum_{j=1}^k \sum_{i=1}^k (x_{ij} - x_{..})^2$$

MS = Mean Square

VR = Variance Ratio

where X_{ij} = Observed Value at Treatment j
 i = 1, 2, ..., n
 j = 1, 2, ..., k

$$T_{.j} = \sum_{i=1}^{n_j} x_{ij}$$

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

$$T_{..} = \sum_{j=1}^k T_{.j}$$

$$\bar{X}_{..} = \frac{T_{..}}{N}$$

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

Comparing the VR value with the critical value F obtained from table at degree of freedom $(k-1)$ and $(N-k)$:

- If $VR > F_{(table)}$, we reject the null hypothesis that $\mu_1 = \mu_2 = \mu_3 = \dots = \mu_k$ and accept the alternative hypothesis.

- If $VR < F_{(table)}$, the null hypothesis stands.

4. Honestly Significant Difference Test (HSD Test)

$$\text{HSD} = q_{\alpha, k, N-k} \sqrt{\frac{\text{MSE}}{n}}$$

α = significant level

k = number of treatments

n = sample sizes of each treatment

MSE = mean square of error from ANOVA table

Value q obtained from table at degree of freedom k and $(N-k)$ and HSD obtained from calculation.

If the difference between treatment means (absolute value) of each pair of treatments is more than HSD value, therefore, this test finds this pair of treatments to be significantly different.

Table 33 Analysis of Variance for Dissolution Rate Constants of HCTZ-PVP K-17 Coprecipitates with Various HCTZ:PVP K-17 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:10, 1:20).

Source of Variation	df	SS	MS	VR
Treatment	6	2.0546	0.3424	169.3392
Error	14	0.0283	0.0020	
Total	20	2.0829		

$$F_{0.05(6,14)} = 2.85$$

$$p\text{-value} = 0$$

Table 34 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 minutes of HCTZ-PVP K-17 Coprecipitates with Various HCTZ-PVP K-17 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:5, 1:10 and 1:20).

Source of Variation	df	SS	MS	VR
Treatment	7	21622.60	3088.94	411.8859
Error	16	119.99	7.4995	
Total	23	21742.59		

$$F_{0.05(7,16)} = 2.66$$

$$p \text{ value} = 0$$

Table 35 Analysis of Variance for Dissolution Rate Constants of HCTZ-PVP K-30 Coprecipitates with Various HCTZ:PVP K-30 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:5, 1:10 and 1:20).

Source of Variation	df	SS	MS	VR
Treatment	7	2.3946	0.3421	329.3736
Error	16	0.0166	0.0010	
Total	23	2.4112		

$$F_{0.05(7,16)} = 2.66$$

$$p\text{-value} = 0$$

Table 35 Analysis of Variance for Dissolution Rate Constants of HCTZ-PVP K-30 Coprecipitates with Various HCTZ:PVP K-30 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:5, 1:10 and 1:20).

Source of Variation	df	SS	MS	VR
Treatment	7	2.3946	0.3421	329.3736
Error	16	0.0166	0.0010	
Total	23	2.4112		

$$F_{0.05(7,16)} = 2.66$$

$$p\text{-value} = 0$$

Table 36 Analysis of Variance for Dissolution Rate Constants of HCTZ-PVP K-90 Coprecipitates with Various HCTZ:PVP K-90 Ratios (1:0, 2:1, 1:1, 1:2, 1:3, 1:4).

Source of Variation	df	SS	MS	VR
Treatment	5	0.1495	0.0299	19.0944
Error	12	0.0188	0.0016	
Total	17	0.1683		

$$F_{0.05(5,12)} = 3.11$$

$$p\text{-value} = 0.0001$$

Table 37 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:5 HCTZ-PVP K-17, 1:5 HCTZ-PVP K-30 and 1:1 HCTZ-PVP K-90 Coprecipitates.

Source of Variation	df	SS	MS	VR
Treatment	2	3519.9920	1759.9960	117.9680
Error	6	89.5156	14.9193	
Total	8	3609.5076		

$$F_{0.05(2,6)} = 5.14$$

$$p\text{-value} = 0.0001$$

Table 38 Analysis of Variance for Dissolution Rate Constants of HCTZ-PEG 4000 Melts with Various HCTZ:PEG 4000 Ratios (1:0, 1:10, 1:20).

Source of Variation	df	SS	MS	VR
Treatment	2	0.9573	0.4786	166.8989
Error	6	0.0172	0.0029	
Total	8	0.9745		

$$F_{0.05(2,6)} = 5.14$$

$$p\text{-value} = 0.0001$$

Table 39 Analysis of Variance for Dissolution Rate Constants of HCTZ-PEG 6000 Melts with Various HCTZ:PEG 6000 Ratios (1:0, 1:5, 1:10, 1:20).

Source of Variation	df	SS	MS	VR
Treatment	3	1.5621	0.5207	123.4323
Error	8	0.0337	0.0042	
Total	11	1.5958		

$$F_{0.05(3,8)} = 4.07$$

$$p\text{-value} = 0$$

Table 40 Analysis of Variance for Dissolution Rate Constants of HCTZ-PEG 20000 Melts with Various HCTZ:PEG 20000 Ratios (1:0, 1:5, 1:10, 1:20).

Source of Variation	df	SS	MS	VR
Treatment	3	0.0960	0.0320	38.3510
Error	8	0.0067	0.0008	
Total	11	0.1026		

$$F_{0.05(3,8)} = 4.07$$

$$p\text{-value} = 0.0002$$

Table 41 Analysis of Variance for Dissolution Rate Constants of 1:10 HCTZ-PEG 4000, 1:10 HCTZ-PEG 6000, and 1:10 HCTZ-PEG 20000 Melts.

Source of Variation	df	SS	MS	VR
Treatment	2	0.8401	0.4200	86.3683
Error	6	0.0292	0.0049	
Total	8	0.8639		

$$F_{0.05(2,6)} = 5.14$$

$$p\text{-value} = 0.0002$$

Table 42 Analysis of Variance for Dissolution Rate Constants of Pure HCTZ and 1:1 HCTZ-Urea Melt.

Source of Variation	df	SS	MS	VR
Treatment	1	0.0002	0.0002	17.1023
Error	4	4.8×10^{-5}	1.2×10^{-5}	
Total	5	0.0002		

$$F_{0.05(1,4)} = 7.71$$

$$p\text{-value} = 0.0155$$

Table 43 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 Minutes of HCTZ-Urea Melts with Various HCTZ:Urea Ratios (1:0, 1:1, 1:2, 1:3, 1:5, 1:10, 1:20).

Source of Variation	df	SS	MS	VR
Treatment	6	15391.14	2565.19	1617.46
Error	14	22.2031	1.5859	
Total	20	15413.34		

$$F_{0.05(6,14)} = 2.85$$

$$p\text{-value} = 0$$

Table 44 Analysis of Variance for Dissolution Rate Constants of HCTZ-Urea Coprecipitates with Various HCTZ:Urea Ratios (1:0, 1:1, 1:3, 1:5, 1:10).

Source of Variation	df	SS	MS	VR
Treatment	4	0.1223	0.0306	269.99
Error	10	0.0011	0.0001	
Total	14	0.1234		

$$F_{0.05(4,10)} = 3.48$$

$$p\text{-value} = 0$$

Table 45 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:3 HCTZ-Urea Melt, 1:3 HCTZ-Urea Coprecipitate and 1:20 HCTZ-Urea Coprecipitate.

Source of Variation	df	SS	MS	VR
Treatment	2	1052.3590	526.1797	227.5372
Error	6	13.875	2.3125	
Total	8	1066.2340		

$$F_{0.05(2,6)} = 5.14$$

$$p\text{-value} = 0.0001$$

Table 46 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:5 HCTZ-PVP K-17 Coprecipitate, 1:10 HCTZ-PEG 4000 Melt and 1:3 HCTZ-Urea Melt.

Source of Variation	df	SS	MS	VR
Treatment	2	63.9922	31.9961	38.2162
Error	6	5.0234	0.8372	
Total	8	69.0156		

$$F_{0.05(2,6)} = 5.14$$

$$p\text{-value} = 0.0008$$

Table 47 Analysis of Variance for Dissolution Rate Constants of Pure HCTZ, 1:5 HCTZ-PVP K-17, 1:5 HCTZ-PVP K-30, 1:1 HCTZ-PVP K-90, 1:10 HCTZ-PEG 4000, 1:10 HCTZ-PEG 6000, 1:10 HCTZ PEG 20000, and 1:3 HCTZ-Urea Physical Mixtures.

Source of Variation	df	SS	MS	VR
Treatment	7	0.0002	2.6×10^{-5}	2.9088
Error	16	0.0001	9.1×10^{-6}	
Total	23	0.0003		

$$F_{0.05(7,16)} = 2.66$$

$$p\text{-value} = 0.0362$$

Table 48 Analysis of Variance for Percentage Labeled Amount of Pure Drug after Storage under Various Conditions (0 day, Dry Storage, 10 and 30 days, Accelerated Storage 10 and 30 days, and Moist Storage 5, 10, 20, and 30 days).

Source of Variation	df	SS	MS	VR
Treatment	8	0.1719	0.02148	0.2292
Error	9	0.8438	0.09375	
Total	17	1.0157		

$$F_{0.05(8,9)} = 3.23$$

$$p\text{-value} = 0.9747$$

Table 49 Analysis of Variance for Percentage HCTZ Labeled Amount of 1:3 HCTZ-Urea Melt after Storage under Various Conditions (0 day, Dry Storage 10 and 30 days, Accelerated Storage 10 and 30 days, and Moist Storage 5, 10, 20 and 30 days).

Source of Variation	df	SS	MS	VR
Treatment	8	1.5938	0.1992	0.918
Error	9	1.9531	0.2170	
Total	17	3.5469		

$$F_{0.05(8,9)} = 3.23$$

$$p\text{-value} = 0.5426$$

Table 50 Analysis of Variance for Dissolution Rate Constants of Pure Drug after Storage under Various Conditions (0 day, Dry Storage 10 and 30 days, Accelerated Storage 10 and 30 days, and Moist Storage 5, 10, 20 and 30 days).

Source of Variation	df	SS	MS	VR
Treatment	8	1.96×10^{-4}	2.45×10^{-5}	1.3029
Error	18	3.39×10^{-4}	1.88×10^{-5}	
Total	26	5.35×10^{-4}		

$$F_{0.05(8,18)} = 2.51$$

$$p\text{-value} = 0.3025$$

Table 51 Analysis of Variance for Percentage Amount of HCTZ Dissolved at 5 minutes of 1:3 HCTZ-Urea Melt with Various Storage Conditions (0 day, Dry Storage 10 and 30 days, Accelerated Storage 10 and 30 days, and Moist Storage 5, 10, 20 and 30 days).

Source of Variance	df	SS	MS	VR
Treatment	9	15120.36	1680.04	3238.631
Error	20	10.375	0.5188	
Total	29	15130.735		

$$F_{0.05(9,20)} = 2.39$$

$$p\text{-value} = 0$$



VITA

Miss Kawunchit Oungbho was born on September 2, 1962, in Bangkok. She got her degree in Bachelor of Science in Pharmacy (second class honour) in 1985, from Faculty of Pharmacy, Prince of Songkhla University.

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