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APPENDICES

APPENDIX A

PLURONIC F-127 AND SODIUM BISULFITE

Pluronic F-127

Pluronic F-127 or Poloxamer 407, is one of the series of poloxamer ABA block copolymers with the general formula (BASF Corporation, 1987; Gilbert, Richardson et al., 1987; Gilbert, Washington et al., 1987) :

$$H(O\text{-}CH_2\text{-}CH_2)_A\text{-}(O\text{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{-}CH_2)_B\text{-}(O\text{-}CH_2\text{-}CH_2)_A\text{-}OH$$

It contains polyoxyethylene-polyoxypropylene units (ratio 7:3) (Lenaerts et al., 1987; Miyazaki et al., 1986).

Molecular weight	:	12600
Description	:	white, waxy, free-flowing granules; practically tasteless and odourless.
Solubility	:	soluble in water and ethanol.
Melting point	:	56°C
HLB-Value	:	18-23
Use	:	Pluronic F-127 is an non-ionic surfactant. It is the most efficient gellant in the

Pluronic series (BASF Corporation, 1987). It has a high solubilizing capacity, consequently Pluronic F-127 gels have been widely studied as potential controlled release drug delivery system. (Gilbert, Richardson et al., 1987; Gilbert, Washington et al., 1987; Lenaerts et al., 1987; Miyazaki et al., 1986).

Sodium Bisulfite

Sodium bisulfite is one of sulfurous acid salts.

Chemical formula : $NaHSO_3$

Molecular weight : 104.07

Description : white crystalline powder, sulfurous odour and acid saline taste.

Solubility : soluble in water, slightly soluble in alcohol, produces solution of acidic pH (Akers, 1982; Windholz et al., eds., 1983).

Use : used as a reducing agent in pharmaceutical products e.g.,

steroids (Decadron(R)), antibiotics (Neomycin(R), Garamycin(R), Kanatrex(R), Amikin(R)), adrenergic (Neosynephrine(R), Intropin(R), Aldomet(R)), and other drugs (procainamide, dextrose, para-aminobenzoic acid, morphine) (Akers, 1982).

APPENDIX B

DETERMINATION OF NIFEDIPINE CONCENTRATIONS

Scanning curve of nifedipine solution before and after irradiation by fluorescent light and typical data for determination of nifedipine concentrations in various media were presented in Figure 10 and Table 16-20, respectively.

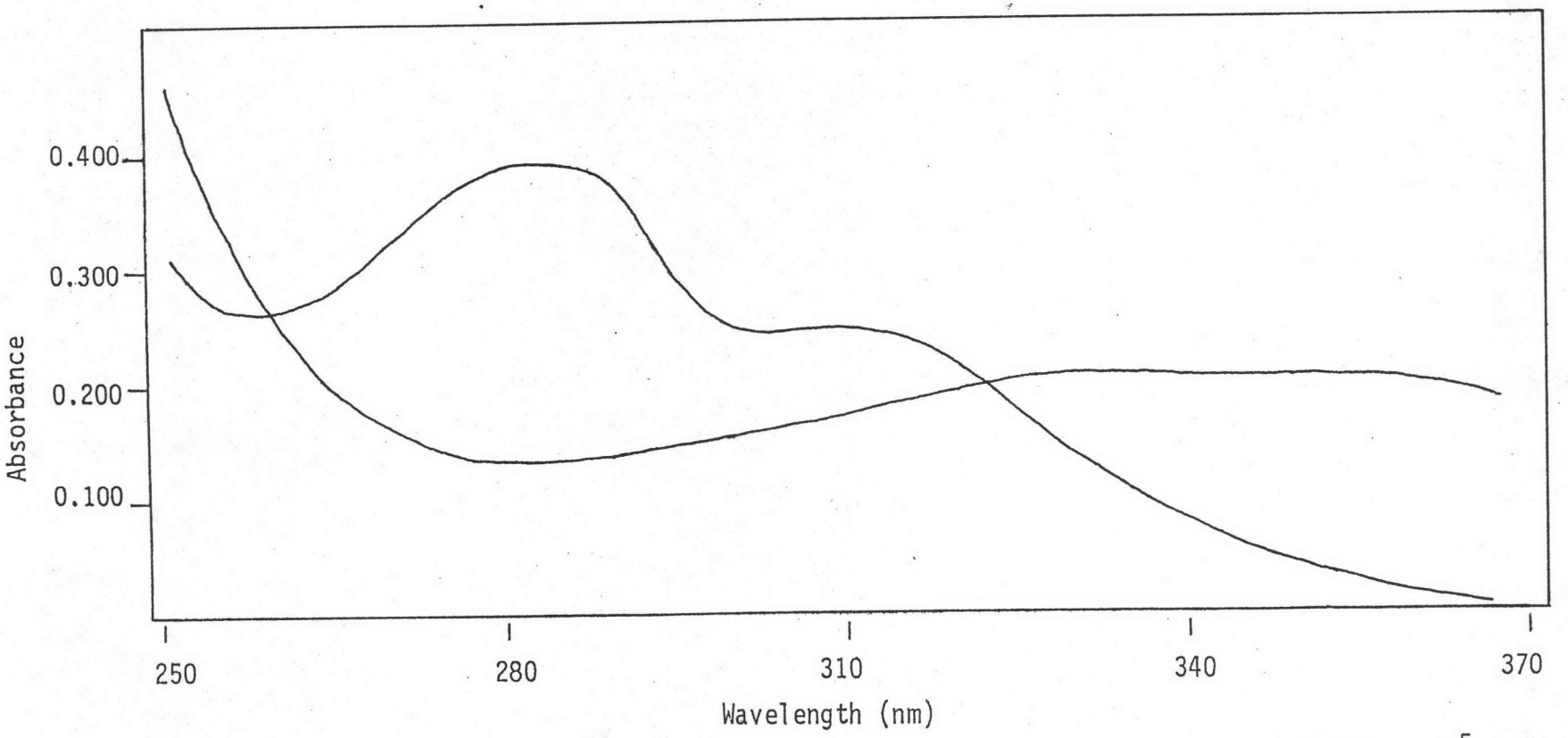

Figure 10 Scanning Curve of 50-ml Solution of Nifedipine with Concentration of 3.403×10^{-5}M in the Solution Mixture of 95% Ethanol and 0.198 g 40% w/w Pluronic F-127 Gel by UV Spectrophotometer

(a) before exposure to fluorescent light

(b) after exposure to fluorescent light for 4 hours

Table 16 Typical Data for Nifedipine in the 50-ml Solution of 0.198 g of 40% w/w Pluronic F-127 Gel in 95% Ethanol (Corresponding to Nifedipine Gel in Formulation I)

Conc.x10^{-5} (M)	Absorbance at 334 nm	Absorbance at 281 nm	Inversely Estimated Conc.x10^{-5} (M)[a]	% Theory[b]
1.701	0.127	0.083	1.751	102.93
3.403	0.212	0.137	3.473	102.05
5.671	0.303	0.195	5.315	93.72
8.506	0.483	0.311	8.950	105.21
11.341	0.571	0.368	10.725	94.56
14.178	0.756	0.488	14.455	101.95
			Mean	100.07
			S.D.	4.74
			C.V.[c]	4.73%

a Inversely estimated conc. = conc. of the reduced form of nifedipine

$$= \frac{(9293.3141 \times A_{334})-(2788.1096 \times A_{281})-298.6771}{37124381.79}$$

The equation above was obtained from :

time zero (reduced form)

at 334 nm : $y = 0.0389+4951.3791x$ $r^2 = .9932^d$

at 281 nm : $y = 0.0255+3188.6621x$ $r^2 = .9928^d$

time infinity (oxidized form)

at 334 nm : $y = 0.0194+2788.1096x$ $r^2 = .9944^d$

at 281 nm : $y = 0.0617+9293.3141x$ $r^2 = .9936^d$

b % Theory $= \frac{\text{Inversely Estimated Conc.}}{\text{Known Conc.}} \times 100$

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

d The curve was obtained from the plot of absorbances at specific wavelength versus molar concentrations of nifedipine solution, estimated using linear regression.

Table 17 Typical Data for Nifedipine in the 50-ml Solution of 0.1979 g of 40% w/w Pluronic F-127 Gel in 95% Ethanol with 0.0001 g of Sodium Bisulfite (Corresponding to Nifedipine Gel Containing Sodium Bisulfite 0.05% w/w in Formulation II)

Conc.x10^{-5} (M)	Absorbance at 334 nm	Absorbance at 281 nm	Inversely Estimated Conc.x10^{-5} (M)[a]	% Theory[b]
1.701	0.119	0.075	1.675	98.47
3.403	0.208	0.131	3.474	102.08
5.671	0.322	0.200	5.798	102.23
8.506	0.502	0.316	9.414	110.67
11.341	0.573	0.361	10.846	95.63
14.178	0.749	0.475	14.378	101.41
			Mean	101.74
			S.D.	5.06
			C.V.[c]	4.97%

a Inversely estimated conc. = conc. of the reduced form of nifedipine

$$= \frac{(9327.7538 \times A_{334}) - (2817.6750 \times A_{281}) - 272.1068}{37390029.09}$$

The equation above was obtained from :

time zero (reduced form)

at 334 nm : $y = 0.0418+4959.0723x$ $r^2 = .9910^d$

at 281 nm : $y = 0.0246+3146.9124x$ $r^2 = .9910^d$

time infinity (oxidized form)

at 334 nm : $y = 0.0177+2817.6750x$ $r^2 = .9904^d$

at 281 nm : $y = 0.0758+9327.7538x$ $r^2 = .9906^d$

b % Theory $= \frac{\text{Inversely Estimated Conc.}}{\text{Known Conc.}} \times 100$

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

d The curve was obtained from the plot of absorbances at specific wavelength versus molar concentrations of nifedipine solution, estimated using linear regression.

Table 18 Typical Data for Nifedipine in the 50-ml Solution of 0.1978 g of 40% w/w Pluronic F-127 Gel in 95% Ethanol with 0.0002 g of Sodium Bisulfite (Corresponding to Nifedipine Gel Containing Sodium Bisulfite 0.10% w/w in Formulation III)

Conc.x10^{-5} (M)	Absorbance at 334 nm	Absorbance at 281 nm	Inversely Estimated Conc.x10^{-5} (M)[a]	% Theory[b]
1.701	0.122	0.078	1.722	101.23
3.403	0.208	0.133	3.450	101.38
5.671	0.323	0.207	5.757	101.51
8.506	0.500	0.320	9.316	109.52
11.341	0.575	0.369	10.815	95.36
14.178	0.755	0.485	14.425	101.74
			Mean	101.79
			S.D.	4.50
			C.V.[c]	4.42%

a Inversely estimated conc. = conc. of the reduced form of nifedipine

$$= \frac{(9249.6510 \times A_{334})-(2868.0366 \times A_{281})-269.2941}{36900292.67}$$

The equation above was obtained from :

time zero (reduced form)

at 334 nm : $y = 0.0417+4982.5974x$ $r^2 = .9920^d$

at 281 nm : $y = 0.0261+3203.2347x$ $r^2 = .9922^d$

time infinity (oxidized form)

at 334 nm : $y = 0.0186+2868.0366x$ $r^2 = .9942^d$

at 281 nm : $y = 0.0748+9249.6510x$ $r^2 = .9919^d$

b % Theory $= \frac{\text{Inversely Estimated Conc.}}{\text{Known Conc.}} \times 100$

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

d The curve was obtained from the plot of absorbances at specific wavelength versus molar concentrations of nifedipine solution, estimated using linear regression.

Table 19 Typical Data for Nifedipine in the 50-ml Solution of 0.1974 g of 40% w/w Pluronic F-127 Gel in 95% Ethanol with 0.0006 g of Sodium Bisulfite (Corresponding to Nifedipine Gel Containing Sodium Bisulfite 0.30% w/w in Formulation IV)

Conc.x10^{-5} (M)	Absorbance at 334 nm	Absorbance at 281 nm	Inversely Estimated Conc.x10^{-5} (M)[a]	% Theory[b]
1.701	0.134	0.087	1.604	94.29
3.403	0.220	0.144	3.321	97.59
5.671	0.332	0.215	5.582	98.43
8.506	0.519	0.337	9.331	109.69
11.341	0.588	0.382	10.714	94.47
14.178	0.764	0.495	14.256	100.55
			Mean	99.17
			S.D.	5.68
			C.V.[c]	5.72%

a Inversely estimated conc. = conc. of the reduced form of nifedipine

$$= \frac{(9291.2331 \times A_{334})-(2872.8368 \times A_{281})-401.28}{37001910.4}$$

The equation above was obtained from :

time zero (reduced form)

at 334 nm : $y = 0.0543+4979.4450x$ $r^2 = .9904$[d]

at 281 nm : $y = 0.0359+3224.4344x$ $r^2 = .9904$[d]

time infinity (oxidized form)

at 334 nm : $y = 0.0306+2872.8368x$ $r^2 = .9900$[d]

at 281 nm : $y = 0.0990+9291.2331x$ $r^2 = .9904$[d]

b % Theory = $\frac{\text{Inversely Estimated Conc.}}{\text{Known Conc.}} \times 100$

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

d The curve was obtained from the plot of absorbances at specific wavelength versus molar concentrations of nifedipine solution, estimated using linear regression.

Table 20 Typical Data for Nifedipine in the 50-ml Solution of 0.197 g of 40% w/w Pluronic F-127 Gel in 95% Ethanol with 0.001 g of Sodium Bisulfite (Corresponding to Nifedipine Gel Containing Sodium Bisulfite 0.50% w/w in Formulation V)

Conc.x10^{-5} (M)	Absorbance at 334 nm	Absorbance at 281 nm	Inversely Estimated Conc.x10^{-5} (M)[a]	% Theory[b]
1.701	0.131	0.083	1.744	102.52
3.403	0.211	0.132	3.396	99.79
5.671	0.323	0.206	5.665	99.89
8.506	0.507	0.325	9.414	110.67
11.341	0.574	0.368	10.782	95.07
14.178	0.751	0.482	14.392	101.50
			Mean	101.57
			S.D.	5.13
			C.V.[c]	5.05%

a Inversely estimated conc. = conc. of the reduced form of nifedipine

$$= \frac{(9252.3860 \times A_{334})-(2825.1298 \times A_{281})-341.6350}{36445128.55}$$

The equation above was obtained from :

time zero (reduced form)

at 334 nm : $y = 0.0498+4905.8962x$ $r^2 = .9902^d$

at 281 nm : $y = 0.0295+3166.6215x$ $r^2 = .9900^d$

time infinity (oxidized form)

at 334 nm : $y = 0.0212+2825.1298 \times$ $r^2 = .9900^d$

at 281 nm : $y = 0.0821+9252.3860 \times$ $r^2 = .9900^d$

b % Theory $= \frac{\text{Inversely Estimated Conc.}}{\text{Known Conc.}} \times 100$

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

d The curve was obtained from the plot of absorbances at specific wavelength versus molar concentrations of nifedipine solution, estimated using linear regression.

APPENDIX C

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. Testing the difference of two means, Student's t-test is used.

μ_1, μ_2 = Population means

x_1, x_2 = Sample means

σ_1, σ_2 = Polulation variances

N_1, N_2 = Sample size

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

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

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

3.1 If $\sigma_1^2 \neq \sigma_2^2$,

$$t = \frac{\bar{x}_1 - \bar{x}_2}{S_p}$$

where S_p^2 = pooled variance

$$S_p^2 = \frac{(S_1)^2}{N_1} + \frac{(S_2)^2}{N_2}$$

with the degree of freedom, df :

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

3.2 If $\sigma_1^2 = \sigma_2^2$,

$$t = \frac{\bar{x}_1 - \bar{x}_2}{S_p}$$

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

with the degree of freedom, df :

$$df = N_1 + N_2 - 2$$

This t-value is compared with $t_{(tab)}$ which is obtained from the table.

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. Analysis of variance (ANOVA)

ANOVA TABLE

Source of Variation	df	Sum of Square	Mean Square	Variance Ratio
Among Groups	k-1	$\sum_{j=1}^{k} n_j (x_{.j}-x_{..})^2$	$\frac{SS_{among}}{k-1}$	V.R. = $\frac{MS_{among}}{MS_{within}}$
Within Group	N-k	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (x_{ij}-x_{.j})^2$	$\frac{SS_{within}}{N-k}$	
Total	N-1	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (x_{ij}-x_{..})^2$		

where x_{ij} = observed value i at treatment j

$i = 1,2,.....,n$

$j = 1,2,.....,k$

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

$$x_{.j} = \frac{T_{.j}}{n_j}$$

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

$$x_{..} = \frac{T_{..}}{N}$$

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

In this study "k" represents number of formulations studied

"N" represents total number of samples

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.

5. Duncan's New Multiple Range Test

If the alternative hypothesis from 4 is accepted, Duncan's New Multiple Range Test is used to test the difference between means of two formulations.

$$S_{\bar{x}} = \sqrt{MS_{within} / n}$$

with the degree of freedom, df = N-k

$$LSR = SSR \times S_{\bar{x}}$$

where LSR = Least significant range

SSR = Significant studentized range, obtained from the table at df = N-k

The means of all formulations are ranked from minimum to maximum, and then they were compared. If the difference between two means of each pair of formulations is more than LSR, this pair is decided to be significantly different.

6. Correlation Coefficient Test

The correlation coefficient is a quantitative measure of the relationship of correlation between two variables, 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 = 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 $H_o : \rho = o$

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

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

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 Khanittha Pongpaln was born on May 24, 1965 in Udornthani. She received her bachelor of Science in Pharmacy in 1988 from the Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen.