CHAPTER IV

RESULTS AND DISCUSSION

Preparation of Nifedipine - Pluronic F-127 Gel

Physical appearances of all nifedipine gel preparations were yellow according to the color of drug. The effects of the six surfactants of three concentrations to clarity, air bubble and rigidity were visually observed and showed in Table 1. All of the six surfactants had no effects to physical appearance, except 5% benzalkonium chloride. The preparation with 5% benzalkonium chloride was translucent, another preparations were transparent. All preparations had no air bubble after refrigeration. They had no residue, and no difference in rigidity was observed.

Analytical Quantitation of Nifedipine

1 Determination of the Maximum Absorption of Nifedipine

Nifedipine was dissolved in the medium with concentration of 0.05 mg/ml. The maximum absorption of nifedipine was detected at the wavelength of 332 nm. by Spectronic 2000. The Pluronic F-127 did not show the absorption at this wavelength (Appendix A).

2 The Calibration Curve

The plots of nifedipine concentration versus absorbance in the medium of EtOH:PEG 400 (1:1) in Table 2, showed a linear relationship with the correlation coeffient of 0.9997. The calibration curve of nifedipine after regression analysis was illustrated in Figure 11. The analysis of nifedipine in this investigation was leased on the measurement

Table 1 Physical Appearances of Nifedipine-Pluronic F-127 Gels Containing Various Concentrations of Surfactants

Preparations	Clarity	Air Bubble	Rigidity
0% (Control)	+	-	+
1% Brij 35	+	-	+
3% Brij 35	+	-	+
5% Brij 35	+	-	+
1% Tween 80	+	-	+
3% Tween 80	+	-	+
5% Tween 80	+	-	+
1% Dioctyl Sodium Sulfosuccinate	+	-	+
3% Dioctyl Sodium Sulfosuccinate	+	-	+
5% Dioctyl Sodium Sulfosuccinate	+	-	+
1% Sodium Lauryl Sulfate	+	-	+
3% Sodium Lauryl Sulfate	+	-	+
5% Sodium Lauryl Sulfate	+	-	+
1% Benzalkonium Chloride	+	-	+
3% Benzalkonium Chloride	+	-	+
5% Benzalkonium Chloride	-	-	+
1% Chlorhexidine Diacetate	+	-	+
3% Chlorhexidine Diacetate	+	-	+
5% Chlorhexidine Diacetate	+	-	+

a clarity : (+) = transparent, (-) = translucent

b air bubble : (+) = with, (-) = without

c rigidity : (+) = rigid, (-) = liquefied

Table 2 Calibration Data of Nifedipine in 1:1 Ethanol : PEG 400 at 332 nm.

Concentration (mcg./ml.)	Absorbance	Inversely Estimate Conc. (mcg./ml.)	% Theory
0.00	0.000	0.00	100.00
10.01	0.139	9.93	99.19
20.02	0.286	20.43	102.05
30.03	0.417	29.79	99.19
40.04	0.552	39.43	98.48
50.05	0.702	50.13	100.19
60.06	0.851	60.79	101.21
70.07	0.976	69.72	99.50
		Mean	99.98
		S.D.	1.0935
		%C.V.	1.0938

a avearage of three determinations

b Inversely Estimate Concentration = (Absorbance + 0.00009166)/0.01402

c % Theory = (Inversely Estimated Conc./Known Conc.)x100

d %C.V. = (S.D./Mean) x 100

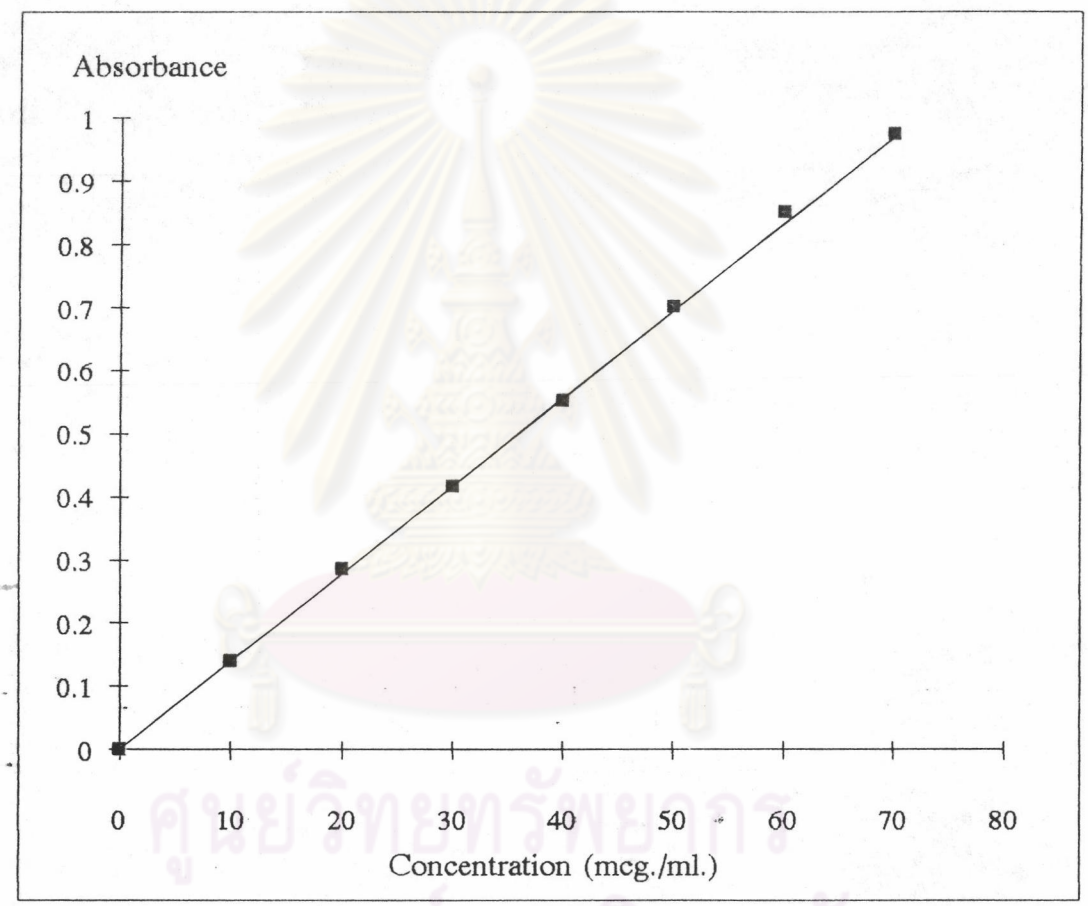

Figure 11 Calibration Curve of Nifedipine in 1:1 Ethanol : PEG 400

of absorbance value at 332 nm. The concentration of nifedipine was then calculated by using equation from calibration curve.

Study of Nifedipine Release from Pluronic F-127 Gel

Amount of nifedipine and percentage labeled amounts of all preparations of nifedipine gels were shown in Table 3. In this study, nifedipine gel without surfactants was compared with other formulations as control. The average percentage of the drug release versus time profile of preparations containing six surfactants were shown in Table 4 to 9 and Figure 12 to 17 respectively. For 24 hours, the control preparations with no surfactants presented the percentage of drug release about 33%.

From Table 4, the percentage of nifedipine release from the preparations containing 1%W/W Brij 35 was 33.35% at 24 hours. The preparations containing 3% and 5% W/W Brij 35 released nifedipine at 24 hours 36.39% and 38.79% respectively. Table 5 showed the percentage of nifedipine release at 24 hours from preperations containing of 1%, 3% and 5% W/W Tween 80 were 34.42%, 37.43 and 37.39% respectively. These percentages of drug release, both Brij 35 and Tween 80, had no statistically significant differences from the control ($P > 0.01$). The effect of nonionic surfactants in this study was similar to Tween 20. It had no effect on the permeation of naloxone [Aungst, B. J., Rogers, N.J., and Shefter, E., 1986]. But, naproxen was enhanced the percutaneous absorption by Tween 60 [Chowhan, Z.T. and Pritchard, R., 1978]. The skin penetration rate of chloramphenicol was increased by Tween 80 at concentrations of 0.5% and 1%, but at lower concentration caused a slight reduction [Aguiar, A.J. and Weiner, M.A., 1969]. The mode of action of nonionic surfactants was the ability to partition into the intercellular lipid

Table 3 Amounts of Nifedipine and % Labeled Amounts of Nifedipine Preparations

Preparations	Amount of Nifedipine (mg./g.)	% Labeled Amount
0% (Control)	10.09 [a] (0.11)	100.91 [a] (1.05)
1% Brij 35	10.23 (0.15)	102.31 (1.52)
3% Brij 35	10.08 (0.13)	100.82 (1.28)
5% Brij 35	10.05 (0.11)	100.53 (1.13)
1% Tween 80	10.10 (0.10)	101.04 (0.98)
3% Tween 80	9.99 (0.13)	99.87 (1.34)
5% Tween 80	10.06 (0.08)	100.63 (0.75)
1% Dioctyl Sodium Sulfosuccinate	9.98 (0.09)	99.79 (0.88)
3% Dioctyl Sodium Sulfosuccinate	10.20 (0.14)	102.01 (1.43)
5% Dioctyl Sodium Sulfosuccinate	10.03 (0.12)	100.31 (1.19)
1% Sodium Lauryl Sulfate	10.03 (0.09)	100.30 (0.88)
3% Sodium Lauryl Sulfate	10.09 (0.12)	100.91 (1.23)
5% Sodium Lauryl Sulfate	10.05 (0.06)	100.50 (0.65)
1% Benzalkonium Chloride	10.09 (0.09)	100.87 (0.85)
3% Benzalkonium Chloride	10.11 (0.08)	101.13 (0.75)
5% Benzalkonium Chloride	10.09 (0.08)	100.91 (0.82)
1% Chlorhexidine Diacetate	10.01 (0.11)	100.14 (1.09)
3% Chlorhexidine Diacetate	9.98 (0.09)	99.80 (0.87)
5% Chlorhexidine Diacetate	10.05 (0.14)	100.53 (1.39)

a = Mean (S.D.) (n=3)

Table 4 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Brij 35

Time	Percent of Nifedipine Release[b]			
(hr.)	0%	1%	3%	5%
0.5	0.26[a] (0.38)	0.31 (0.52)	0.54 (0.25)	0.46 (0.09)
1	0.91 (0.28)	1.18 (0.26)	1.57 (0.15)	1.45 (0.10)
1.5	1.71 (0.20)	1.99 (0.19)	2.45 (0.10)	2.45 (0.14)
2	2.48 (0.16)	2.77 (0.16)	3.26 (0.11)	3.33 (0.14)
3	4.05 (0.13)	4.51 (0.13)	4.92 (0.13)	5.11 (0.13)
4	5.37 (0.10)	6.01 (0.13)	6.46 (0.11)	6.65 (0.10)
5	6.06 (0.09)	7.04 (0.12)	7.71 (0.10)	8.96 (0.08)
6	7.98 (0.10)	8.76 (0.11)	9.38 (0.10)	9.99 (0.07)
8	10.03 (0.09)	12.01 (0.10)	12.33 (0.10)	12.80 (0.05)
10	12.95 (0.09)	14.38 (0.10)	14.91 (0.10)	15.66 (0.07)
12	15.26 (0.13)	16.66 (0.08)	17.34 (0.08)	18.22 (0.07)
14	17.17 (0.09)	18.57 (0.09)	19.45 (0.08)	20.79 (0.06)
16	20.26 (0.09)	21.26 (0.09)	22.75 (0.10)	23.75 (0.06)
18	22.53 (0.07)	23.50 (0.07)	25.91 (0.10)	28.08 (0.07)
20	25.46 (0.08)	27.09 (0.06)	30.14 (0.09)	31.70 (0.05)
22	29.05 (0.09)	30.36 (0.05)	32.53 (0.09)	35.25 (0.03)
24	33.67 (0.07)	33.35 (0.05)	36.39 (0.08)	38.79 (0.05)

a = Mean (S.D.) (n=6)

b = (Amount of Drug in Receptor Medium)/(Amount of Drug in Preparations)x100

Table 5 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Tween 80

Time	Percent of Nifedipine Release[a]			
(hr.)	0%	1%	3%	5%
0.5	0.26 (0.38)	0.47 (0.11)	0.44 (0.19)	0.41 (0.12)
1	0.91 (0.28)	1.27 (0.05)	1.41 (0.10)	1.33 (0.06)
1.5	1.71 (0.20)	2.11 (0.06)	2.52 (0.11)	2.50 (0.06)
2	2.48 (0.16)	2.81 (0.05)	3.38 (0.11)	3.39 (0.06)
3	4.05 (0.13)	4.14 (0.03)	4.98 (0.14)	4.93 (0.02)
4	5.37 (0.10)	5.37 (0.01)	6.50 (0.10)	6.71 (0.01)
5	6.06 (0.09)	6.80 (0.01)	8.06 (0.09)	8.01 (0.02)
6	7.98 (0.10)	7.97 (0.01)	9.32 (0.05)	9.61 (0.03)
8	10.03 (0.09)	10.81 (0.02)	12.48 (0.07)	12.56 (0.03)
10	12.95 (0.09)	13.56 (0.02)	15.06 (0.07)	15.13 (0.03)
12	15.26 (0.13)	15.96 (0.01)	18.03 (0.06)	17.70 (0.01)
14	17.17 (0.09)	18.68 (0.01)	20.38 (0.05)	19.30 (0.02)
16	20.26 (0.09)	21.90 (0.01)	23.52 (0.06)	22.41 (0.04)
18	22.53 (0.07)	24.54 (0.01)	26.49 (0.06)	26.46 (0.05)
20	25.46 (0.08)	28.41 (0.02)	29.85 (0.08)	30.84 (0.04)
22	29.05 (0.09)	31.91 (0.03)	33.78 (0.06)	33.78 (0.03)
24	33.67 (0.07)	34.42 (0.01)	37.34 (0.06)	37.39 (0.03)

a = Mean (S.D.) (n=6)

Table 6 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Sodium Lauryl Sulfate

Time	Percent of Nifedipine Release[a]			
(hr.)	0%	1%	3%	5%
0.5	0.26 (0.38)	0.18 (0.40)	0.39 (0.32)	0.30 (0.10)
1	0.91 (0.28)	0.90 (0.35)	1.17 (0.31)	1.04 (0.13)
1.5	1.71 (0.20)	1.67 (0.31)	1.86 (0.34)	2.33 (0.14)
2	2.48 (0.16)	2.52 (0.23)	2.75 (0.29)	3.48 (0.09)
3	4.05 (0.13)	3.50 (0.12)	4.65 (0.19)	6.07 (0.10)
4	5.37 (0.10)	5.30 (0.18)	6.35 (0.12)	8.27 (0.10)
5	6.06 (0.09)	6.31 (0.18)	8.17 (0.13)	10.37 (0.08)
6	7.98 (0.10)	7.81 (0.16)	10.01 (0.13)	13.06 (0.08)
8	10.03 (0.09)	9.84 (0.16)	12.82 (0.12)	17.54 (0.05)
10	12.95 (0.09)	12.10 (0.15)	16.25 (0.12)	21.75 (0.08)
12	15.26 (0.13)	14.53 (0.14)	18.69 (0.11)	25.04 (0.10)
14	17.17 (0.09)	17.16 (0.17)	21.71 (0.10)	28.29 (0.08)
16	20.26 (0.09)	20.30 (0.18)	25.17 (0.14)	31.10 (0.06)
18	22.53 (0.07)	22.60 (0.14)	27.07 (0.09)	34.91 (0.05)
20	25.46 (0.08)	24.02 (0.14)	31.05 (0.07)	37.91 (0.05)
22	29.05 (0.09)	26.86 (0.14)	34.56 (0.04)	40.49 (0.04)
24	33.67 (0.07)	28.71 (0.11)	36.51 (0.04)	42.88 (0.02)

a = Mean (S.D.) (n=6)

Table 7 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Dioctyl Sodium Sulfosuccinate

Time	Percent of Nifedipine Release[a]			
(hr.)	0%	1%	3%	5%
0.5	0.26 (0.38)	0.40 (0.28)	0.36 (0.27)	0.45 (0.19)
1	0.91 (0.28)	1.16 (0.18)	1.11 (0.16)	1.21 (0.23)
1.5	1.71 (0.20)	1.88 (0.16)	1.86 (0.16)	1.97 (0.22)
2	2.48 (0.16)	2.68 (0.13)	2.64 (0.16)	2.77 (0.22)
3	4.05 (0.13)	4.02 (0.13)	4.19 (0.14)	4.27 (0.21)
4	5.37 (0.10)	5.68 (0.10)	5.72 (0.15)	5.72 (0.20)
5	6.06 (0.09)	6.92 (0.09)	6.81 (0.21)	6.98 (0.18)
6	7.98 (0.10)	8.29 (0.11)	8.75 (0.10)	8.56 (0.16)
8	10.03 (0.09)	11.09 (0.10)	11.62 (0.09)	11.17 (0.19)
10	12.95 (0.09)	13.87 (0.11)	14.50 (0.07)	14.77 (0.14)
12	15.26 (0.13)	16.77 (0.10)	17.52 (0.10)	18.00 (0.14)
14	17.17 (0.09)	19.90 (0.12)	21.31 (0.11)	22.10 (0.12)
16	20.26 (0.09)	22.20 (0.09)	24.64 (0.09)	26.81 (0.12)
18	22.53 (0.07)	25.39 (0.08)	28.04 (0.09)	29.58 (0.12)
20	25.46 (0.08)	28.53 (0.08)	31.31 (0.08)	33.75 (0.11)
22	29.05 (0.09)	33.52 (0.04)	34.07 (0.06)	37.57 (0.10)
24	33.67 (0.07)	36.21 (0.04)	37.49 (0.05)	41.27 (0.06)

a = Mean (S.D.) (n=6)

Table 8 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Benzalkonium Chloride

Time	Percent of Nifedipine Release[a]			
(hr.)	0%	1%	3%	5%
0.5	0.26 (0.38)	0.23 (0.16)	0.43 (0.06)	0.55 (0.31)
1	0.91 (0.28)	0.99 (0.12)	1.57 (0.10)	1.87 (0.18)
1.5	1.71 (0.20)	1.88 (0.14)	2.58 (0.10)	3.16 (0.21)
2	2.48 (0.16)	2.63 (0.15)	3.47 (0.06)	4.30 (0.20)
3	4.05 (0.13)	4.28 (0.18)	5.37 (0.05)	6.70 (0.21)
4	5.37 (0.10)	5.89 (0.14)	6.75 (0.10)	9.07 (0.22)
5	6.06 (0.09)	7.40 (0.16)	8.54 (0.10)	11.49 (0.18)
6	7.98 (0.10)	9.00 (0.16)	10.05 (0.10)	13.47 (0.16)
8	10.03 (0.09)	12.24 (0.15)	12.59 (0.09)	17.32 (0.17)
10	12.95 (0.09)	14.64 (0.13)	16.25 (0.06)	21.45 (0.17)
12	15.26 (0.13)	17.42 (0.10)	18.64 (0.07)	25.07 (0.15)
14	17.17 (0.09)	20.27 (0.14)	21.59 (0.06)	27.95 (0.15)
16	20.26 (0.09)	23.01 (0.11)	23.64 (0.09)	32.25 (0.15)
18	22.53 (0.07)	25.75 (0.13)	26.71 (0.07)	35.85 (0.14)
20	25.46 (0.08)	27.82 (0.14)	28.12 (0.07)	38.81 (0.14)
22	29.05 (0.09)	30.52 (0.14)	32.14 (0.08)	42.46 (0.11)
24	33.67 (0.07)	32.76 (0.14)	35.79 (0.06)	47.17 (0.14)

a = Mean (S.D.) (n=6)

Table 9 The Average Percentage of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Chlorhexidine Diacetate

Time	Percent of Nifedipine Release[a]			
(hr.)	0%	1%	3%	5%
0.5	0.26 (0.38)	0.28 (0.30)	0.23 (0.33)	0.46 (0.20)
1	0.91 (0.28)	0.95 (0.23)	0.79 (0.18)	1.31 (0.11)
1.5	1.71 (0.20)	1.83 (0.10)	1.56 (0.08)	2.16 (0.10)
2	2.48 (0.16)	2.54 (0.10)	2.35 (0.09)	2.97 (0.09)
3	4.05 (0.13)	3.86 (0.10)	3.88 (0.09)	4.29 (0.07)
4	5.37 (0.10)	5.28 (0.08)	5.39 (0.10)	5.48 (0.07)
5	6.06 (0.09)	6.47 (0.08)	6.49 (0.09)	6.70 (0.07)
6	7.98 (0.10)	7.68 (0.09)	7.92 (0.11)	7.72 (0.06)
8	10.03 (0.09)	9.69 (0.07)	10.16 (0.11)	9.92 (0.06)
10	12.95 (0.09)	12.36 (0.08)	12.33 (0.10)	11.84 (0.05)
12	15.26 (0.13)	14.37 (0.09)	14.30 (0.11)	13.77 (0.04)
14	17.17 (0.09)	16.23 (0.09)	16.07 (0.11)	15.32 (0.07)
16	20.26 (0.09)	18.32 (0.09)	17.85 (0.13)	17.62 (0.06)
18	22.53 (0.07)	20.65 (0.07)	19.86 (0.17)	19.37 (0.06)
20	25.46 (0.08)	22.44 (0.08)	21.59 (0.17)	21.25 (0.08)
22	29.05 (0.09)	25.76 (0.09)	23.38 (0.16)	23.29 (0.05)
24	33.67 (0.07)	28.06 (0.09)	26.48 (0.18)	26.21 (0.05)

a = Mean (S.D.) (n=6)

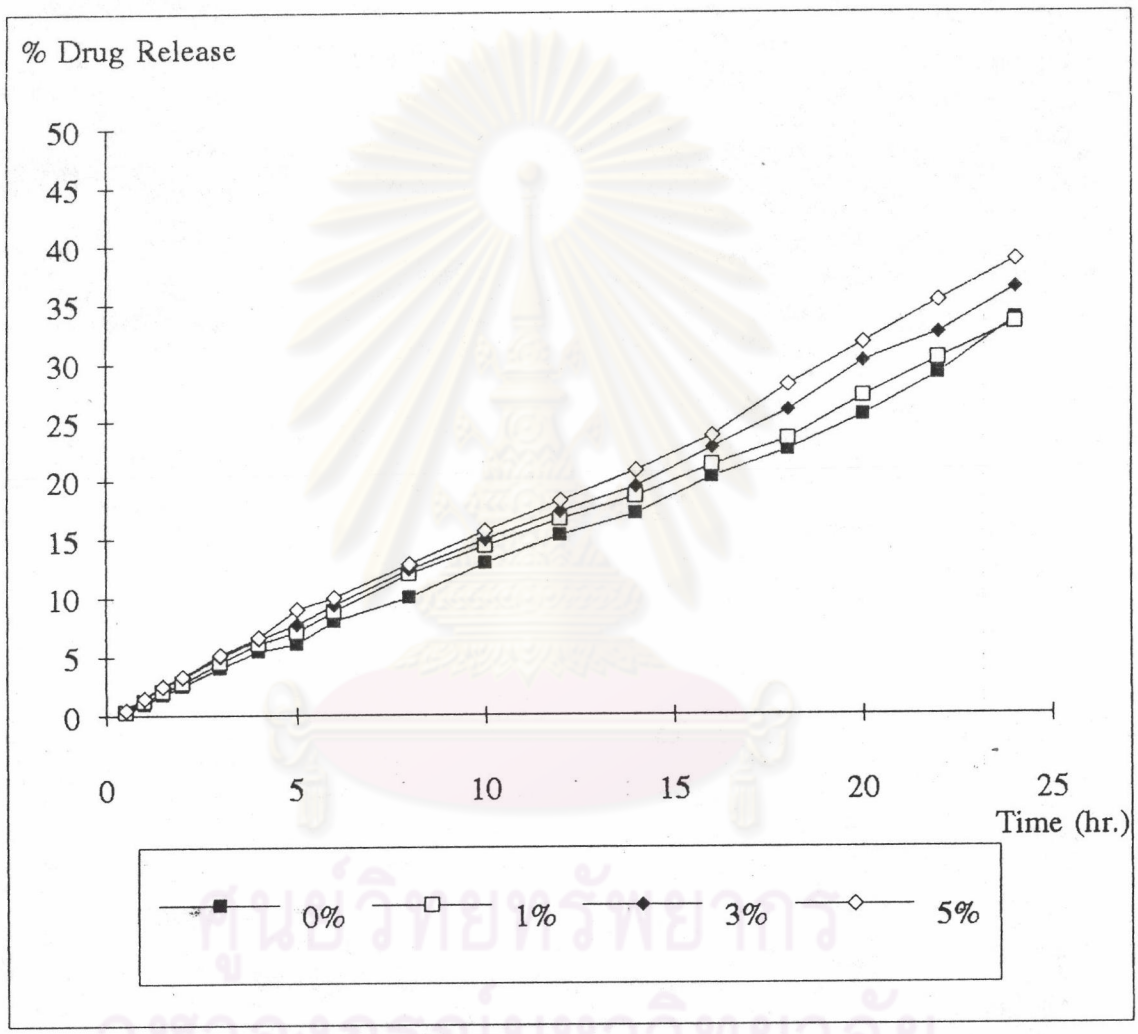

Figure 12 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Brij 35

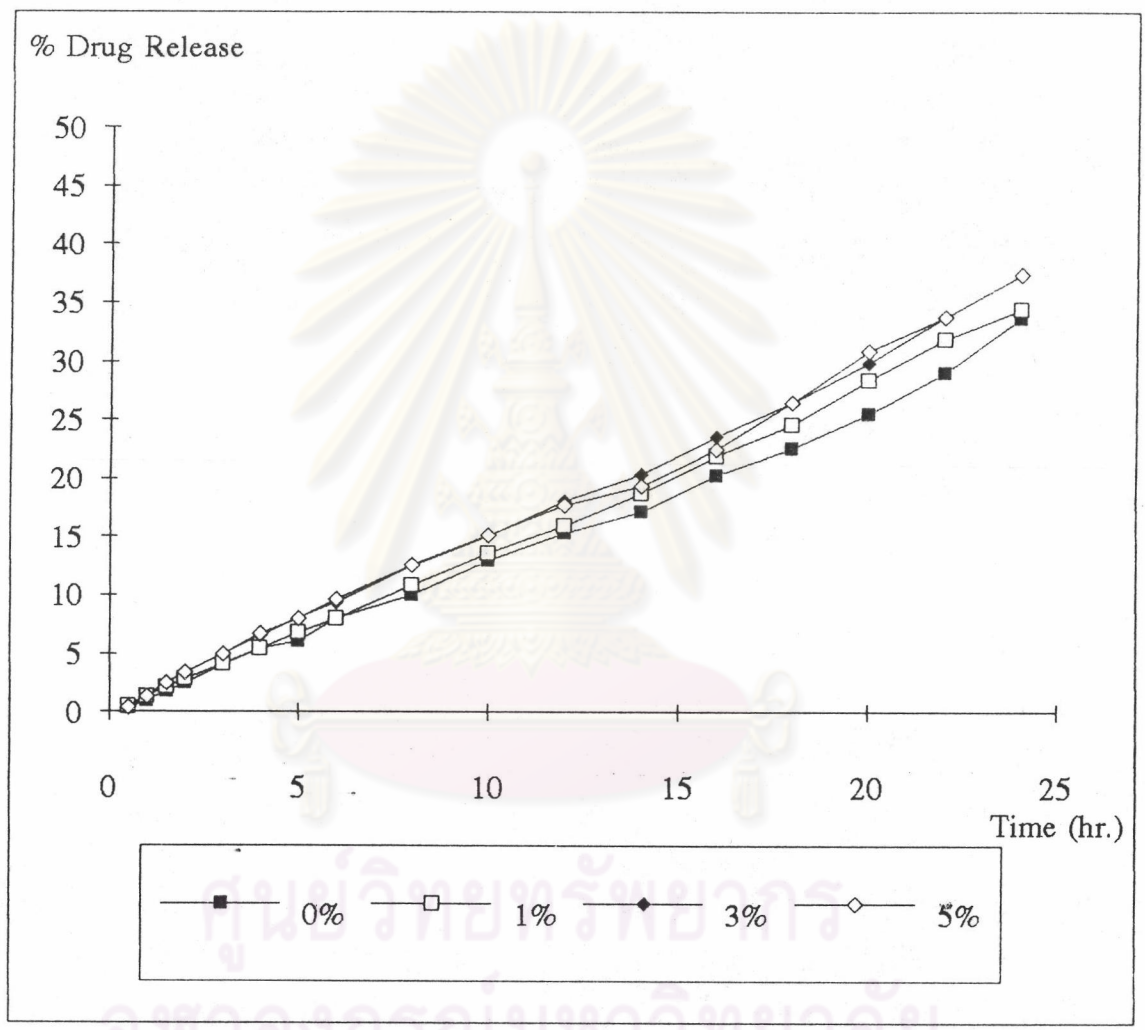

Figure 13 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Tween 80

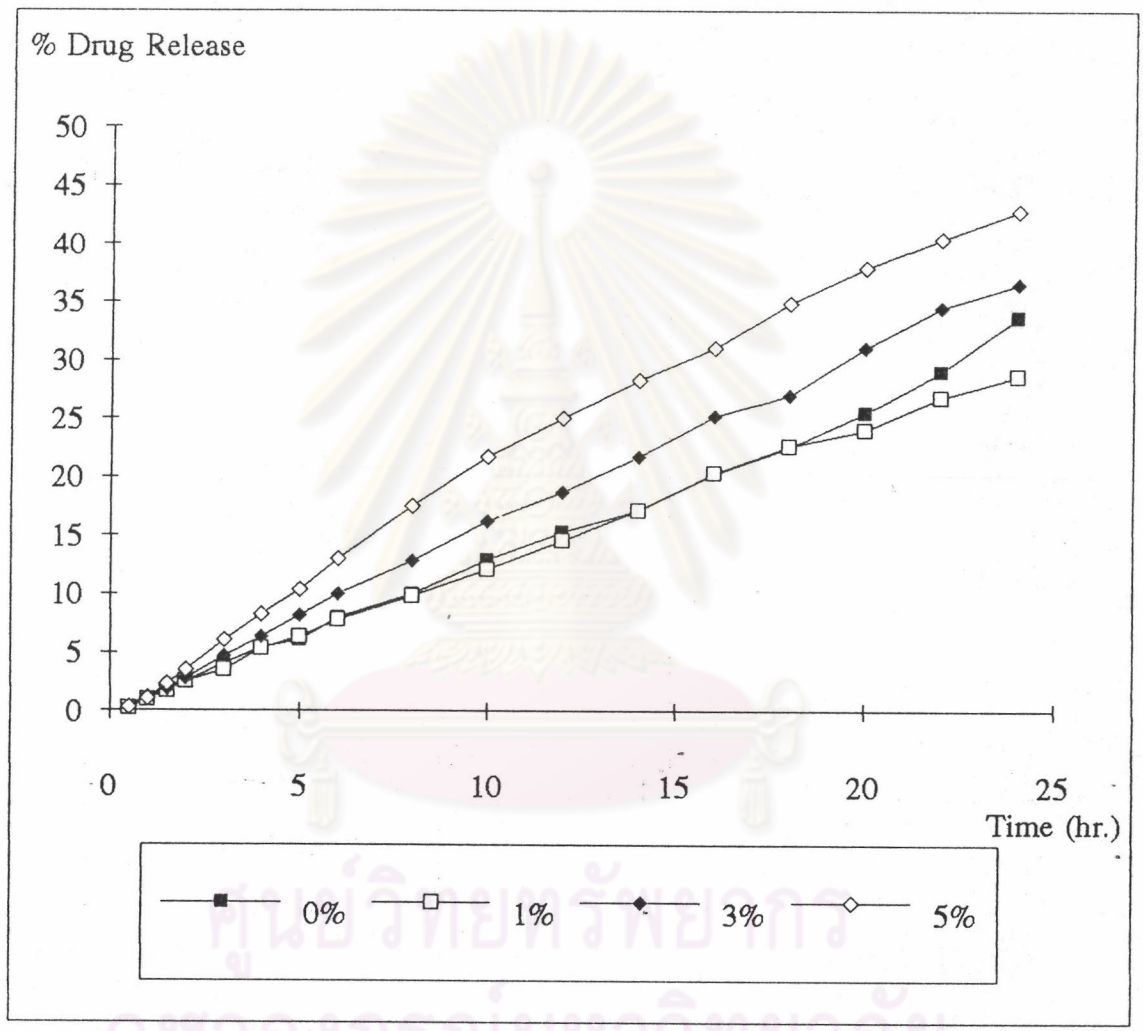

Figure 14 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Sodium Lauryl Sulfate

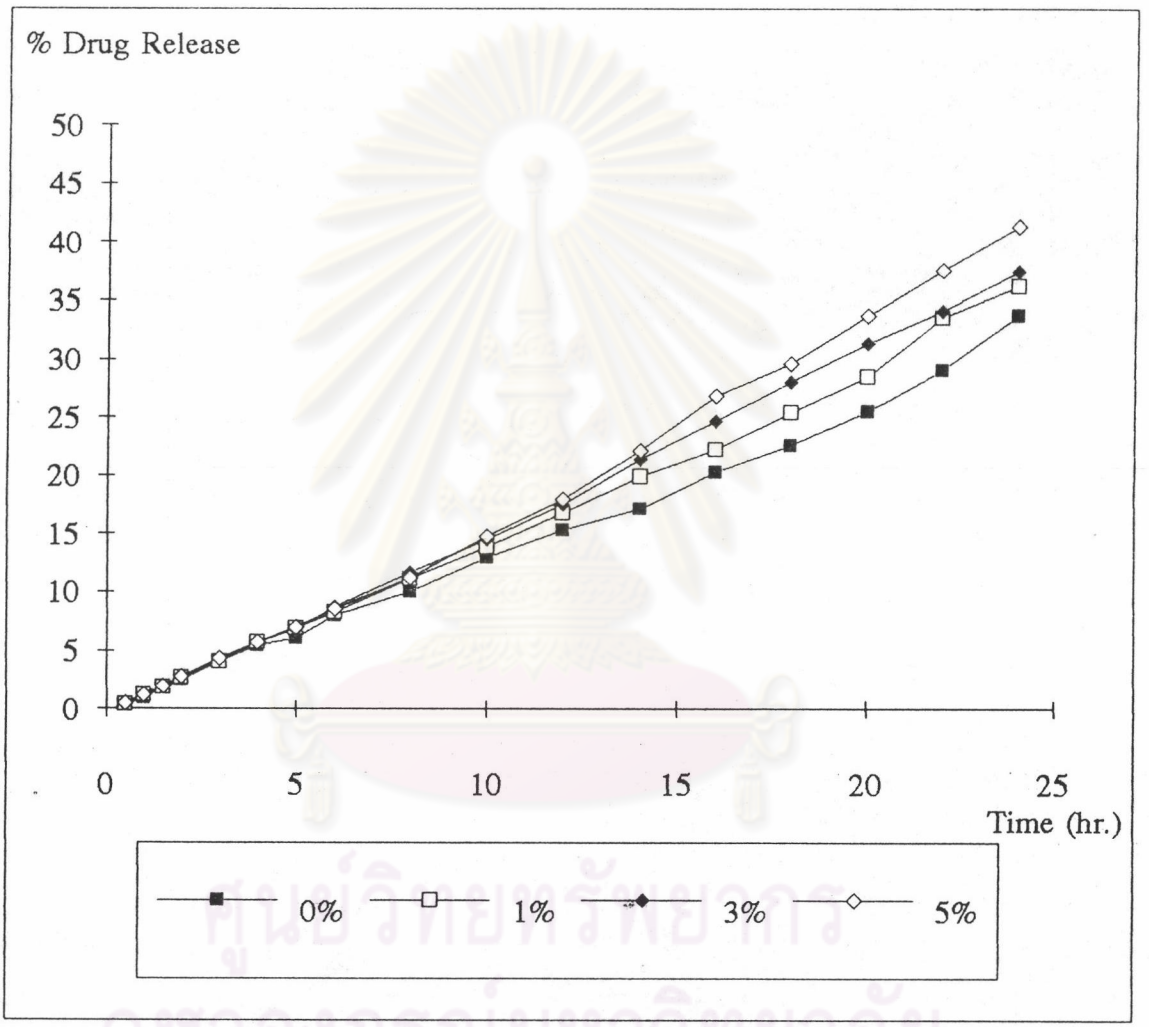

Figure 15 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Dioctyl Sodium Sulfosuccinate

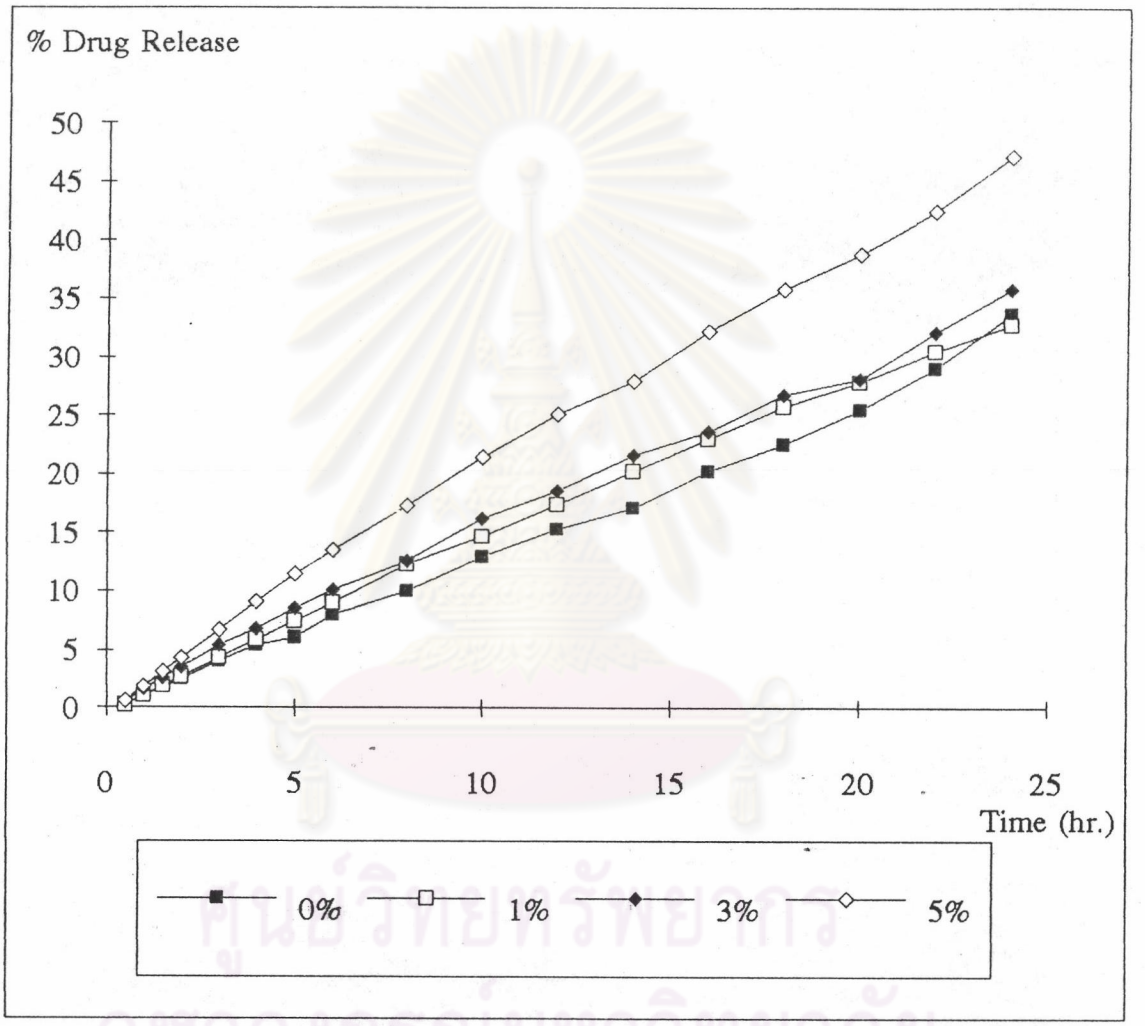

Figure 16 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Benzalkonium Chloride

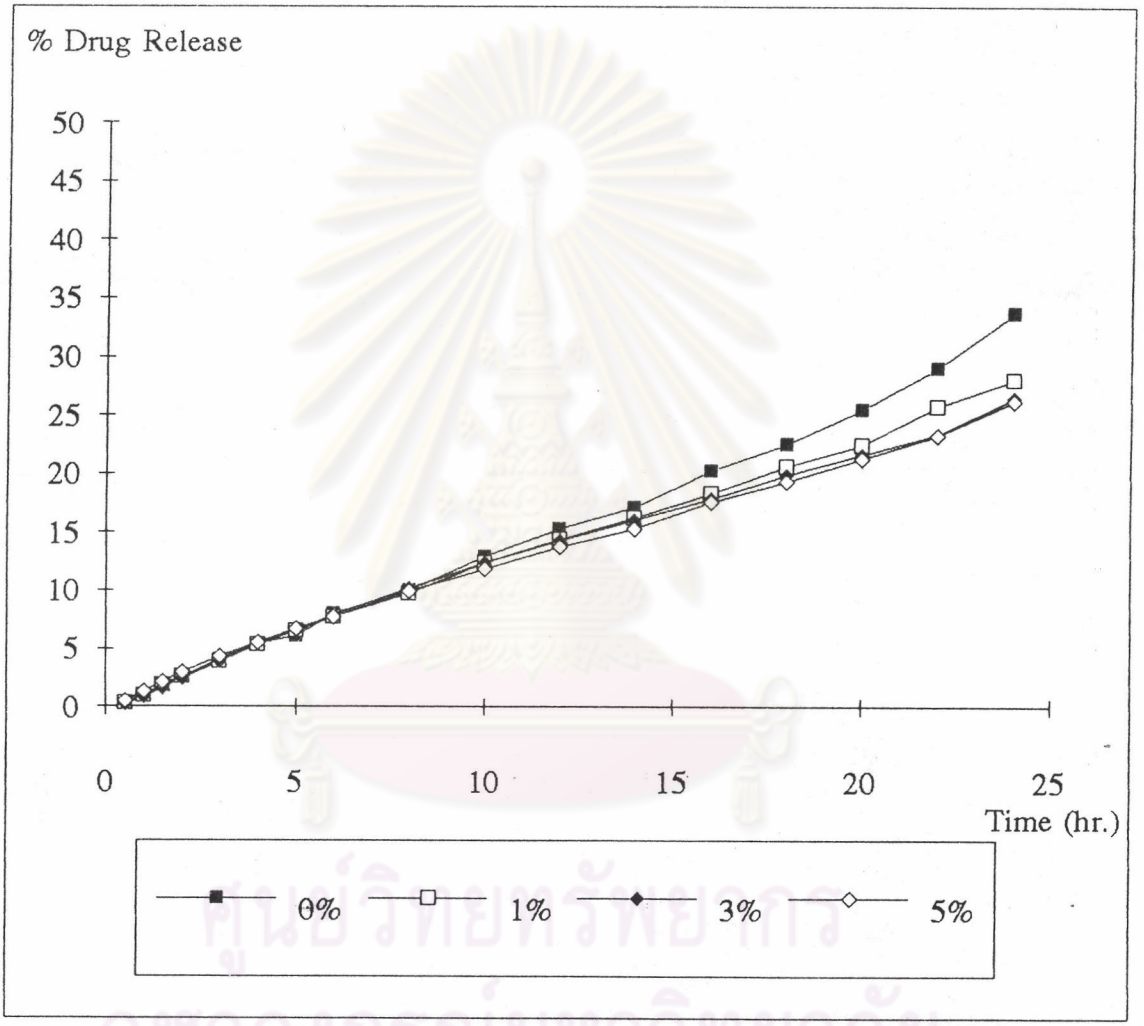

Figure 17 Percent Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Chlorhexidine Diacetate

phases of the stratum corneum, which increased fluidity in this region and presumably reduced diffusional resistances. In this study, because it was *in vitro* study, thus there was on effect on the skin of surfactants. The enhancing effect did not obtain in this study.

From Table 6, the percentage of nifedipine release from the preparations containing 1%W/W sodium lauryl sulfate was 28.71 at 24 hours. The preparations containing 3% and 5% W/W sodium lauryl sulfate released nifedipine at 24 hours 36.51% and 42.88% respectively. There was no statistically significant difference between 1% W/W sodium lauryl sulfate and the control ($P > 0.01$). However, there were statistically significant difference between the control preparations and containing 3%, 5% W/W ($P < 0.01$).

Table 7 showed the percentage of nifedipine release from the preparations containing 1% and 3% W/W dioctyl sodium sulfosuccinate, at 24 hours, was 36.21 and 37.49 respectively. The preparations containing 5% W/W dioctyl sodium sulfosuccinate released nifedipine 41.27%. There was no statistically significant difference between 1%, 3% W/W dioctyl sodium sulfosuccinate and the control preparations ($P > 0.01$). There was statistically significant difference between the control preparations and the preparations containing 5% W/W ($P < 0.01$). However, there was no statistically significant difference between 3% W/W dioctyl sodium sulfosuccinate and 3% W/W sodium lauryl sulfate preparation ($P > 0.01$).

The alkyl sulfates were the most widely studied anionic surfactants, which could penetrate and destroy the integrity of the stratum corneum [Hadgraft, J. and Guy, R.H., 1989]. Similar to this study, sodium

lauryl sulfate enhanced the penetration of naproxen [Chowhan, Z.T. and Pritchard, R. 1978.], chloramphenicol [Aguiar, A.J. and Weiner, M.A., 1969] and naloxone [Aungst, B. J., Rogers, N.J., and Shefter, E., 1986].

From Table 8, the percentage of nifedipine release from the preparetions containing 1% and 3%W/W benzalkonium chloride were 32.76% and 35.79% respectively. The preparations containing 5%W/W benzalkonium chloride showed 47.17%, the highest percentage of drug release in this study. There was statistically significant difference between the control and the preparation containing 5% W/W ($P < 0.01$).There was no statistically significant difference between preparations containing 1%, 3% W/W benzalkonium chloride and the control preparation ($P > 0.01$).

From Table 9, the percentage of nifedipine release from the preparations containing 1%, 3%, and 5%W/W chlorhexidine diacetate were 28.06%, 26.48% and 26.21% respectively. There were no statistically significant differences among preparations containing 0%, 1%, 3% and 5%W/W chlorhexidine diacetate ($P > 0.01$).

The amount of the drug release versus time profiles were shown in Table 10 to 15 and Figure 18 to 23. To determine the drug release rate constant, plots of released drug amount versus time and released drug amount versus square root of time were compared. Linear regression was used to determine the coefficients of determination (r^2) which were then compared as shown in Appendix B.

The results indicated that the coefficients of determination which were nearest to 1 were obtained from plots of released drug amount

Table 10 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Brij 35

Time	Amount of Nifedipine Release[a] (mg./sq.cm.)			
(hr.)	0%	1%	3%	5%
0.5	0.52 (0.38)	0.63 (0.52)	1.07 (0.25)	0.93 (0.09)
1	1.82 (0.28)	2.36 (0.26)	3.14 (0.15)	2.90 (0.10)
1.5	3.41 (0.20)	3.97 (0.19)	4.89 (0.10)	4.90 (0.14)
2	4.95 (0.16)	5.55 (0.16)	6.52 (0.11)	6.66 (0.14)
3	8.11 (0.13)	9.03 (0.13)	9.84 (0.13)	10.21 (0.13)
4	10.74 (0.10)	12.03 (0.13)	12.92 (0.11)	13.29 (0.10)
5	13.20 (0.09)	14.80 (0.12)	15.42 (0.10)	17.92 (0.08)
6	15.95 (0.10)	17.51 (0.11)	18.76 (0.10)	19.97 (0.07)
8	20.06 (0.09)	24.02 (0.10)	24.66 (0.10)	25.61 (0.05)
10	25.90 (0.09)	28.76 (0.10)	29.81 (0.10)	31.32 (0.07)
12	30.52 (0.13)	33.32 (0.08)	34.69 (0.08)	36.48 (0.07)
14	35.41 (0.09)	37.14 (0.09)	38.90 (0.08)	41.58 (0.06)
16	40.52 (0.09)	42.52 (0.09)	45.49 (0.10)	47.51 (0.06)
18	45.06 (0.07)	46.99 (0.07)	51.82 (0.10)	56.16 (0.07)
20	50.94 (0.08)	54.17 (0.06)	60.27 (0.09)	63.41 (0.05)
22	58.10 (0.09)	60.72 (0.05)	65.05 (0.09)	70.50 (0.03)
24	67.33 (0.07)	66.71 (0.05)	72.77 (0.08)	77.59 (0.05)

a = Mean (S.D.) (n=6)

Table 11 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Tween 80

Time (hr.)	Amount of Nifedipine Release[a] (mg./sq.cm.)			
	0%	1%	3%	5%
0.5	0.52 (0.38)	0.94 (0.11)	0.89 (0.19)	0.83 (0.12)
1	1.82 (0.28)	2.55 (0.05)	2.83 (0.10)	2.66 (0.06)
1.5	3.41 (0.20)	4.23 (0.06)	5.04 (0.11)	5.00 (0.06)
2	4.95 (0.16)	5.62 (0.05)	6.77 (0.11)	6.77 (0.06)
3	8.11 (0.13)	8.29 (0.03)	9.97 (0.14)	9.86 (0.02)
4	10.74 (0.10)	10.74 (0.01)	13.09 (0.10)	13.42 (0.01)
5	13.20 (0.09)	13.60 (0.01)	16.13 (0.09)	16.02 (0.02)
6	15.95 (0.10)	15.93 (0.01)	18.64 (0.05)	19.22 (0.03)
8	20.06 (0.09)	21.61 (0.02)	24.96 (0.07)	25.12 (0.03)
10	25.90 (0.09)	27.12 (0.02)	30.12 (0.07)	30.26 (0.03)
12	30.52 (0.13)	31.92 (0.01)	36.07 (0.06)	35.40 (0.01)
14	35.41 (0.09)	37.36 (0.01)	40.76 (0.05)	38.59 (0.02)
16	40.52 (0.09)	43.80 (0.01)	47.04 (0.06)	44.82 (0.04)
18	45.06 (0.07)	49.08 (0.01)	52.98 (0.06)	52.92 (0.05)
20	50.94 (0.08)	56.82 (0.02)	59.70 (0.08)	61.69 (0.04)
22	58.10 (0.09)	63.81 (0.03)	67.57 (0.06)	67.57 (0.03)
24	67.33 (0.07)	68.84 (0.01)	74.68 (0.06)	74.79 (0.03)

a = Mean (S.D.) (n=6)

Table 12 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Sodium Lauryl Sulfate

Time	Amount of Nifedipine Release[a] (mg./sq.cm.)			
(hr.)	0%	1%	3%	5%
0.5	0.52 (0.38)	0.35 (0.40)	0.79 (0.32)	0.60 (0.10)
1	1.82 (0.28)	1.80 (0.35)	2.35 (0.31)	2.09 (0.13)
1.5	3.41 (0.20)	3.33 (0.31)	3.73 (0.34)	4.67 (0.14)
2	4.95 (0.16)	5.03 (0.23)	5.50 (0.29)	6.97 (0.09)
3	8.11 (0.13)	6.99 (0.12)	9.30 (0.19)	12.14 (0.10)
4	10.74 (0.10)	10.60 (0.18)	12.70 (0.12)	16.54 (0.10)
5	13.20 (0.09)	12.61 (0.18)	16.34 (0.13)	20.74 (0.08)
6	15.95 (0.10)	15.62 (0.16)	20.03 (0.13)	26.13 (0.08)
8	20.06 (0.09)	19.67 (0.16)	25.63 (0.12)	35.09 (0.05)
10	25.90 (0.09)	24.20 (0.15)	32.50 (0.12)	43.50 (0.08)
12	30.52 (0.13)	29.06 (0.14)	37.39 (0.11)	50.09 (0.10)
14	35.41 (0.09)	34.32 (0.17)	43.41 (0.10)	56.58 (0.08)
16	40.52 (0.09)	40.61 (0.18)	50.34 (0.14)	62.19 (0.06)
18	45.06 (0.07)	45.21 (0.14)	54.14 (0.09)	69.83 (0.05)
20	50.94 (0.08)	48.04 (0.14)	62.10 (0.07)	75.81 (0.05)
22	58.10 (0.09)	53.71 (0.14)	69.12 (0.04)	80.98 (0.04)
24	67.33 (0.07)	57.43 (0.11)	73.01 (0.04)	85.77 (0.02)

a = Mean (S.D.) (n=6)

Table 13 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Dioctyl Sodium Sulfosuccinate

Time (hr.)	Amount of Nifedipine Release[a] (mg./sq.cm.)			
	0%	1%	3%	5%
0.5	0.52 (0.38)	0.81 (0.28)	0.72 (0.27)	0.90 (0.19)
1	1.82 (0.28)	2.32 (0.18)	2.21 (0.16)	2.43 (0.23)
1.5	3.41 (0.20)	3.77 (0.16)	3.73 (0.16)	3.95 (0.22)
2	4.95 (0.16)	5.36 (0.13)	5.28 (0.16)	5.55 (0.22)
3	8.11 (0.13)	8.04 (0.13)	8.38 (0.14)	8.53 (0.21)
4	10.74 (0.10)	11.35 (0.10)	11.43 (0.15)	11.44 (0.20)
5	13.20 (0.09)	13.84 (0.09)	13.63 (0.21)	13.96 (0.18)
6	15.95 (0.10)	16.59 (0.11)	17.51 (0.10)	17.12 (0.16)
8	20.06 (0.09)	22.19 (0.10)	23.25 (0.09)	22.35 (0.19)
10	25.90 (0.09)	27.75 (0.11)	28.99 (0.07)	29.55 (0.14)
12	30.52 (0.13)	33.55 (0.10)	35.03 (0.10)	36.01 (0.14)
14	35.41 (0.09)	39.80 (0.12)	42.61 (0.11)	44.20 (0.12)
16	40.52 (0.09)	44.39 (0.09)	49.28 (0.09)	53.62 (0.12)
18	45.06 (0.07)	50.78 (0.08)	56.09 (0.09)	59.16 (0.12)
20	50.94 (0.08)	57.06 (0.08)	62.63 (0.08)	67.51 (0.11)
22	58.10 (0.09)	67.05 (0.04)	68.14 (0.06)	75.14 (0.10)
24	67.33 (0.07)	72.41 (0.04)	74.98 (0.05)	82.53 (0.06)

a = Mean (S.D.) (n=6)

Table 14 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Benzalkonium Chloride

Time (hr.)	Amount of Nifedipine Release[a] (mg./sq.cm.)			
	0%	1%	3%	5%
0.5	0.52 (0.38)	0.46 (0.16)	0.86 (0.06)	1.11 (0.31)
1	1.82 (0.28)	1.93 (0.12)	3.13 (0.10)	3.75 (0.18)
1.5	3.41 (0.20)	3.75 (0.14)	5.17 (0.10)	6.31 (0.21)
2	4.95 (0.16)	5.33 (0.15)	6.94 (0.06)	8.60 (0.20)
3	8.11 (0.13)	8.56 (0.18)	10.75 (0.05)	13.41 (0.21)
4	10.74 (0.10)	11.77 (0.14)	13.51 (0.10)	18.14 (0.22)
5	13.20 (0.09)	14.80 (0.16)	17.08 (0.10)	22.99 (0.18)
6	15.95 (0.10)	18.00 (0.16)	20.11 (0.10)	26.94 (0.16)
8	20.06 (0.09)	24.49 (0.15)	25.17 (0.09)	34.64 (0.17)
10	25.90 (0.09)	29.27 (0.13)	32.50 (0.06)	42.89 (0.17)
12	30.52 (0.13)	34.83 (0.10)	37.28 (0.07)	50.14 (0.15)
14	35.41 (0.09)	40.54 (0.14)	43.17 (0.06)	55.91 (0.15)
16	40.52 (0.09)	46.01 (0.11)	47.29 (0.09)	64.51 (0.15)
18	45.06 (0.07)	51.49 (0.13)	53.42 (0.07)	71.70 (0.14)
20	50.94 (0.08)	55.63 (0.14)	56.24 (0.07)	77.63 (0.14)
22	58.10 (0.09)	61.04 (0.14)	64.28 (0.08)	84.93 (0.11)
24	67.33 (0.07)	65.51 (0.14)	71.59 (0.06)	94.35 (0.14)

a = Mean (S.D.) (n=6)

Table 15 The Average Amount of Nifedipine Release from Pluronic F-127 Gel Containing Various Concentrations of Chlorhexidine Diacetate

Time	Amount of Nifedipine Release[a] (mg./sq.cm.)			
(hr.)	0%	1%	3%	5%
0.5	0.52 (0.38)	0.57 (0.30)	0.45 (0.33)	0.92 (0.20)
1	1.82 (0.28)	1.90 (0.23)	1.58 (0.18)	2.61 (0.11)
1.5	3.41 (0.20)	3.65 (0.10)	3.12 (0.08)	4.33 (0.10)
2	4.95 (0.16)	5.08 (0.10)	4.71 (0.09)	5.94 (0.09)
3	8.11 (0.13)	7.73 (0.10)	7.76 (0.09)	8.57 (0.07)
4	10.74 (0.10)	10.57 (0.08)	10.78 (0.10)	10.96 (0.07)
5	13.20 (0.09)	12.95 (0.08)	12.98 (0.09)	13.40 (0.07)
6	15.95 (0.10)	15.37 (0.09)	15.83 (0.11)	15.43 (0.06)
8	20.06 (0.09)	19.37 (0.07)	20.32 (0.11)	19.83 (0.06)
10	25.90 (0.09)	24.71 (0.08)	24.66 (0.10)	23.68 (0.05)
12	30.52 (0.13)	28.73 (0.09)	28.61 (0.11)	27.54 (0.04)
14	35.41 (0.09)	32.45 (0.09)	32.15 (0.11)	30.63 (0.07)
16	40.52 (0.09)	36.63 (0.09)	35.71 (0.13)	35.23 (0.06)
18	45.06 (0.07)	41.29 (0.07)	39.72 (0.17)	38.73 (0.06)
20	50.94 (0.08)	44.89 (0.08)	43.19 (0.17)	42.50 (0.08)
22	58.10 (0.09)	51.52 (0.09)	46.77 (0.16)	46.58 (0.05)
24	67.33 (0.07)	56.13 (0.09)	52.96 (0.18)	52.42 (0.05)

a = Mean (S.D.) (n=6)

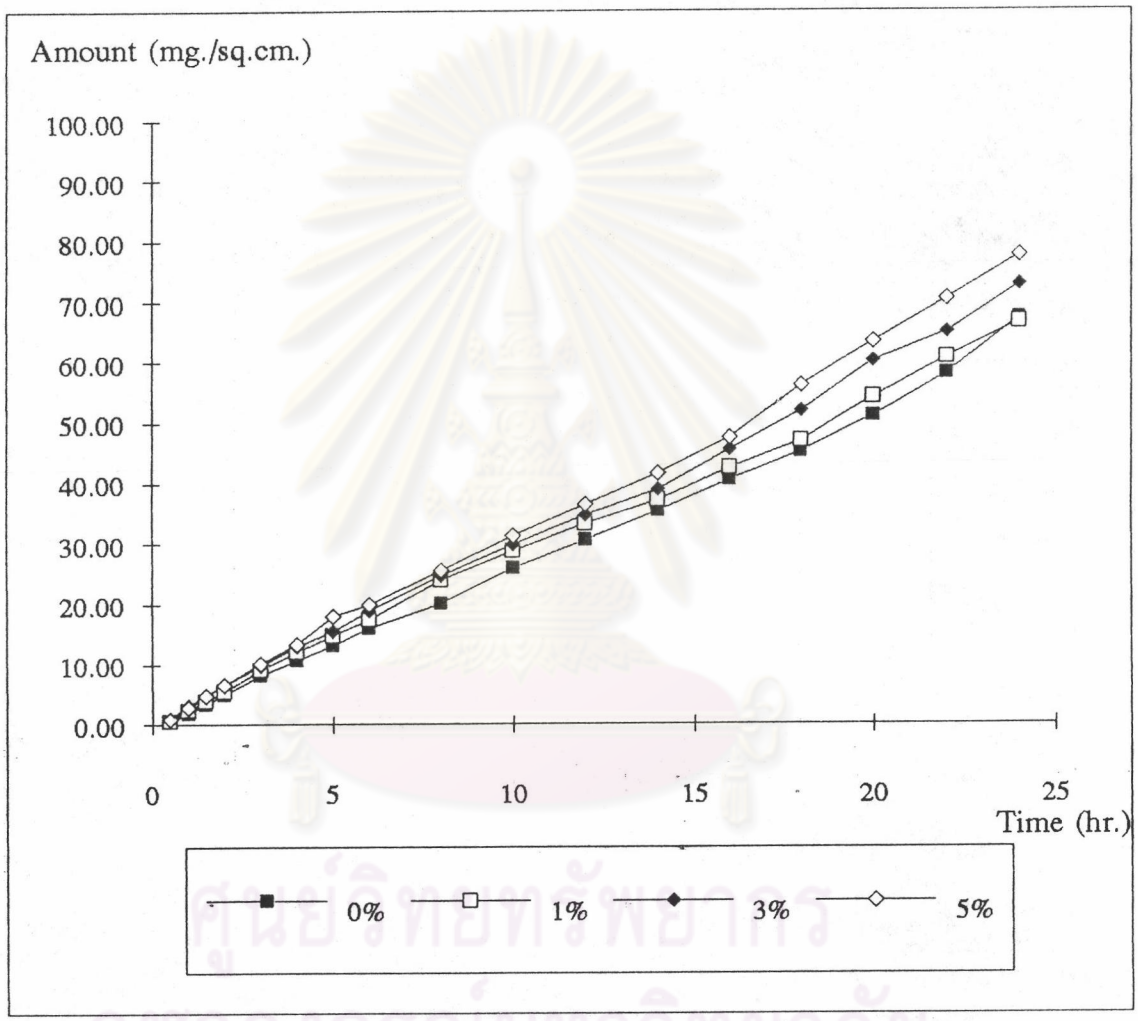

Figure 18 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Brij 35

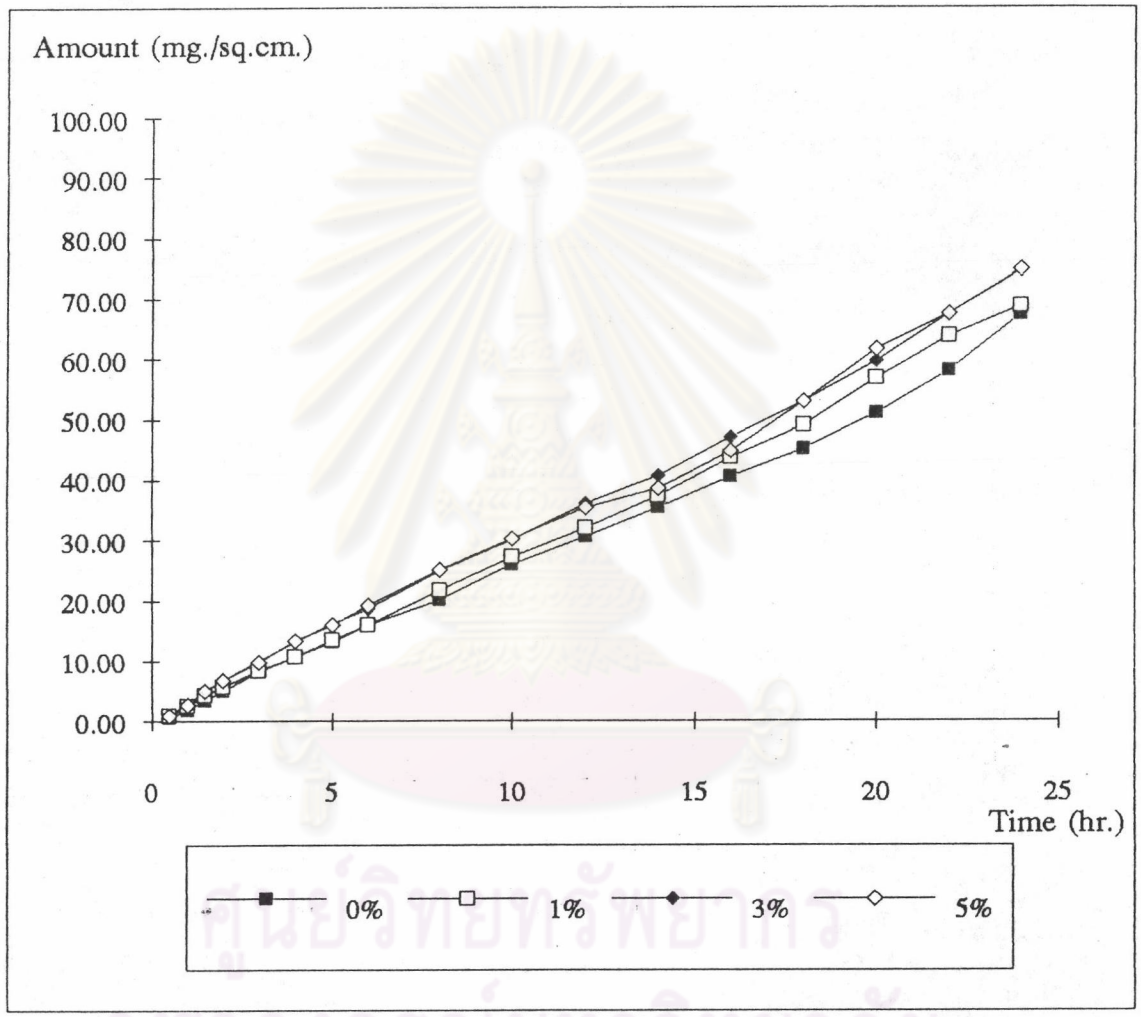

Figure 19 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Tween 80

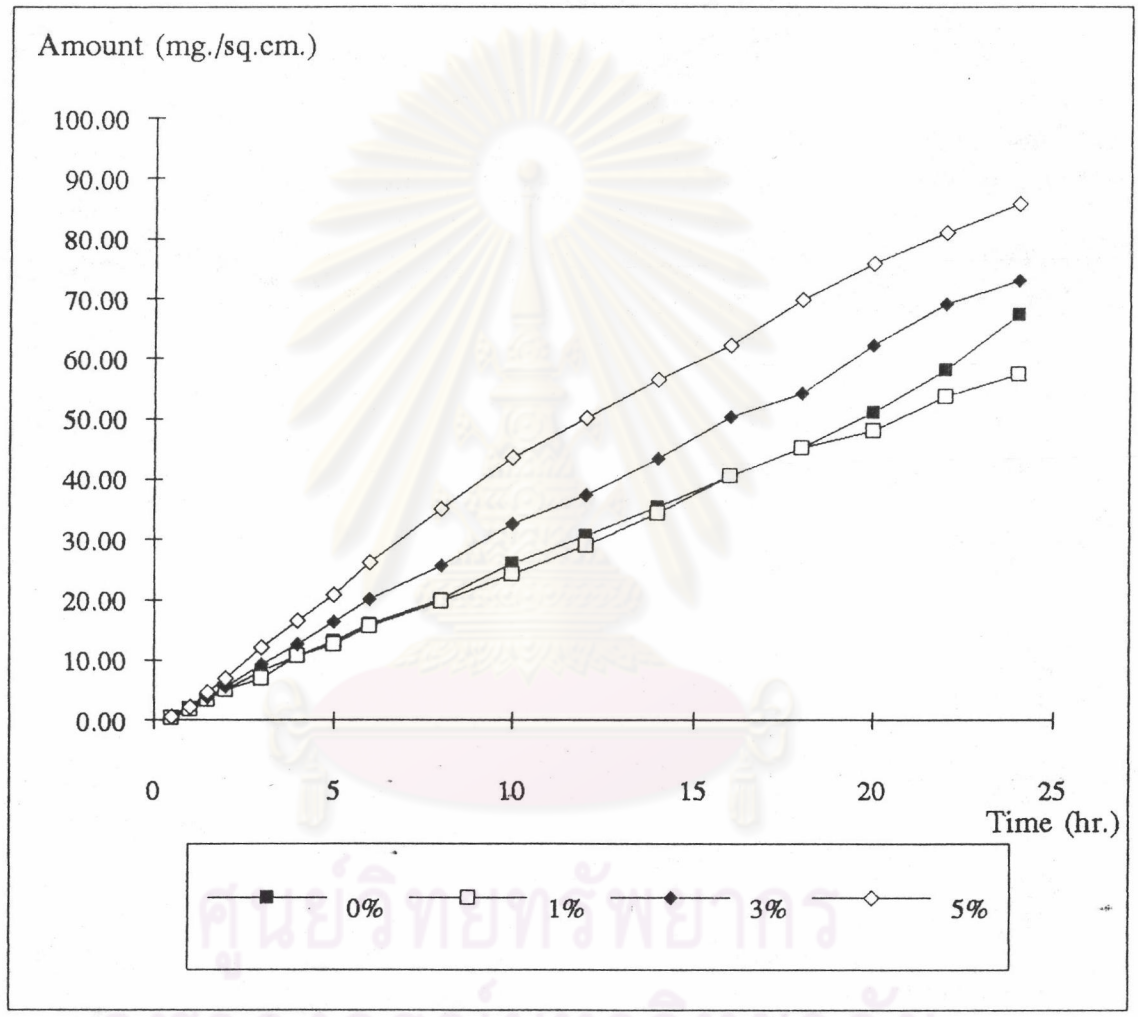

Figure 20 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Sodium Lauryl Sulfate

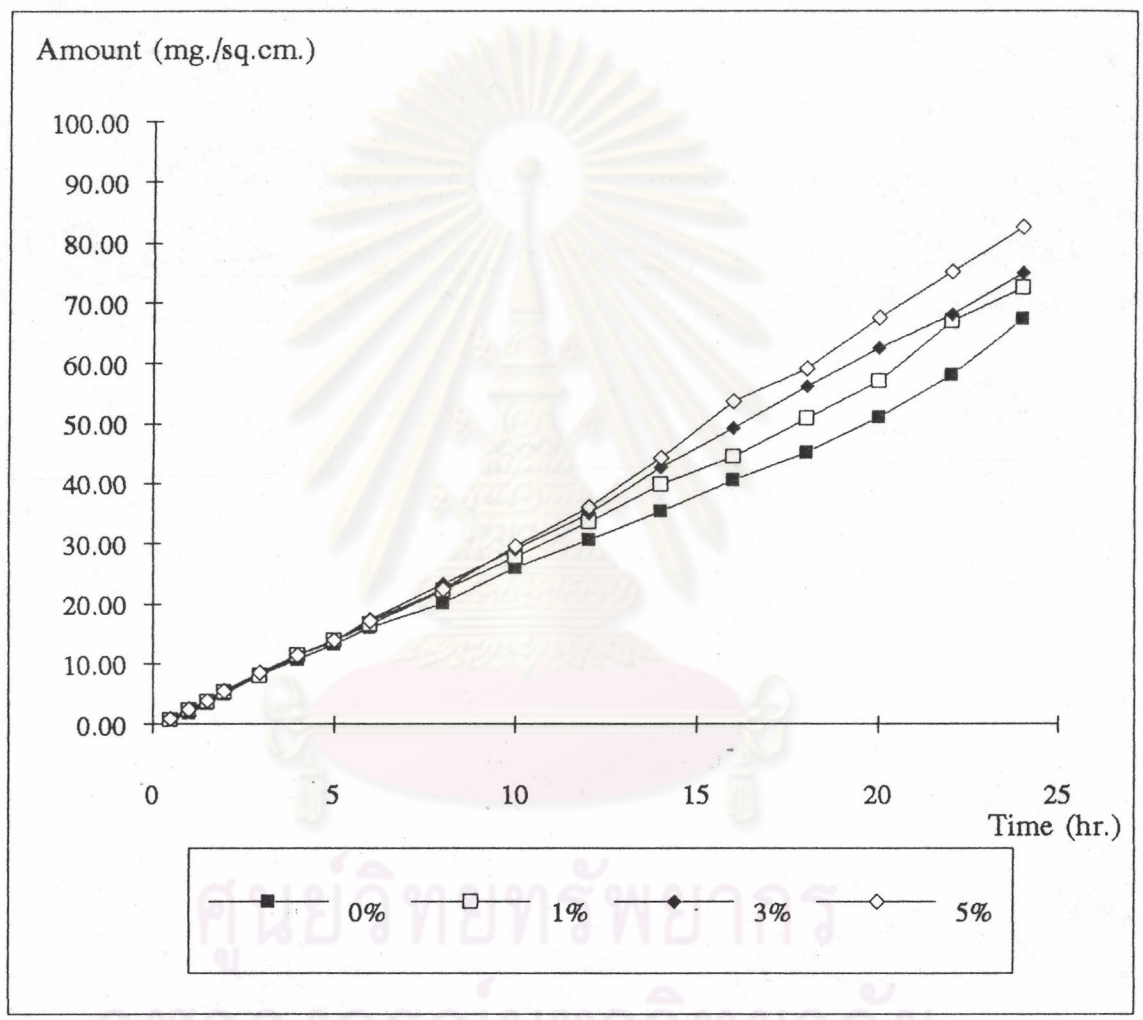

Figure 21 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Dioctyl Sodium Sulfosuccinate

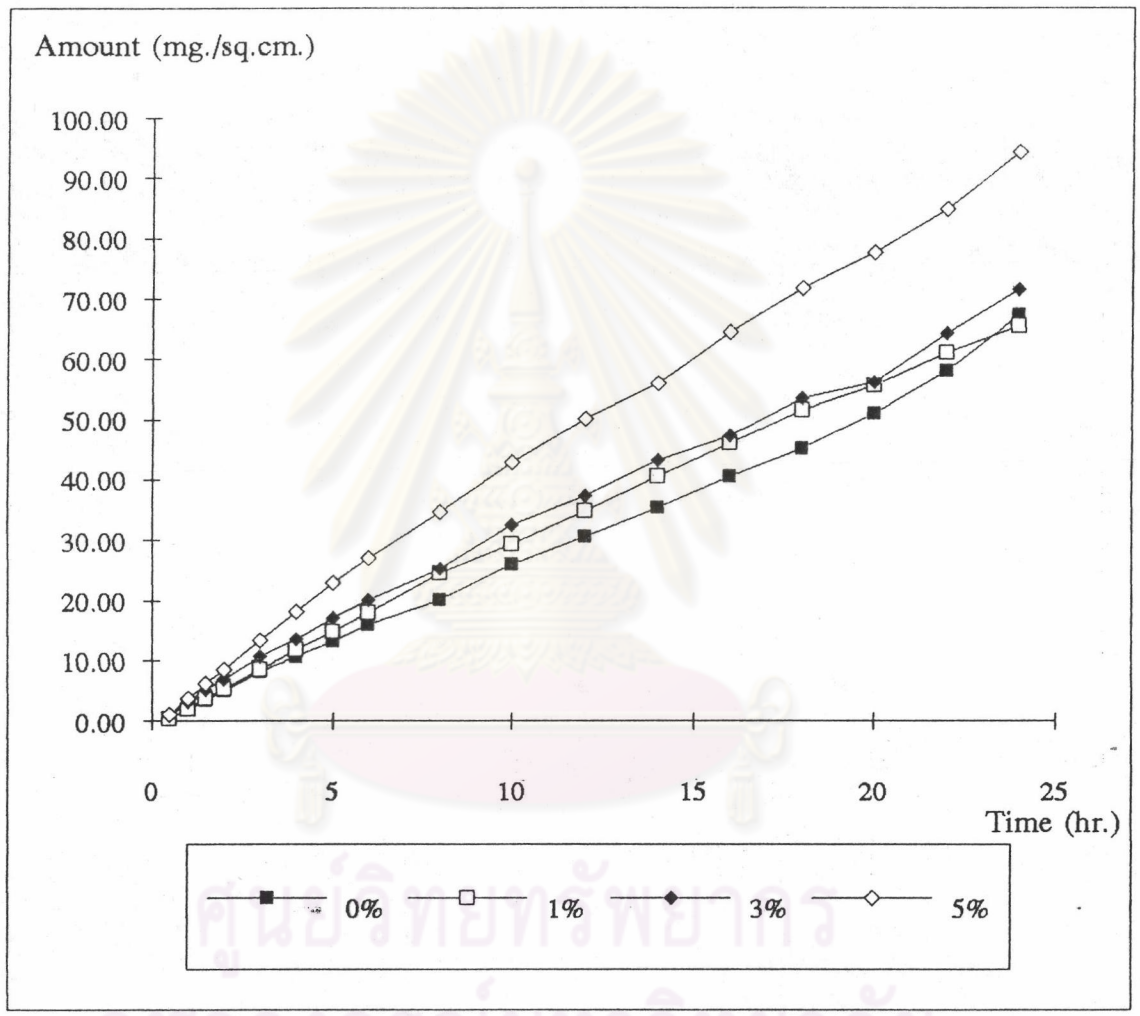

Figure 22 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Benzalkonium Chloride

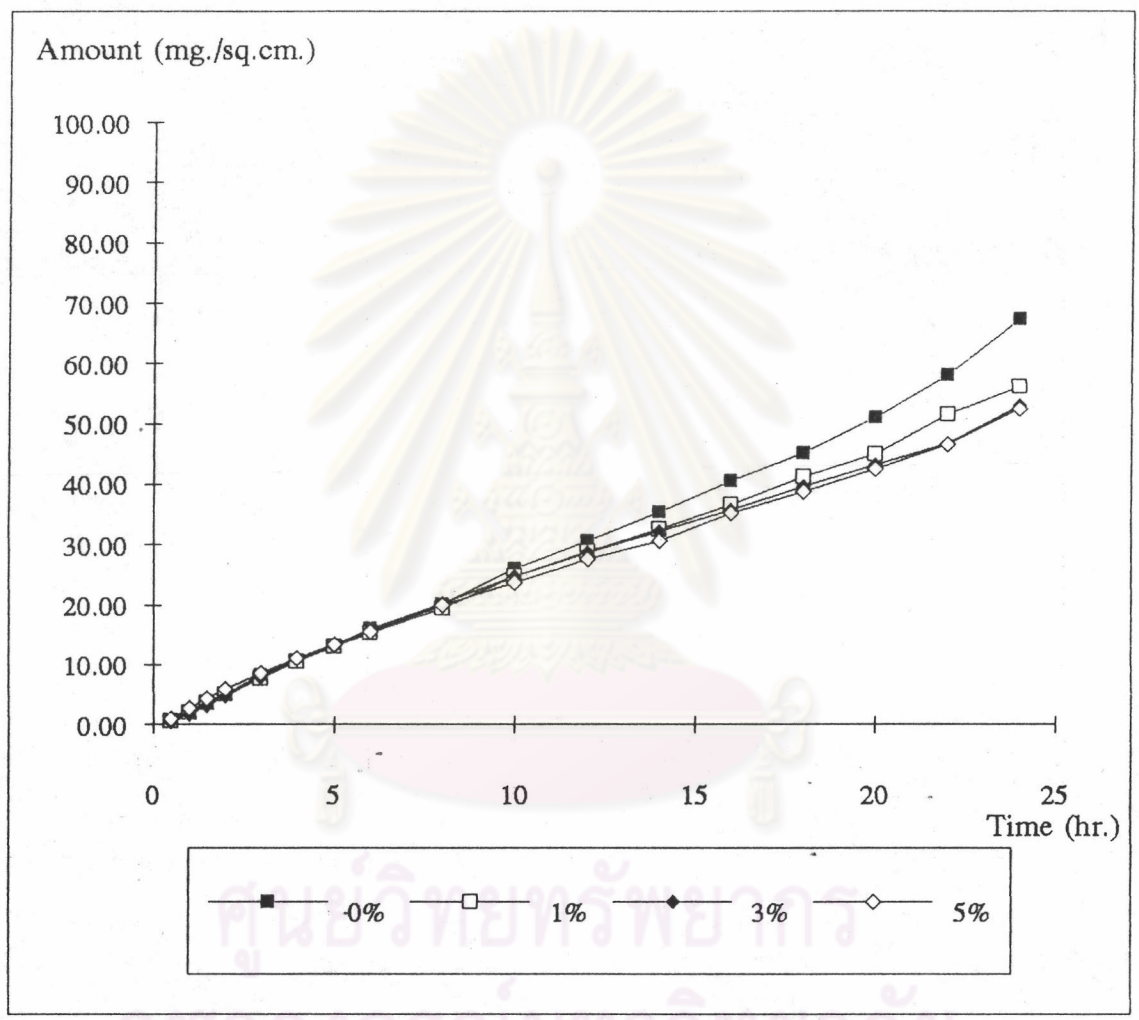

Figure 23 Amount Release - Time Profile of Nifedipine - Pluronic F-127 Gel Containing Various Concentrations of Chlorhexidine Diacetate

versus time. The coefficients of determination of amount drug release time profile of nifedipine showed that the release kinetics of nifedipine from various preparations of Pluronic F-127 gels studied were found to be zero-order kinetics.

The drug release rate constant was obtained from the slope of the plots of released drug amount versus time as shown in Table 16. The influence of types and concentrations of surfactants on nifedipine release rate constants were noted. Student's t-test comparison of drug release rate constants of nifedipine gels containing various types and concentrations of surfactants with preparations containing 0% surfactants as the control, were showed in Table 17.

There was no statistically significant difference between control and preparations containing all concentrations of Brij 35, Tween 80 and chlorhexidine diacetate ($P > 0.01$). However, statistically significant differences were observed between control and preparations containing certain concentrations of dioctyl sodium sulfosuccinate, sodium lauryl sulfate and benzalkonium chloride ($P < 0.01$).

The non-ionic surfactants in this study, Brij 35 and Tween 80, three concentrations, 1% 3% and 5%W/W, did not enhance the rate of the drug release. Aguiar, A.J. and Weiner, M.A. (1969) found that, at the concentrations of 0.5% and 1% of Tween 80 increased the skin penetration of chloramphenicol, but at lower concentrations caused a slight reduction. Similar to the study, Tween 20 had no effect on the permeation of naloxone [Aungst, et.al. 1986].

Table 16 Release Rate Constants of Nifedipine from Various Preparations

Preparations	Release Rate Constant [a] (mg.)/(sq.cm.)(hr.)
0% (Control)	2.66 (0.19)
1% Brij 35	2.71 (0.14)
3% Brij 35	2.93 (0.25)
5% Brij 35	3.09 (0.15)
1% Tween 80	2.85 (0.04)
3% Tween 80	3.01 (0.18)
5% Tween 80	3.00 (0.11)
1% Dioctyl Sodium Sulfosuccinate	2.97 (0.15)
3% Dioctyl Sodium Sulfosuccinate	3.16 (0.22)
5% Dioctyl Sodium Sulfosuccinate	3.46 (0.29)
1% Sodium Lauryl Sulfate	2.44 (0.13)
3% Sodium Lauryl Sulfate	3.10 (0.14)
5% Sodium Lauryl Sulfate	3.73 (0.14)
1% Benzalkonium Chloride	2.80 (0.17)
3% Benzalkonium Chloride	2.87 (0.21)
5% Benzalkonium Chloride	3.88 (0.25)
1% Chlorhexidine Diacetate	2.29 (0.20)
3% Chlorhexidine Diacetate	2.16 (0.38)
5% Chlorhexidine Diacetate	2.16 (0.20)

a = Mean (S.D.) (n=6)

Table 17 Comparison of Rate Constants of Nifedipine Release from Various Concentration of Surfactants with Control, Using Student's t-test.

Preparations	t- value (calculated)	Statistical Significance
1% Brij 35	0.460	N
3% Brij 35	1.945	N
5% Brij 35	3.991	N
1% Tween 80	2.115	N
3% Tween 80	3.002	N
5% Tween 80	2.947	N
1% Dioctyl Sodium Sulfosuccinate	2.858	N
3% Dioctyl Sodium Sulfosuccinate	3.857	N
5% Dioctyl Sodium Sulfosuccinate	5.169	S
1% Sodium Lauryl Sulfate	1.331	N
3% Sodium Lauryl Sulfate	4.168	S
5% Sodium Lauryl Sulfate	10.133	S
1% Benzalkonium Chloride	0.692	N
3% Benzalkonium Chloride	1.691	N
5% Benzalkonium Chloride	5.065	S
1% Chlorhexidine Diacetate	2.955	N
3% Chlorhexidine Diacetate	2.659	N
5% Chlorhexidine Diacetate	4.001	N

t (table) = 4.032

S = Significant at $P < 0.01$

N = Not Significant at $P > 0.01$

Anionic surfactants, 3%, 5%W/W of sodium lauryl sulfate, and 5%W/W of dioctyl sodium sulfosuccinate enhanced the release rate constants. However, there was no statistically significant difference between 3%W/W sodium lauryl sulfate and 3%W/W dioctyl sodium sulfosuccinate ($P > 0.01$). It was indicated that the high concentrations of sodium lauryl sulfate and dioctyl sodium sulfosuccinate enhanced the rate constant of nifedipine from Pluronic F-127 gels.

For cationic surfactants, the certain concentration, 5%W/W of benzalkonium chloride enhanced the release rate constant ($P < 0.01$). The preparations containing 1% and 3%W/W benzalkonium chloride had no statistically significant difference from the control ($P > 0.01$). In contrast, the effect of chlorhexidine diacetate did not enhance the release rate constant of nifedipine gels. It seemed to reduce the rate constant. However, there was no statistically significant difference among the preparations containing various concentrations of chlorhexidine diacetate ($P > 0.01$). The conflicting results for cationic surfactants might be partially explained that the high concentration of benzalkonium chloride was incompatible with Pluronic F-127 while chlorhexidine diacetate was not.

The rate constants of nifedipine release from preparations with surfactants were plotted versus concentration in Figure 24 to 29. As shown from slopes of the correlation in Table 18, it seemed that the increase of concentration of dioctyl sodium sulfosuccinate, sodium lauryl sulfate and benzalkonium chloride trended to increase release rate constant of nifedipine. While increased concentrations of Brij 35 and Tween 80 had

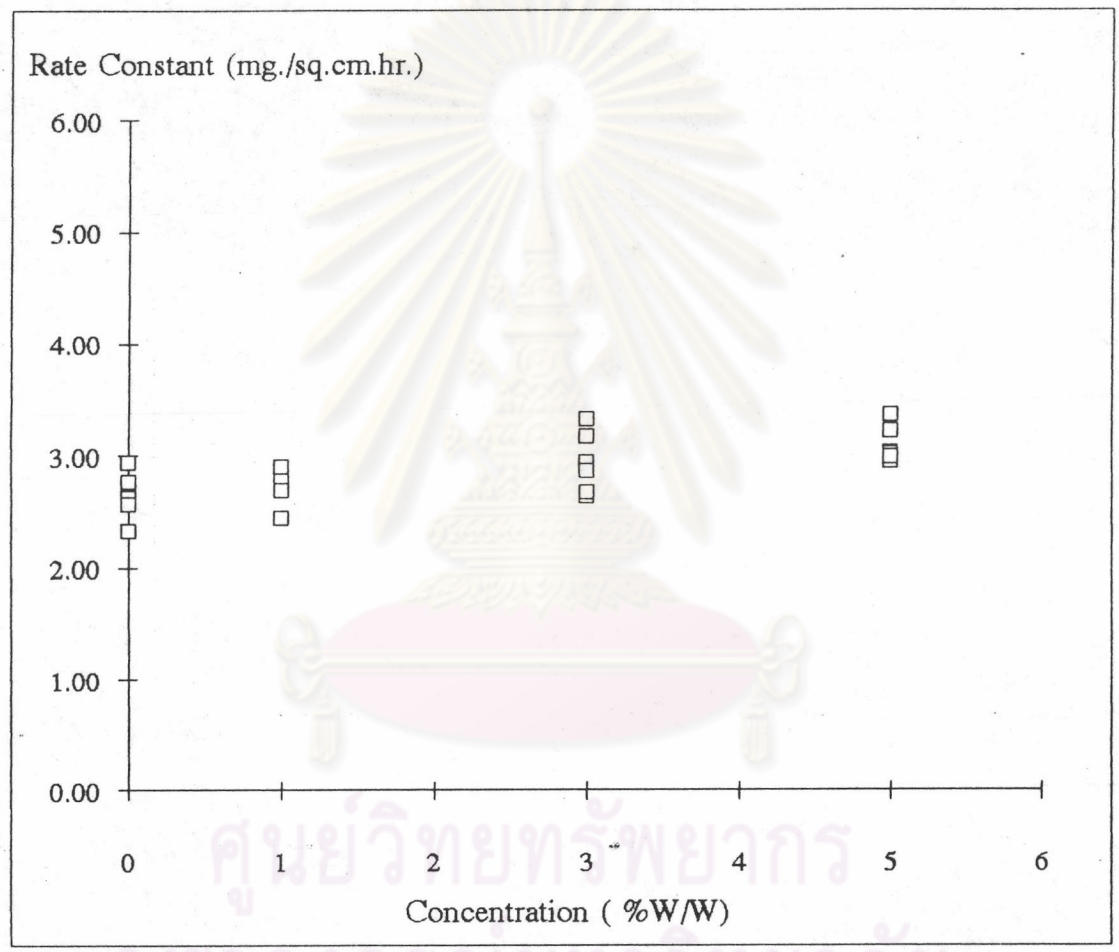

Figure 24 Effect of Concentration of Brij 35 on Nifedipine Release Rate Constant

Plot of Rate Constant versus Concentration of Brij 35.

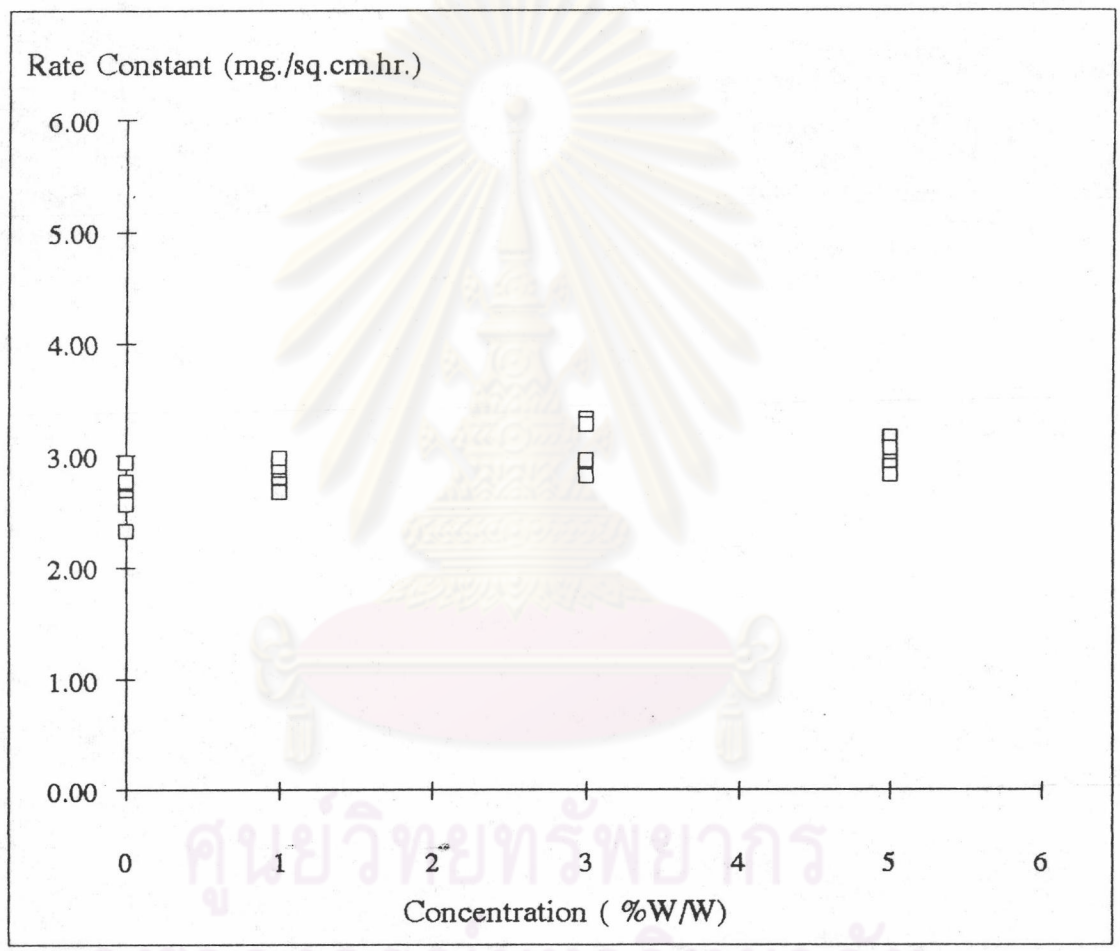

Figure 25 Effect of Concentration of Tween 80 on Nifedipine Release Rate Constant

Plot of Rate Constant versus Concentration of Tween 80

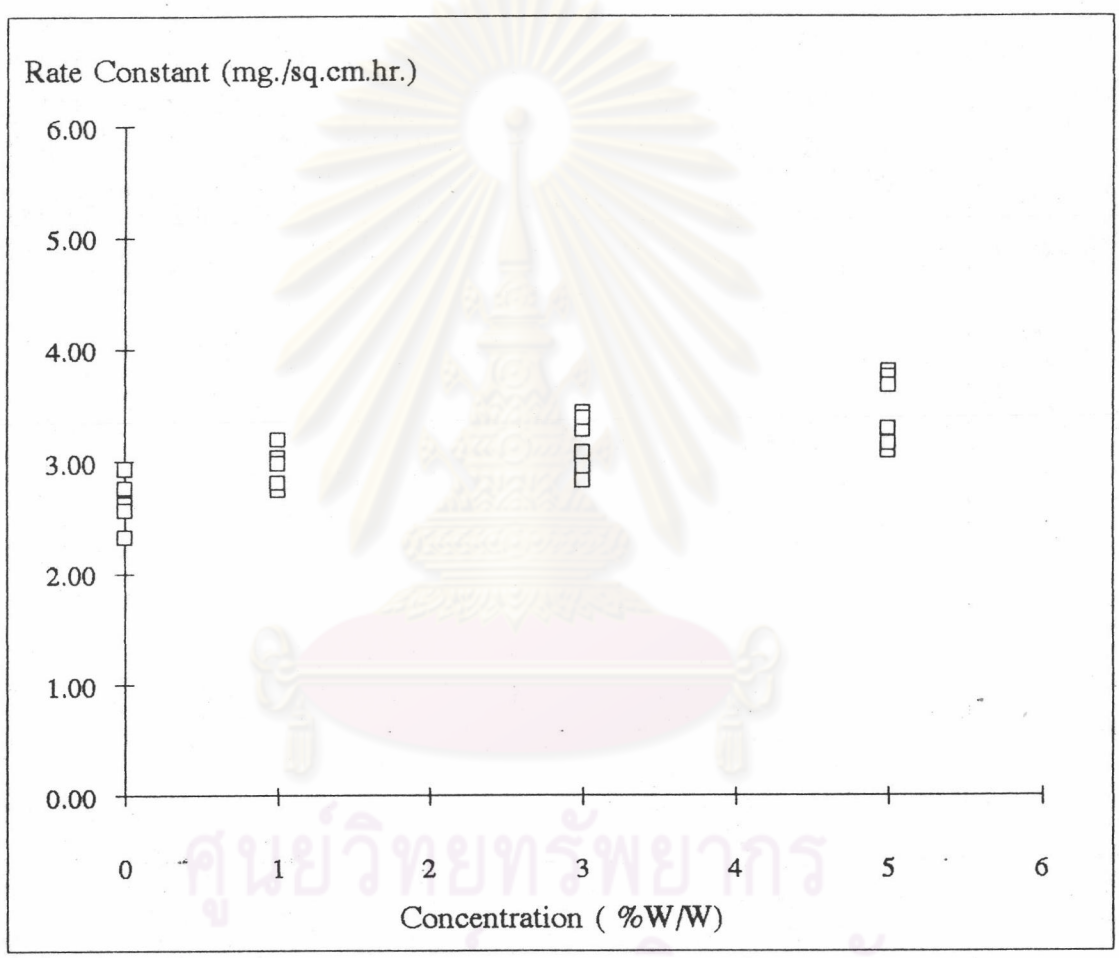

Figure 26 Effect of Concentration of Dioctyl Sodium Sulfosuccinate on Nifedipine Release Rate Constant. Plot of Rate Constant versus Concentration of Dioctyl Sodium Sulfosuccinate

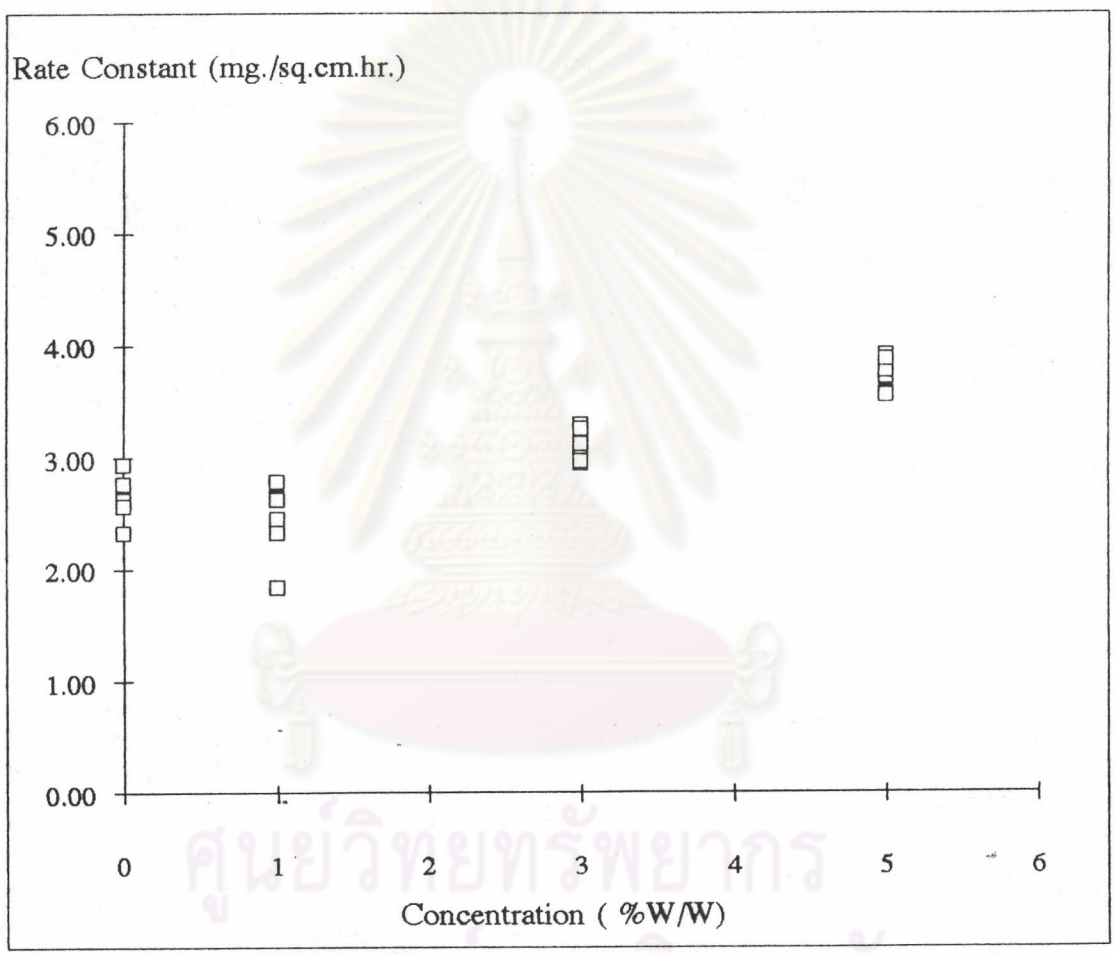

Figure 27 Effect of Concentration of Sodium Lauryl Sulfate on Nifedipine Release Rate Constant. Plot of Rate Constant versus Concentration of Sodium Lauryl Sulfate

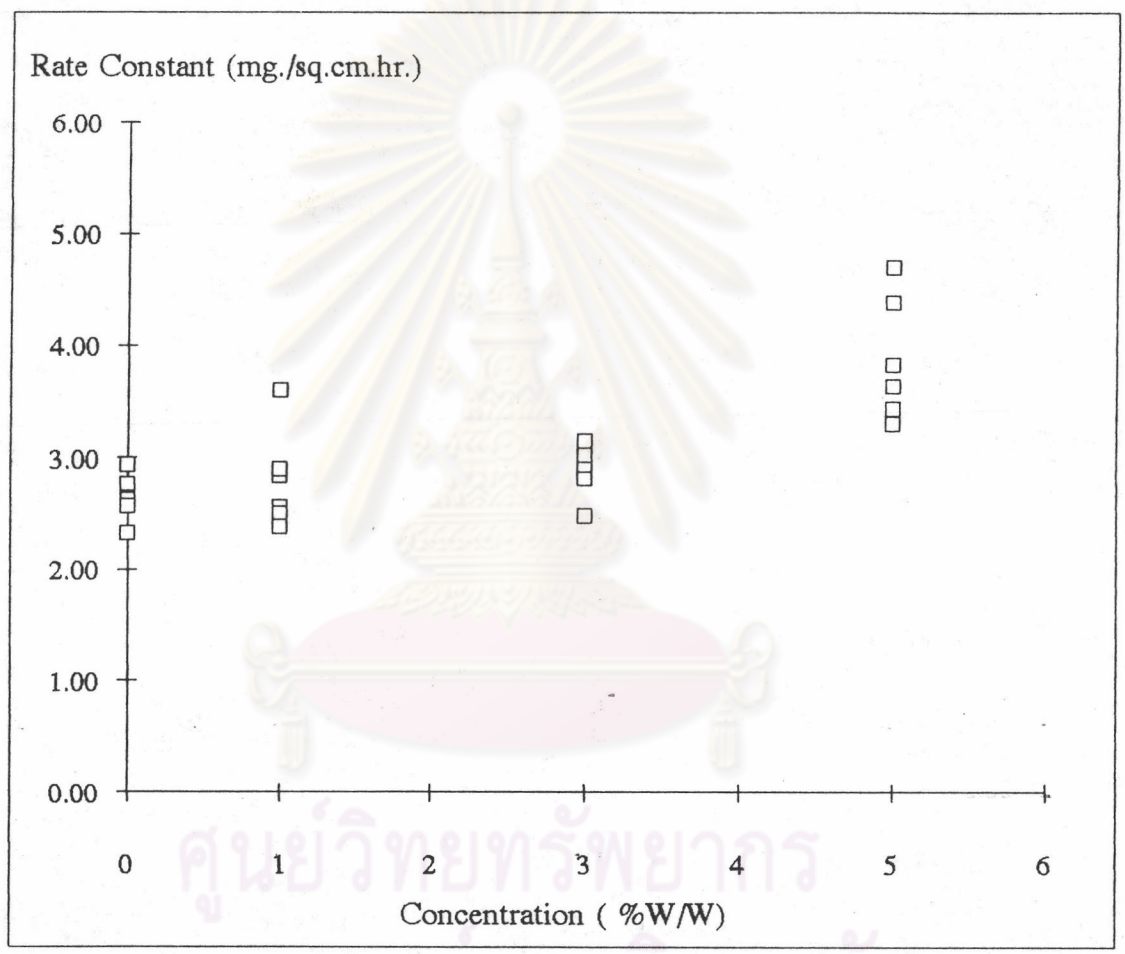

Figure 28 Effect of Concentration of Benzalkonium Chloride on Nifedipine Release Rate Constant. Plot of Rate Constant versus Concentration of Benzalkonium Chloride

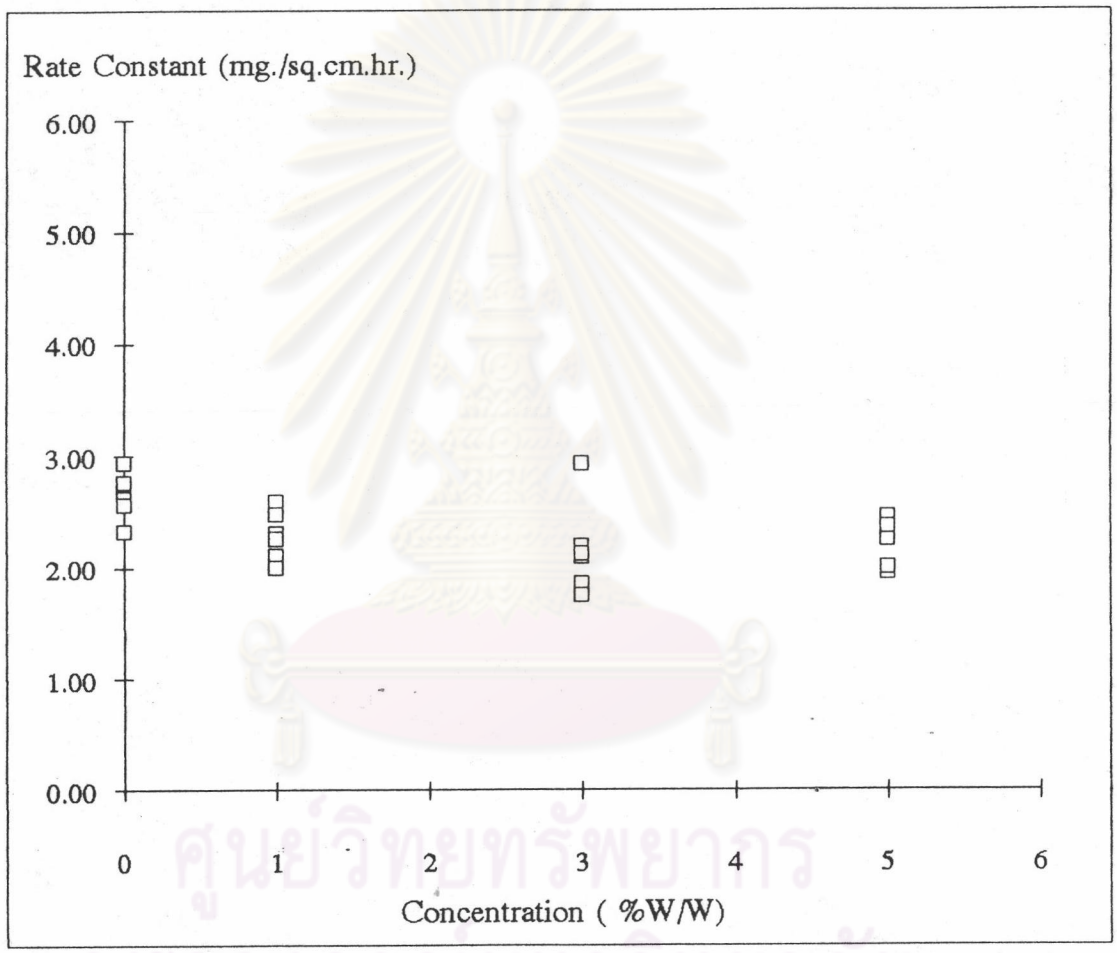

Figure 29 Effect of Concentration of Chlorhexidine Diacetate on Nifedipine Release Rate Constant. Plot of Rate Constant versus Concentration of Chlorhexidine Diacetate.

Table 18 The Correlation between Surfactant Concentrations and Nifedipine Release Rate Constants

Surfactants	Correlation Coefficient[a]	Slope
Brij 35	0.991	0.090
Tween 80	0.775	0.065
Dioctyl Sodium Sulfosuccinate	0.960	0.148
Sodium Lauryl Sulfate	0.879	0.241
Benzalkonium Chloride	0.807	0.226
Chlorhexidine Diacetate	0.670	-0.087

a = The results obtained from 6 samples.

no effect on rate constants. In contrast, it seemed that the increase of concentrations of chlorhexidine diacetate trended to decrease release rate constants.

From the results of this study, the surfactants which could enhanced the amount of nifedipine release from Pluronic F-127 gels, were dioctyl sodium sulfosuccinate, sodium lauryl sulfate and benzalkonium chloride. However, it is unlikely that they will find a use in transdermal therapeutics systems because of their irritation potential. For further studies, irritation effects of these surfactants to skin should be investigated.