CHAPTER III

RESULTS

1. Solubility of Nifedipine

The solubilities of NFP in varicus solvents including water was shown in Table 10. It was found that the solubilities of NFP in various solvents were greater than in water and phosphate buffer pH 7.4 solution (PBS). The results indicated that NFP was practically insoluble in water, PBS and the mixture of 20% v/v PEG 400 in phosphate buffer pH 7.4 solution, the elution medium for skin permeation study of this reseach. Its solubilities in these three solvents were about 7.79×10^{-5}, 7.25×10^{-5} and 8.61×10^{-4} g/100 ml, respectively. However, NFP showed a substantially more soluble in the elution medium than in pure PBS. In a report by Chien (1982), the addition of a co-solvent into the elution medium increased the solubility of drug, thus the addition of PEG 400 into PBS as the elution medium, might provide and maintain a sink condition required for *in-vitro* skin permeation study for NFP transdermal delivery system.

Table 10 The Solubilities of Nifedipine in Water and Other Solvents at 37°C

	Solvent	conc.of NFP* (mcg/ml)	Solubility	
			g/100 ml	
1	Reverse osmosis treated water	0.7785 ± 0.0496	7.79×10^{-5}	Practical insoluble (1:1,283,697)
2	Phosphate buffer pH 7.4 Solution	0.7248 ± 0.0175	7.25×10^{-5}	Practical insoluble (1:1,379,310)
3	Mixture of PBS + PEG 400 20% v/v	8.6141 ± 0.8391	8.61×10^{-4}	Practical insoluble (1:116,144)
4	Glycerol	0.7928 ± 0.0816	7.9×10^{-5}	Practical insoluble (1:1,261,034)
5	Mixture of glycerol + water (1:1)	2.8751 ± 0.1069	2.88×10^{-4}	Practical insoluble (1:347,222)
6	Propylene glycol (PG)	53.4696+ 6.2621	5.35×10^{-3}	Practical insoluble (1:18,691)
7	Mixture of PG + water (1:1)	43.07093 ± 3.2255	4.31×10^{-3}	Practical insoluble (1:23,201)
8	Absolute alcohol (Abs.Alc)	69.7814 ± 2.3752	9.68×10^{-3}	Very slightly soluble (1:10,330)
9	Mixture of Abs.Alc + water (1:1)	94.2763 ± 2.0405	9.43×10^{-3}	Very slightly soluble (1:10604)

*average concentration of NFP from Triplicate run (N = 3)

2. Physical characteristics of Nifedipine Transdermal delivery system

All NFP preparations exhibited yellowish gel according to the color of the drug.

2.1 Pluronic F-127 gel matrix

From the physical characteristics showed in Table 11, 12 and 13, the consistency of gel increased with increasing the concentration of PF-127. Small air bubbles appeared during preparing process and were prominent at higher concentration of gelling agents. However, these air bubbles disappeared when stored the mixture in refigerator. The highest concentration, 50% w/w, of PF-127 was very difficult to prepare. It took much more times to be completly dispersed but it provided higher consistency than the lower concentrations, 30% w/w and 40% w.w. The residue of gel matrix when applied on the surface of skin was observed. It was found that the residue increased when decreasing the concentration of PF-127. Incorporation of PG, glycerol, or PEG 400 could reduce this problem and improve the consistency of prepartation.

After stored in refigerator, preparation of 30% w/w and 40% w/w polymer completely dispersed within 24 hours, while that of 50% w/w polymer took more times,

Table 11 Physical Characteristics Obtained from 30% w/w Pluronic F-127 gel matrices.

Physical Characteristics \ Prep. No	1	2	3	4	5	6	7	8	9	10	12	13	14
Difficulty in preparing[1]	-	-	-	-	-	-	-	-	-	-	-	-	-
Clarity[2]	+	+	+	+	+	+	+	+	+	+	+	+	+
Air bubble[1]	-	-	-	-	-	-	-	-	-	-	-	-	-
Residue[1] on Application	+4	+4	+3	+3	+3	+4	+4	+4	+4	+4	+4	+4	+4
Consistency[3]	+2	+2	+2	+2.5	+2	+2.5	+2-	+2	+2	+2	+2	+2	+2.5

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

Table 12 Physical Characteristics Obtained from 40% w/w Pluronic F-127 gel matrices.

Physical Characteristics \ Prep. No	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Difficulty in preparing[1]	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Clarity[2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Air bubble[1]	+	+	-	-	-	-	-	-	-	+	-	-	-	-
Residue[1] on Application	+3	+3	+3	+2	+3	+3	+3	+3	+3.	+3	+3	+2	+3	+3
Consistency[3]	+2.5	+3	+3	+3	+3	+3.5	+3	+3	+3.5	+3	+3	+3	+3	+3

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

Table 13 Physical Characteristics Obtained from 50% w/w Pluronic F-127 gel matrices.

Physical Characteristics \ Prep. No	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Difficulty in preparing[1]	++	+	+	-	+	+	-	+	-	-	-	-	-	-
Clarity[2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Air bubble[1]	+	-	-	+	-	-	-	-	-	-	+	-	-	-
Residue[1] on Application	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Consistency[3]	+3	+3.5	+3.5	+3.5	+3	+3.5	+3.5	+3	+3	+3	+3.5	+3	+3	+3

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

about 36 hours. However, all preparations exhibited clear, yellowish gel without precipitation of NFP after incubated for 24 hours at room temperature.

2.2 Aerosil A-200 gel matrix

The physical characteristics of NFP transdermal preparation containing Ae-200 were shown in Tables 14 and 15. No air bubbles was obtained in these gels. The preparation of 30% w/w polymer showed better consistency and better physical appearance, however, it was more difficult to prepare than the other, 20% w/w of Ae-200. This problem might be reduced by incorporating PEG 400. PEG 400 might also improve the clarity of gel matrices. The consistency of gel matrices which dued to the properties of PG and glycerol was observed. It was found that suitable concentrations of both organic modifiers ranged from > 25% w/w to < 45% w/w. Concentration lower than 25% w/w provided rigid gel which might crack when stored at room temperature. In addition, concentration higher than 45% w/w provided liquid gel whick took much more time, over 72 hours to transform to hard gel. Thus, the precipitation of NFP in gel matrix might occur. Suitable concentrations of PEG 400 were not more than 35%w/w, since higher concentration might also provide soft gel.

Table 14 Physical Characteristics Obtained from 20% w/w Aerosil A-200 gel matrices.

Physical Characteristics \ Prep. No	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Difficulty in preparing[1]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+
Clarity[2]	-	-	+	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-
Air bubble[1]	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-
Residue[1]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-
Consistency[3]	+3	+3	+3	+3	+3	+3	+3	+3	+3.5	+3	+3	+3.5	+3	+3.5	+4	+4.5	+4	+4.5
Transformation times (hours)	24	>24 <36	>36	24	>36	>36	>24 <36	>36	>36	>36	>24 <36	>36	>36	>36	>24 <36	24	>24 <36	24

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

Table 15 Physical Characteristics Obtained from 30% w/w Aerosil A-200 gel matrices.

Physical Characteristics \ Prep. No	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
Difficulty in preparing[1]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	+	+	+
Clarity[2]	-	-	-	-	-	-	-	+	-	+	+	+	+	+	-	-	-	-
Air bubble[1]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Residue[1]	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-
Consistency[3]	+3.5	+3.5	+3	+3.5	+3.5	+3	+3	+3.5	+3.5	+3.5	+3.5	+3.5	+3.5	+4	+4.5	+5	+4.5	+5
Transformation times (hours)	<24	24	>24 <36	24	24	>24 <36	>24 <36	>24 <36	>24	>24 <36	>24 <36	>24 <36	>24 <36	>36	>24	24	>24	24

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

2.3 Pluronic F-127-Aerosil A-200 Gel Matrix

The objective in using combined gelling agents was to improve the physical appearance of gel matrices. Ae-200 could be used as thickening agent for improving the consistency and reducing the transformation time of PF-127 gel. The result was shown in Table 16. The suitable concentration of Ae-200 was below 10% w/w with PF-127 50% w/w.

2.4 The Selected Formulations of NFP Transdermal Deliver Preparations for Permeation Study

From the results of physical characteristies study of NFP transdermal delivery preparations, the desired NFP preparations for evaluation were shown in Tables 17, 18, 19 and 20.

For PF-127 gel matrices (Table 17), the desired preparation composed of 50% w/w of PF-127, 3-6% of Ae-200, 5-10% w/w of glycerol or PG and/or 10-15% w/w of PEG 400. For Ae-200 gel matrices (Table 18), they consisted of 30% w/w Ae-200 as drug carrier. The other additives were glycerol or PG at the range of 27-35% w/w, 15-25% w/w of PEG 400 and/or 1% w/w of HPMC.

Table 16 Physical Characteristics Obtained from Combined Pluronic F-127 30-50% w/w and Aerosil A-200 2-10% w/w Gel Matrices.

Pulronic F-127	30% (w/w)							40% (w/w)							50% (w/w)						
Aerosil A-200 (% w/w)	2	5	10	5	10	5	10	2	5	10	5	10	5	10	2	5	10	5	10	5	10
Prep.No. / Physical Characteristics	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
Difficulty in preparing[1]	+	+	++	+	+	+	+	++	++	++	+	+	+	+	+++	+++	+++	+	+	+	+
Clarity[2]	+	-	-	+	+	+	+	-	-	+	+	+	+	+	-	-	-	+	+	+	+
Air bubble[1]	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	+	+	-	-	-	-
Residue[1]	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Consistency[3]	+2.5	+3	+3	+3	+3	+3	+3	+3	+3	+3.5	+4	+4	+4	+4	+3.5	+4	+4.5	+4.5	+4.5	+4.5	+4.5

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

Table 17 The Desired Preparations of Nifedipine-TDDs Using Pluronic F-127 Gel as Drug Carrier.

Ingredients	percent of ingredients in each preparation (% w/w)									
	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10
Nifedipine	1	1	1	1	1	1	1	1	1	1
Pluronic F-127	50	50	50	50	50	50	50	50	50	50
Glycerine	-	-	10	7.5	7.5	7.5	-	-	-	-
Propyleneglycol	-	-	-	-	-	-	10	7.5	7.5	7.5
PEG 400	-	-	-	-	10	15	-	-	10	15
Aerosil	3	6	6	6	6	6	6	6	6	6

Table 18 The Desired Preparations of Nifedipine-TDDs Using Aerosil A-200 Gel as Drug Carrier.

Ingredients	Percent of ingredients in each preparation (% w/w)											
	A01	A02	A03	A04	A05	A06	A07	A08	A09	A10	A11	A12
Nifedipine	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil A-200	30	30	30	30	30	30	30	30	30	30	30	30
Glycerine	27	35	27	27	27	27	-	-	-	-	-	-
Propyleneglycol	-	-	-	-	-	-	27	35	27	27	27	27
PEG 400	-	-	15	25	15	25	-	-	15	25	15	25
HPMC	-	-	-	-	1	1	-	-	-	-	1	1

Table 19 Physical Characteristics Obtained from Desired Nifedipine-TDDs Preparations Using Pluronic F-127 Gel as Drug Carrier.

Physical Characteristics \ Prep. No.	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10
Dificulty in Preparing[1]	++	++	-	+	-	-	-	+	-	-
Clarity[2]	+	+	+	+	+	+	+	+	+	+
Air bubble[1]	-	-	-	-	-	-	-	-	-	-
Residue on Application[1]	+	-	-	-	-	-	-	-	-	-
Consitency[3]	+4	+4.5	+4.5	+4.5	+4	+4	+4	+4	+4	+4

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.

Table 20 Physical Characteristics Obtained from Desired Nifedipine-TDDs Preparations Using Aerosil A-200 Gel as Drug Carrier.

Physical Characteristics \ Prep. No.	A01	A02	A03	A04	A05	A06	A07	A08	A09	A10	A11	A12
Dificulty in Preparing[1]	-	-	-	-	-	+	-	+	-	-	+	+
Clarity[2]	+	+	+	+	+	+	+	+	+	+	+	+
Air bubble[1]	-	-	-	-	-	-	-	-	-	-	-	-
Residue on Application[1]	-	+	-	+	-	-	-	+	+	+	-	-
Consitercy[3]	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4
Transformation Times (hours)	24	24	24	24	24	24	24	24	24	24	24	24

1. The number of the symbols of (+) and (-) showed a degree of intensity and no appearance, respectively.

2. Clarity : (+) = transparent, (-) = translucent.

3. Consistency : observed by hand-pressed with scoring as follow
   a) +5 = solid firmed matrix and leaved no impression when pressed.
   b) +4 = solid firmed matrix and leaved impression when pressed.
   c) +3 = hard gel.
   e) +2 = soft gel.
   d) +1 = cream liked.

All twenty two selected preparations provided good physical appearance, good consistency and took a short time for gel transformation.

3. Permeation Study

3.1 Determination of Optimal Stirring Rate

The results for the determination of optimal stirring rate for each diffusion cell was run by the method of Gummer and et.al., (1987) were shown in Table 21. The results indicated that the suitable stirring rate, for each assembly, which completely dispersed of mauve coloration from permanganate crystal within 30 seconds was 90 rpm. by external driving unit. This stirring rate provided good hydrodynamics of elution medium to reduce the effect of aqueous boundary layer. It was the stirring rate used for the *in-vitro* skin permeation of NFP-TDDs preparation for this research study.

3.2 Determination of Temperature Control

To determine the optimal temperature for the *in-vitro* skin permeation study, the temperature of elution medium, "inner temperature, IT", and the temperature of water in the water jacket," outer temperature, OT", that correlated to the scale of temperature adjustable knob

Table 21 The Average Time to Disperse of Mauve Coloration from The Permanganate Crystal Obtained from Each *in-vitro* Permeation Apparatus.

Diffusion cell	A					B					C				
stirring rate (rpm.)	60	70	80	90	100	60	70	80	90	100	60	70	80	90	100
Times (second)*	85	63	47	29	22	103	74	37	26	23	91	61	44	27	23

* Each data represents the mean of triplicate determination

were detected. The results from three diffusion cells were shown in Table 22. It was found that the scale of adjustable knob of each external thermostatic plate, A, B, C that could provide and maintain a constant temperature of diffusion cell at 37 $\pm$ 1^{o}C for at least 24 hours of experiment were 1.3, 1.5 and 1.3, individually. The mean different temperature between "IT" and "OT" in each diffusion cell, A, B, C was 0.9, 0.8 and 0.9, respectively. These scales, 1.3, 1.5 and 1.3, of individual external thermostatic plate were maintained throughout is research study.

4. Quantitative Analysis of Nifedipine-TDDs Preparation

4.1 Determination of Maximum Absorption Wavelength of NFP

By UV scanning for maximum absorption wavelength of NFP and IS, the result in Figure 11, indicated that both NFP and IS had two maxima absorptions. Their maxima UV-absorptions were detected at the wavelength of 358,237 and 341,242.5 nm, respectively. The absorbances of NFP and IS at maximum wavelength, 237 and 341 nm, were 1.38 and 1.14, respectively. However, the wavelength at 238 nm was preferred for NFP detection in high performance liquid chromatographical method to determine the quantities of NFP by several investigators and by USP. Thus, in this research study, the quantitative analysis of NFP from NFP-

Table 22 The Temperature of Elution Medium and Water in Water Jacket Obtained from Each Diffusion Cell by Controlling with Individual External Thermostatic Plate at Various Degree of Adjustable Knob.

Diffusion cell	A*									B*									C*								
Scale	1.0			1.3			1.5			1.0			1.3			1.5			1.0			1.3			1.5		
Time(h)	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif	IT	OT	Dif
0.5	34.3	35.6	1.3	36.7	37.7	1.0	38.8	40.2	1.4	32.1	33.0	1.1	35.1	35.9	0.8	36.3	37.1	0.8	33.2	34.2	1.2	36.4	37.3	0.9	37.5	38.6	0.9
3.0	34.7	35.9	1.2	37.1	37.8	0.7	39.2	40.3	1.1	32.7	33.5	1.2	35.7	36.6	0.9	37.1	37.8	0.7	34.0	35.2	1.2	36.9	38.1	1.2	38.3	39.4	1.1
6.0	35.2	36.0	0.8	37.3	38.1	0.8	40.1	40.8	0.7	33.1	34.2	1.1	35.9	36.7	0.8	37.3	37.9	0.6	35.4	36.1	0.7	37.2	38.0	0.8	38.7	39.7	1.0
9.0	35.0	36.2	1.2	37.2	38.0	0.8	40.4	41.1	0.7	33.3	34.4	1.1	36.1	36.9	0.8	37.5	38.8	0.6	35.5	36.3	0.8	37.3	38.1	0.8	39.0	39.9	0.9
12.0	35.2	36.2	1.0	37.4	38.2	0.8	40.7	41.3	0.6	33.5	34.5	1.0	36.2	36.8	0.6	37.4	38.2	0.8	35.9	36.9	1.0	37.4	38.3	0.9	39.2	40.0	0.8
16.0	35.1	34.3	1.2	37.5	38.5	1.0	40.5	41.3	-0.8	33.6	34.4	1.0	36.3	36.9	0.6	37.4	38.6	0.8	36.0	36.9	0.9	37.4	38.3	0.9	39.2	40.1	0.9
20.0	35.2	36.2	1.0	37.4	38.5	1.1	40.6	41.5	0.9	33.6	34.6	1.0	36.4	37.0	0.6	37.5	38.6	1.1	36.2	37.0	0.8	37.5	38.5	1.0	39.3	40.0	0.7
24.0	35.0	36.2	1.2	37.5	38.6	1.1	40.7	41.6	0.9	33.6	34.6	1.0	36.3	37.2	0.9	37.9	38.5	1.0	36.1	37.0	0.9	37.5	38.6	0.9	39.3	40.2	0.9
mean dif.temp.			1.1			0.9			0.9			1.1			0.8			0.8			0.9			0.9			0.9

* Each data represent the mean of duplicate determination and the hydrodynamics of eluting medium in each diffusion cell was maintained at 30 rpm. of stirring rates.

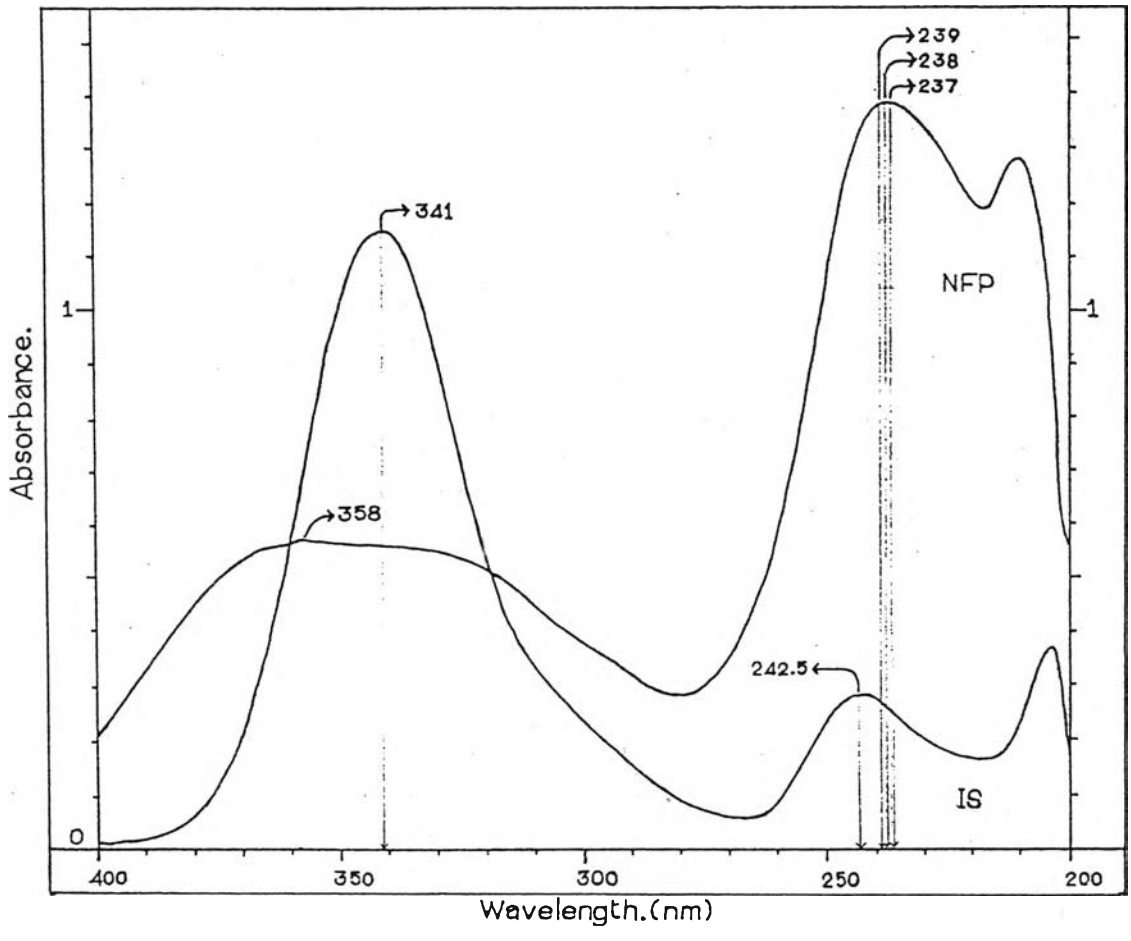

Figure 11 UV-Scanning Curve of Nifedipine (NFP) and 4-Dimethyl aminobenzaldehyde (IS) in Methanol by UV-Spectrophotometer. NFP = 39.68 ug/ml; IS = 4.03 ug/ml. Maximum Absorbance of NFP at 341,237 nm; IS at 358 and 242.5 nm.

TDDs by HPLC were performed at the wavelength of 238 nm of UV-detector.

4.2 Chromatographic Conditions

Isocratic reversed-phase HPLC and designed chromatographic conditions, e.g., mixture of 0.01 M acetate buffer pH 6.1 and methanol in the ratio of 35 : 65, as mobile phase and the wavelength of 238 nm of UV-detector, could provide good resolution between NFP and IS. The run time per sample was within 12 minutes. Their chromatogram of HPLC was shown in Figure 12 presented the good resolution between NFP and IS and the interval of retention time was about 1.24 - 1.29 minutes.

4.3 Calibration Curve

The calibration curve of NFP was constructed by plotting the ratio of peak area (PAR) of NFP and IS against the NFP concentration. A typical calibration plot (Figure 13), showed a linear relationship between the ratio of AUC and NFP concentration with the correlation coefficient by a least square fitted was 0.9982. For the calculation of the concentration of NFP in *in-vitro* skin-permeation study, the calibration plots in the range 0.02 - 0.24 ug/ml NFP was repeated every course of the analysis and each x-coefficient of a least square fitted was used to calculate the amount of NFP in each elution sample.

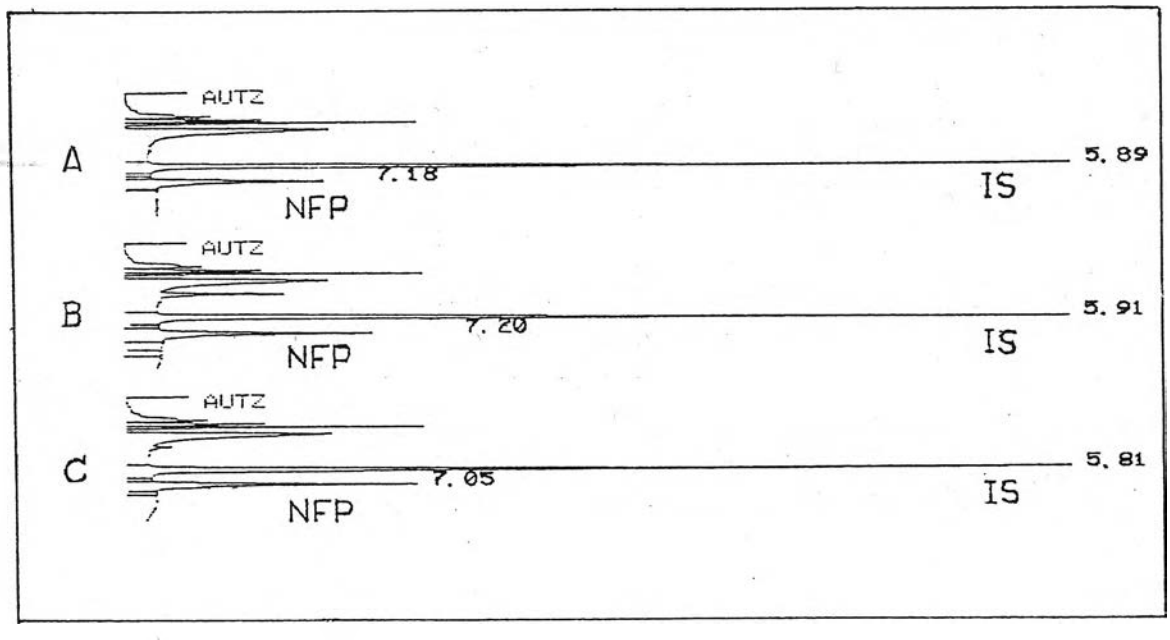

Figure 12 High Performance Liquid Chromatogram of Nifedipine (NFP) and 4-Dimethylaminobenzaldehyde (IS) at 238 nm. Each Sample Contained Fixed Concentration of IS as 0.12 ug/ml with various concentrations of NFP; [A] 0.04 ug/ml; [B] 0.06 ug/ml and [C] 0.08 ug/ml.

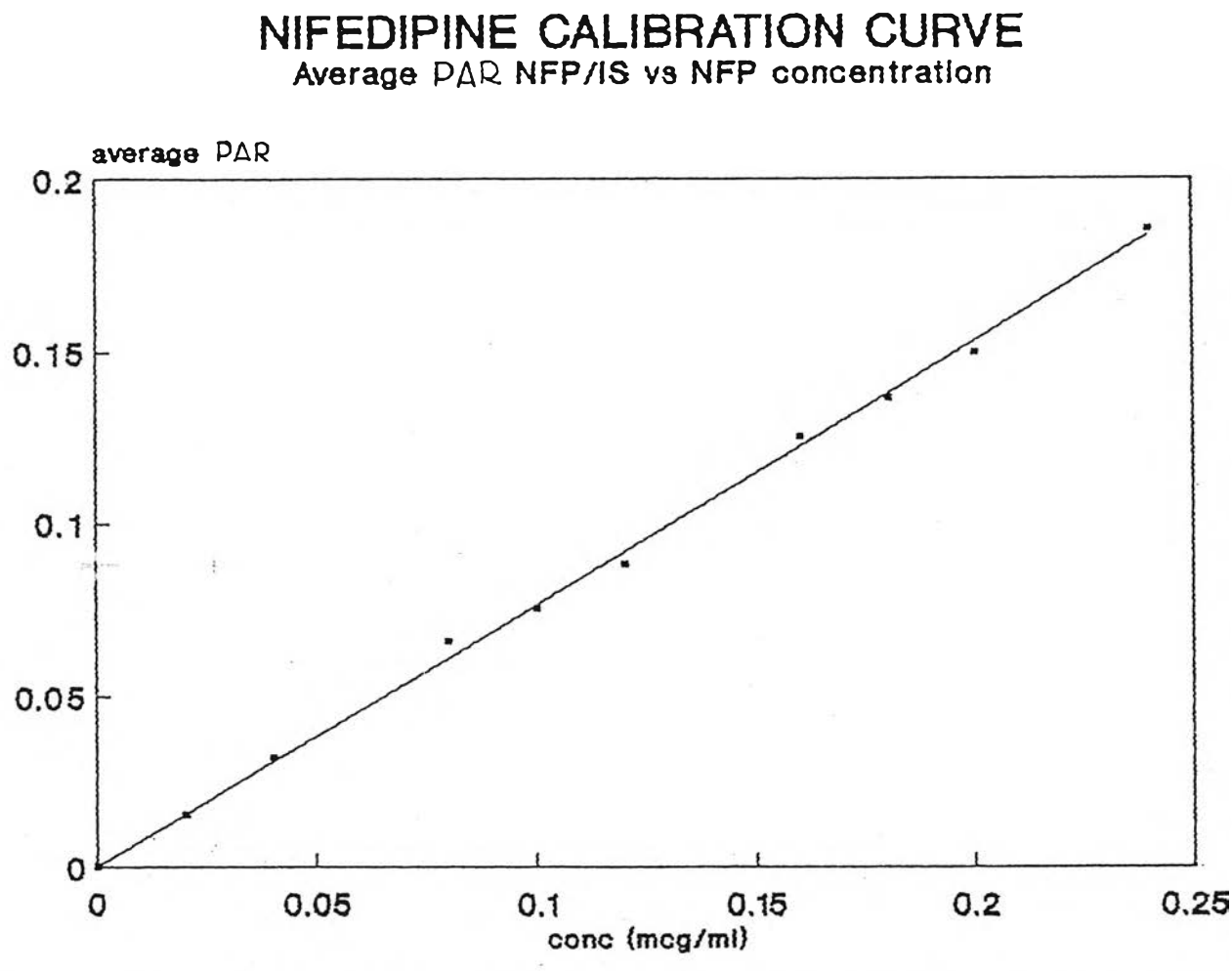

Figure 13 Calibration Curve of Nifedipine (NFP) - Internal Standard (IS) Peak Area Ratio (PAR) as A function of NFP Concentration Range of 0.02 - 0.24 ug/ml Determined by HPLC at 238 nm UV detector.
(Y = 0.75981X + 0.000768 R-square = 0.9982 n = 2).

5 In vitro Evaluation of Nifedipine TDDs Preparations

From in-vitro skin permeation experiment which used miniature pig's skin as barrier, the skin permeation profile data and of NFP from saturated solution and from twenty-two desired preparations were illustrated in Appendices I-XXV, Figures 14 - 47 and Tables 23 - 25. All data were presented as average cumulative permeation of NFP through a unit surface area of pig's skin [Qs]. The relationship between Qs vs time (t) or vs square root of time (sqrt t) and between logarithm of remained drugs (RQs) per area vs t of each formula were exhibited for the observation of permeation pattern, permeation mechanism, rate of skin permeation and correlation coefficient to indicate the effect of gelling agents and other additives. The result of these relationships were shown in Tables 26, 27.

5.1 Saturated Nifedipine Solution

The permeation data and profile of saturated NFP solution was presented in Appendix I, Table 23, and Figures 14-16 the results indicated that the maximum Qs was 0.1837 mcg/cm^2. The relationship between Qs vs t indicated that permeation pattern of NFP from saturated solution was non-linear, the drug rapidily permeated for the first two hours and followed by a slow permeation till 24 hours with a constant rate. From the relationships

TABLE 23 The Average Cumulative Amount of Nifedipine per Surface Area of Pig's Skin (mcg/cm^2) Permeated from Nifedipine Saturated Solution by in-vitro Skin Permeation Experiments.(n=3)

Time (hr)	PERMEATION AMOUNT[mcg/cm^2]				
	CELL A	CELL B	CELL C	AVERAGE	SD
0	0	0	0	0	0
0.5	0.1010	0.0324	0.0325	0.0553	0.0368
1	0.1833	0.0793	0.0613	0.1079	0.0659
2	0.2051	0.1087	0.0468	0.1202	0.0767
3	0.1383	0.1699	0.1312	0.1465	0.0650
4	0.1530	0.1628	0.0658	0.1272	0.0667
5	0.1481	0.1445	0.0720	0.1215	0.0607
6	0.1817	0.1605	0.1477	0.1633	0.0717
8	0.1100	0.1314	0.0837	0.1084	0.0498
10	0.1081	0.2076	0.0952	0.1369	0.0735
12	0.1315	0.2146	0.1101	0.1521	0.0765
15	0.1316	0.1901	0.1048	0.1422	0.0688
18	0.1590	0.2953	0.1140	0.1894	0.1057
21	0.1471	0.2834	0.1193	0.1833	0.1007
24	0.1464	0.3173	0.1247	0.1961	0.1130

SD = STANDARD DEVIATION

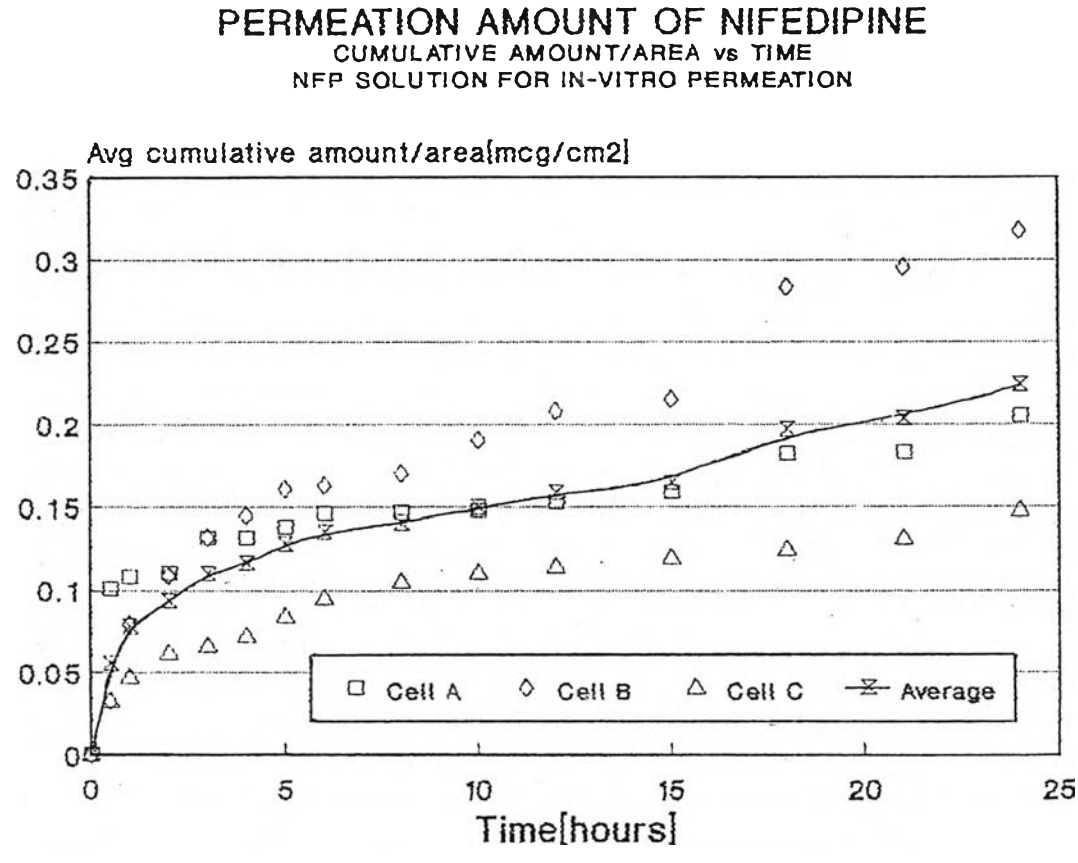

Figure 14 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from Saturated Solution.

[Y = 0.0060X + 0.0834, R-square = 0.9344 n = 3].

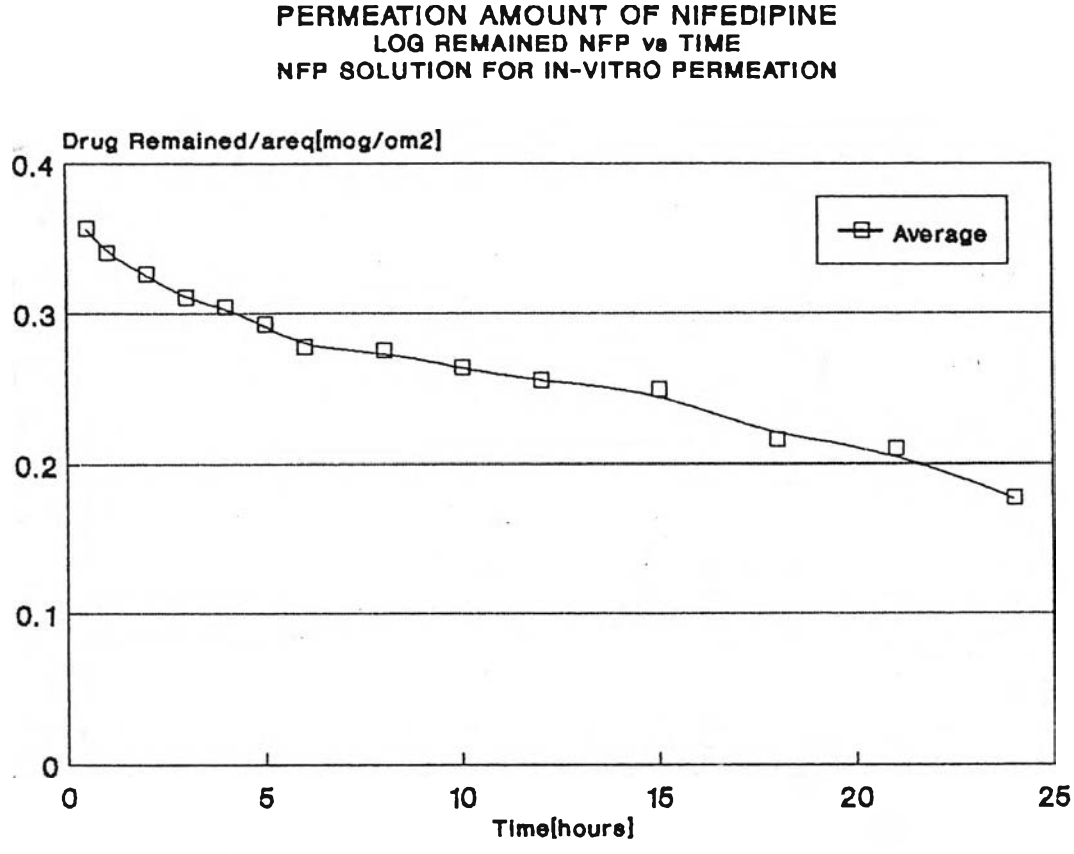

Figure 15 First-Order Plot of Nifedipine Permeation [mcg/cm^2] from Saturated Solution.
[Y = 0.0356X - 1.063, R-square = 0.8034 n = 3].

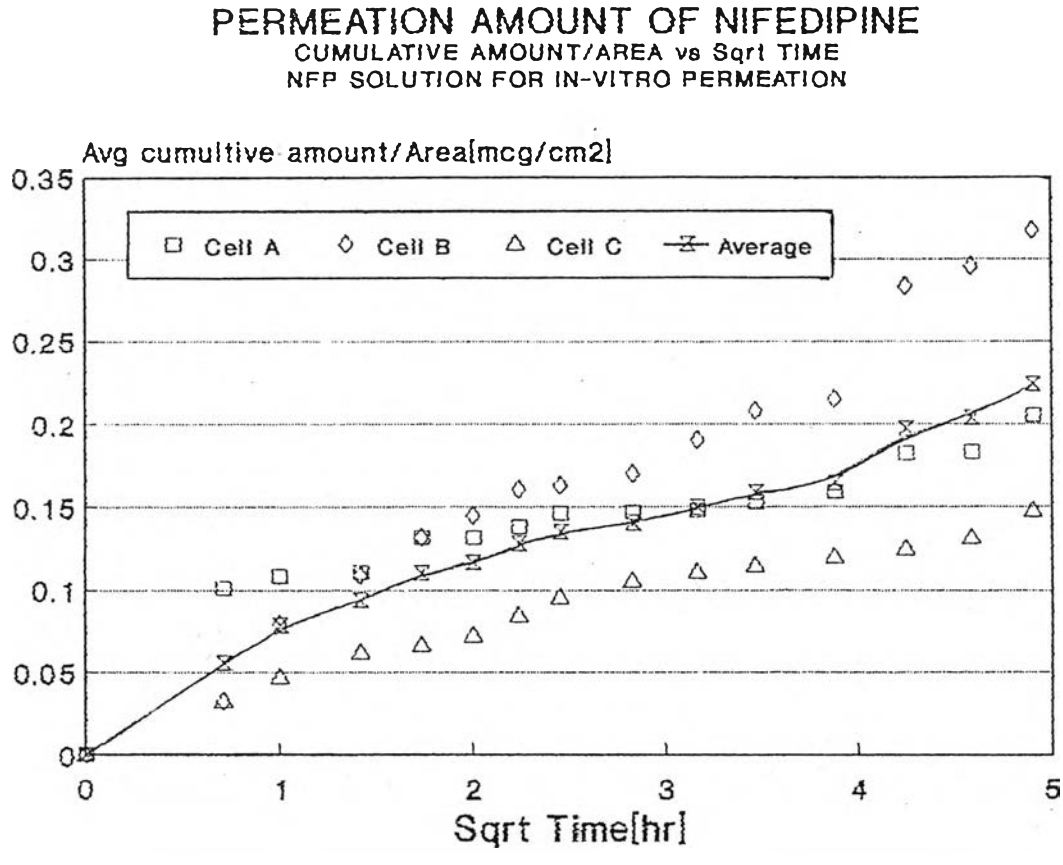

Figure 16 Hiquchi's Plot of Nifedipine Permeation [mcg/cm^2] from Saturated Solution.
[Y = 0.0356X + 0.0411, R-square = 0.9789 n = 3].

between Qs vs t, logarithm of RQs vs t and Qs vs Sqrt t (Table 26 and Figure 14 - 16), the value of each correlation coefficient was observed from a linear relationship which established from the data generated. The results were 0.9344, 0.9344 and 0.9789, respectively, indicated that the skin permeation pattern of NFP from the saturated solution by in-vitro skin permeation study seemed to be the Higuchi's model kinetics with 0.0356 $mcg/cm^2-h^{1/2}$ of slope and 0.0411 mcg/cm^2 of Y-intercept.

5.2 **NFP-Pluronic F-127 TDDs Preparations**

The permeation-Time data and permeation-Time profile of NFP from ten preparations of NFP-TDDs using PF-127 gel as drug carriers were illustrated in Appendices II - XII Table 24, and Figure 17 - 32. All preparations, exactly, sustained permeation of NFP over 24 hours. The maximum permeation amount was observed from preparation P03 to be 194.13 mcg/cm^2, while the minimum was 2.0635 mcg/cm^2 from P10. they could be ranked in the following order; P03 > P02 > P01 > P09 > P05 > P04 > P06 > P07 > P08 > P10. From the skin permeation rate of NFP from each preparation, which observed from the slope of Qs vs time plot (Figures 17 - 19, 24-25 and Table 26), it was found that P03 exhibited must superior skin permeation rate than the others, and the maximum permeation rate was 8.1598 mcg/cm^2-h.

TABLE 24 The Average Cumulative Amount of Nifedipine per Surface Area of Pig's Skin (mcg/cm^2) Permeated from Nifedipine-TDDs Using Pluronic F-127 Gel as Drug Carrier by in-vitro Skin Permeation Experiments (n = 3)

Time [hr]	Average Cumulative NFP Amount/Surface Area[mcg/cm^2]									
	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10
0	0	0	0	0	0	0	0	0	0	0
0.5	0.3509	0.2452	2.5233	1.3569	0.8340	0.4093	0.8009	0.6892	0.9346	0.4110
1	0.5212	0.3534	3.4171	1.5366	1.0769	0.4808	1.2209	0.8471	1.9874	0.5566
2	1.2522	0.3780	4.0440	1.6942	1.3061	0.5339	1.4678	1.1046	3.6267	0.6138
3	1.4858	0.6925	5.4976	1.8551	1.6084	0.5944	1.6781	1.1745	3.7820	0.7108
4	1.9184	1.8483	8.4156	2.2172	2.5723	0.6167	1.7868	1.4484	4.4797	0.8122
5	2.9805	2.3509	12.126	2.7766	3.5388	0.6788	2.0846	1.5276	5.3651	0.8972
6	3.8582	3.0305	18.579	3.0178	4.1656	0.6992	2.3882	1.6937	6.6196	0.9296
8	7.0290	6.1343	37.311	3.3737	5.5316	0.7594	2.7110	1.8124	7.1747	0.9814
10	10.936	10.210	59.653	3.9264	6.6066	0.8169	2.9324	2.0161	8.2825	1.0667
12	16.643	11.604	71.257	4.2324	7.5533	0.8799	3.2585	2.3305	9.3054	1.2655
15	24.974	19.872	94.292	4.3264	8.5049	1.0014	3.7173	2.5904	11.307	1.3402
18	30.815	32.794	122.98	5.4623	9.1185	1.1674	4.4228	2.6967	15.217	1.4407
21	35.133	38.371	157.95	6.6237	9.8893	4.2754	4.6186	3.3735	15.940	1.5698
24	43.367	46.124	194.13	9.6988	11.810	8.0727	5.4985	3.6851	17.830	2.0635

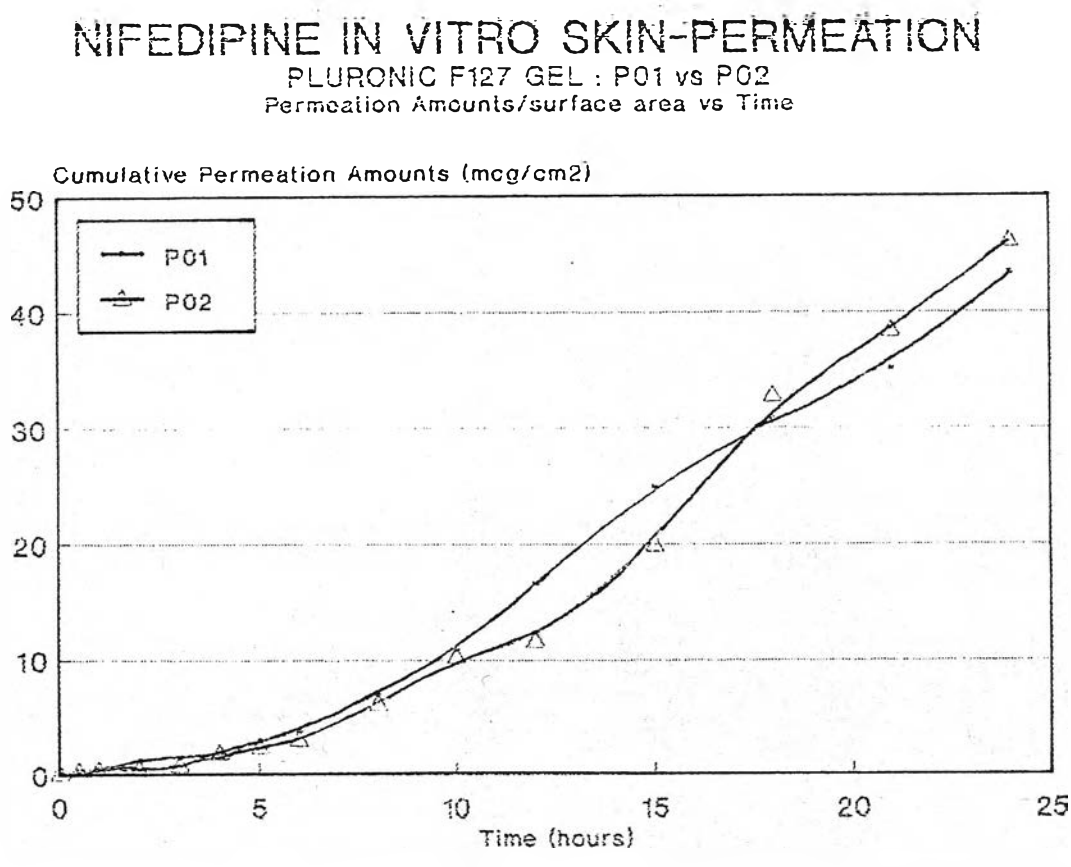

Figure 17 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from P01 and P02 Contained Aerosil A-200 3% w/w and 6% w/w Respectively.

[P01 : Y = 1.8894X - 4.5295, R-square = 0.9717;
P02 : Y = 1.9842X - 5.9247, R-square = 0.9433].

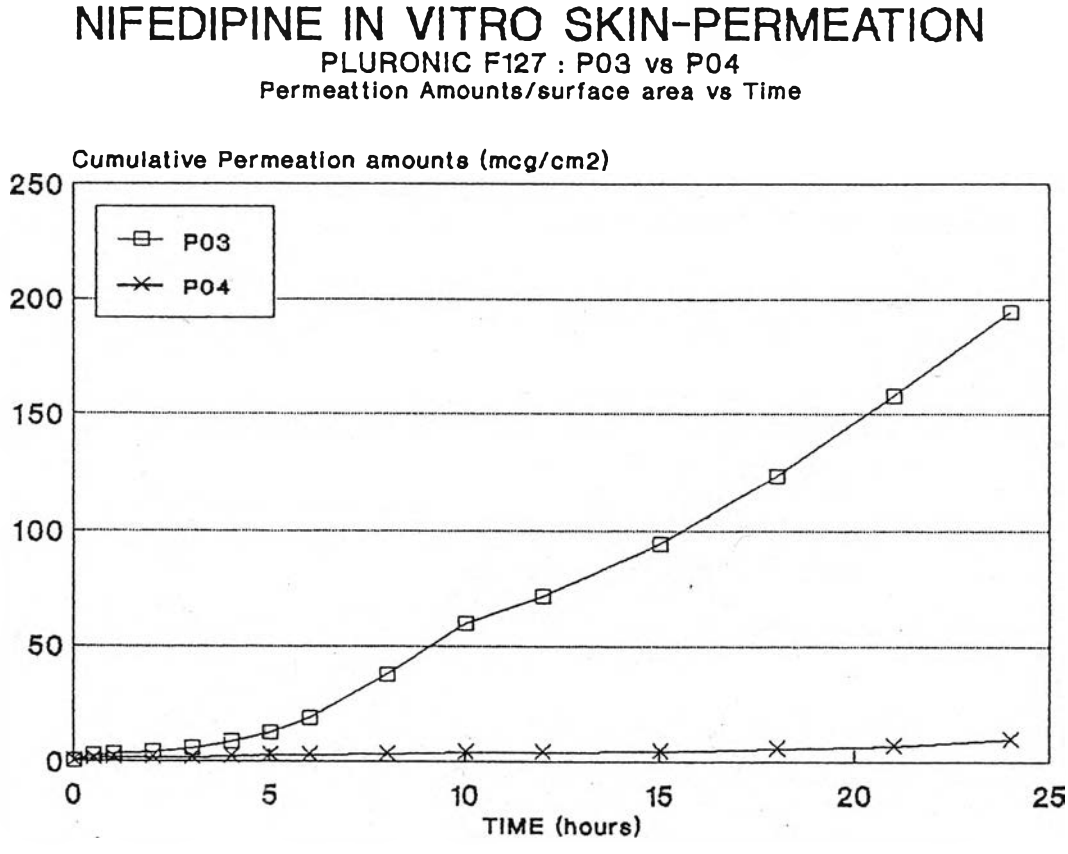

Figure 18 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from P03 and P04 Contained Glycerol 10% w/w and 7.5% w/w, Respectively.

[P03 : Y = 8.1598X - 18.8938 R-square = 0.9735;

P04 : Y = 0.2896X + 1.0423 R-square = 0.9250].

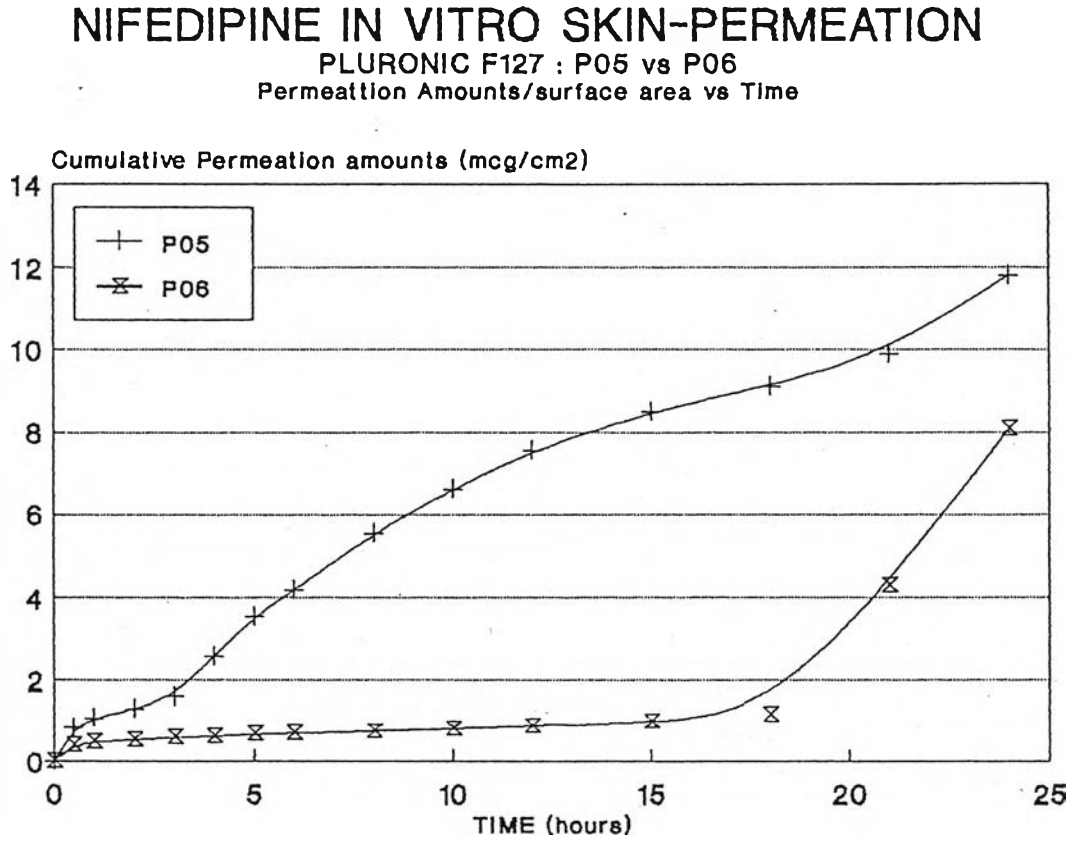

Figure 19 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from P05 and P06 Contained PEG 400 10% w/w and 15% w/w, Respectively.

[P05 : Y = 0.4692X + 0.9532, R-square = 0.9694;

P06 : Y = 0.2136X - 0.4758, R-square = 0.5954].

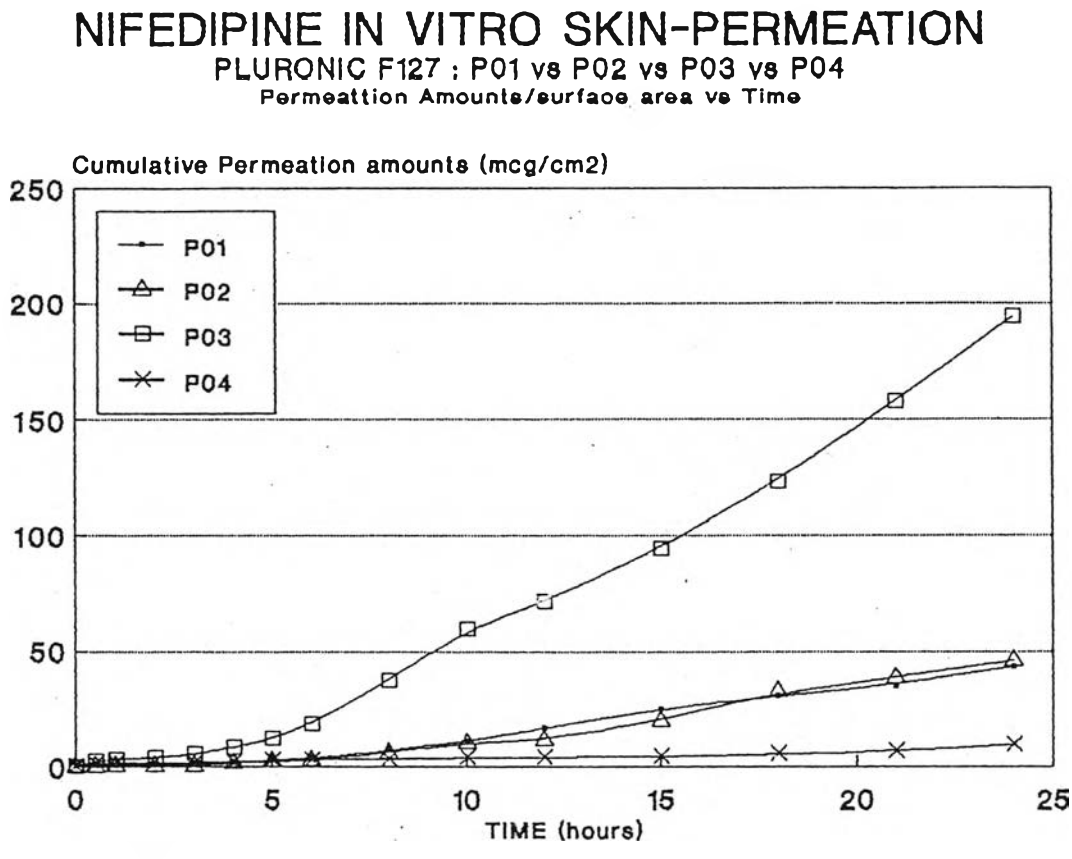

Figure 20 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P03, P04.

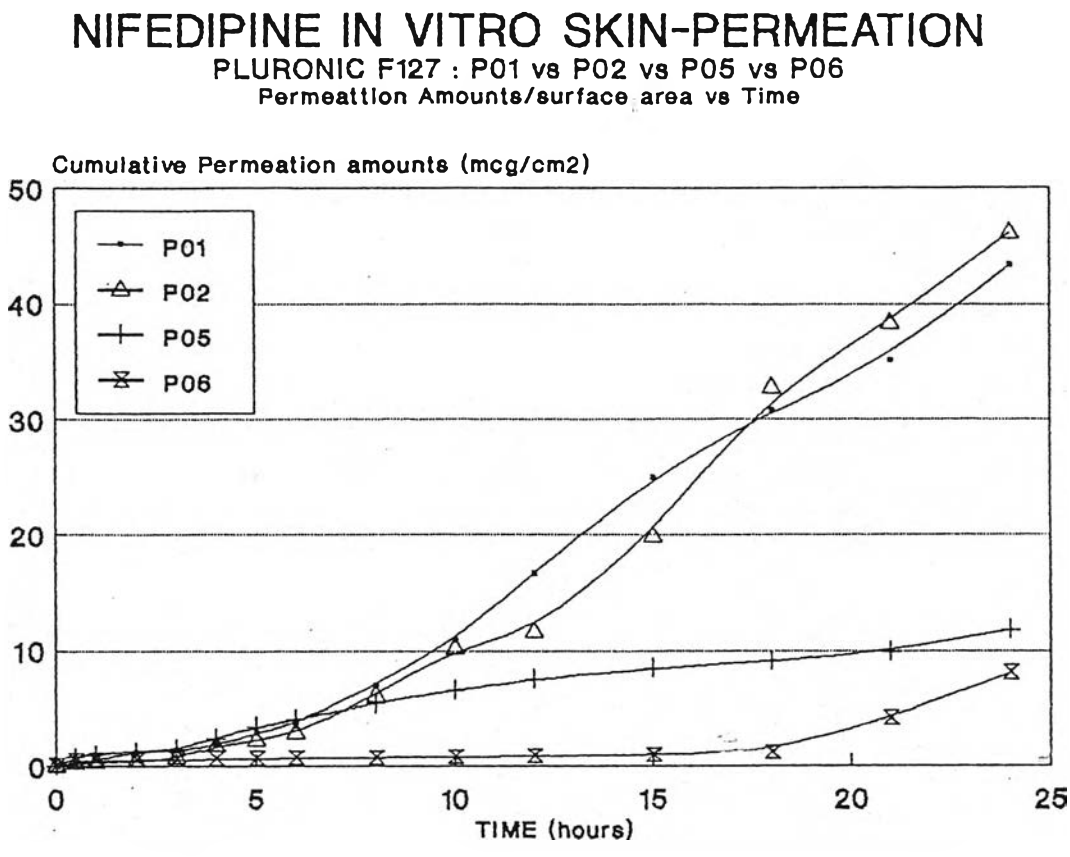

Figure 21 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P05, P06.

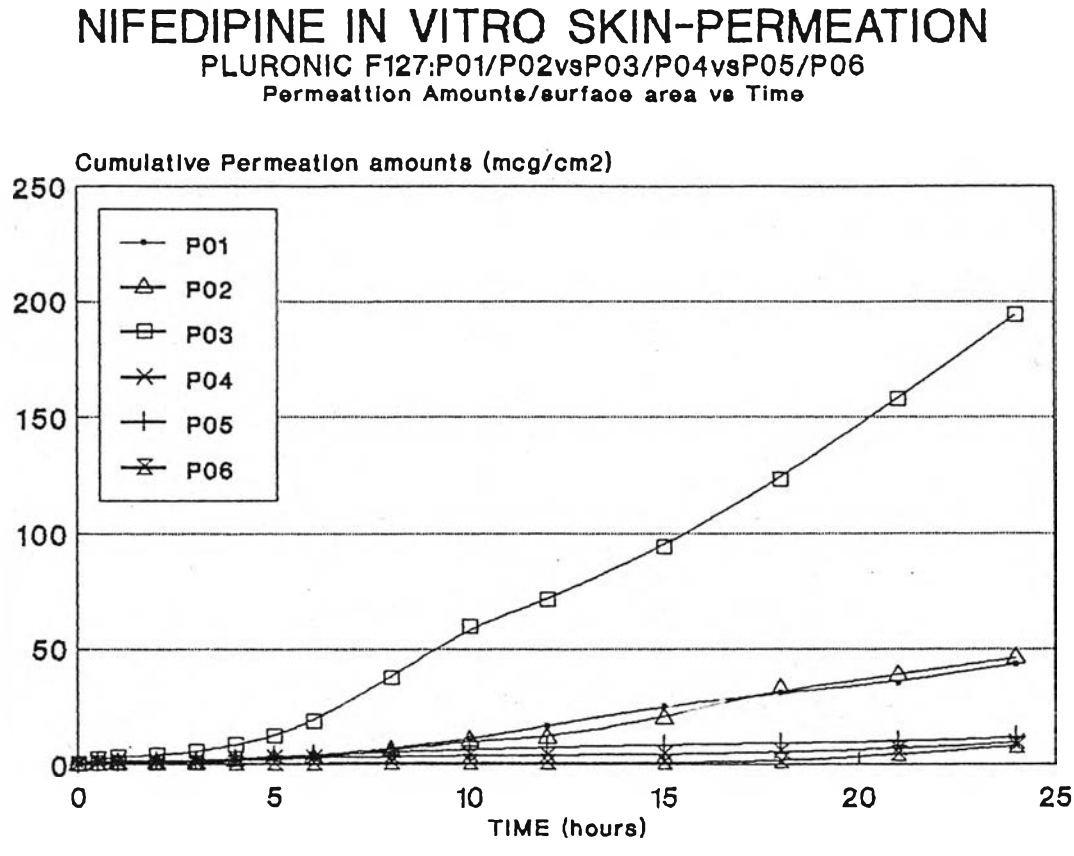

Figure 22 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P03, P04 vs P05, P06.

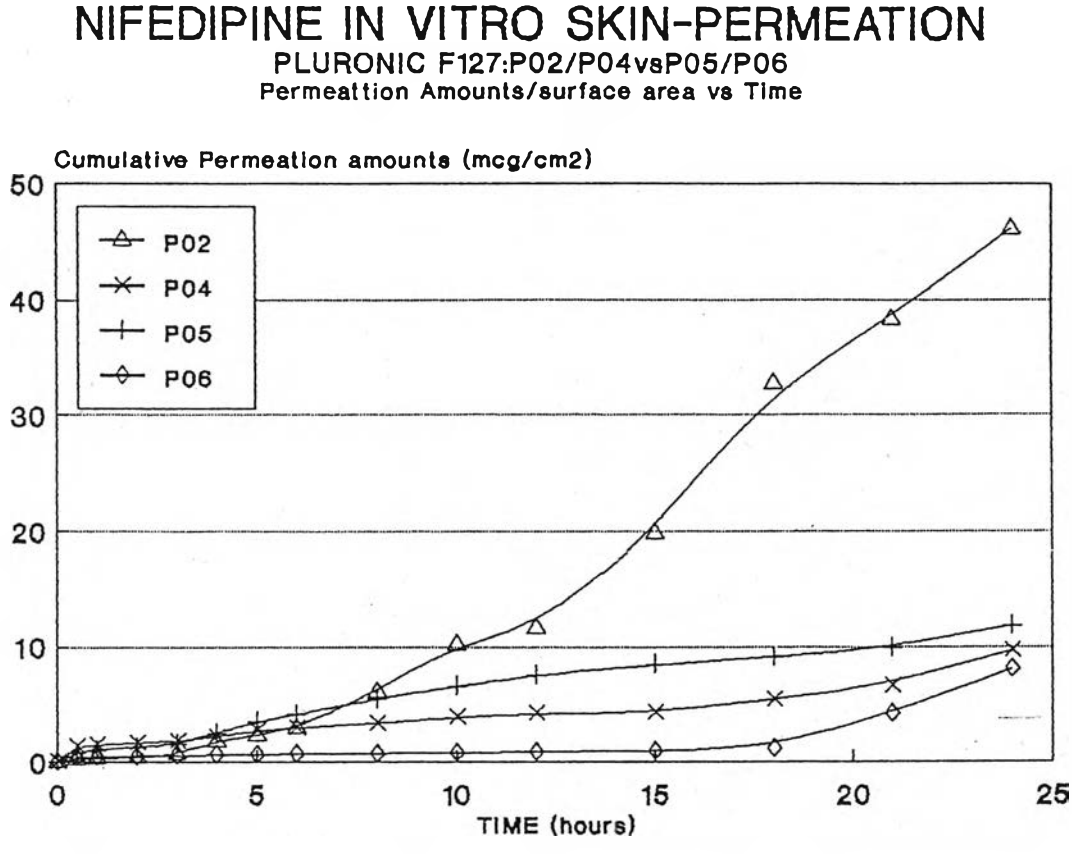

Figure 23 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P02 vs P04 vs P05, P06.

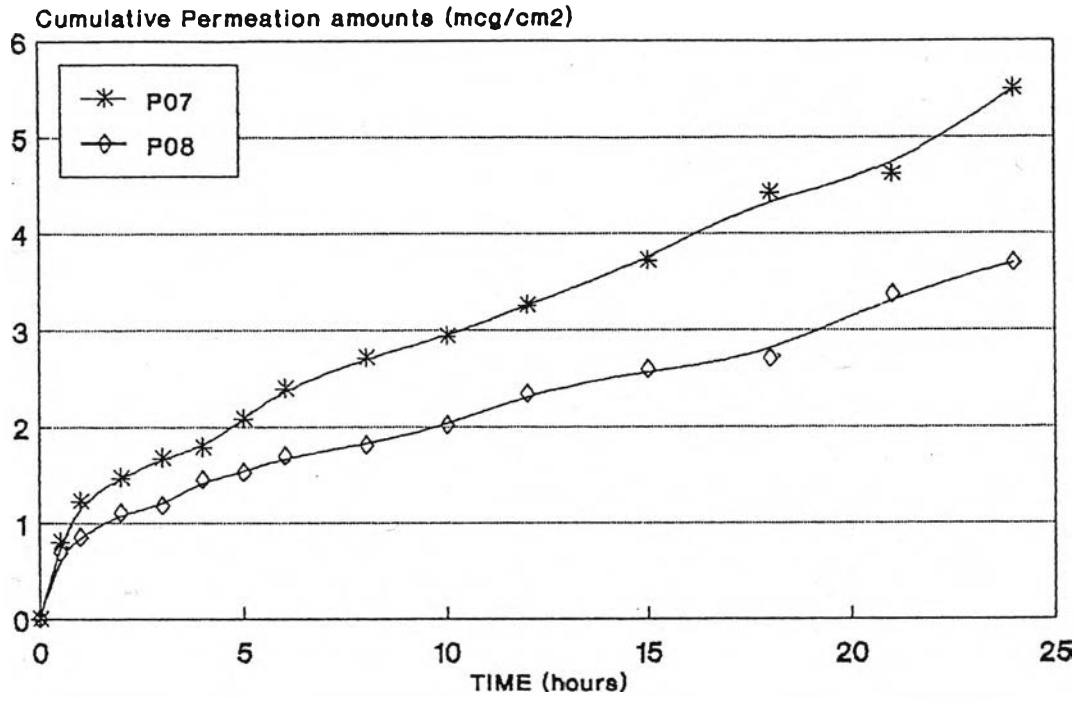

Figure 24 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from P07 and P08 Contained Propylene glycol 10% w/w and 7.5% w/w, Respectively.

[P07 : Y = 0.1811X + 1.0806, R-square = 0.9872;
P08 : Y = 0.1175X + 0.8409, R-square = 0.9825].

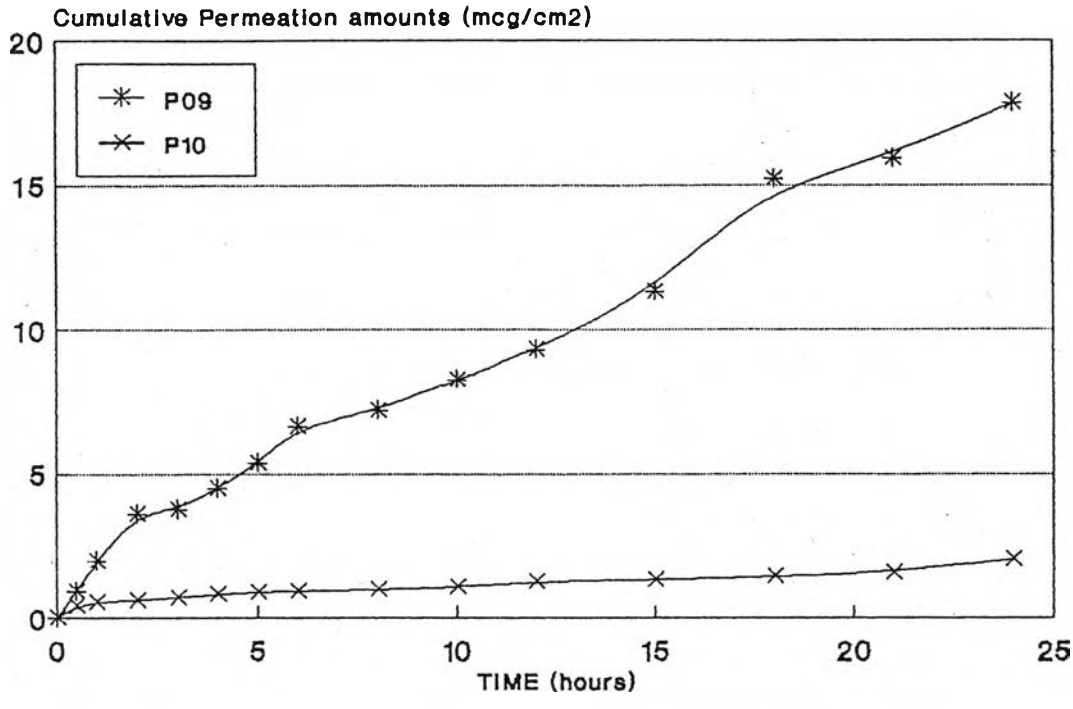

Figure 25 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from P09 and P10 Contained PEG 400 10% w/w and 15% w/w, Respectively.

[P09 : Y = 0.6893X + 1.6133, R-square = 0.9870;

P10 : Y = 0.0574X + 0.5159, R-square = 0.9596].

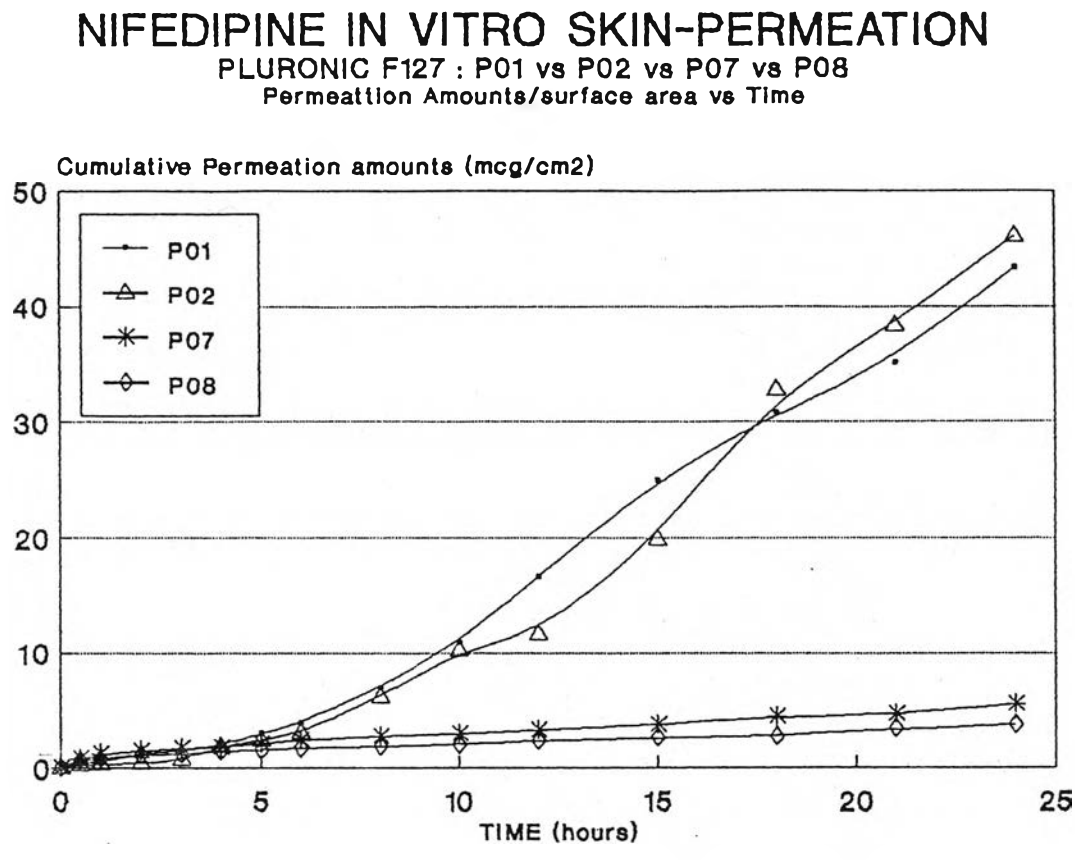

Figure 26 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P07, P08.

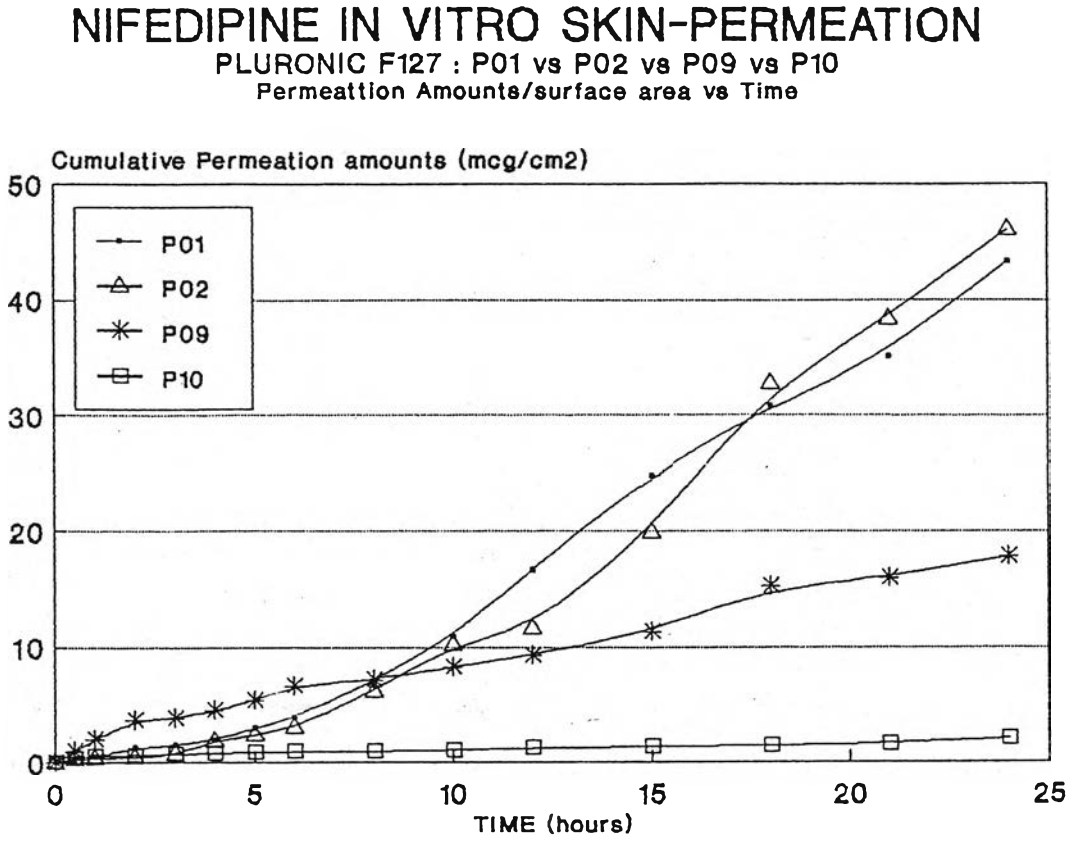

Figure 27 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P09, P10

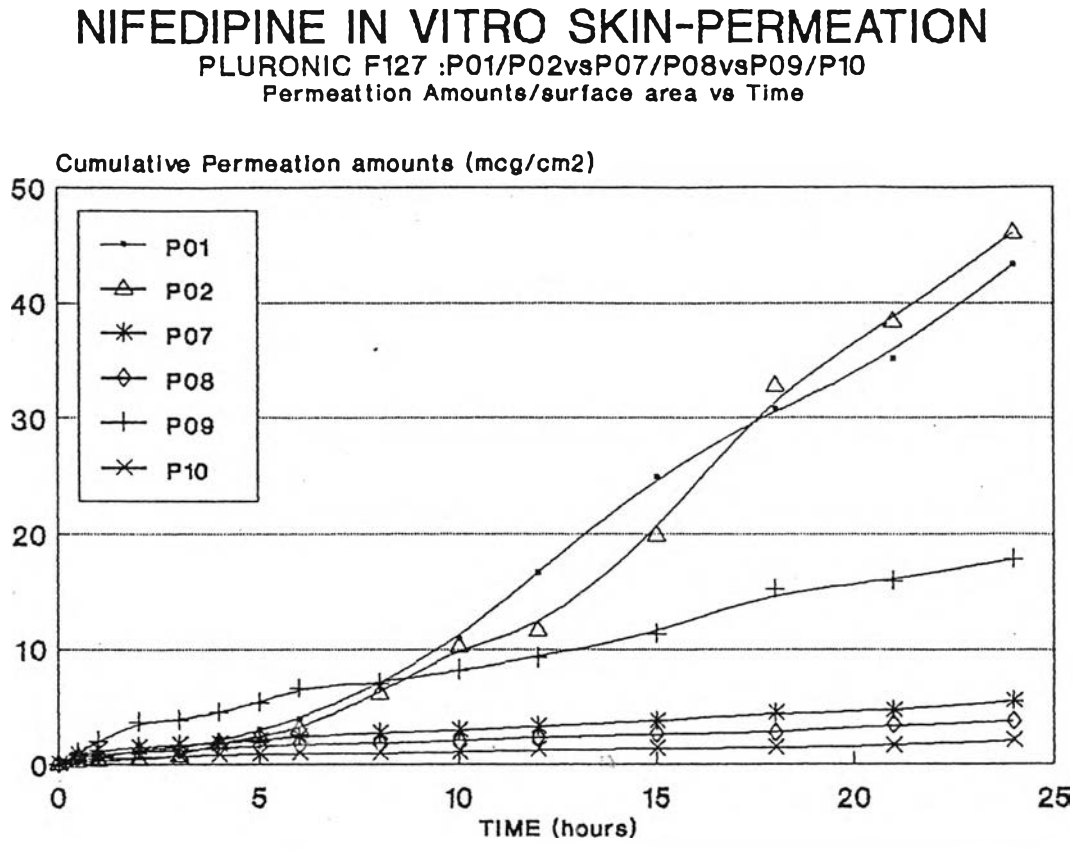

Figure 28 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P07, P08 vs P09, P10.

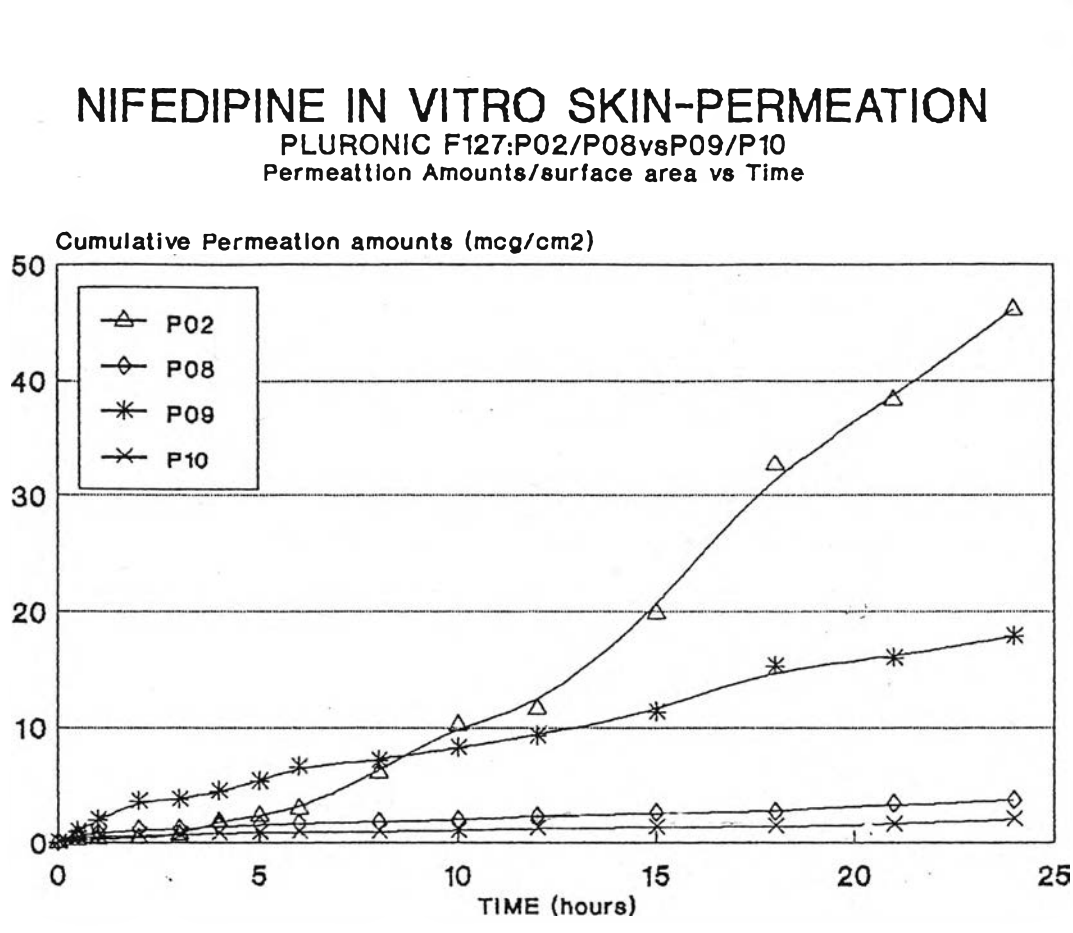

Figure 29 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P02 vs P08, vs P09, P10.

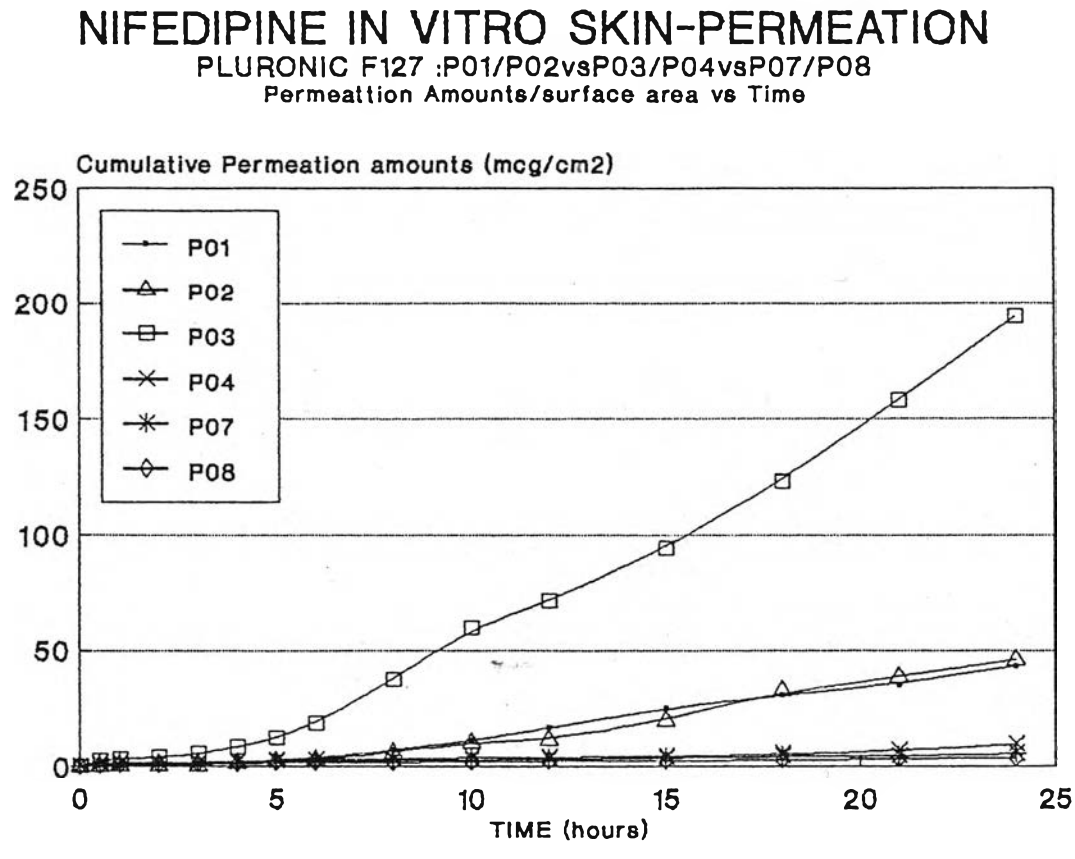

Figure 30 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P03, P04 vs P07, P08.

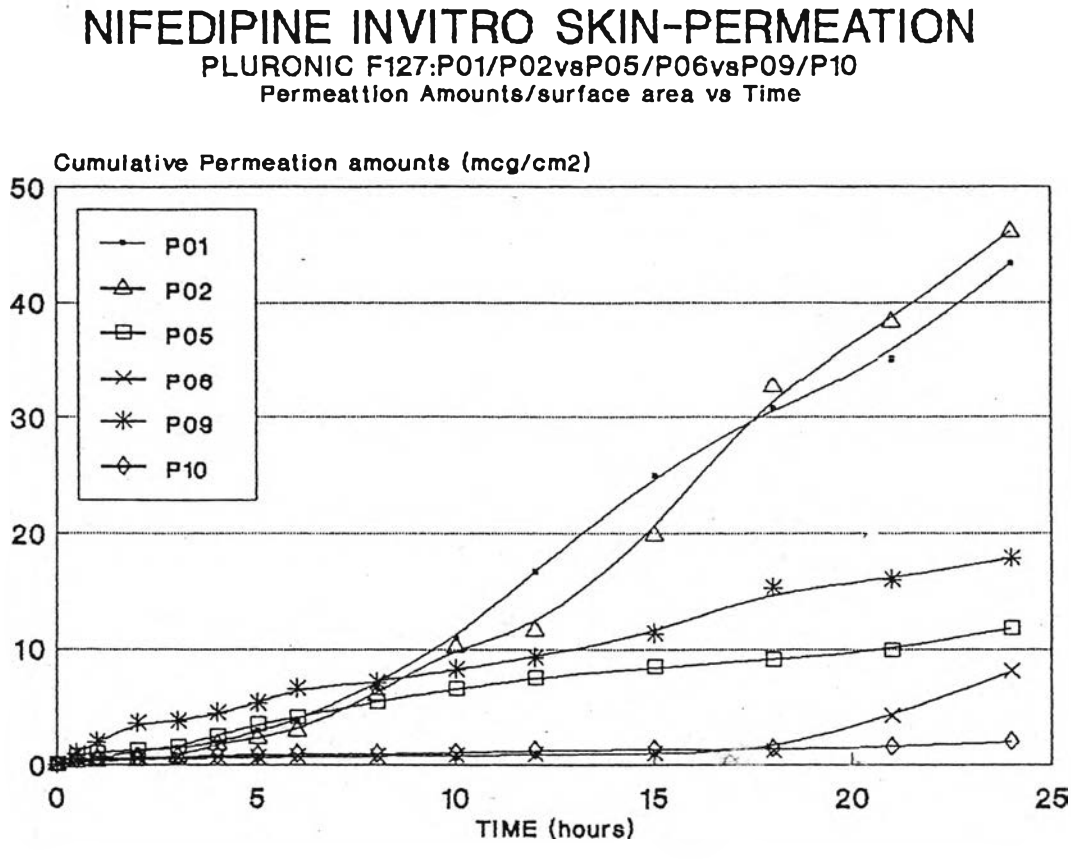

Figure 31 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P05, P06 vs P09, P10.

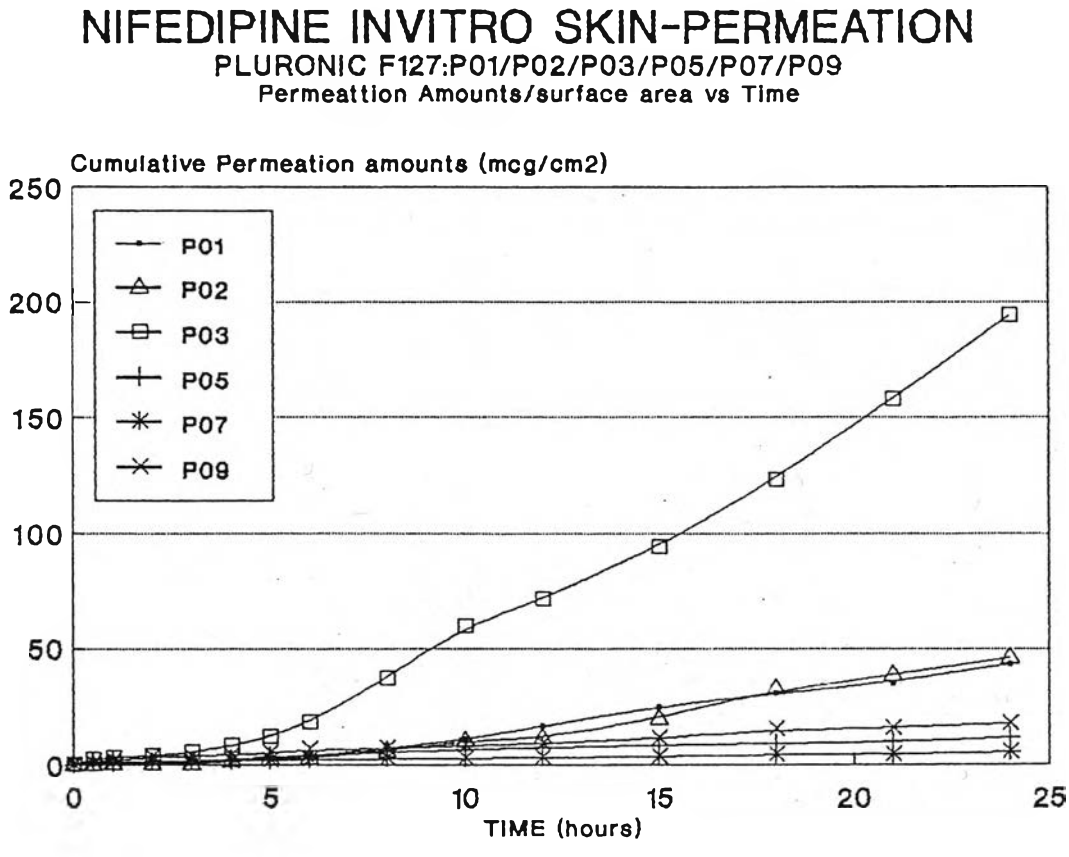

Figure 32 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared P01, P02 vs P03, vs P05, vs P07 vs P09.

To evaluated skin permeation pattern of NFP from PF-127 gel matrices, the linear relationship from the correlation of % Qs vs time, logarithm of remains % Qs vs time and % Qs vs square root time were observed and the kinetic patterns of each preparations were analysed. The results (Table 27), indicated that the skin permeation pattern of P01, P02 and P03 tended to be zero order kinetic P05, P08 was of Higuchi's model and all others might be zero order kinetic or first order kinetic.

The effects of organic modifiers on skin permeation of NFP were investigated by comparing the linear relationship of drug permeation-time profiles which obtained from the preparation P03, P04, contained 10% w/w and 7.5% w/w of glycerol, respectively and from P07, P08 which contained 10% w/w and 7.5% w/w of PG. The results were illustrated in Figures 20, 22, 26, 28, 30. The obtained permeation profiles from P03 and P04 (Figure 18), showed quite different pattern. The permeation rate which obtained from P03, 8.1598 mcg/cm^2/h, was higher than from P04 and increased about 4 times in permeation rate when compared to P01 and P02 which had no organic modifier Figure 20. However, the addition of 7.5% w/w glycerol, P04, decreased the permeation rate of NFP approximately 10 folds. Two permeation patterns were similarly depicted from P07 and P08, in Figure 24, these results indicated that higher concentration of PG exhibited higher permeation rate of NFP, about 0.1811 mcg/cm^2/h and 0.1175

mcg/cm^2/h, respectively. However, the comparison in skin permeation profile from these preparations (Figure 30) indicated that glycorol could increase the permeation rate of NFP when used more than 7.5% w/w while the addition of PG might decrease the NFP-permeation from PF-127 matrices that a 10-fold decrease in permeation rate was obtained from P07, P08 when compared to P01 and P02.

The effects of PEG 400, which combined with organic modifiers, glycerol and PG, on the skin permeation profile of NFP were observed. Figure 19 showed the obtained profiles from two different concentration of added co-solvent 10% w/w PEG 400 for P05 and 15% w/w PEG 400 for P06, combined with a fixed concentration of glycerol as 7.5% w/w. The results indicated quite different permeation profile, the profile from P05 was closed to Higuchi's model while two different slopes were observed from P06 that the quite low permeation rate of NFP was detected for the first eighteen hour and then the rate was quite higher over 24 hours. The result of increasing a 1 fold in permeation rate of NFP was observed from P05 when compared to P04 (Figure 23), which contained only glycerol 7.5% w/w but the decreasing in permeation rate of NFP was obtained from P06, a higher concentation of PEG 400 containing (Figure 30).

These phenomenon was also observed from P09 and P10 that PEG 400 was added to the preparation of fixed concentration of PG, 7.5% w/w, as 10% w/w and 15% w/w, respectively (Figures 25, 29),the NFP skin permeation rate was 6-fold increased and 0.5 fold decreaed from P09 and P10, respectively, when compared to P08. With comparison to P01 and P02 (Figure 27), the results indicated that the adding of co-solvent, PEG 400, to PF-127-PG gel matrices could not increase the permeation rate of NFP but all of these preparation could prolong the penetration of NFP from devices over 24 hours.

The effects of organic modifier and co-solvent on skin permeation profile of NFP from PF-127 gel matrices by *in-vitro* permeation experiments (Figures 22, 28),could be concluded that the permeation rate of NFP was increased when the preparations were added with only glycerol with the concentration of 10% w/w, but the lower concentration of glycerol, as 7.5% w/w, might decrease the rate. The skin permeation rate of NFP might be decreased when the preparations were added with PG at both designed concentrations. The addition of PEG 400 could not increase the permeation rate of NFP, however the results for this investigation was shown that the low concentration of PEG 400 combined with both organic modifiers could exhibit faster NFP-permeation rate from PF-127 matrix devices when compared to their preparations contained high concentration.

5.3 NFP-Aerosil A-200 TDDs Preparations

The cumulative permeation-time data and profiles of NFP from twelve preparation of NFP-TDDs using Ae-200 gel matrices as drug carrier were presented in Appendices XIII - XXV (Table 25 and Figures 33-47). The skin permeation pattern and the rate of skin permeation rate of NFP from these TDDs could be fitted to a linear of Qs vs time relationship, except the preparations A03 and P10 in which their permeation profiles were more closely to Higuchi's model kinetics, Qs vs $t^{1/2}$. These results indicated that Aerosil gel matrices could give a sustain-release characteristic with a constant NFP-permeation rate overs 24 hours except the specified preparations, A03 and A10. The maximum permeation was clearly depicted from A10 with a 156.11 mcg/cm^2 of permeation amount and a 32.854 mcg/cm^2/$h^{1/2}$ of permeation rate while the minimum permeation was observed from A08 of which the permeation amount and permeation rate were 5.1962 mg/cm^2 and 0.2265 mcg/cm^2/h, respectively.

Different pattern of skin permeation profile of NFP from A10 and A03 was noticed that each permeation pattern had two different slopes, during the first six hour and the rest of time interval which both tended. These slopes were 13.326 mcg/cm^2/h and 3.7941 mcg/cm^2/h from P10 while those from P03 were 6.0937 mcg/cm^2/h and 3.4779 mcg/cm^2/h, respectively. With respect to Qs vs t

relationship, these preparations could be ranked according to the permeation rate of NFP as the following order; A10 > A09 > A03 > A12 > A07 > A01 > A06 > A04 > A11 > A02 > A05 > A08.

The effect of organic modifiers on the rate of skin permeation of NFP were investigated from the permeation profiles which obtained from A01, A02 for glycerol and A07, A08 for PG as depicted in Figures 33, 39 and 45. The patterns of these profiles were similar and the results indicated that skin permeation rate was constant and faster permeation rate was achieved from lower concentration of organic modifiers, A01 and A07. The increasing in the concentration of glycerol from 27% w/w (A01) to 35% w/w (A02) a 5-fold decrease in skin permeation rate was obtained, to a permeation rate of 2.3239 mcg/cm^2/h. Similarly to A07 vs A08, a 12-fold decrease in skin permeation rate occurred when increasing PG concentration from 27% w/w to 35% w/w, with the permeation rate of NFP from P07 was 2.4250 mcg/cm^2/h. At high concentration of organic modifiers, A02 vs A08, the permeation rate affected from glycerol was faster than that from PG while at low concentration, A01 vs A07, the obtained permeation profile and rate were quite close similar (Figure 45).

TABLE 25 The Average Cumulative Amount of Nifedipine per Surface Area of Pig's Skin (mcg/cm^2) Permeated from Nifedipine-TDDs Using Aerosil A-200 Gel as Drug Carrier by in-vitro Skin Permeation Experiments (n = 3)

Time [hr]	Average Cum Amount of NFP/area[mcg/cm2]					
	A01	A02	A03	A04	A05	A06
0	0	0	0	0	0	0
0.5	0.8012	1.3632	4.9598	1.3464	0.5037	1.5952
1	1.2084	1.4073	8.5581	2.9075	0.5044	2.6769
2	2.3253	2.7195	15.598	2.9251	0.8629	4.0566
3	3.2836	2.5685	22.388	3.7747	1.2728	5.7343
4	4.4138	2.5850	26.207	4.8656	1.6350	7.2995
5	5.7015	3.1217	32.197	5.9894	1.8005	9.3784
6	7.5208	3.3408	39.614	8.2131	1.8417	12.949
8	15.158	4.5614	47.144	10.312	2.2946	19.777
10	22.230	5.5368	51.226	16.463	2.5193	22.362
12	27.053	5.9714	61.736	23.861	3.9477	25.699
15	33.543	8.2736	76.861	25.744	4.1999	32.219
18	38.349	9.7129	88.240	27.133	5.1392	35.533
21	45.584	10.153	95.577	37.140	6.7239	41.347
24	52.430	11.095	96.136	39.831	7.8871	47.092
	A07	A08	A09	A10	A11	A12
0	0	0	0	0	0	0
0.5	1.3364	0.5420	3.4807	15.440	0.8482	2.0134
1	1.4312	0.5044	4.6777	24.144	1.0626	4.0808
2	3.2503	0.4482	6.8830	39.658	1.2812	5.4307
3	6.1928	0.5232	7.8530	54.681	1.9990	7.3030
4	7.3592	0.9517	10.191	62.977	2.0776	8.4933
5	9.1694	1.0109	14.455	78.444	2.5189	10.187
6	11.851	1.1284	20.139	89.592	3.8693	12.451
8	17.598	1.6247	38.414	90.712	4.9710	19.581
10	20.278	2.2340	41.906	96.881	6.3227	26.701
12	27.192	3.0355	53.864	114.44	9.0580	32.080
15	35.070	3.1577	65.792	131.93	11.192	40.553
18	43.096	5.1782	79.079	130.44	15.475	48.361
21	50.788	4.6085	84.499	140.49	18.959	70.858
24	55.546	5.1962	101.67	156.11	23.919	72.007

SD : STANDARD DEVIATION.

TABLE 26 The Correlation Coefficient of Nifedipine Saturated Solution and Nifedipine-TDDs Preparations
[A] : Avg Cum Permeation Amount of NFP per Suface Area [Qs] vs Time
[B] : Log Remained Amount of NFP per Surface Area [RQs] vs Time
[C] : Avg Cum Permeation Amount of NFP per Suface Area [Qs] vs Square root of Time

	Saturated NFP Solution								
	[A] : Qs vs Time			[B] : log RQs vs Time			[C] : Qs vs sqrt Time		
	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2
	0.0060	0.0834	0.9344	-0.005	0.3141	0.9344	0.0356	0.0410	0.9789
	NFP-Pluronic F-127 TDDs								
Prep No.	[A] : Qs vs Time			[B] : log RQs vs Time			[C] : Qs vs sqrt Time		
	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2
P01	1.8894	-4.529	0.9717	-0.002	2.1597	0.9712	10.311	-15.47	0.8720
P02	1.9842	-5.924	0.9433	-0.002	2.1848	0.9423	10.669	-16.98	0.8219
P03	8.1598	-18.89	0.9761	-0.009	2.0853	0.9728	44.502	-66.08	0.8784
P04	0.2896	1.0423	0.9594	-0.005	2.1297	0.9594	1.5979	-0.683	0.9449
P05	0.4692	0.9532	0.9694	-0.003	2.1340	0.9681	2.7141	-2.187	0.9780
P06	0.2135	-0.475	0.5957	-0.006	2.1977	0.5964	1.0777	-1.471	0.4588
P07	0.1811	1.0806	0.9874	-0.007	2.1398	0.9874	1.0371	-0.102	0.9751
P08	0.1175	0.8409	0.9831	-0.009	2.1529	0.9831	0.6727	0.0735	0.9669
P09	0.6893	1.6133	0.9870	-0.001	2.1088	0.9871	3.9201	-2.816	0.9618
P10	0.0574	0.5159	0.9596	-0.012	2.1772	0.9594	0.3280	0.1429	0.9449
	NFP-Aerosil A-200 TDDs								
Prep No.	[A] : Qs vs Time			[B] : log RQs vs Time			[C] : Qs vs sqrt Time		
	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2	X-COEF	Y-INT	R^2
A01	2.3239	-2.952	0.9887	-0.003	2.1197	0.9884	12.990	-17.26	0.9321
A02	0.4344	1.1535	0.9866	-0.003	2.1226	0.9884	2.4490	-1.578	0.9444
A03	4.0842	9.8237	0.9742	-0.006	2.0302	0.9884	23.676	-17.66	0.9866
A04	1.7151	-0.828	0.9787	-0.002	2.1045	0.9780	9.5810	-11.37	0.9208
A05	0.2988	0.1736	0.9885	-0.005	2.1633	0.9808	1.6590	-1.635	0.9127
A06	1.9778	0.8274	0.9914	-0.002	2.0889	0.9891	11.251	-11.89	0.9701
A07	2.4250	-1.705	0.9961	-0.003	2.0995	0.9952	13.568	-16.67	0.9362
A08	0.2265	0.0573	0.9564	-0.006	2.1818	0.8744	1.2633	-1.329	0.8200
A09	4.3602	-2.266	0.9877	-0.006	2.0666	0.9867	24.517	-29.51	0.9387
A10	5.4845	36.836	0.9082	-0.007	1.9833	0.9142	32.854	-2.993	0.9819
A11	0.9468	-1.361	0.9687	-0.000	2.1430	0.9646	5.1570	-6.818	0.8626
A12	3.0886	-2.848	0.9777	-0.004	2.0821	0.9759	17.044	-21.26	0.8969

TABLE 27 The Analysis Of ermeation Kinetic and Mechanism Of Nifedipine following Linear Regression for ach reparation

No.	%Qs vs Time	log%RQs vs Time	%Qs vs sqTime	Analysis Mt/Mα=kt^n n	k Kinetic Constant	r Square	dQ/dt vs Q	dQ/dt vs 1/Q	Kinetic Pattern	Mechanism Pattern
NFP-Pluronic F-127 TDDs										
P01	0.9717	0.9712	0.8720	1	0.0159	0.9319	0.5620	0.3394	zero	case II
P02	0.9433	0.9423	0.8219	1	0.0159	0.8834	0.5928	0.3478	zero	case II
P03	0.9761	0.9728	0.8784	1	0.0691	0.9364	0.6715	0.4875	zero	case II
P04	0.9594	0.9594	0.9449	0.75	0.0063	0.8846	0.0026	0.1625	zero/first	nonFickian
P05	0.9694	0.9681	0.9780	0.75	0.0107	0.9843	0.1569	0.2157	Higuchi´s	Fickian
P06	0.5957	0.5964	0.4588	0.25	0.0232	0.9655	0.6837	0.1946	-	nonFickian
	0.9820	0.9571	0.9688	-	-	-	-	-	zero	case II
	0.9965	0.8915	0.9838	-	-	-	-	-	zero	case II
P07	0.9874	0.9874	0.9751	0.55	0.0088	0.9793	0.2650	0.7376	zero/first	nonFickian
P08	0.9831	0.9831	0.9669	0.5	0.0069	0.9692	0.2122	0.5621	Higuchi´s	Fickian
P09	0.9870	0.9871	0.9618	0.75	0.0161	0.9849	0.9975	0.4374	zero/first	nonFickian
P10	0.9596	0.9594	0.9449	0.45	0.0042	0.9341	0.1881	0.5893	zero/first	nonFickian
NFP-Aerosil A-200 TDDs										
No.	%Q vs Time	log%RQs vs Time	%Q vs sqTime	Analysis Mt/Mα=kt^n n	k Kinetic Constant	r Square	dQ/dt vs Q	dQ/dt vs 1/Q	Kinetic Pattern	Mechanism Pattern
A01	0.9887	0.9884	0.9321	1	0.0213	0.9773	0.2163	0.2227	zero	case II
A02	0.9866	0.9884	0.9444	0.75	0.0103	0.9753	0.0633	0.1855	zero/first	nonFickian
A03	0.9742	0.9884	0.9866	0.75	0.0958	0.9909	0.6029	0.5307	first	nonFickian
	0.9947	0.9037	0.9820	-	-	-	-	-	-	case II
	0.9640	0.9399	0.9590	-	-	-	-	-	-	case II
A04	0.9787	0.9780	0.9208	1	0.0166	0.9771	0.0082	0.0050	zero	case II
A05	0.9885	0.9808	0.9127	1	0.0031	0.9768	0.0061	0.0386	zero	case II
A06	0.9914	0.9891	0.9701	0.95	0.0234	0.9929	0.0506	0.0848	zero	case II
A07	0.9961	0.9952	0.9362	1	0.0231	0.9927	0.0597	0.1430	zero	case II
A08	0.9564	0.8744	0.8200	1	0.0023	0.9560	0.0001	0.0005	zero	case II
A09	0.9877	0.9867	0.9387	1	0.0421	0.9859	0.0232	0.0066	zero	case II
A10	0.9082	0.9142	0.9819	0.5	0.3196	0.9811	0.6392	0.7631	Higuchi´s	Fickian
	0.9940	0.9139	0.9891	-	-	-	-	-	-	case II
	0.9530	0.9392	0.9421	-	-	-	-	-	-	case II
A11	0.9687	0.9646	0.8626	1	0.0086	0.9545	0.3091	0.0441	zero	case II
A12	0.9777	0.9759	0.8969	1	0.0291	0.9718	0.0589	0.0067	zero	case II

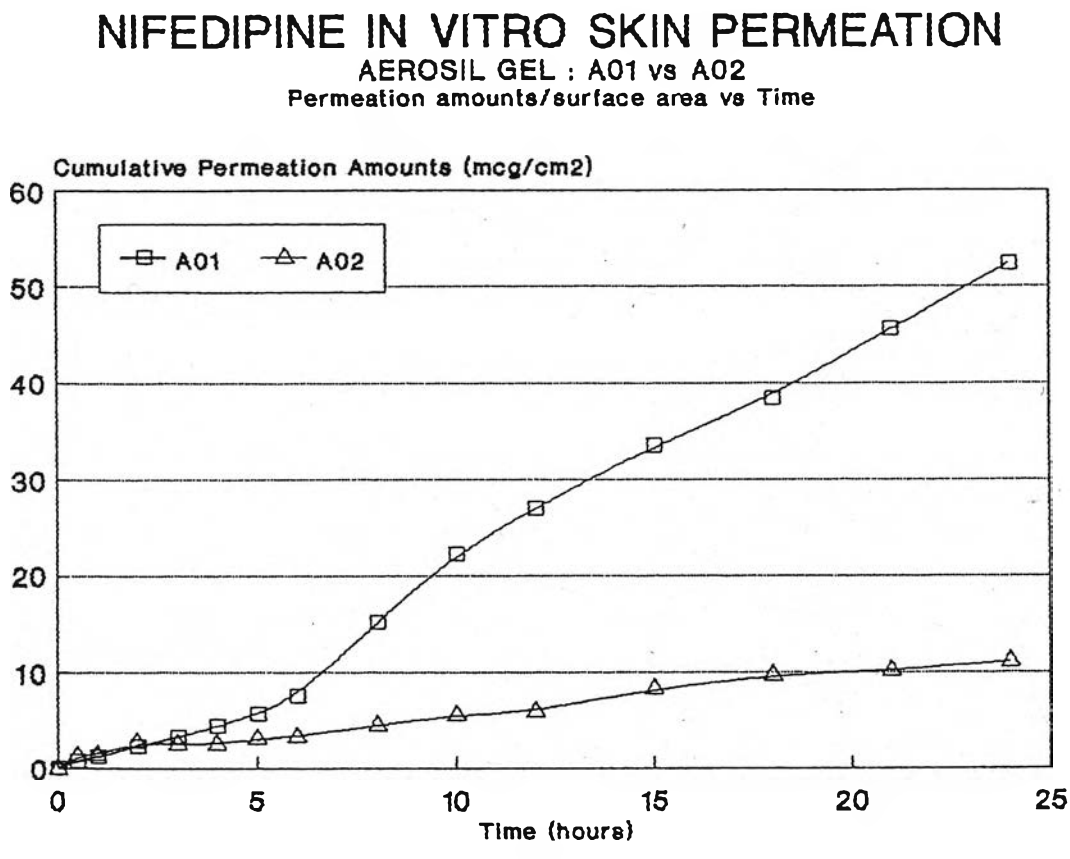

Figure 33 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A01 and A02 Contained Glycerol 27% w/w and 35% w/w, Respectively.

[A01 : Y = 2.3239X - 2.9529, R-square = 0.9887;

A02 : Y = 0.4344X - 1.1535, R-square = 0.9852].

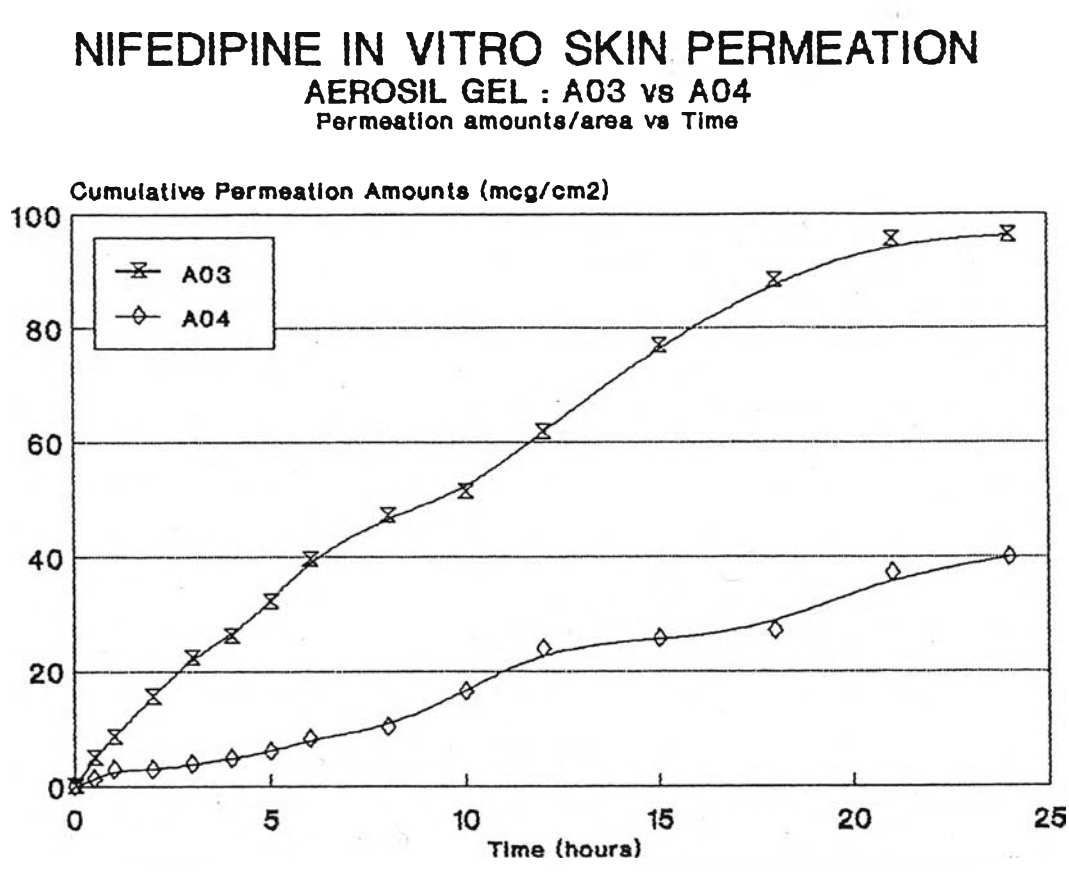

Figure 34 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A03 and A04 Contained PEG 400 15% w/w and 25% w/w, Respectively.

[A03 : Y = 4.0842X + 9.8237, R-square = 0.9742;

A04 : Y = 1.7151X - 0.828, R-square = 0.9787].

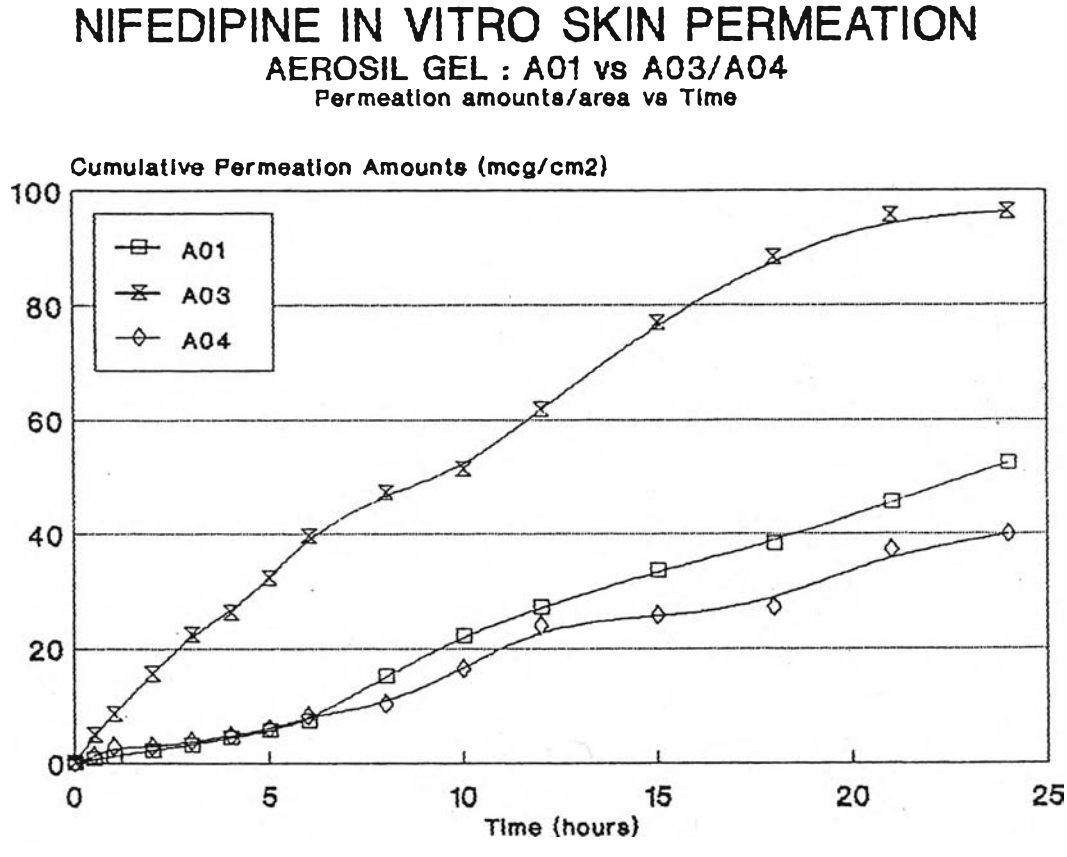

Figure 35 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared A01 vs A03, P04.

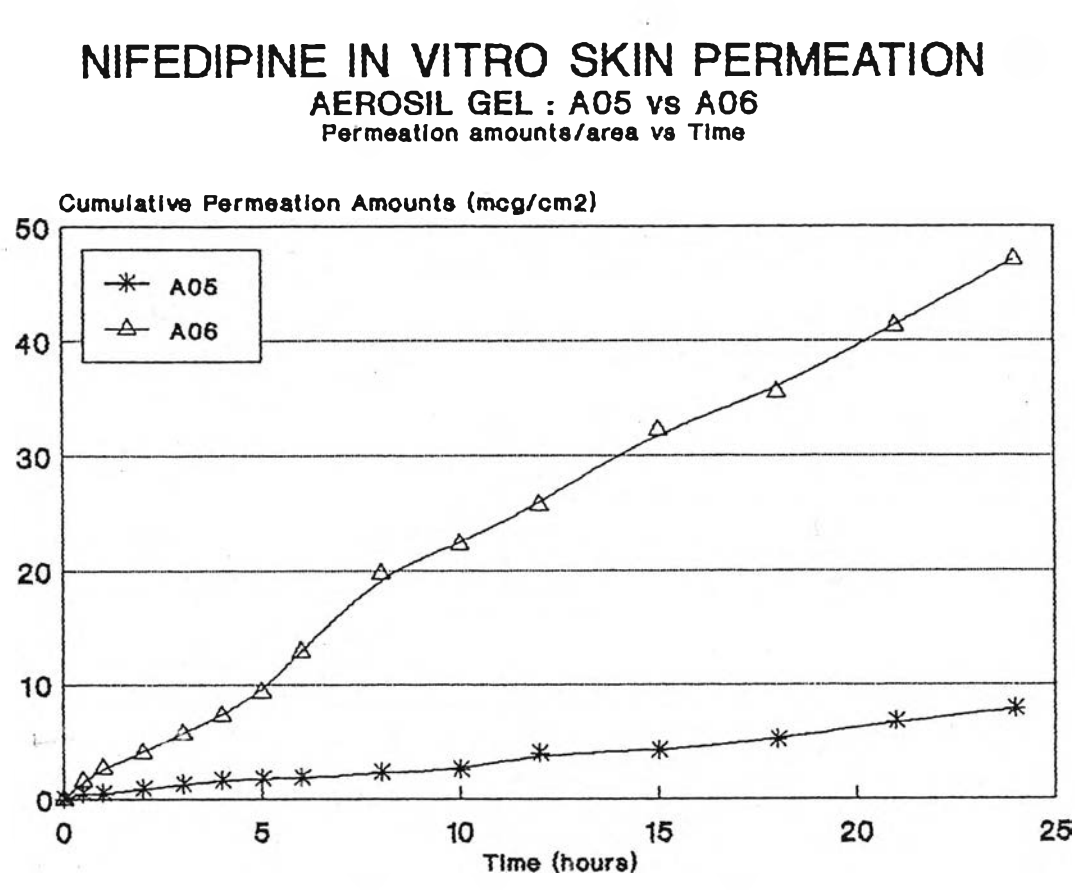

Figure 36 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A05 and A06 Contained PEG 400 15% w/w, HPMC 1% w/w and PEG 400 25% w/w, HPMC 1% w/w, Respectively.

[A05 : Y = 0.2988X + 0.1736, R-square = 0.9791;

A06 : Y = 1.9778X + 0.8274, R-square = 0.9914].

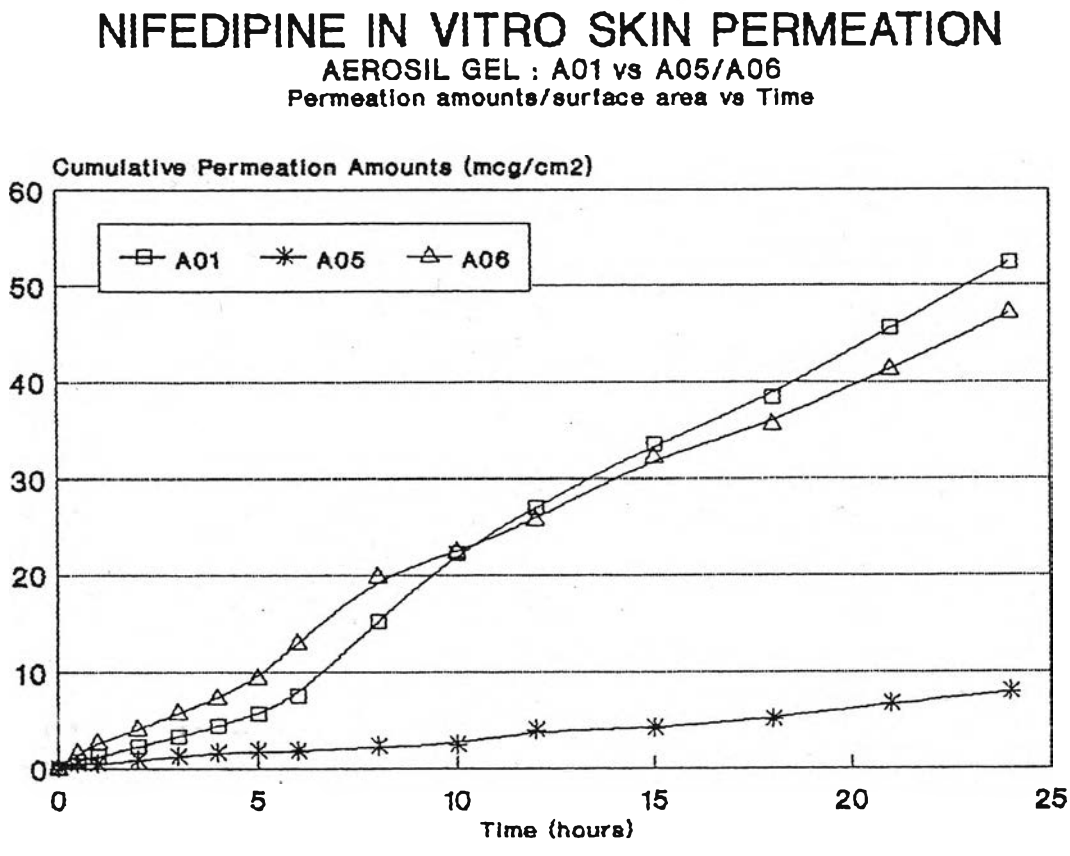

Figure 37 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared A01 vs A05, A06.

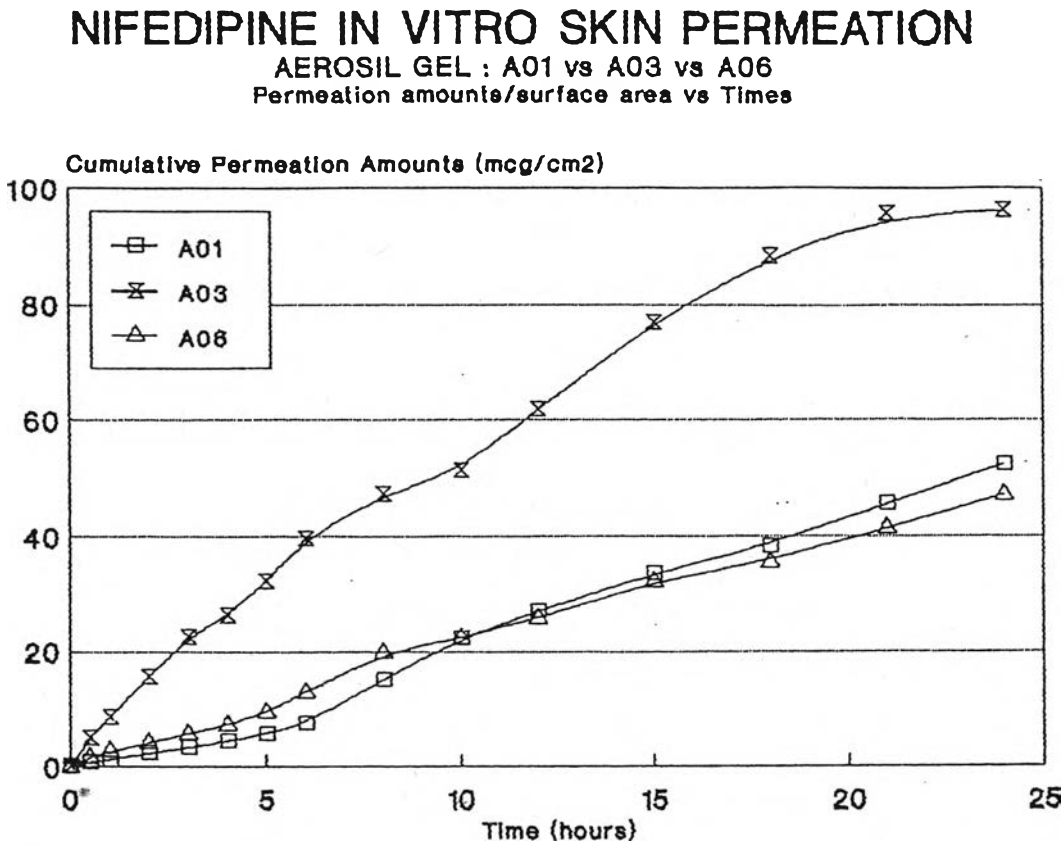

Figure 38 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared A01 vs A03 vs A06.

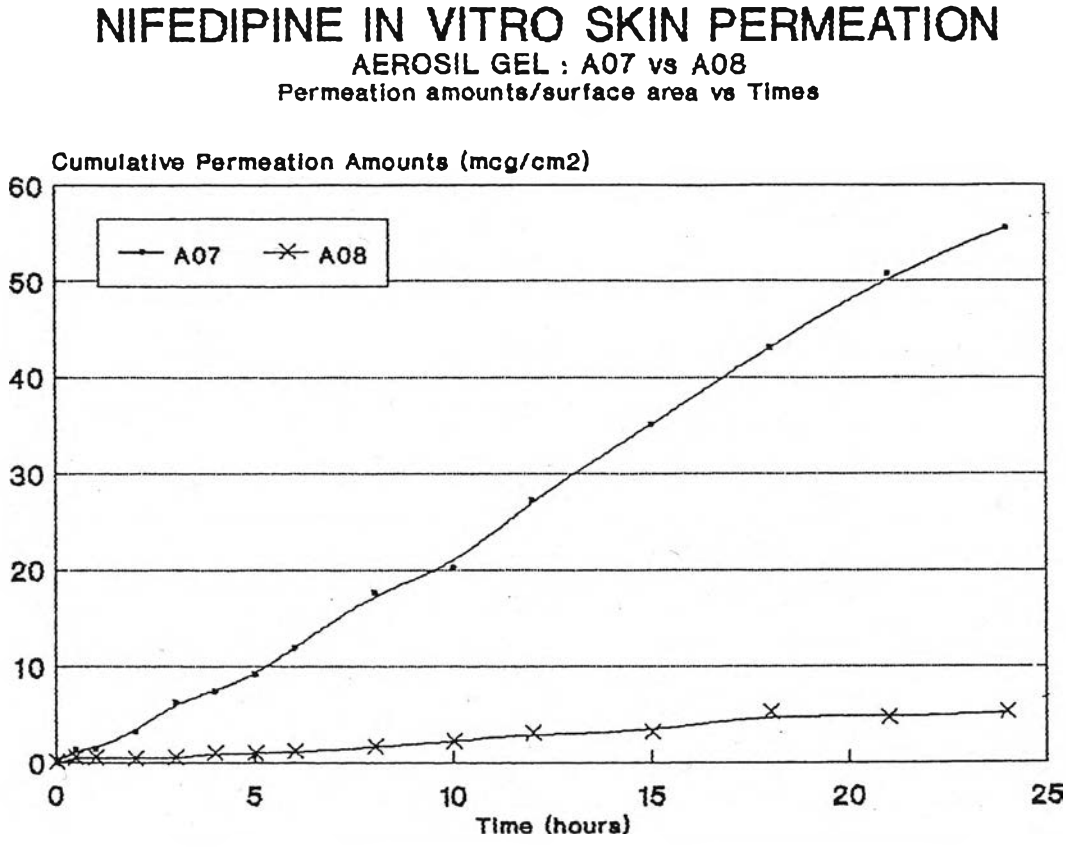

Figure 39 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A07 and A08 Contained Propylene glycol 27% w/w, and 35% w/w, Respectively.

[A07 : Y = 2.4250X - 1.705, R-square = 0.9961;

A08 = 0.2265X + 0.0573, R-square = 0.9654].

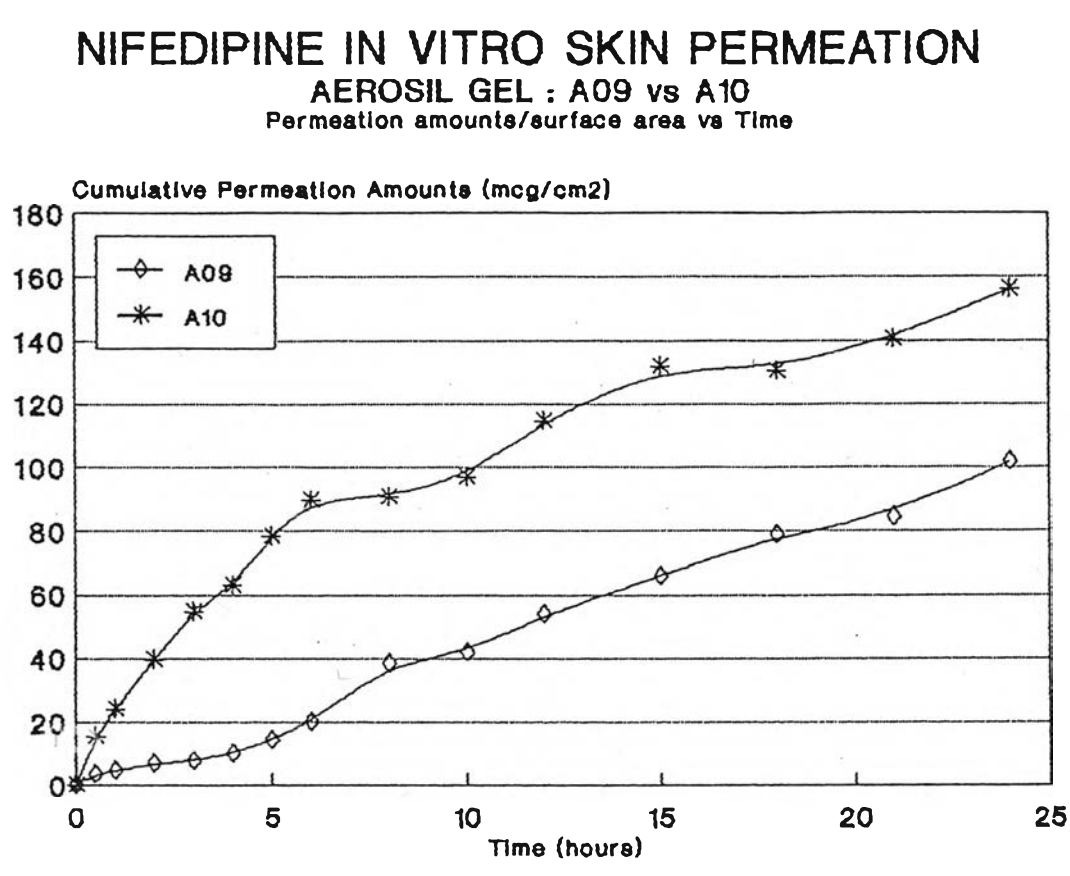

Figure 40 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A09, A10 Contained PEG 400 15% w/w and 25 w/w Respectively.

[A09 : Y = 4.3602X - 2.266, R-square = 0.9877;

A10 : Y = 5.4845X + 36.836, R-square = 0.9080].

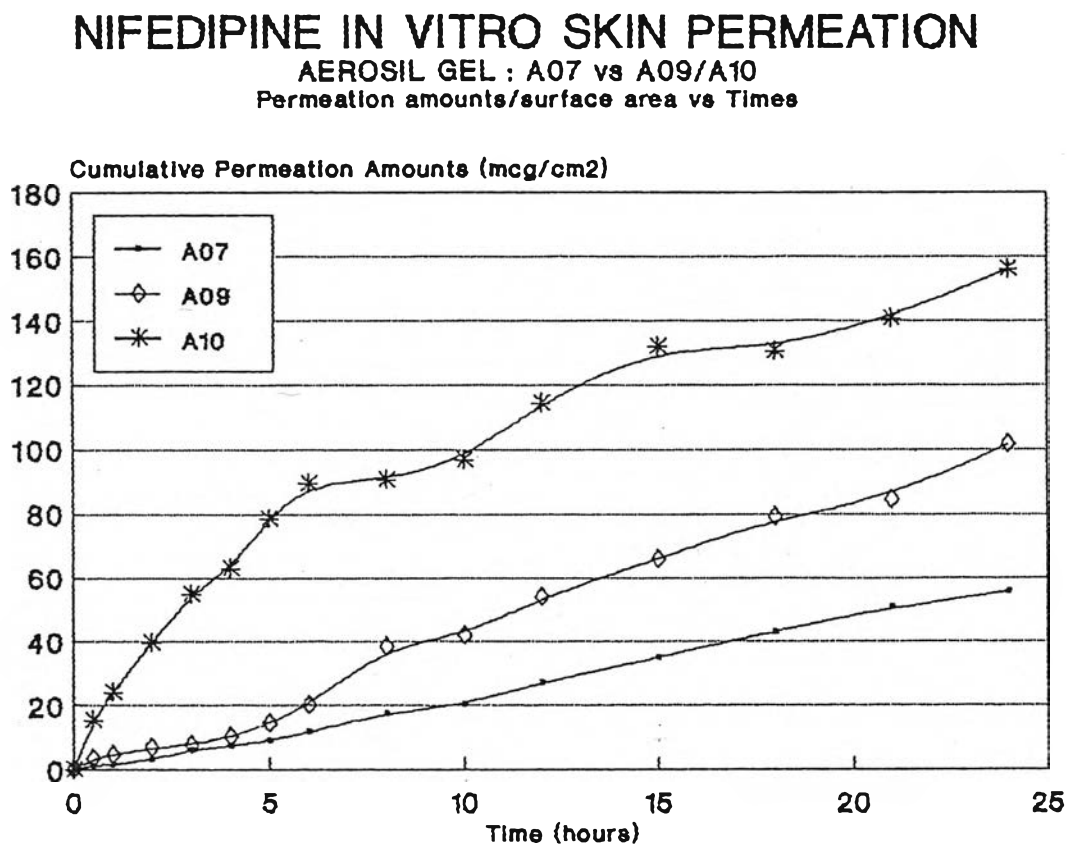

Figure 41 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] Compared A07 vs A09, A10.

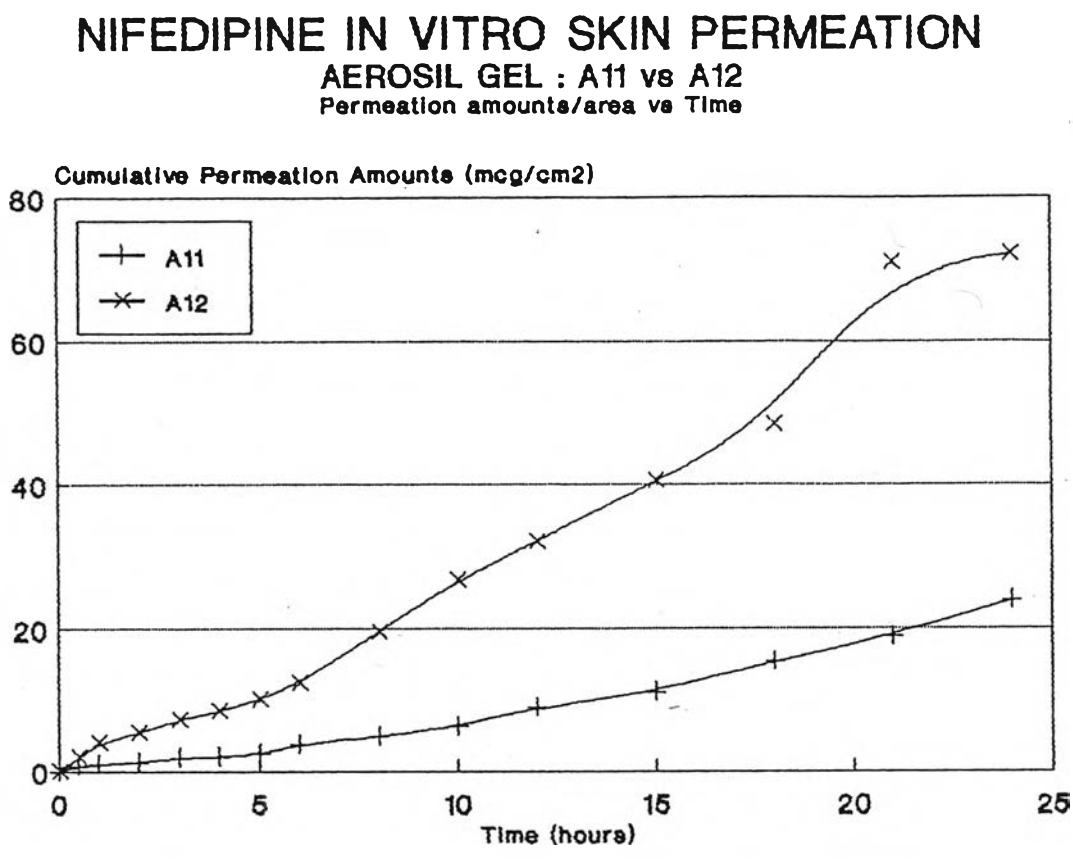

Figure 42 Drug Permeation-Time Profile of Nifedipine [mcg/cm^2] from A11 and A12 Contained PEG 400 15% w/w, HPMC 1% w/w and PEG 400 25% w/w, Respectively.

[A11 : Y = 0.9468X - 1.361, R-square = 0.9687;

A12 : Y = 3.0886X - 2.848, R-square = 0.977].

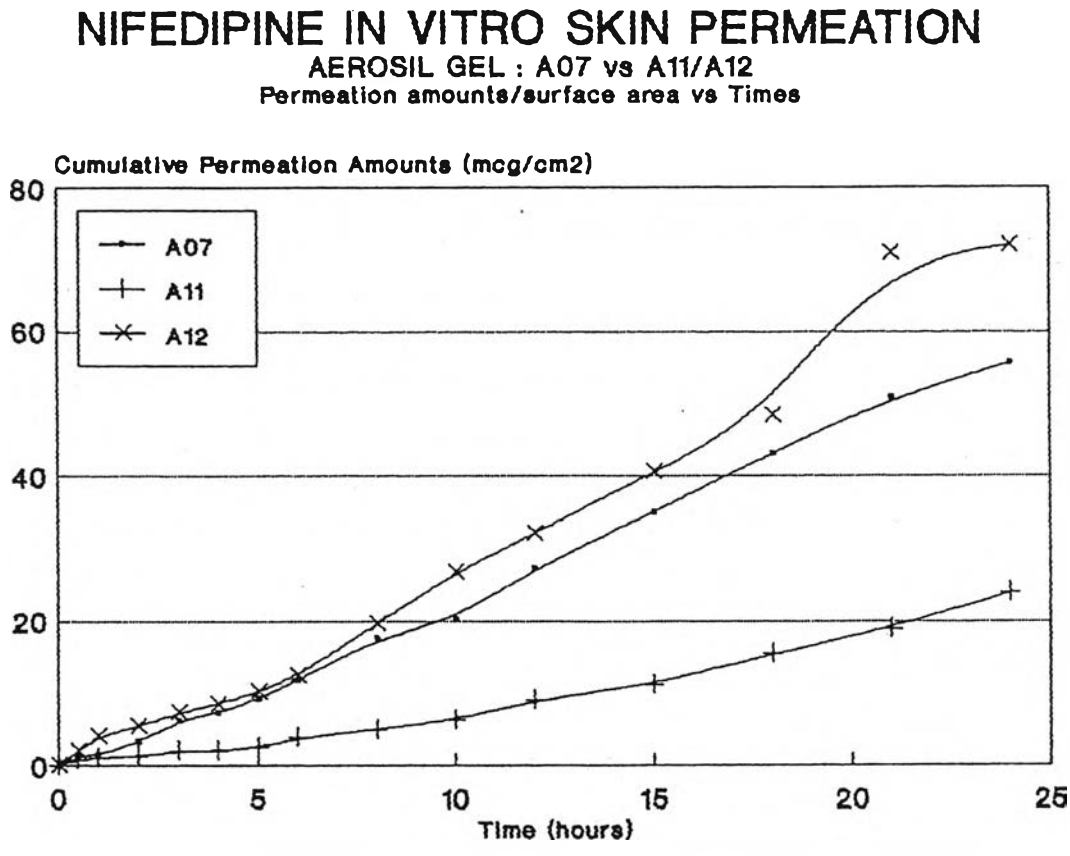

Figure 43 Drug Permeation-Profile of Nifedipine Compared A07 vs A11, A12.

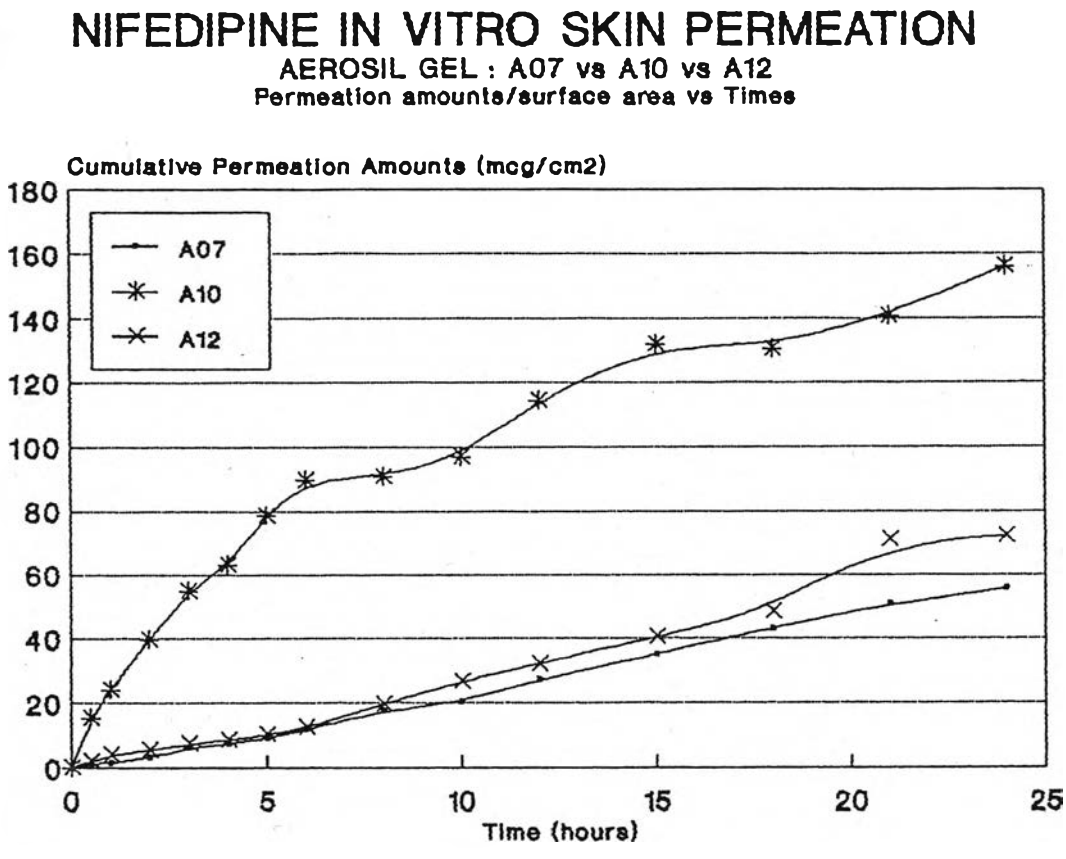

Figure 44 Drug Permeation-Profile of Nifedipine Compared A07 vs A10 vs A12.

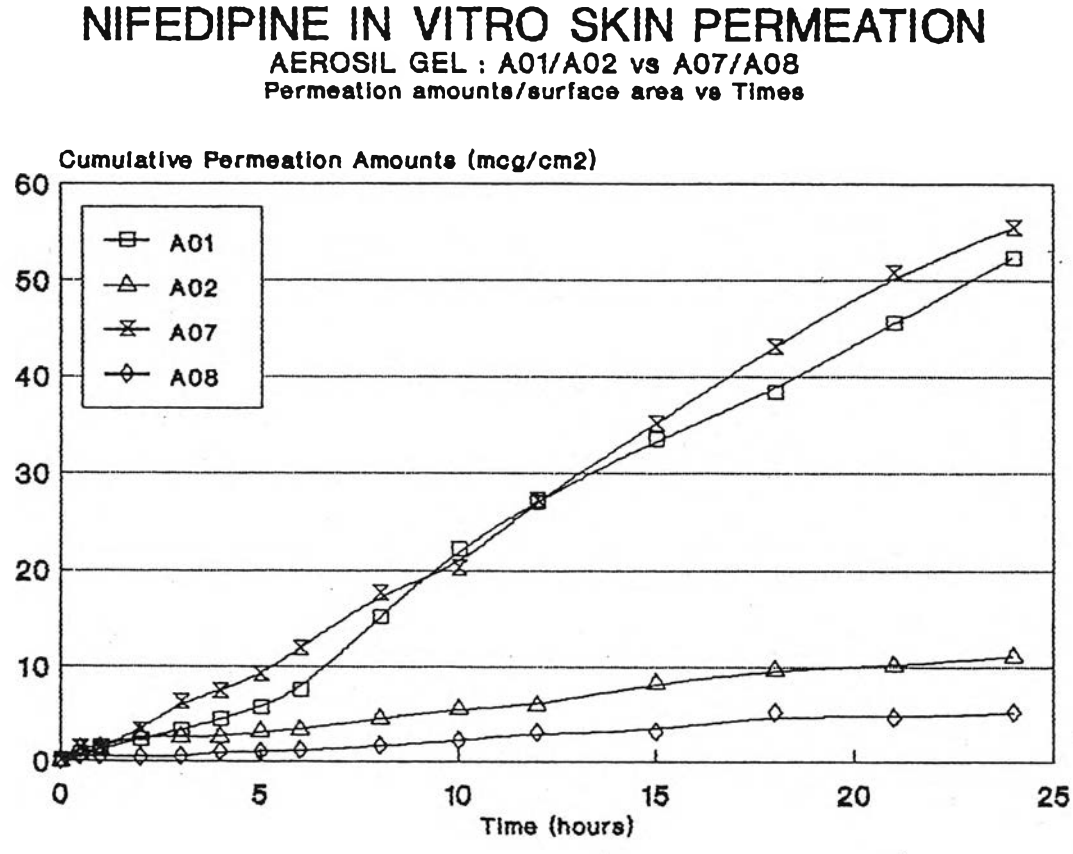

Figure 45 Drug Permeation-Profile of Nifedipine Compared A01, A02 vs A07, A08.

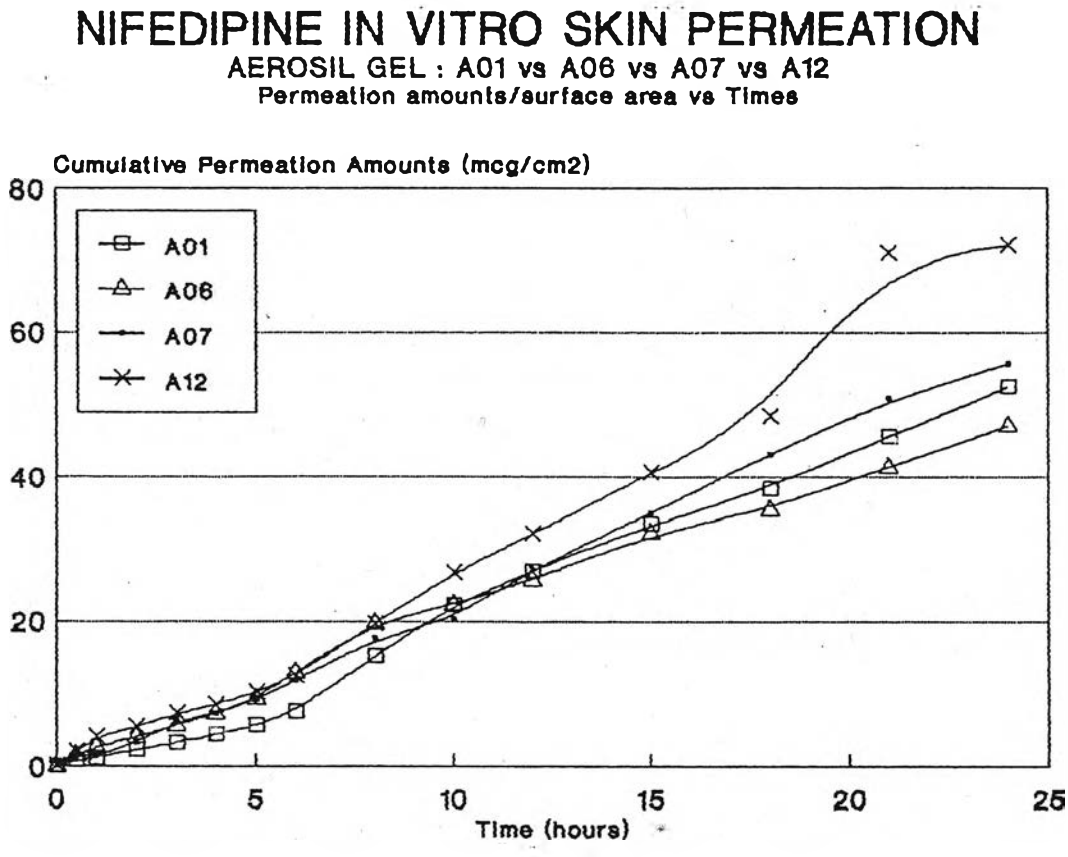

Figure 46 Drug Permeation-Profile of Nifedipine Compared A01 vs A06 vs A07 vs A12.

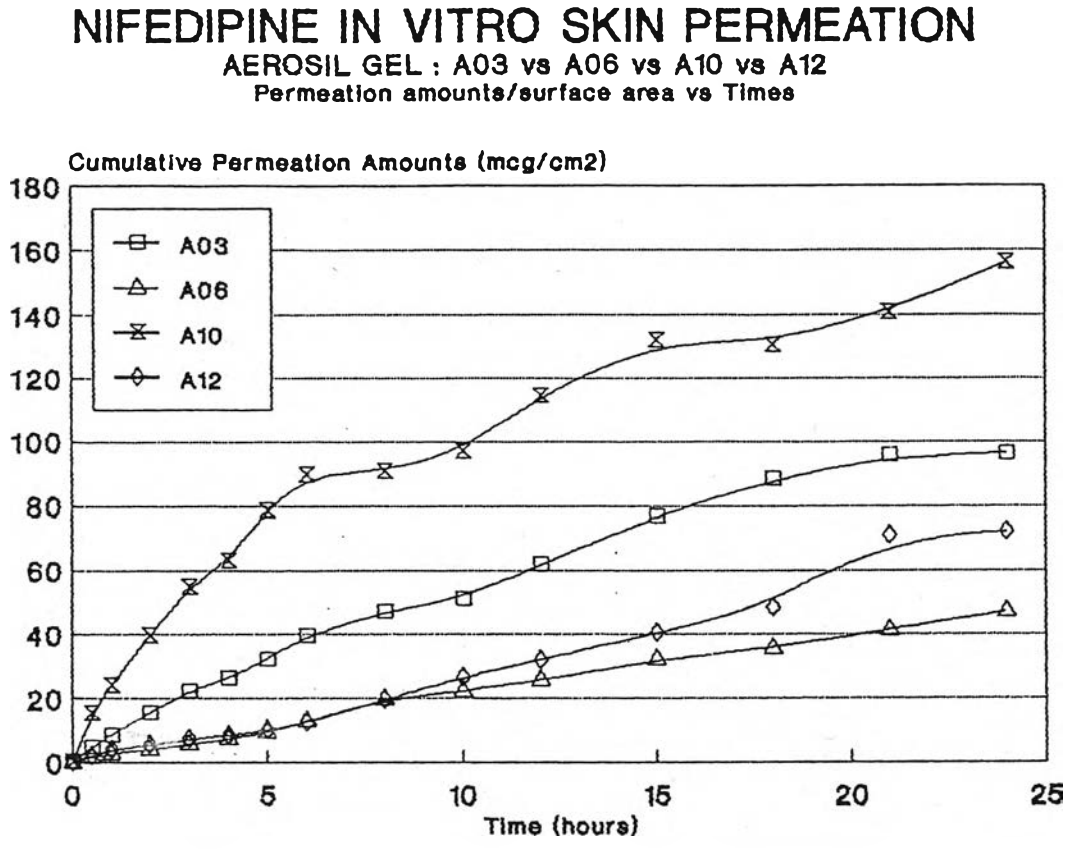

Figure 47 Drug Permeation-Profile of Nifedipine Compared A03 vs A06 vs A10 vs A12.

The effect of PEG 400 concentration on the rate of skin permeation and permeation profile was also examined. The increase in skin permeation rate of NFP was observed to be dependent upon the PEG 400 concentration (Figures 34, 40). For preparations A03 and A04 (Figures 34, 35) which contained 27% w/w glycerol, the high permeation rate of NFP was achieved from the lower concentration of PEG 400 with a 2-fold increase in permeation rate of NFP when compared to A01, contained no PEG 400, while the high PEG 400 concentration, A04, exhibited the permeation rate of NFP closely to A01. A contrast phenomenon was observed for the effect of PEG 400 combined with of PG. For preparations A09, A10 (Figures 40, 41), skin permeation rate of NFP was increased as increasing PEG 400 concentration to be a 1.5 and a 2.2 folds for A09 and A10, respectively, when compared to A07. These observations could be ranked according to the skin permeation rate of NFP as the following order A10 > A09 > A03 > A04 with the rates of 5.4845, 4.3603, 4.0842 and 1.7151 mcg/cm^2/h, respectively.

The skin permeation profiles of NFP affected from HPMC as thickening agent, in preparations A05, A06, A11 and A12 were shown in Figures 36, 37, 38, 42, 43 and 44. The results indicated that thickening agent could retard the permeation rate of NFP especially in the preparation containing glycerol. The skin permeation rate of NFP from A05 was clearly decreased of 2.6, 15 and 6 folds when

compared to A01, A03 and A04, respectively. The Ae-200 gel matrices contained 27% glycerol could be ranked according to the skin permeation rate of NFP as the following order, A03 > A01 = A06 > A04 = P05. For the preparation containing PG, the obtained permeation rate from A11 was approximaly 4.6 folds decreased and from A12 was 1.7 fold decreased when compared to A09 and A10, respectively. To compared to A07, the permeation rate achieved from A12 which contained high concentration of PEG 400 and HPMC was little faster than from P07 which had no PEG and HPMC but that from P11 was slower than that from A07 with approximatly 1.6 fold decreasing. The ranking of skin permeation from these preparations were as follow as A10 > A09 > A12 = A07 > A11.

5.4 **The Elucidation of Drug Permeation Model**

In order to determine the effects of different types of gelling agent and different formulation on the model of drug permeation, all of permeation data were fitted to zero order, first order or Higuchi's model. The most linearity which obtained from correlation between % Qs vs time (zero order kinetic), the logarithm of % remained Qs vs time (first order kinetic) and % Qs vs square root of time were used to determine the kinetic of drug permeation model of each preparation. The result of this interpretation was shown in Table 27, it was found that the correlation coefficients of these preparations

were closely to be both zero order and first order kinetics exepted P05, P08, A03, A10. It was difficult to indicate the exact permeation profile of NFP from gel matices devices. However, it could estimate that the permeation rate of NFP from these devices were constant over a peroid of required times. The estimated profile kinetic of NFP permeation was shown in Table 27, it was found that PF-127 gel matrices devices which exhibited a zero order kinetic of NFP permeation was the preparation P01, P02 and P03. Higuchi's model was obtained from P05, P08 and the other tended to be zero order or first order kinetic. For Ae-200 gel matrices devices, the most linearity obtained from all preparations except from A03 and A10 which the correlation coefficients of overall data were closed to first order and Higuchi's model, respectively. However, with observation of permeation profile of both preparation Figures 34 and 40, it showed that A03 and A10 exihibited two permeation slopes, the first six hours of permeation and the rest time interval, their correlation coefficient were closed to zero order kinetic model.

The results of *in-vitro* skin permeation experiment of hydrophilic gel matrices, PF-127, and hydrophobic gel matrices, Ae-200, indicated that different polymer and different concentration of addition produced different both the permeation-time profile and the skin permeation rate. The maximum skin permeation rate of NFP

in the period as required could be observed from PF-127 hydrophilic gel matrices, P03, however the hydrophobic gel matrices produced a rapid onset of permeation of NFP. The results of skin-permeation studies from both types of gel matrices were indicated that they might be able to enhance the bioavailabity of NFP and exhibited a sustain-release characteristic with a constant rate over peroid of 24 hours.