# CHAPTER III

# RESULTS

## 1. Preparation of 1% W/W Nifedipine Transdermal Delivery System

Every nifedipine TDDS preparation was yellow according to the color of drug.

### Pluronic(R) F 127

It was found that no air bubble was obtained in these gel. With increasing the concentration of Pluronic(R) F 127, the increasingly sticky gels were observed. The residue and the rigidity of gel were increased too. From the result in Table 4, the drug formulations containing 35, 40 and 45% w/w of this polymer were selected to further evaluation.

### PEG 4000 : PEG 400 Copolymers

Normally, PEG 4000 and PEG 400 were mixed together to make hydrophilic ointment using 40% and 60% W/W, or in the ratio of 2:3, respectively. In this study, combination of PEG 4000 and PEG 400 were proposed in the ratio of 1:4, 1:2 and 1:1, respectively. Physical appearance of nifedipine TDDS preparation formulated by PEG copolymers was shown in Table 5.

Table 4 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from Pluronic(R) F127 in Various Concentrations

| conc. (%w/w) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 30 | + | - | + | + | + | - |
| 35 | + | - | + | + | + | + |
| 40 | + | - | ++ | + | ++ | ++ |
| 45 | + | - | +++ | ++ | +++ | +++ |
| 50 | - | - | ++++ | +++ | ++++ | ++++ |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

Table 5 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from the Various Ratio of PEG 4000:PEG 400 (A:B)

| ratio (A:B) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 1:4 | - | - | ++ | ++ | ++ | + |
| 1:2 | - | - | ++ | ++ | +++ | + |
| 1:1 | - | - | +++ | ++ | ++++ | + |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

Table 6 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from (1:1) PVA:PVP in Various Concentrations

| conc. (%w/w) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 30 | - | - | - | - | ++ | ++ |
| 40 | - | - | - | - | ++ | +++ |
| 50 | - | - | - | - | ++++ | ++++ |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

Table 7 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from Methocel$^{(R)}$A 4M in Various Concentrations

| conc. (%w/w) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 3 | + | + | + | + | - | - |
| 4 | + | + | + | + | - | - |
| 5 | - | + | ++ | + | + | - |
| 10 | - | + | ++ | ++ | ++ | + |
| 15 | - | + | ++++ | +++ | +++ | ++ |
| 20 | mass | + | ++++ | +++ | ++++ | ++++ |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

PVA-PVP Copolymers

The preparations of PVA and PVP copolymers produced yellow rubber-like translucent gels. As the concentration of these copolymers increased, these gels became rigider. Air bubbles were not noticed in these gels. No residue was left on the skin when applied. Only three concentrations of this copolymers as shown in Table 6 was ability to be prepared. When the concentration of this copolymers was higher than 50% w/w the preparation was too rigid to prepared.

Methocel$^{(R)}$A 4M

From the result in Table 7, the formulation consisted of either 3% or 4% w/w of Methocel$^{(R)}$A 4M was not rigid. Preparation formulated by 20% w/w this polymer was a mass gel in stead of a translucent gel. So, Methocel$^{(R)}$A 4M in the concentration of 5, 10 and 15% w/w were selected.

Methocel$^{(R)}$K 4M

It was intended to formulate and prepare nifedipine TDDS preparartions with Methocel$^{(R)}$K 4M in the same concentration of Methocel$^{(R)}$A 4M. Physical appearance of preparation formulated with Methocel$^{(R)}$K 4M was shown in Table 8.

Methocel$^{(R)}$K 100M

The preparations which contain in concentration of 3, 4 and 5% w/w Methocel$^{(R)}$K 100M could resulted in a translucent gel, but 10% w/w of this polymer gave a mass gel as shown in Table 9. Thus, these three concentrations of Methocel$^{(R)}$K 100M were selected.

Table 8 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from Methocel$^{(R)}$K 4M in Various Concentrations

| conc. (%w/w) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 5 | - | + | ++ | + | ++ | - |
| 10 | - | + | +++ | ++ | +++ | + |
| 15 | - | + | ++++ | +++ | ++++ | ++ |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

Table 9 : Physical Appearance of Nifedipine TDDS Preparatoin Obtained from Methocel$^{(R)}$K 100M in Various Concentrations

| conc. (%w/w) | clarity* | air bubble | sticky | residue | rigidity | difficulty in preparing |
|---|---|---|---|---|---|---|
| 3 | - | + | +++ | ++ | ++ | + |
| 4 | - | + | +++ | ++ | ++ | ++ |
| 5 | - | + | ++++ | ++ | +++ | +++ |
| 10 | mass | + | ++++ | +++ | ++++ | ++++ |

* clarity : (+) = transparent, (-) = translucent
the number of the symbols of (+) and (-) showed a degree of the appearance and no appearance, respectively

From all preparations formulated by various amount of different hydrophilic polymers or copolymers, it was concluded the selected preparations formulated with the single polymer or copolymers in the following:

- Pluronic(R)F127 in water in the concentration of 35, 40 and 45% w/w
- PEG 4000 and 400 copolymer in the ratio of 1:4, 1:2 and 1:1
- copolymers PVA:PVP (1:1) in glycerine & water in the concentration of 30, 40 and 50% w/w
- Methocel(R)A 4M in the concentration of 5, 10 and 15% w/w
- Methocel(R)K 4M in the concentration of 5, 10 and 15% w/w
- Methocel(R)K 100M in the concentration of 3, 4 and 5% w/w

## 2. Analytical Quantitation of Nifedipine

### *2.1. Analysis of Nifedipine in Preparations*

#### 2.1.1 Determination of the UV Absorption Maxima of Nifedipine

When nifedipine was dissolved in the medium which composed of ethanol and PEG 400 in the ratio of 1:1. The uv. maximum absorption of nifedipine was detected at the wavelength of 332 nm as shown in Figure 11. The polymeric matrix base from hydrophilic polymers did not show the absorption at this wavelength.

#### 2.1.2 Calibration Curve

The plot of nifedipine concentration versus its absorbance in the medium of PEG 400:ETOH (1:1) medium in Table 10, showed a linear relationship with the correlation coefficient of 0.9988. The calibration curve of nifedipine after regression analysis was illustrated in Figure 12.

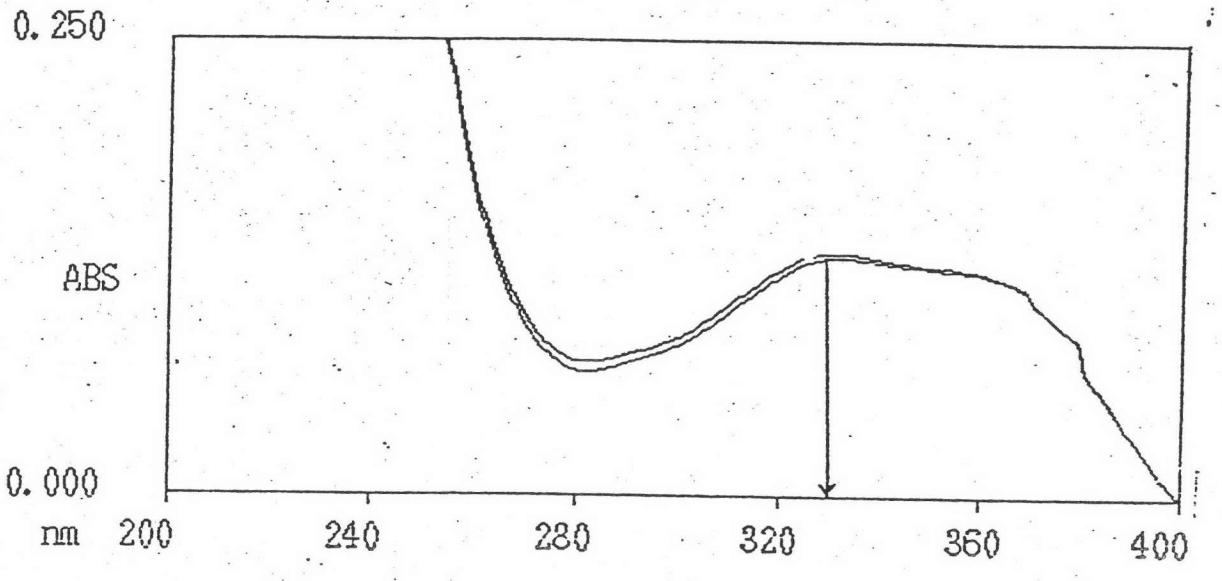


Figure 11 Scanning Curve of Nifedipine in PEG 400 : Ethanol (1:1) by UV Spectrophotometer. (Maximum Wavelength = 332 nm.) (n=2)

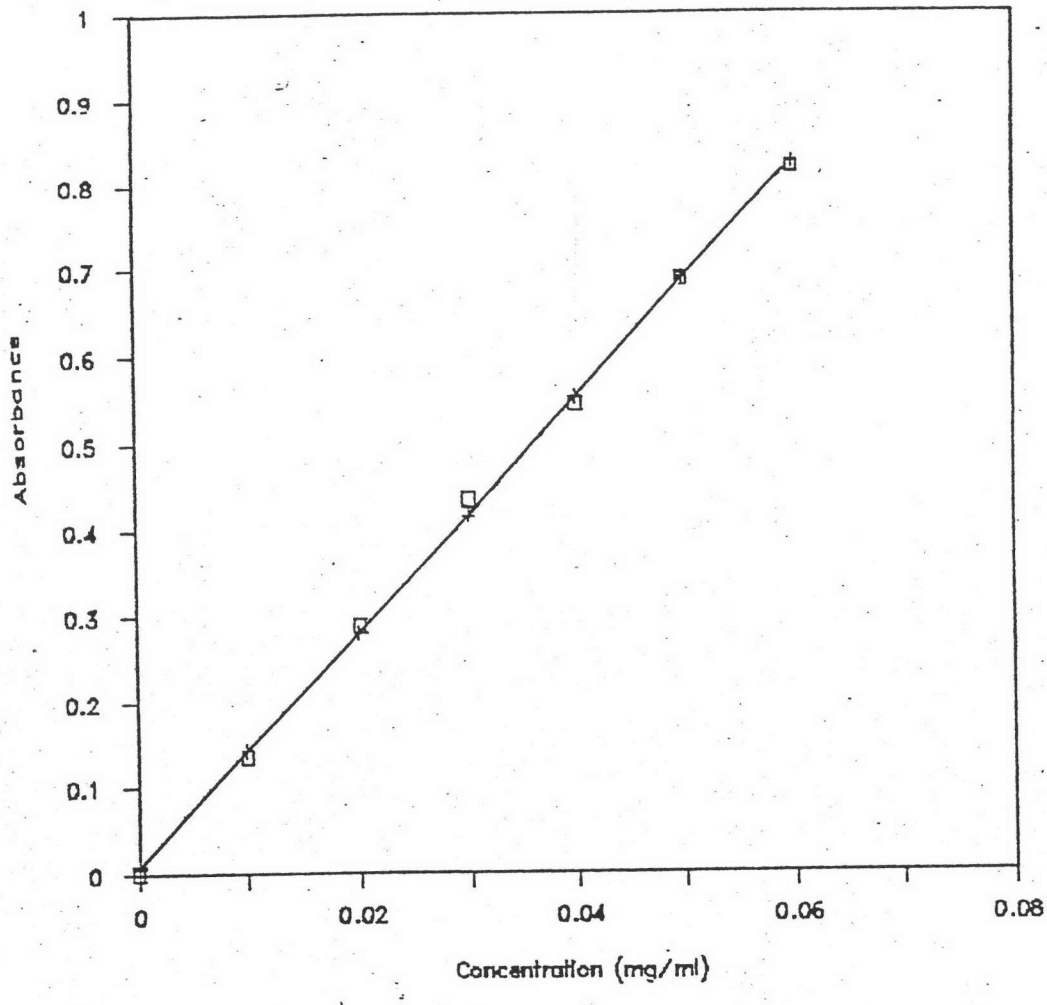


Figure 12 Calibration Curve of Nifedipine in 1:1 PEG 400 : Ethanol at 332 nm. (Y = 13.6536 X + 0.0063, r = 0.9988) (n = 2)

Table 10 : Absorbance of Nifedipine in PEG 400 : Ethanol (1:1) at 332 nm. by UV Spectrophotometry

| concentration of drug (mg/ml) | absorbance* at 332 nm |
|---|---|
| 0 | 0 |
| 0.01 | 0.135 |
| 0.02 | 0.228 |
| 0.03 | 0.435 |
| 0.04 | 0.545 |
| 0.05 | 0.688 |
| 0.06 | 0.820 |

*average of two determinations

## *2.2. Analysis of Nifedipine in Biological Fluids*

### 2.2.1 Serum Analysis

Dichloromethane and pentane in the ratio of 3:7 could extract nifedipine from the serum samples. These extracted solutions could be dried at 40°c within 2 hours. Disodium hydrogen phosphate pH 6.1 and methanol in the ratio of 40:60, as mobile phase dissolving the residue of the extracted solution could seperate nifedipine from the endogenous substance of the serum. No endogenous peak or any other interferences were observed at the same peak time as drug and internal standard. The run time per sample was within 20 minutes. Chromatograme of HPLC as shown in Figure 13 presented the good resolution between drug and the internal standard used. The obtained calibration plotted of relationship between peak area ratio and serum concentration was shown in Figure 14.

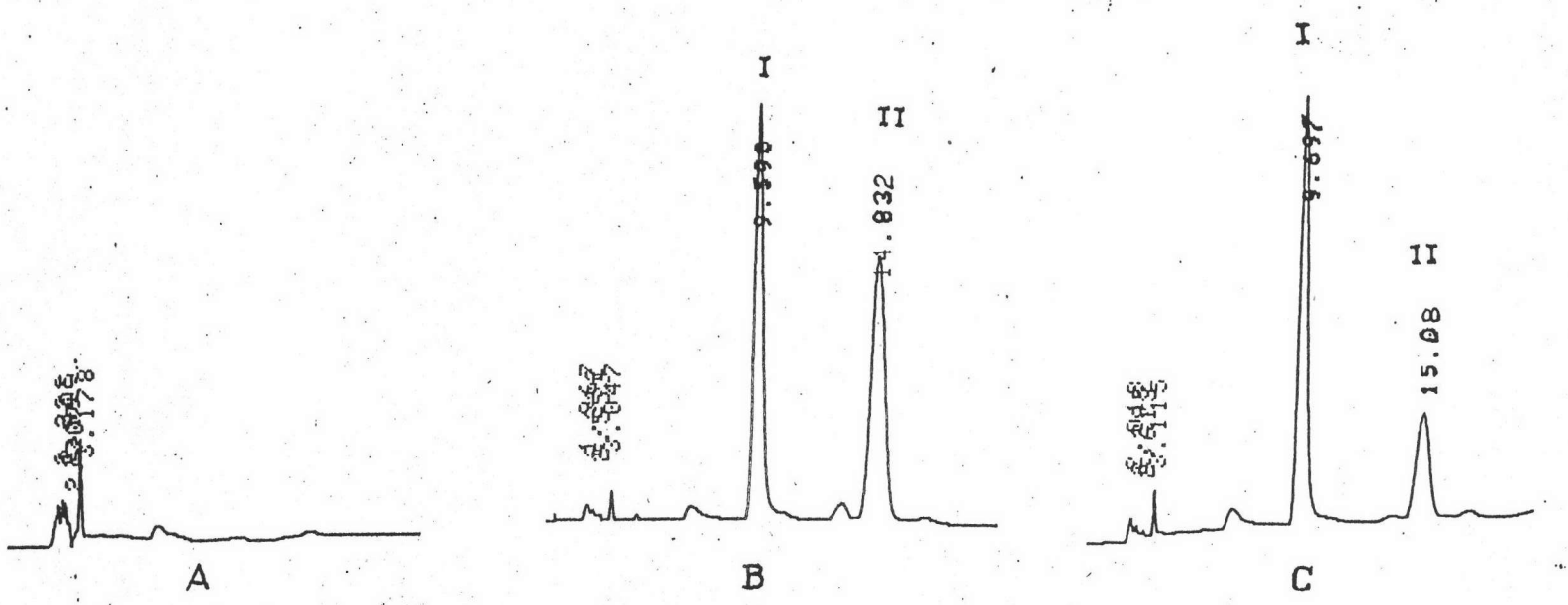


Figure 13 Typical HPLC chromatogram of (A) control rabbit's serum before administration of nifedipine;(B) control serum spiked with 2 ug/ml internal standard (4-dimethylamino-benzaldehyde)(I) and 0.8 ug/ml nifedipine(II); and (C) rabbit's serum taken 1 hour after nifedipine tdds administration prepared from PVA-PVP copolymers

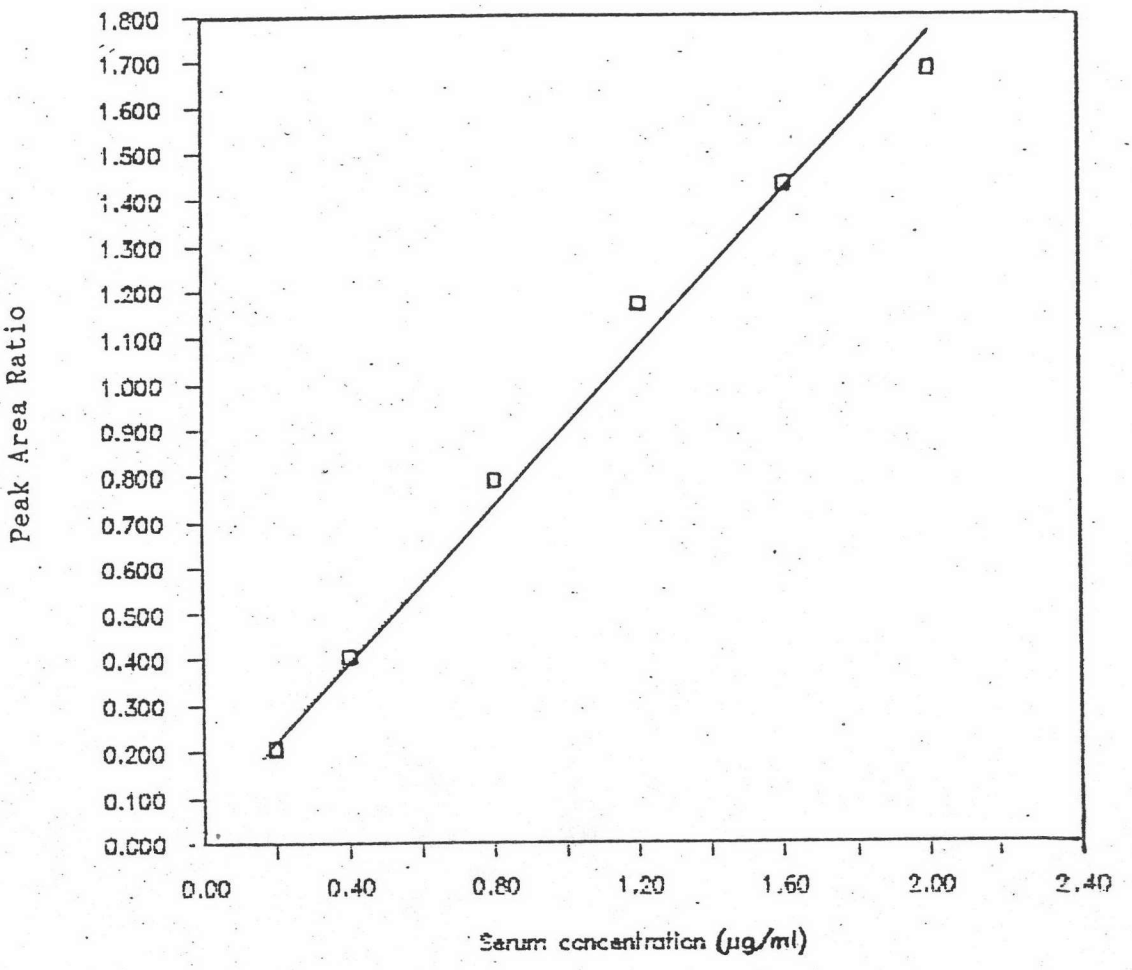


Figure 14 Calibration Curve of Nifedipine-Internal Standard (4-Dimethylaminobenzaldehyde) Ratio As A Function of Serum Nifedipine Concentration at 236 nm.
($y = 0.8544 X + 0.0547$, $r = 0.9916$)

## 3. Evaluation of the Nifedipine TDDS Preparations

### *3.1. In-Vitro Diffusion Stdies.*

The three relationships between the average percentage of drug released vs. time profile from nifedipine TDDS preparations containing Pluronic$^{(R)}$F 127, PEG 4000 : PEG 400 copolymers, PVA-PVP copolymers, Methocel$^{(R)}$A 4M, K 4M, and K 100M were shown in Figure 15-32, respectively. Also, all of the drug release time data from these polymers were showed in Table 11-16 (Appendix 2-7), accordingly.

#### Pluronic$^{(R)}$ F 127

The influence of concentration on the drug released of the preparations containing Pluronic$^{(R)}$F 127 was exhibited. Higher concentration of this polymer produced lower percentage of drug released. For 12 hours, the preparations containing 35% w/w and 45% w/w of this polymer could present the percentage of drug released of 42 and 17, respectively. From the curve shown in Figure 15 and the value of correlation coefficient of the relationship between the percentage drug released versus time in Table 17 was the highest among the other relationships. This result indicated that the release pattern of these preparations seemed to be a zero-order kinetic.

#### PEG 4000 : PEG 400 Copolymers

Very slightly increasing in the percentage of drug was noted when the amount of PEG 400 was increased in the preparation. These preparations containing PEG 4000 : PEG 400 in the

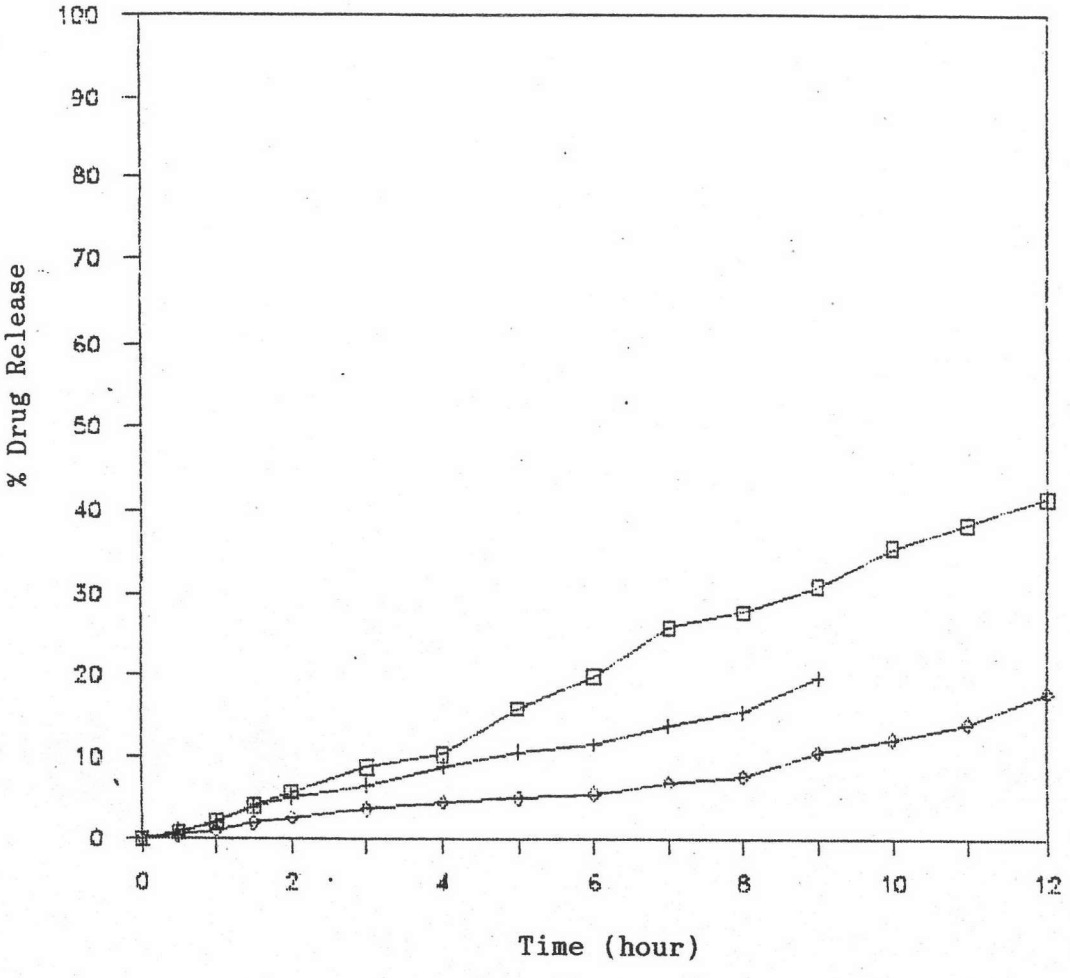


Figure 15 Drug Released-Time Profiles of Nifedipine TDDS Containing Various Concentration of Pluronic$^{(R)}$F 127

(▫——▫ 35%, +——+ 40%, ◇——◇ 45%)

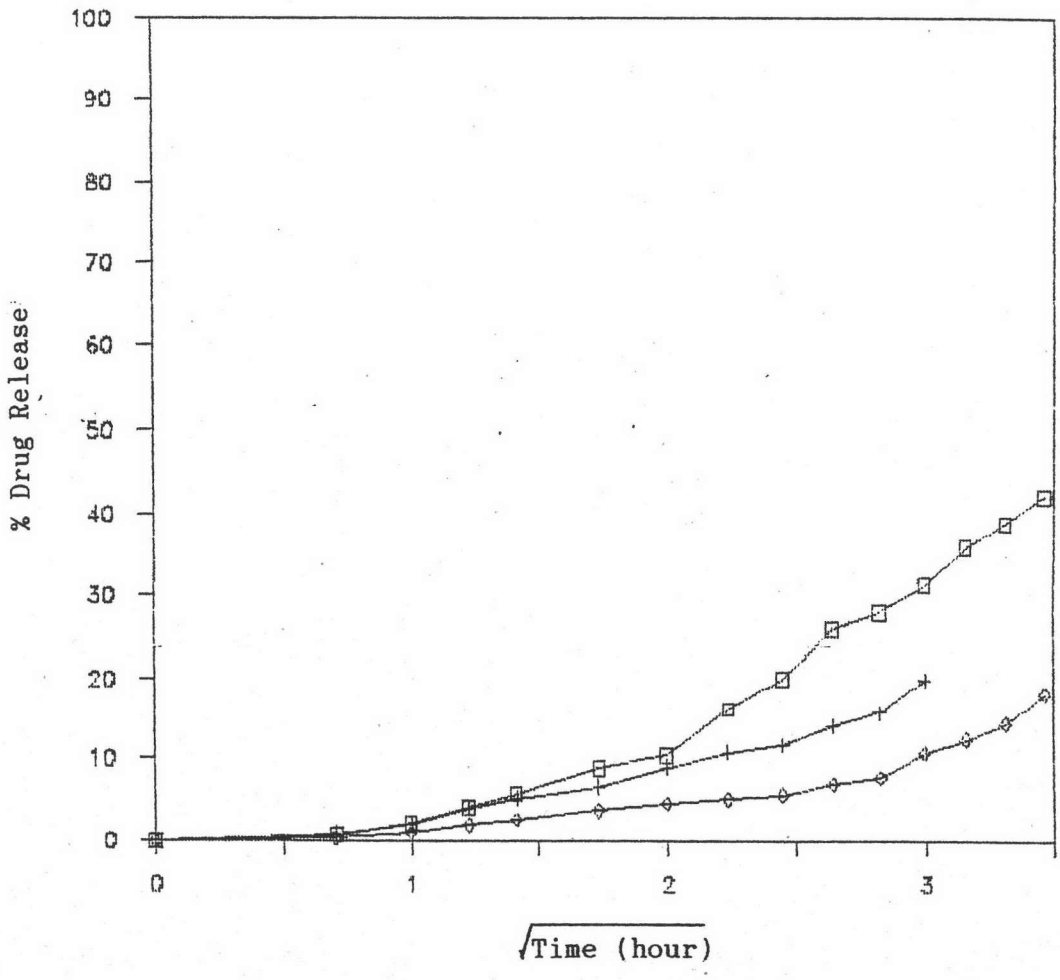


Figure 16 Drug Released-$\sqrt{\text{Time}}$ Profiles of Nifedipine TDDS Containing Various Concentration of Pluronic$^{(R)}$F 127

(□——□ 35%, +——+ 40%, ◇——◇ 45%)

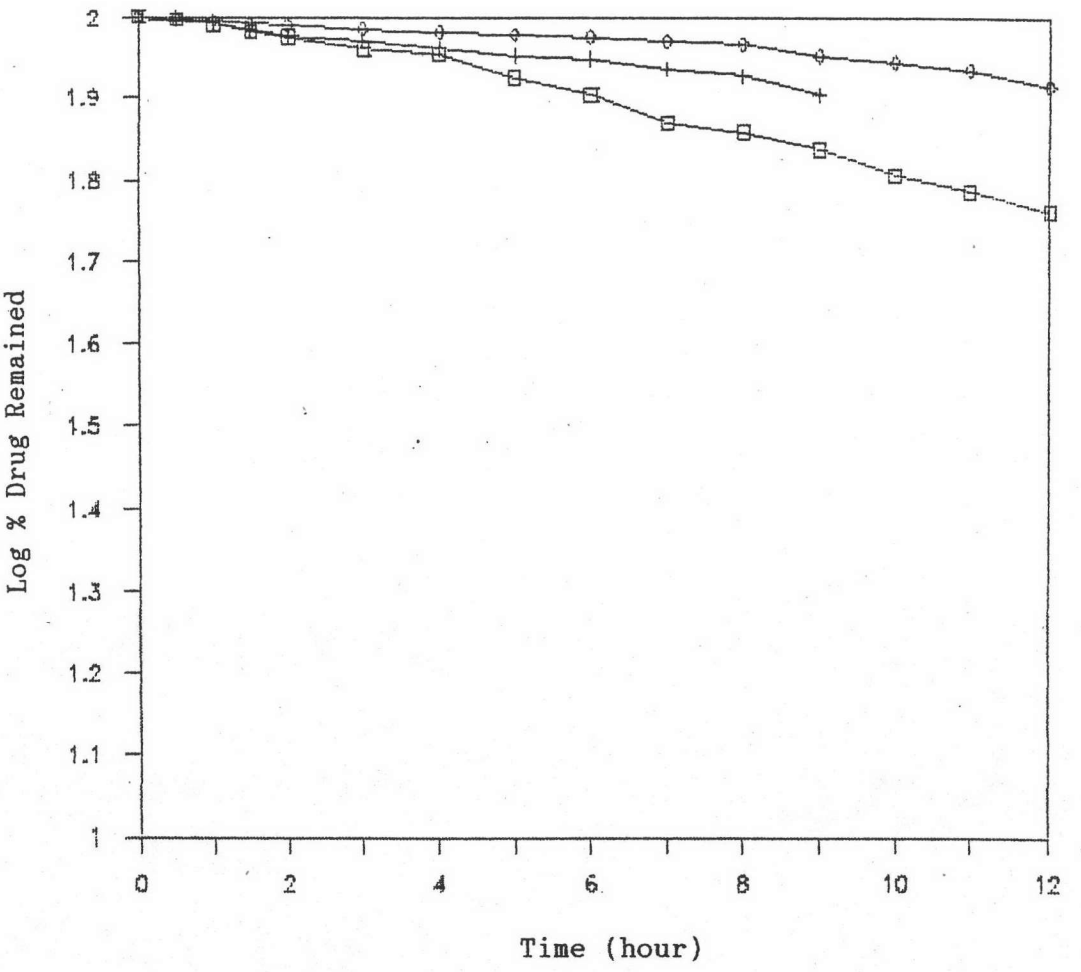


Figure 17 Log Drug Remained-Time Profiles of Nifedipine TDDS Containing Various Concentration of Pluronic$^{(R)}$ F 127 (□——□ 35%, +——+ 40%, ◇——◇ 45%)

ratio of 1:1 and 1:2 and 1:4 produced the percentage of drug released of 10, 11, and 13, respectively in the period of 12 hours. From Figure 20 and Table 17, the maximum correlation coefficient in the range of 0.984-0.988 of the relationship between logarithm of drug release and time was indicated that the first-order kinetic seemed to be the release pattern of the preparation formulated with combination of PEG 4000 and PEG 400.

PVA-PVP Copolymers

In the case of preparation containing PVP-PVA copolymer, non-linear release pattern was observed. Rapidly release of drug was noted from the first hour to the eighth hour and followed by the slow relrase the drug till 12 hours. In the diffusion studies for 12 hours, the percentage of drug released from the preparation containing 30, 40 and 50 %w/w of PVA-PVP copolymer were 88, 59 and 48 respectively. The low concentration of copolymer increased the percentage of drug released. According to the high relationship between the drug released and the square root of time in the range value of correlation coefficient of 0.9472-0.9930 in Table 17 and the curve shown in Figure 22, it was implied that the release pattern of drug from this copolymers tend to be the Higuchi's model.

Methocel$^{(R)}$A 4M

Figure 18 indicated that low concentration of Methocel$^{(R)}$A 4M caused an increasing in the release of drug. The 30%, 28%, and 13% of drug released were observed in the preparation containing 5%, 10% and 15% w/w of this polymer, respectively in the period of 12 hours. It was surprising at the release pattern of this polymer. It was fluctuated during the fourth to the ninth hour. The

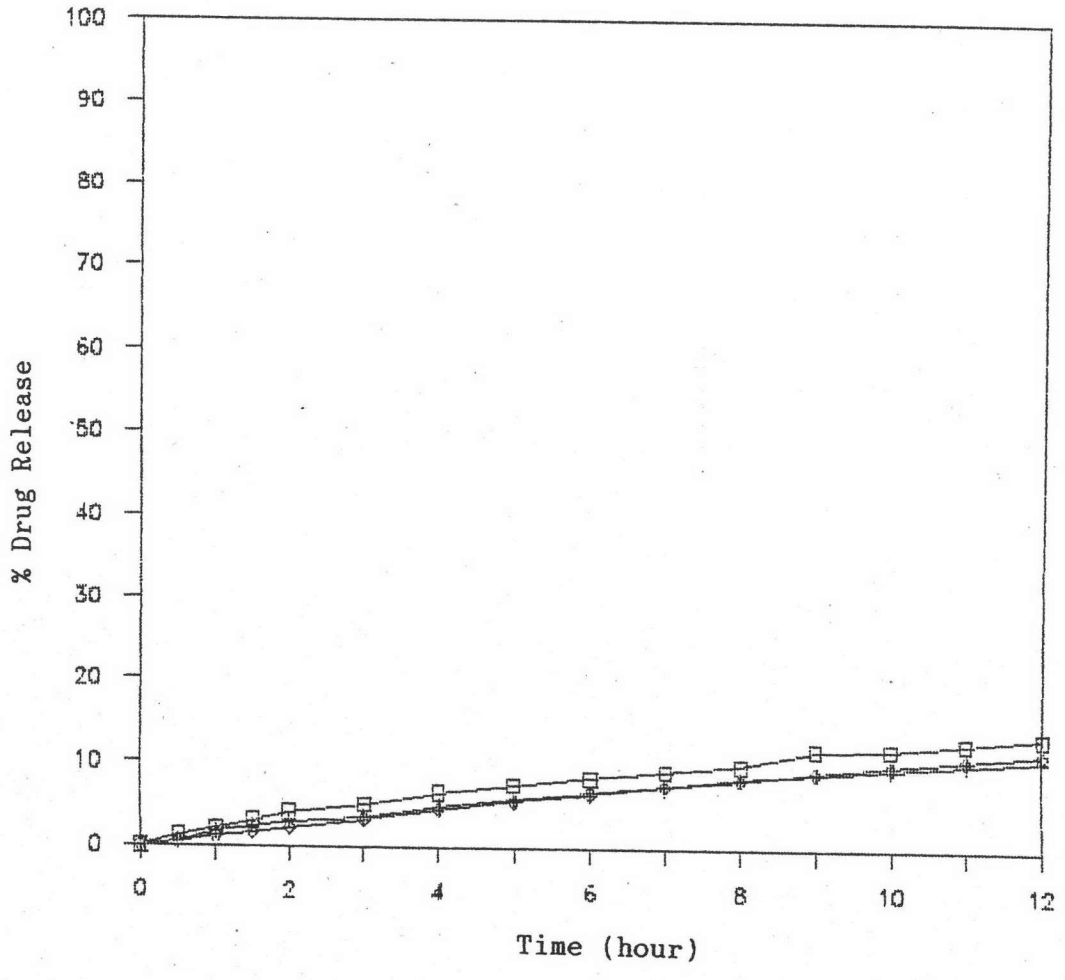


Figure 18 Drug Released-Time Profiles of Nifedipine TDDS Containing Various Ratio of PEG 4000 : PEG 400

( ◇——◇ 1:1, +——+ 1:2, □——□ 1:4)

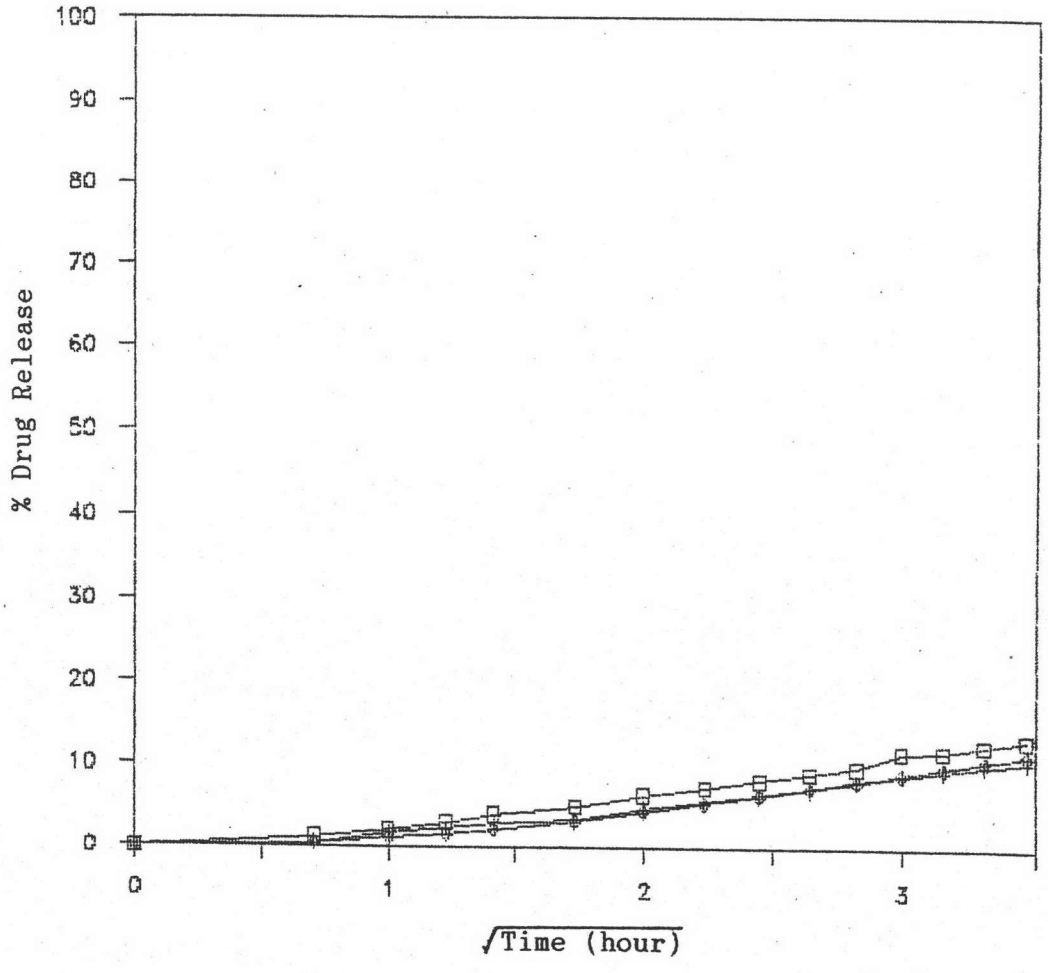


Figure 19 Drug Released-$\sqrt{\text{Time}}$ Profiles of Nifedipine TDDS Containing Various Ratio of PEG 4000 : PEG 400

( ◇——◇ 1:1, +——+ 1:2, □——□ 1:4)

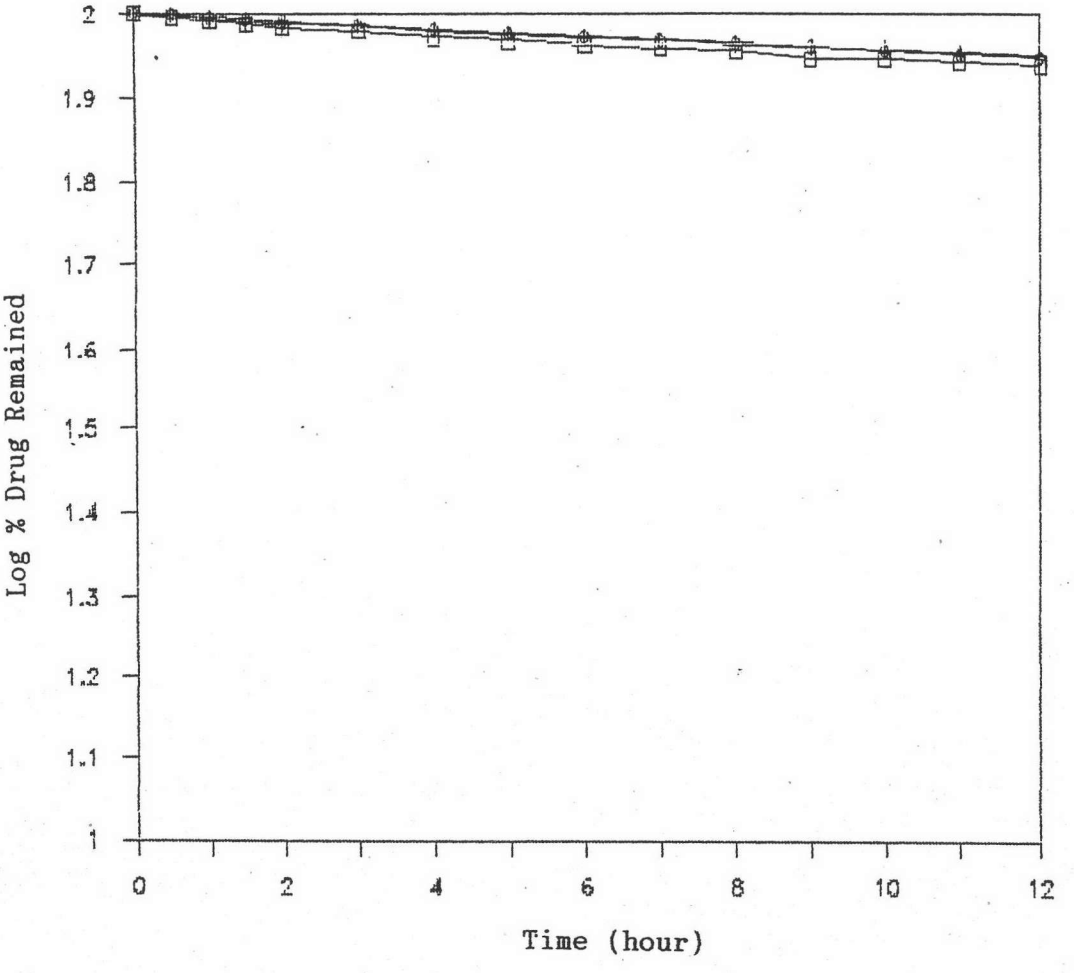


Figure 20 Log Drug Remained-Time Profiles of Nifedipine TDDS Containing Various Ratio of PEG 4000 : PEG 400 ( ◇——◇ 1:1, +——+ 1:2, □——□ 1:4)

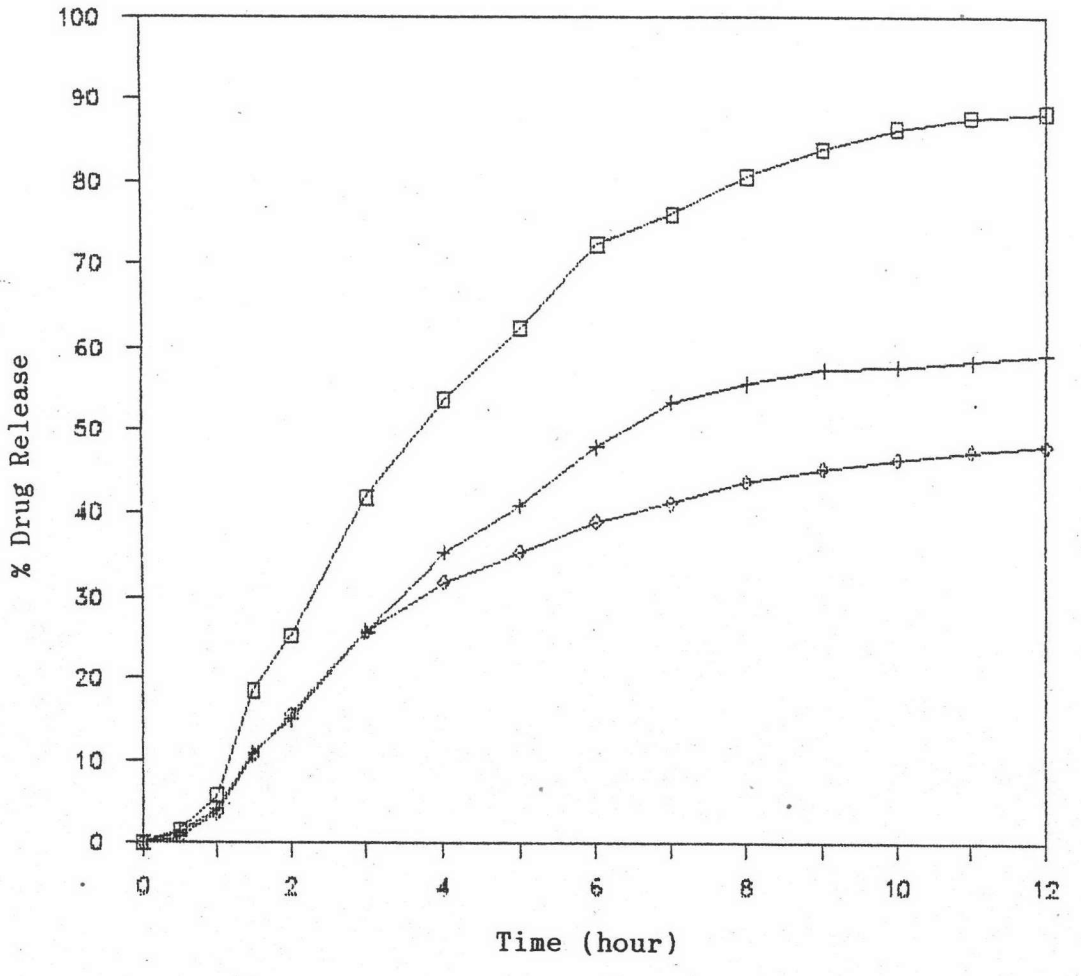


Figure 21 Drug Released-Time Profiles of Nifedipine TDDS Coniaining Various Concentration of PVA-PVP Copolymers (□——□ 30%, +——+ 40%, ◇——◇ 50%)

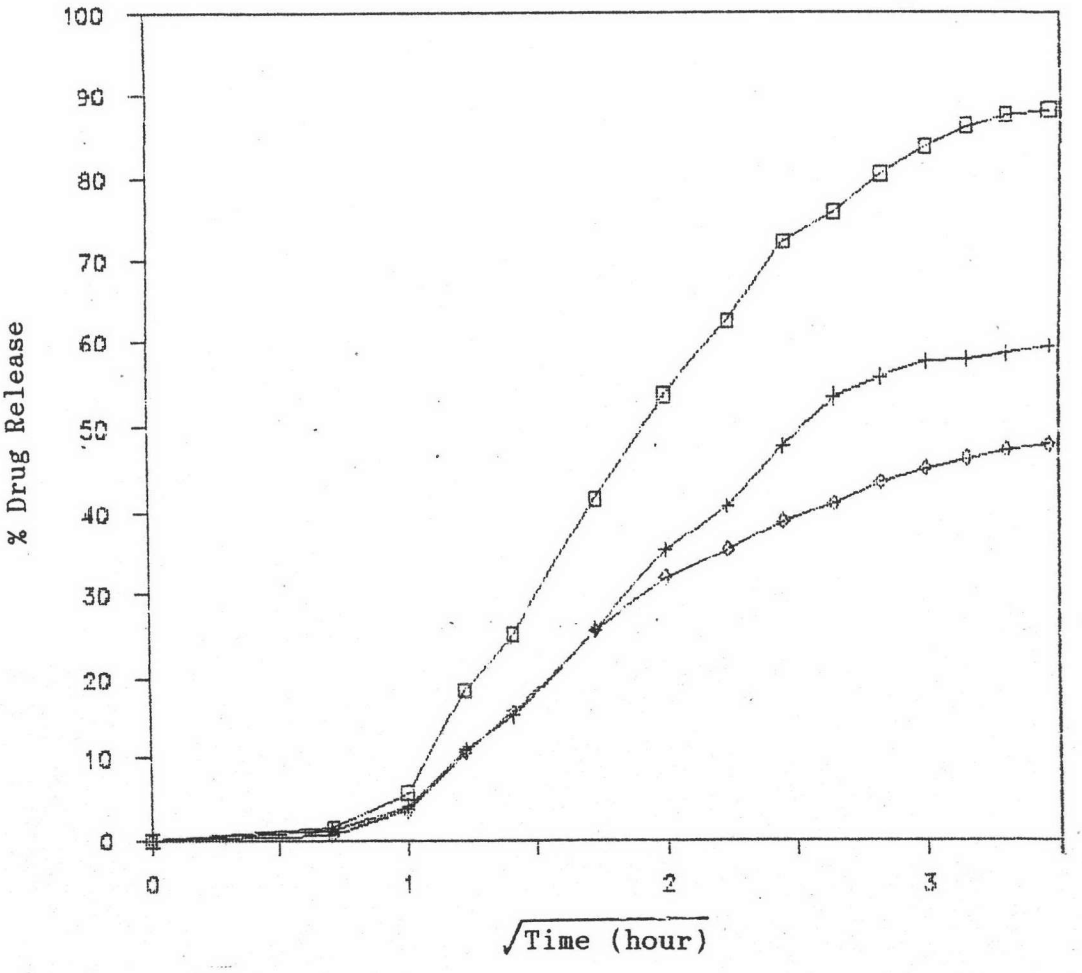


Figure 22 Drug Released-$\sqrt{\text{Time}}$ Profiles of Nifedipine TDDS Coniaining Various Concentration of PVA-PVP Copolymers ( ▫—— ▫ 30%, +——+ 40%, ◇—— ◇ 50%)

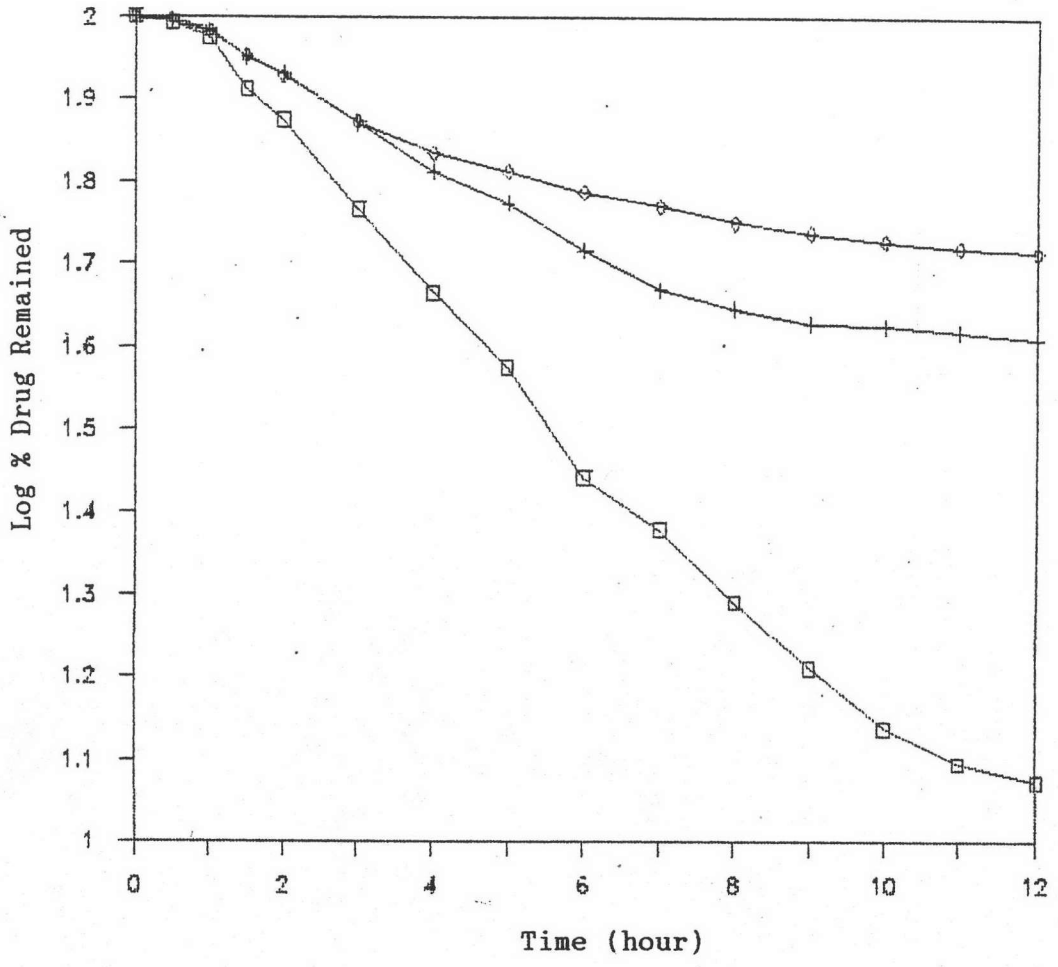


Figure 23 Log Drug Remained-Time Profiles of Nifedipine TDDS Coniaining Various Concentration of PVA-PVP Copolymers (□——□ 30%, +——+ 40%, ◇——◇ 50%)

maximum r value from Table 17 and the curve shown in Figure 24-25 indicated that the tendency of nifedipine released from this polymer may be zero-order kinetic in the concentration of 5 and 10% w/w but follow Higuchi's equation in the concentration of 15% w/w.

Methocel(R) K 4M

The drug released - time profiles from the preparations containing this polymer indicated that the release of drug depended on the concentration. Increasing the concentration of polymer affected decreasing of drug released. The drug released from the preparations composed of 5%, 10% and 15% w/w of this polymer were 24%, 21% and 14%, respectively within 12 hours. Maximum correlation coefficient in Table 17 and the curve shown in Figure 27,29, respectively, indicated that the release of drug this polymer seemed to follow the first-order kinetic in the concentration of 5% and 10% w/w and zero-order kinetic in the concentration of 15% w/w.

Methocel(R) K 100M

In the period of 12 hours, the preparation composed of 3%, 4% and 5% w/w Methocel(R) K 100M presented the amount drug released of 31%, 26% and 21%, respectively. The release pattern of drug from this polymer may be the first-order in the concentration of 3% w/w and seemed to be the Higuchi's model in the concentration of 4% and 5% w/w according to the maximum correlation coefficient in Table 17 and the curve shown in Figure 31,32 respectively.

As these results, it were indicated that the concentration of polymers obviously affected the percentage of drug released and

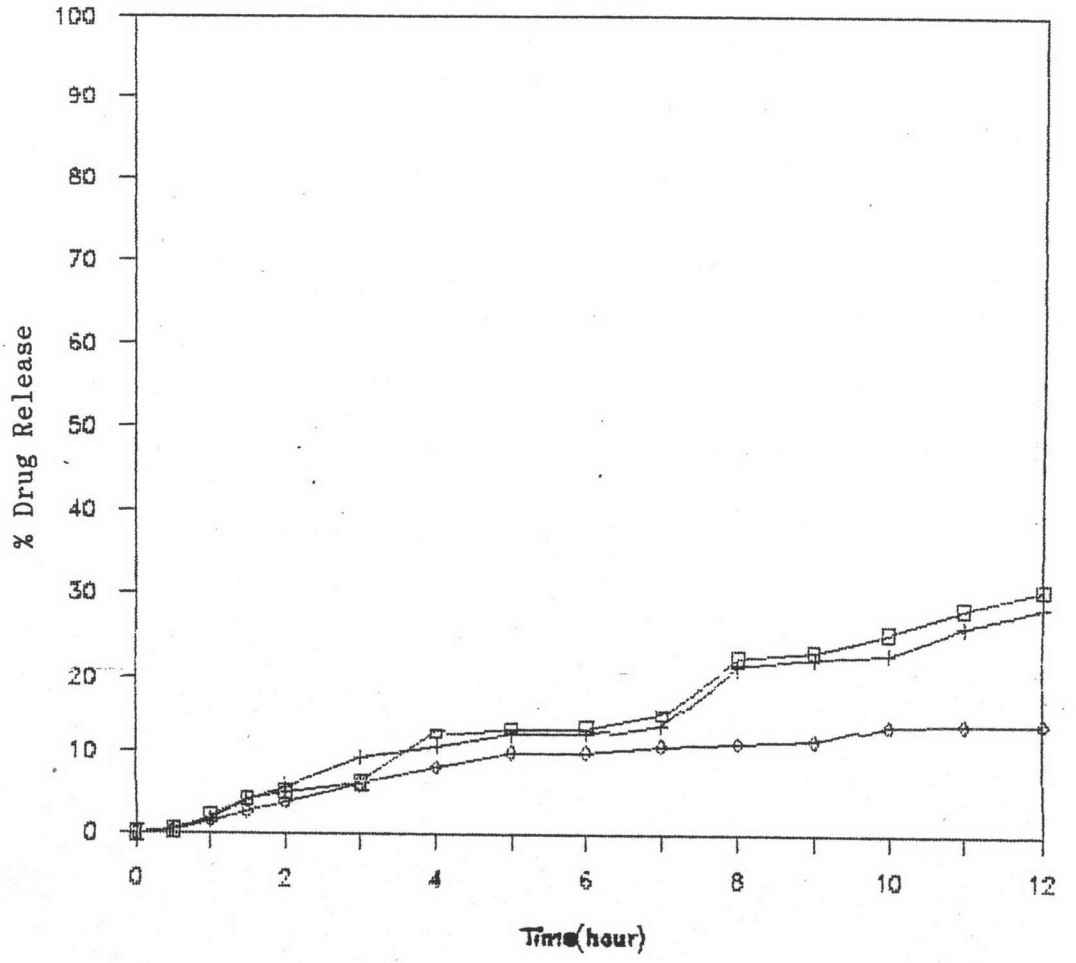


Figure 24 Drug Released-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$A 4M

( □——□ 5%, +——+ 10%, ◇——◇ 15%)

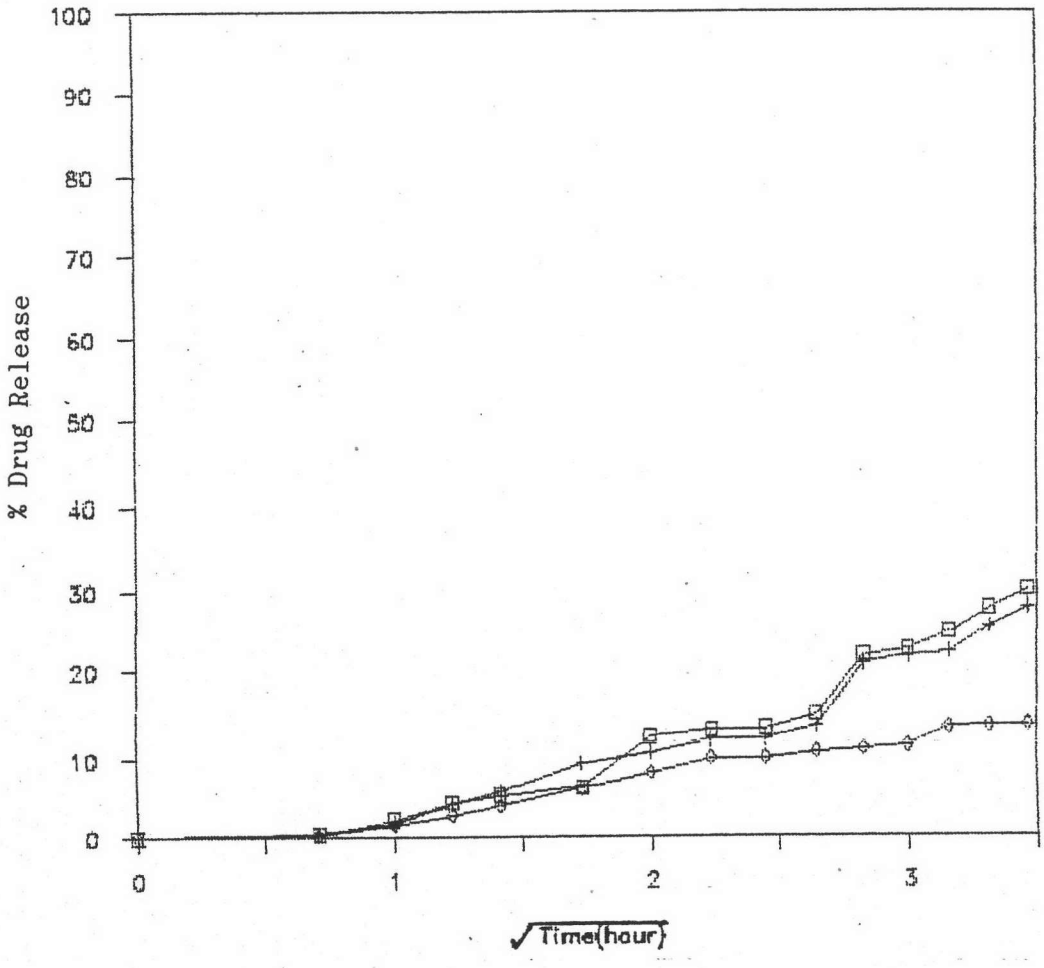


Figure 25 Drug Released-$\sqrt{\text{Time}}$ Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$A 4M

( ——— 5%, ——— 10%, ——— 15%)

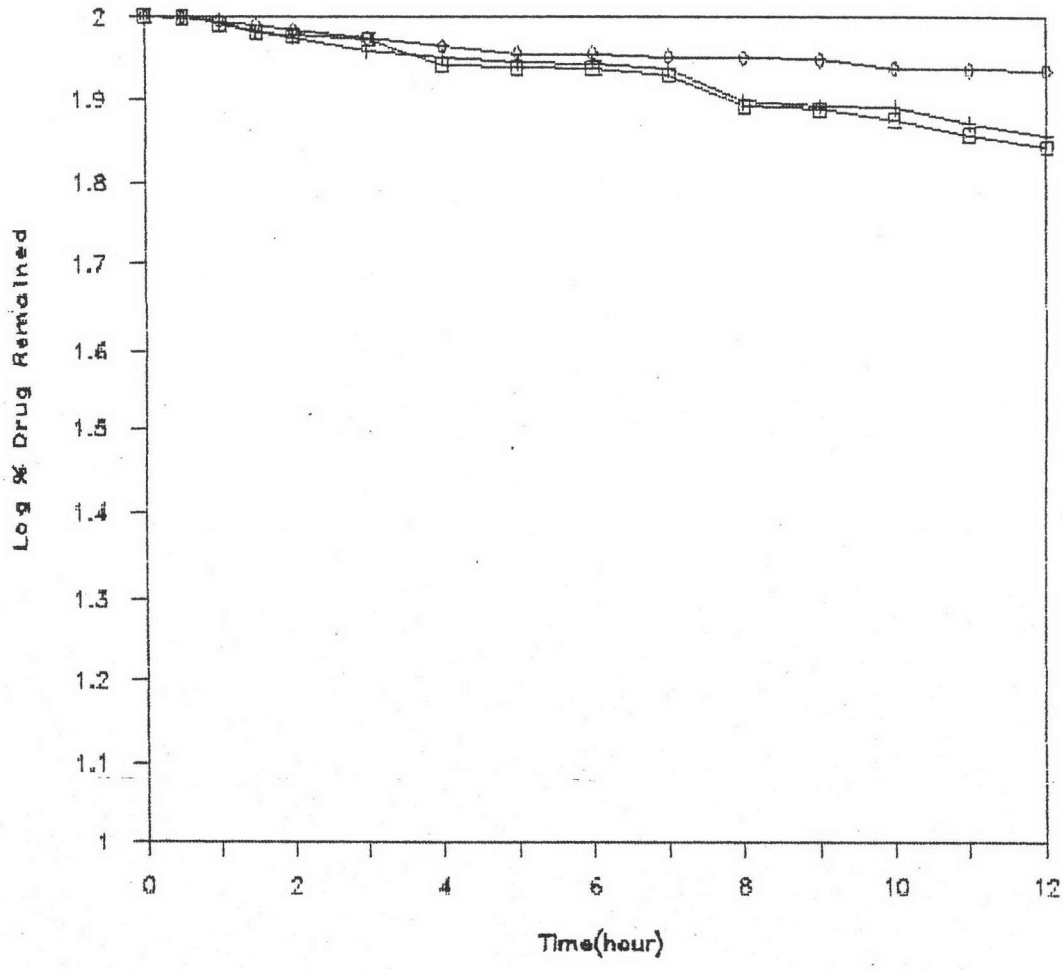


Figure 26 Log Drug Remained-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$A 4M
( ▫——▫ 5%, —+—+— 10%, ◇——◇ 15%)

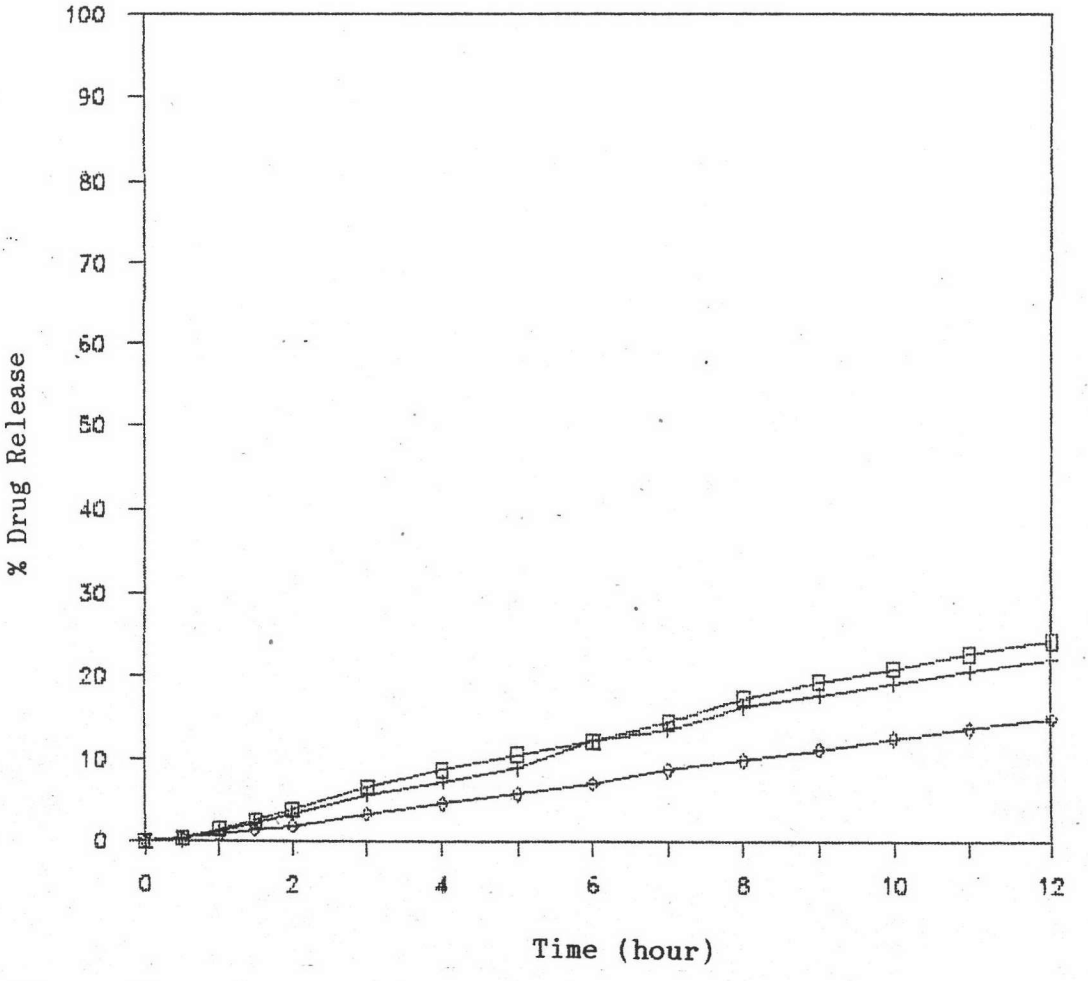


Figure 27 Drug Released-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$K 4M

(□——□ 5%, +——+ 10%, ◇——◇ 15%)

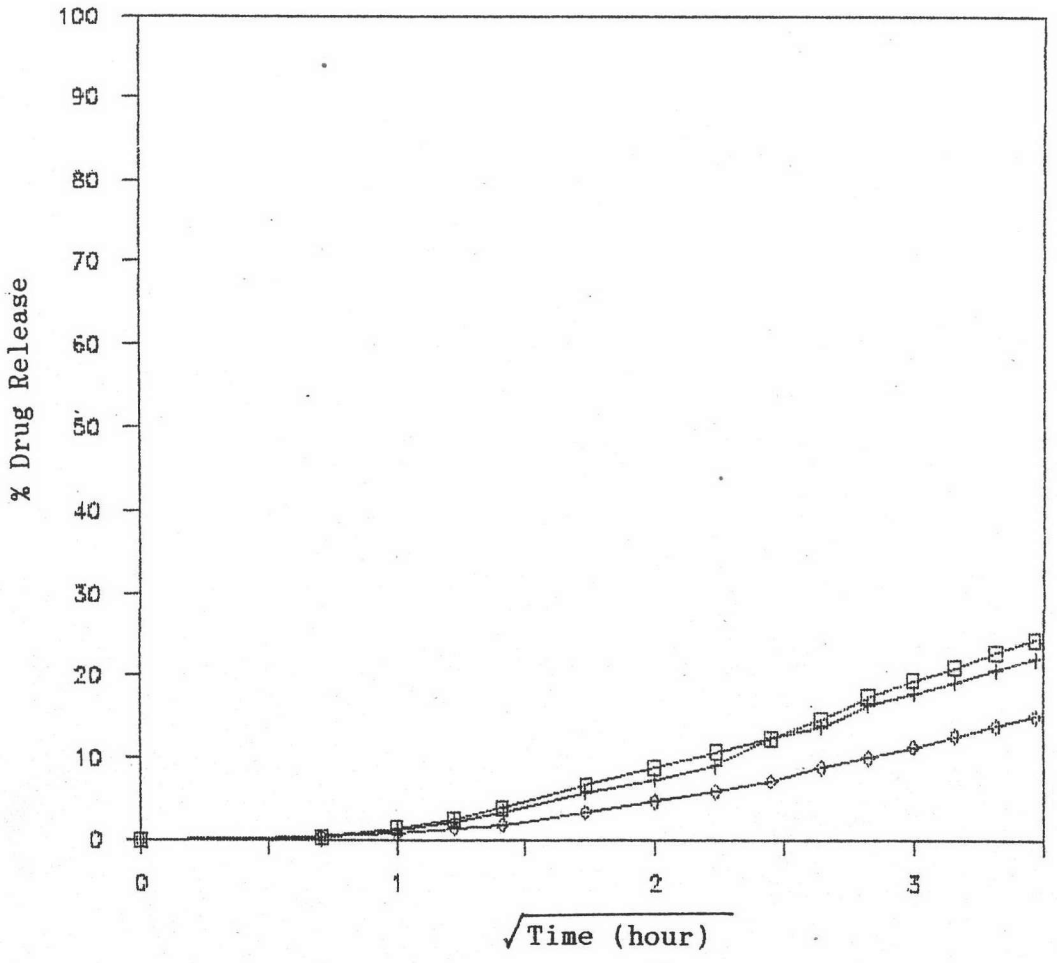


Figure 28 Drug Released-$\sqrt{Time}$ Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$K 4M

(o——□ 5%, +——+ 10%, ◇——◇ 15%)

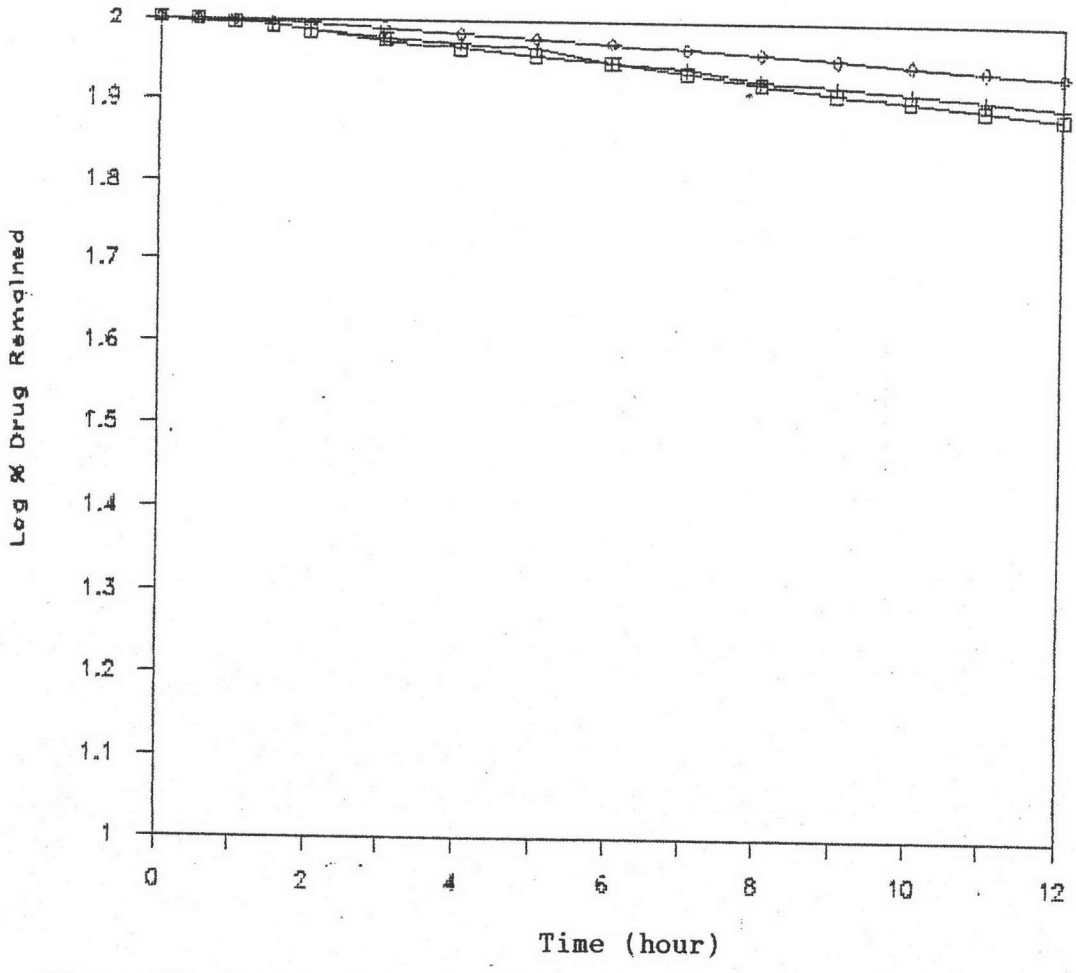


Figure 29 Log Drug Remained-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel(R) K 4M (□——□ 5%, +——+ 10%, ◇——◇ 15%)

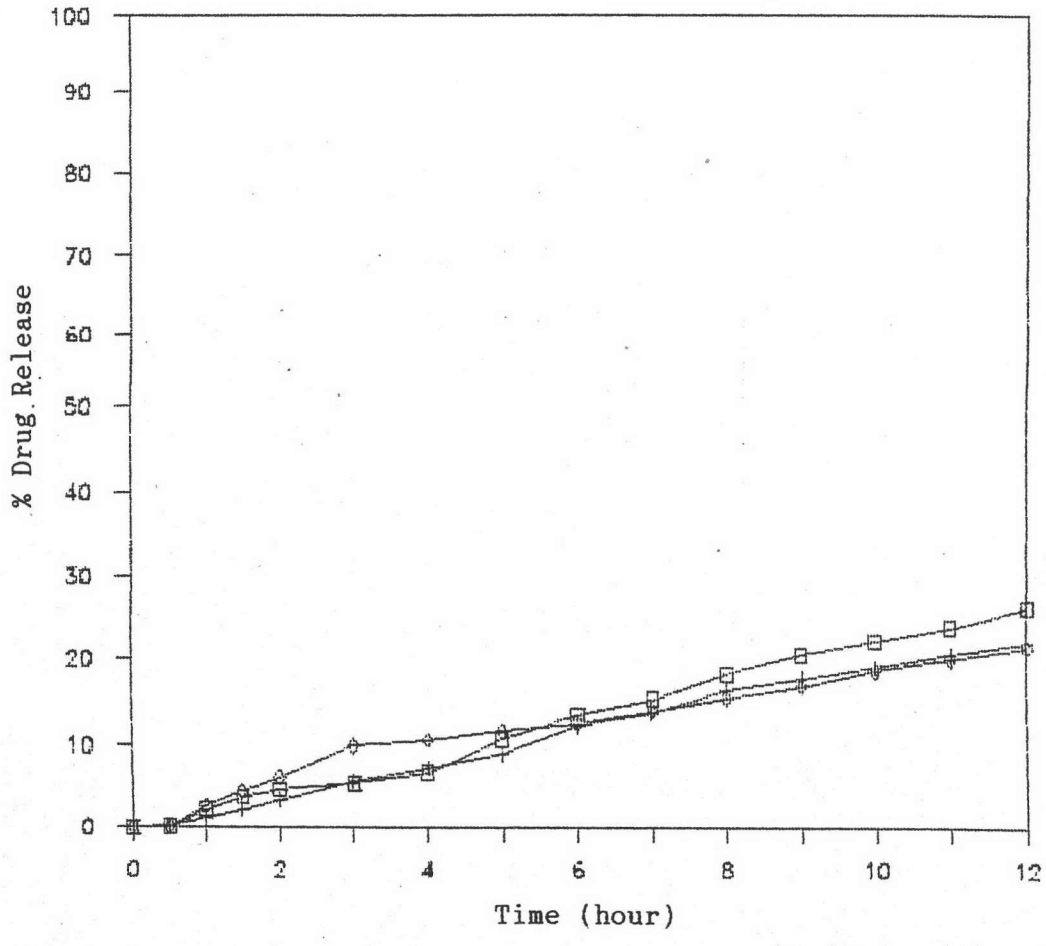


Figure 30 Drug Released-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$K100M

(□——□ 3%, +——+ 4%, ◇——◇ 5%)

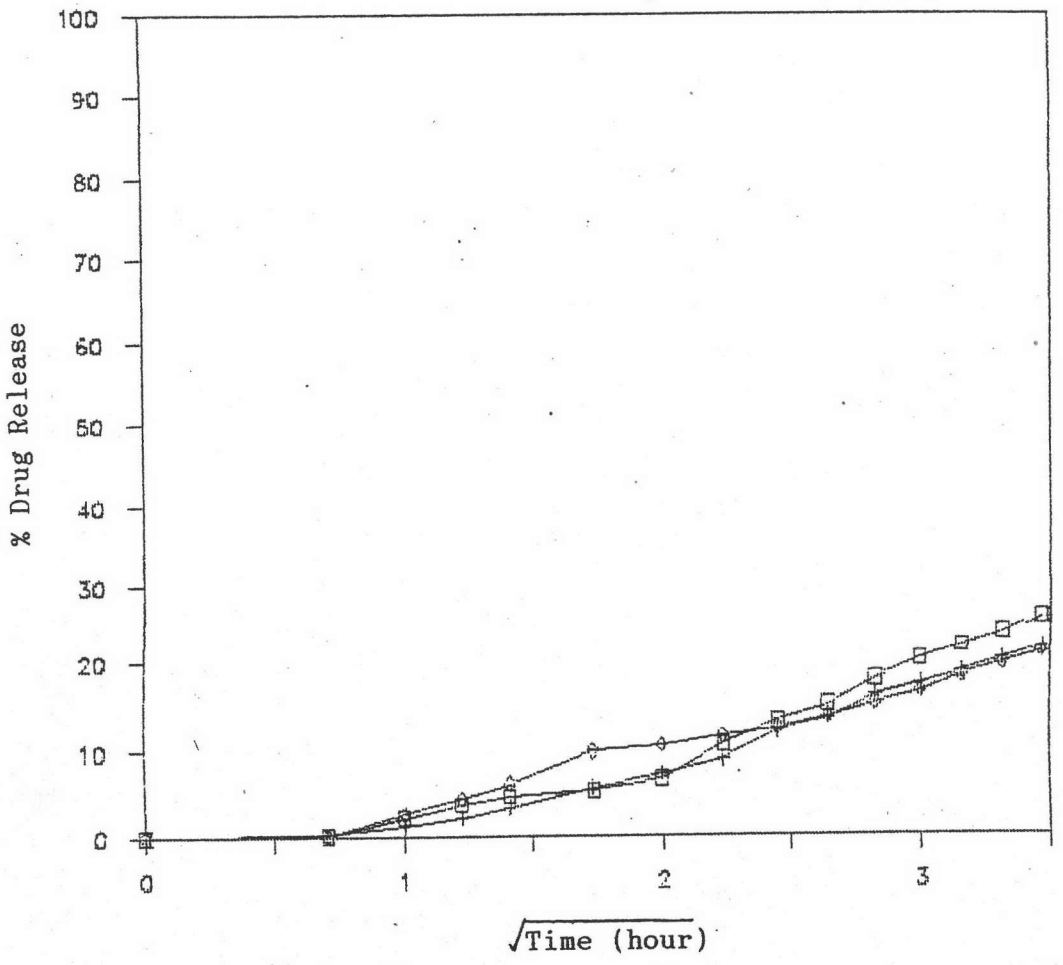


Figure 31 Drug Released-$\sqrt{Time}$ Profiles of Nifedipine TDDS Containing Various Concentration of Methocel$^{(R)}$K100M

( □——□ 3%, +——+ 4%, ◇——◇ 5%)

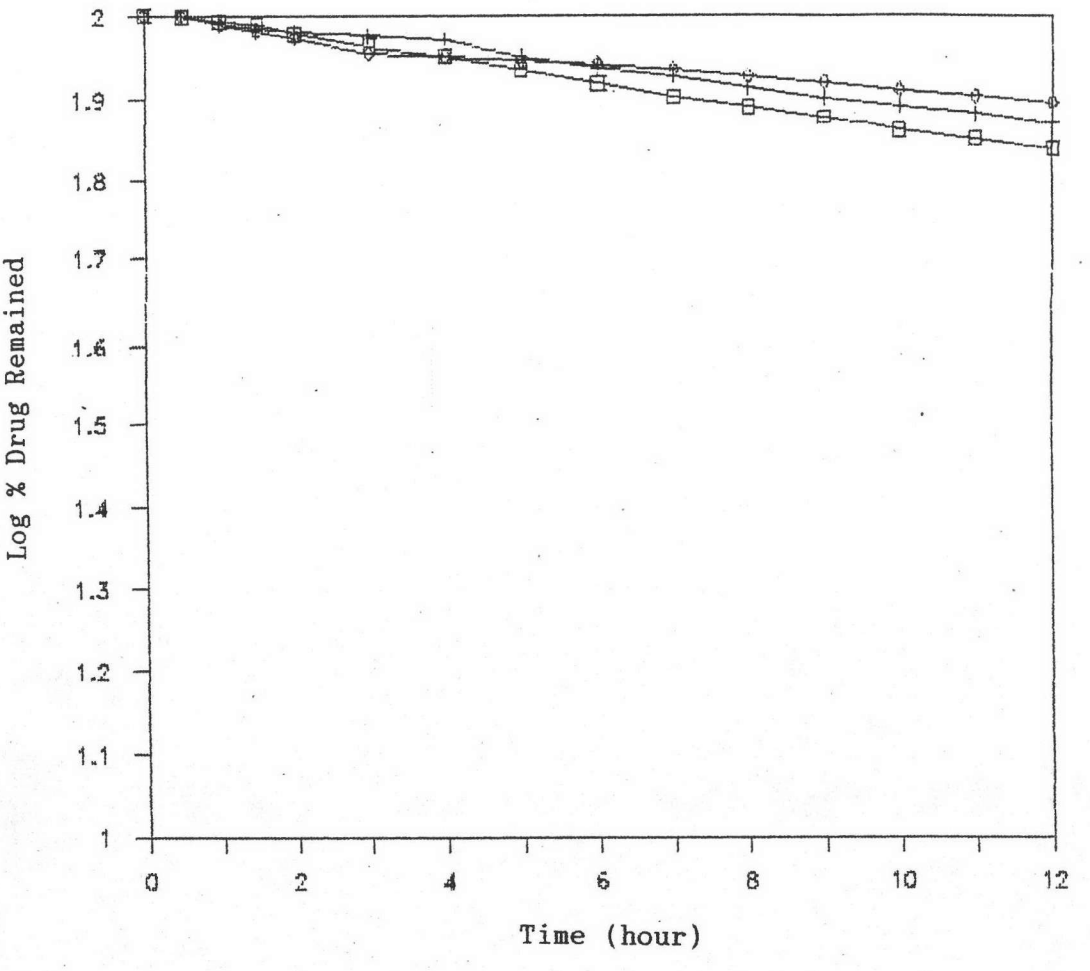


Figure 32 Log Drug Remained-Time Profiles of Nifedipine TDDS Containing Various Concentration of Methocel(R)K100M (o——o 3%, +——+ 4%, ◇——◇ 5%)

Table 17: Correlation Coefficients of the Relationships Between % Drug Released VS. Time (I), %Drug Released VS. $\sqrt{\text{Time}}$ (II), Log % Drug Remained VS. Time (III).

| POLYMER | %,RATIO | I | II | III |
|---|---|---|---|---|
| PF-127 | 35% | 0.9951 | 0.9111 | 0.9880 |
| | 40% | 0.9873 | 0.9344 | 0.9841 |
| | 45% | 0.9463 | 0.8332 | 0.9340 |
| PEG | 1:4 | 0.9795 | 0.9801 | 0.9873 |
| | 1:2 | 0.9805 | 0.9794 | 0.9842 |
| | 1:1 | 0.9850 | 0.9685 | 0.9884 |
| MC A4M | 5 | 0.9563 | 0.9192 | 0.9413 |
| | 10 | 0.9664 | 0.9144 | 0.9631 |
| | 15 | 0.9055 | 0.9482 | 0.9117 |
| MC K4M | 5 | 0.9973 | 0.9397 | 0.9984 |
| | 10 | 0.9939 | 0.9358 | 0.9956 |
| | 15 | 0.9987 | 0.9206 | 0.9977 |
| MC K100M | 3 | 0.9952 | 0.9390 | 0.9978 |
| | 4 | 0.9624 | 0.9736 | 0.9725 |
| | 5 | 0.9252 | 0.9955 | 0.9929 |
| PVP:PVA | 30 | 0.9031 | 0.9930 | 0.9550 |
| | 40 | 0.9024 | 0.9472 | 0.9387 |
| | 50 | 0.8839 | 0.9523 | 0.9249 |

the different polymers produced the different both the released pattern and the drug released-time profile. Moreover, according to find the maximum correlation coefficient it could obtain X-coefficient and Y-intercept of the linear equation of the relationship too. So, the drug release from these hydrophilic polymers in various concentrations at any time could be calculated from these values in Table 18.

From evaluation the preparations *in-vitro* diffusion studies was briefly said that the preparation which displayed the percentage of drug released in the period as required from maximum to minimum were following : PVA-PVP copolymer, Pluronic$^{(R)}$F 127, Methocel$^{(R)}$A 4M, K 4M, K 100M and PEG 4000 : PEG 400 copolymer, respectively. Therefore, the two preparations containing 30% w/w PVA-PVP copolymers and 35% w/w Pluronic$^{(R)}$F 127 were selected to the *in-vivo* diffusion study because these preparations gave the maximum percentage of drug release and could sustain the drug release with a constant rate in the period of 12 hours.

## *3.2. In-Vivo Diffusion Studies.*

### 3.2.1 Application of Nifedipine TDDS Preparations

By the way, the assumption of the *in-vivo* diffusion studies in the application of nifedipine tdds preparations was that these preparations were not lost the water or the polymer base during administration. The only weight loss was the weight of drug penetrated through the skin into blood circulation. Weight of drug preparation before and after application was shown in Table 19 and 20.

Table 18 X-coefficient and Y-intercept of the Linear Relationship with the Maximum Correlation Coefficient of Hydrophilic Polymers

| Polymer | X-coefficient | Y-intercept | Apparent Release Pattern |
|---|---|---|---|
| Puronic(R) F 127 in water (%w/w) | | | |
| 35 | 3.6542 | -1.5663 | zero-order |
| 40 | 1.9732 | 0.6168 | zero-order |
| 45 | 1.2935 | -0.6609 | zero-order |
| PEG 4000:PEG 400 ointment base | | | |
| 1:4 | -0.0049 | 1.9946 | first-order |
| 1:2 | -0.0040 | 1.9963 | first-order |
| 1:1 | -0.0044 | 1.9979 | first-order |
| (1:1)PVA:PVP in glycerine & water (%w/w) | | | |
| 30 | 32.9414 | 4.0283 | Higuchi's model |
| 40 | 21.5787 | -10.1066 | Higuchi's model |
| 50 | 16.9765 | -6.3576 | Higuchi's model |
| Methocel(R) A 4M (%w/w) | | | |
| 5 | 2.4376 | 0.5530 | zero-order |
| 10 | 2.2360 | 0.3702 | zero-order |
| 15 | 4.6188 | -1.9561 | Higuchi's model |
| Methocel(R) K 4M (%w/w) | | | |
| 5 | -0.0104 | 2.0029 | first-order |
| 10 | -0.0095 | 2.0032 | first-order |
| 15 | 1.2827 | -0.4184 | zero-order |
| Methocel(R) K 100M (%w/w) | | | |
| 3 | -0.0142 | 2.005 | first-order |
| 4 | 6.9672 | -3.0418 | Higuchi's model |
| 5 | 6.3783 | -4.3378 | Higuchi's model |

Table 19 Weight of Nifedipine TDDS Preparation Containing 30% w/w PVA-PVP Used in Application on Rabbit's Skin

| Weight of drug preparation | Rabbit Number | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| before application (g) | 13.8769 | 13.9880 | 14.0099 |
| after application (g) | 13.8562 | 13.9706 | 13.9944 |
| penetrated drug (mg) | 20.7 | 17.4 | 15.5 |

Table 20 Weight of Nifedipine TDDS Preparation Containing 35% w/w Pluronic$^{(R)}$F 127 Used in Application on Rabbit's Skin

| Weight of drug preparation | Rabbit Number | | |
|---|---|---|---|
| | 4 | 5 | 6 |
| before application (g) | 15.0774 | 15.6775 | 15.3124 |
| after application (g) | 15.0636 | 15.6684 | 15.3022 |
| penetrated drug (mg) | 13.8 | 9.1 | 10.2 |

The serum concentration-time profiles of nifedipine released from TDDS preparations containing 30% w/w PVA-PVP copolymer and 35% w/w Pluronic$^{(R)}$F 127 were shown in Figure 33 and 34, respectively. Also the complete serum concentration-time data were shown in Table 21 and 22, accordingly.

The observed maximum serum concentration of nifedipine from the preparation containing 30% w/w of PVA-PVP copolymer was detected within 1 hour after application. This preparation could release sustained nifedipine in the period of 24 hours as required. Figure 33 indicated that the drug serum concentration was wide variation among these rabbits.

Nifedipine released from TDDS containing 35% w/w of Pluronic$^{(R)}$F 127 also showed high variation between two rabbits. The serum samples from the other rabbit were not refrigerated kept so they were not taken to determine the drug released. The observed maximum serum concentration of nifedipine in rabbit # 4 was 2.8 µg/ml after 4 hours of drug application. Then the serum concentration was slowly decreased and still detectable at 24 hours with the concentration of 0.75 µg/ml. For rabbit # 5, the serum concentration of nifedipine could be observed within 24 hours clearly showed that the drug released was within the range of 0.123 µg/ml to 0.538 µg/ml.

From the serum concentration-time profiles and the data, it was briefly said that nifedipine from TDDS preparations containing either PVA-PVP copolymer or Pluronic$^{(R)}$F 127 could be released and penetrated through the rabbit's skin into blood circulation. These polymers could sustained release nifedipine in the period of 24 hours and it was observed that the serum drug concentration from nifedipine tdds preparation containing 30%w/w PVA-PVP copolymers was more than that containing 35%w/w Pluronic$^{(R)}$ F127.

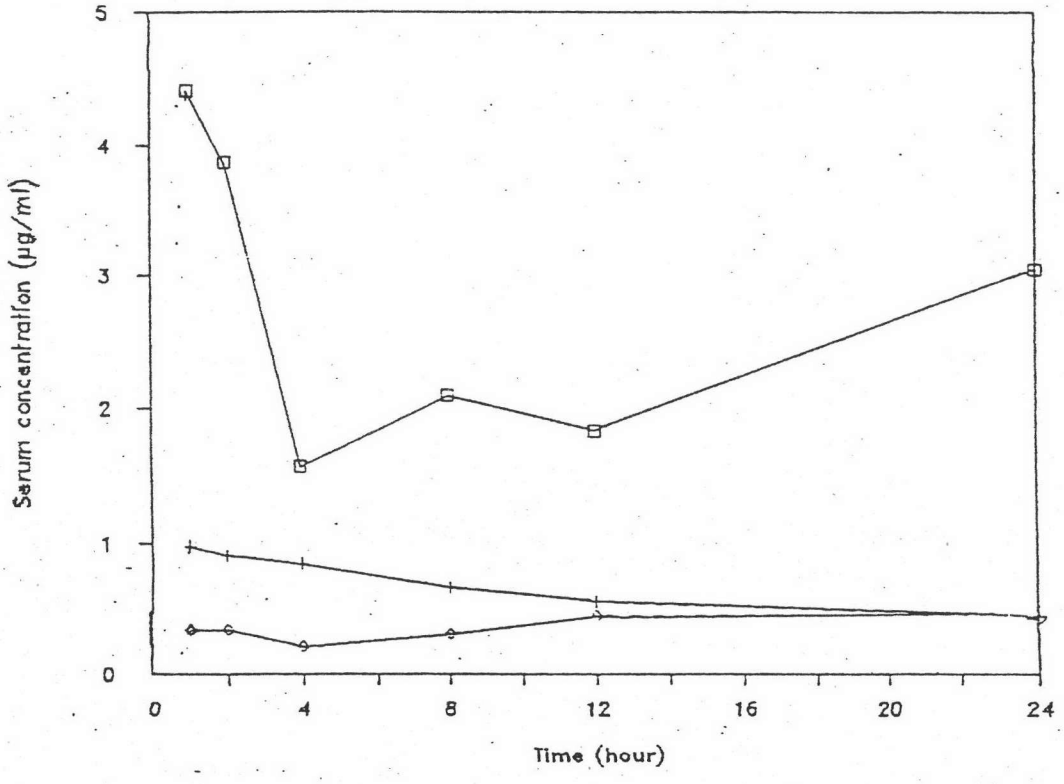


Figure 33 Serum Drug Concentration-Time Profiles of Nifedipine TDDS Containing 30% of PVA-PVP Copolymers in Three Rabbits ( □——□ No.1, +——+ No.2, ◇—◇ No.3)

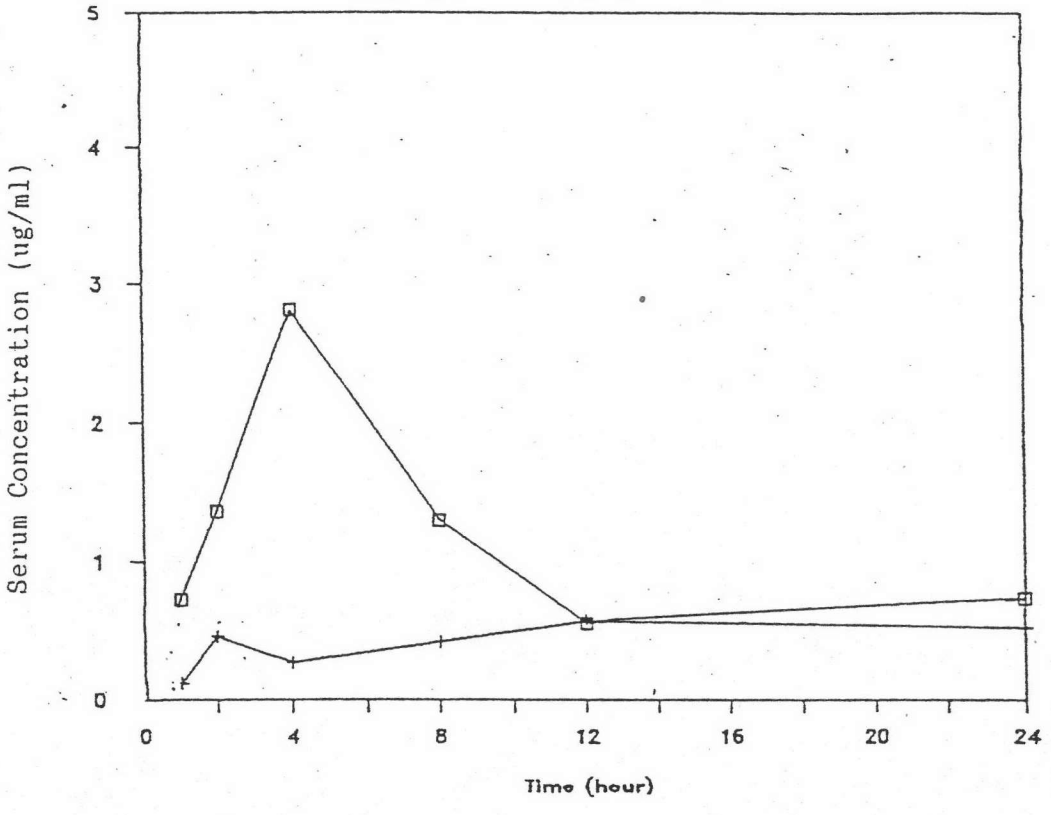


Figure 34 Serum Drug Concentration-Time Profiles of Nifedipine TDDS Containing 35% of Pluronic$^{(R)}$F 127 in Three Rabbits ( o——o No.4, +——+ No.5)

(Sample serum of rabbit No.6 was damaged)

Table 21: Serum Concentration-Time Data of Nifedipine Released from TDDS Containing 30 % w/w PVA-PVP Copolymer in Three Rabbits

| Rabbit number | 1 | 2 | 3 |
|---|---|---|---|
| Weight of Nifedipine (mg) | 20.7 | 17.4 | 15.5 |
| Time (hr) | Conc. (µg/ml) | Conc. (µg/ml) | Conc. (µg/ml) |
| 1 | 4.414 | 0.973 | 0.339 |
| 2 | 3.875 | 0.905 | 0.336 |
| 4 | 1.564 | 0.841 | 0.211 |
| 8 | 2.095 | 0.656 | 0.304 |
| 12 | 1.834 | 0.554 | 0.444 |
| 24 | 3.049 | 0.438 | 0.424 |

Table 22: Serum Concentration-Time Data of Nifedipine Released from TDDS Containing 35 % w/w Pluronic F127 in Three Rabbits

| Rabbit number | 4 | 5 | 6* |
|---|---|---|---|
| Weight of Nifedipine (mg) | 13.8 | 9.1 | 10.2 |
| Time (hr.) | Conc. (µg/ml) | Conc. (µg/ml) | Conc. (µg/ml) |
| 1 | 0.739 | 0.123 | - |
| 2 | 1.368 | 0.467 | - |
| 4 | 2.814 | 0.274 | - |
| 8 | 1.311 | 0.427 | - |
| 12 | 0.565 | 0.584 | - |
| 24 | 0.751 | 0.538 | - |

* serum samples were non-refrigerated

### 3.2.2 Intravenous Administration

By intravenous route of nifedipine administration, the serum concentration-time profile data was quite strange as the concentration detected in both rabbit #7 & 8. For rabbit #9, he was dead after the administration of the drug, so no data can be determined.