CHAPTER IV

DISCUSSION AND CONCLUSION

Discussion

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

Owing to the result of drug preparing and the obtained physical appearance from the preparations containing the selected concentration of the hydrophilic polymers, it was said that these polymers could produce the pleasant physical appearance of tdds preparations. In the selected range of concentration of the polymer was expected that the polymer could sustain the drug release in the periods of time as required

2. Analytical Quantitation of Nifedipine

2.1. Analysis of Nifedipine in Preparations

2.1.1 Determination of the UV Absorption Maxima of Nifedipine

The uv absorption maxima of nifedipine in the medium of PEG400:ethanol in the ratio 1:1 was observed at the wavelength of 332 nm and the polymer bases were not absorbed at this wavelength. It was sure that the obtained data could indicated the release of only drug without any interference from the polymer bases.

2.2. Analysis of Nifedipine in Biological Fluids

2.2.1 Serum Analysis

The objective of this *in-vivo* diffusion studies was to determine whether nifedipine from the selected polymer *in-vitro* diffusion studies could be penetrated through the skin into blood circulation. It did not emphasize on the analytical method needed. This analytical method was not validated and % recovery had not been calculated. Therefore, the analytical procedure must be improved in the further study. The possibly errors depended upon various factors such as ; the organic solvent could not completely extract the drug from the serum sample, the extraction time was not enough, the evaporation time was not equal in each serum sample, the concentration range of standard solution was not corresponding enough to determine the serum concentration and the serum concentration data as shown in Table 21-22 were base on the linear regression obtained from the calibration data. Therefore, these obtained serum contration-time profiles could only be roughly indicated the penetration of nifedipine TDDS through the skin.

3. Evaluation of the Nifedipine TDDS Preparations

3.1. In-Vitro Diffusion Stdies.

Pluronic$^{(R)}$F 127

Pluronic$^{(R)}$F 127 was a copolymer blocking surfactant. Both the hydrophobic and the hydrophilic chains had either linkages which could from hydrogen bond with water molecules. This allowed

this polymer to dissolve and form the micelles in water (27,28). As the temperature of a cold aqueous surfactant solution was raised. These hydrogen bonds were broken. The water molecules in the hydrophobic that were released as their bonds were broken or weakened were trapped and caused the polymer to become rigid (51).

Nifedipine was increasing soluble in Pluronic$^{(R)}$F 127 surfactant solution because it was held into the micelle of this polymer. Moreover, the drug outside of micelles was gradually release to the medium in recepter compartment. The drug in micelles was then released to matrix according to drug concentration gradient. Therefore, drug concentration in matrix outside of micelle was constant. The release of drug from matrix to the medium was constant. Thus, the release pattern of nifedipine from Pluronic$^{(R)}$F 127 in this *in-vitro* diffusion studies would possibly be a zero-order kinetic.

The effect of Pluronic$^{(R)}$F 127 concentrations on the percentages of nifedipine released was noted. With increasing concentration of this polymer, the percentages of drug released were decreased. The reason for a reducing of drug release may be due to the reduction of the size and number of water channel within the gel matrix and increasing in the micro-viscosity of the channel of the gel (28,29). It was reported that the higher Pluronic$^{(R)}$F 127 concentration, the greater the gel strength or viscosity (30). If the gel strength increased, it became more difficult to disrupt the structure of gel matrix that as an increasingly resistant barrier to drug diffusion.

PEG 4000 : PEG 400 Copolymers

The slowly release of nifedipine were displayed in the preparations containing PEG 4000 and PEG 400 copolymers. It could be attributed that when PEG and nifedipine were melted and solidified,

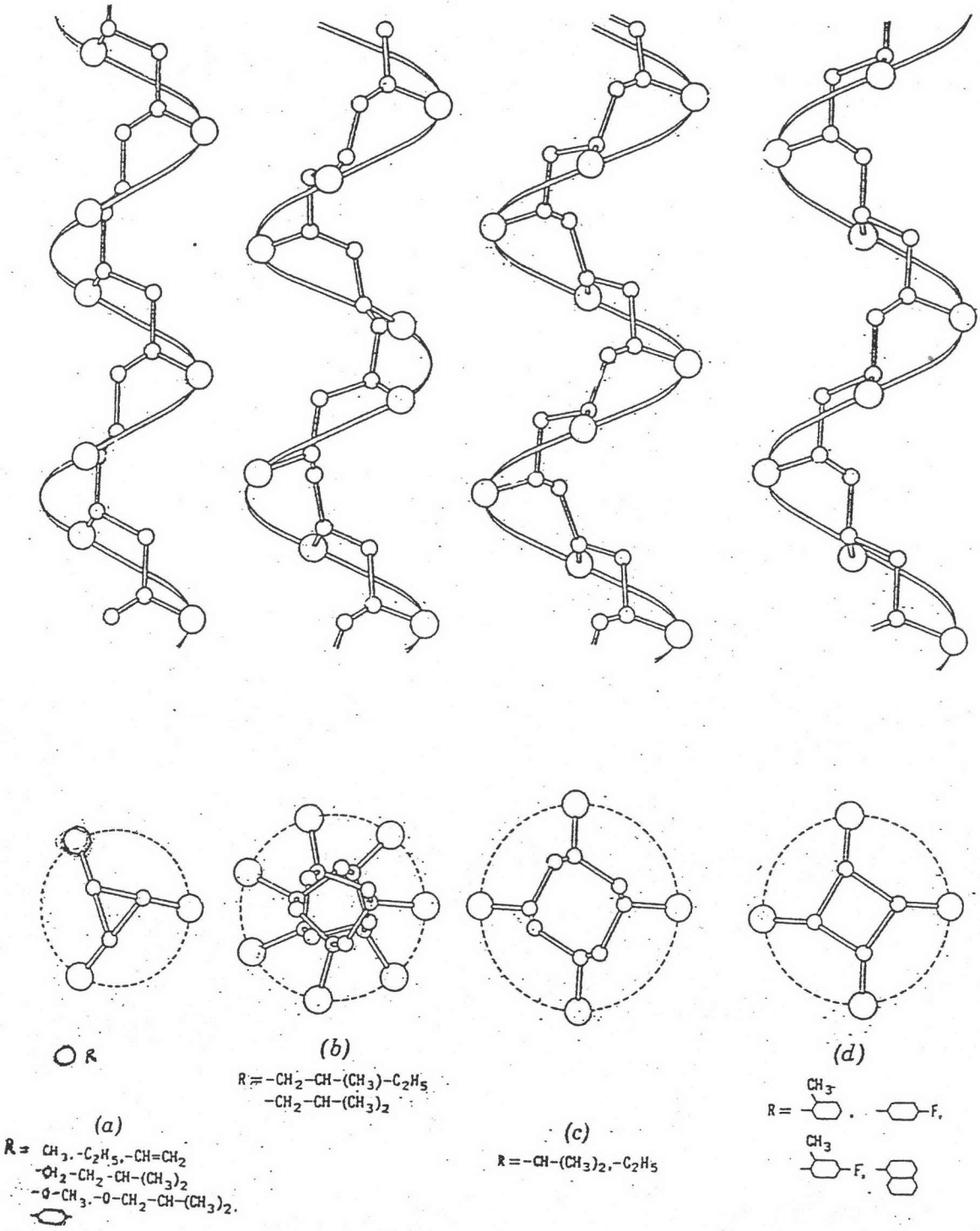


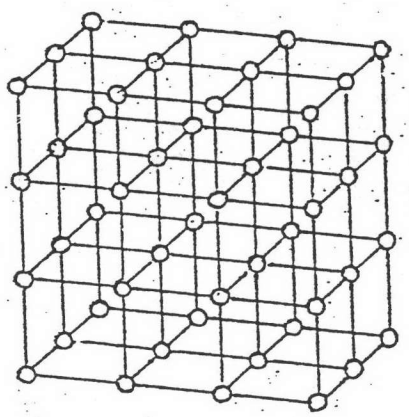
Figure 35 Helical Conformation of Polymers

the drug was trapped in the interstitial space of the matrix formed by the two paralleled helix of PEG (77). This helical structure was one of those as shown in Figure 35 (78). From the structure of PEG, OH-groups were not too the bulkly side group, the helix may have three units per turn and the arrangement may be similar to that Figure 35-a. If the side group was not bulkly, the tighter helices would be formed(78). It was possibly that the drug was trapped and hold in the tightly helical matrix, so the drug was released rather difficult and slow.

When the ratio of PEG 4000 : PEG 400 was changed from 1:1 to 1:2 and 1:4, the percentages of drug released were increasing, respectively. This was due to the reduction of matrix strength or viscosity of the preparation because PEGs with low molecular weight were decreasing in viscosity (17,32).

PVA-PVP Copolymers

The drug release-time profile of nifedipine TDDS preparations containing PVA-PVP copolymers was obviously shown that these copolymers could release high percentage of drug and the release rate seemed to be fast within 8 hours. This result was ascribed. These copolymers could form the lattice structure in the matrix (18,33,36). The lattice structure was shown in Figure 36 (79). According to the structure of both PVA and PVP, it was observed that the side group of PVP was bulkly. More bulkly side groups required more space, resulting in the formation of loose lattice (78). Therefore, the interstitial space in the lattice was wide. When nifedipine was trapped within this lattice structure, the drug could be released easily and diffuse into the medium. Moreover in this matrix glycerine was used as the plasticizer for this



System	Edge Lengths	Angles
Cubic	$a = b = c$	$\alpha = \beta = \gamma = 90°$
Tetragonal	$a = b \neq c$	$\alpha = \beta = \gamma = 90°$
Orthorhombic	$a \neq b \neq c$	$\alpha = \beta = \gamma = 90°$
Monoclinic	$a \neq b \neq c$	$\alpha = \beta = 90° \neq \gamma$
Triclinic	$a \neq b \neq c$	$\alpha \neq \beta \neq \gamma$
Rhombohedral	$a = b = c$	$\alpha = \beta = \gamma \neq 90°$
Hexagonal	$a = b \neq c$	$\alpha = \beta = 90°; \gamma = 120°$

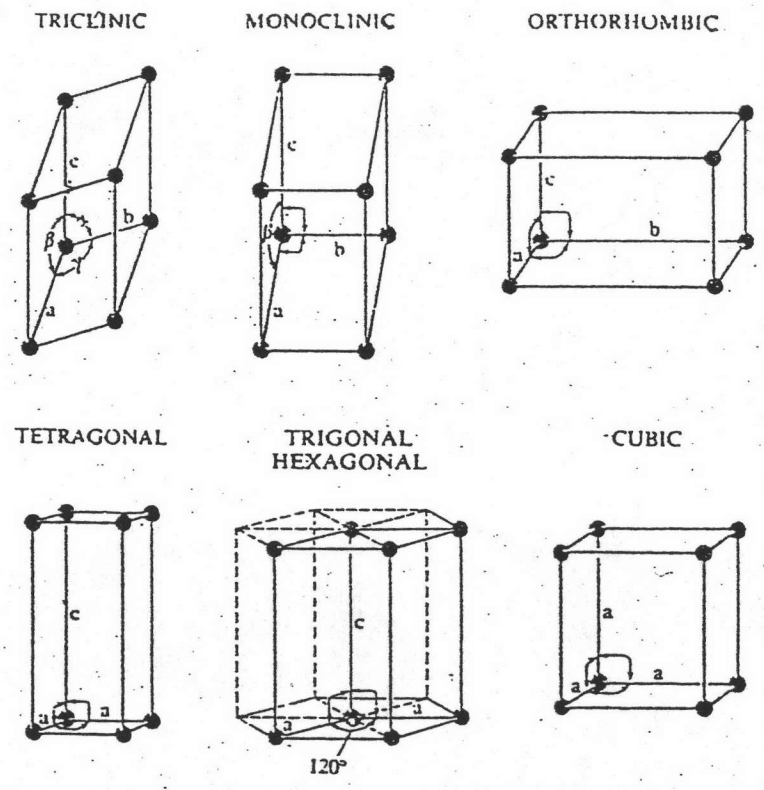


Figure 36 Lattice Structure of Polymer

copolymer. It could impart flexibility to the polymer by interposing itself between the polymer chain and interacted with the force which held the chains together. Thus, the polymeric matrix was extended and softened (80). Therefore, nifedipine was fast released and its percentage of drug release was high.

It was found that the drug was decreasingly released when the concentration of this copolymer was increased. This was ascribed that the viscosity of the matrix was increased according to increasing the concentration of the polymer, and the matrix was not increasingly extended and softened because the amount of glycerine was still constant.

Methocel$^{(R)}$A 4M, K 4M, and K 100M

For hydrophilic cellulose derivatives the increasing concentration of either Methocel$^{(R)}$A or Methocel$^{(R)}$K in formulation decreased the percentage of drug released. The reason was that increasing concentration of these polymers increased the viscosity which affected to the gel strength as a barrier of drug diffusion into the medium (17). Also, with the same concentration of 5% w/w Methocel$^{(R)}$K 100M released the percentage of drug less than Methocel$^{(R)}$K 4M according to the high viscosity. This could be attributable that Methocel$^{(R)}$K 100M had a number of anhydroglucose units more than Methocel$^{(R)}$K 4M, although both of them had the same type and the number of substituent groups (D.S.) on the unit. The present of more anhydroglucose units, the higher result in the molecular weight and viscosity.

Comparison between the drug release from Methocel$^{(R)}$A 4M and Methocel$^{(R)}$K 4M, they had the same viscosity and molecular weight but they were different in both D.S.value and type of

substituent groups. Many hydroxypropoxyl groups were existed in Methocel$^{(R)}$K 4M, It was proposed that nifedipine may interact with these substituent groups at the position of secondary hydroxyl groups. The drug would like to exist in the matrix of Methocel$^{(R)}$K 4M more than those of Methocel$^{(R)}$A 4M. Therefore, Methocel$^{(R)}$A 4M could release drug more than Methocel$^{(R)}$K 4M in the same concentration.

It was observed that the release of drug from these cellulose derivatives was not consistent because there were a few of small air bubbles in these preparations.

From this *in-vitro* diffusion studies, it could be concluded that polymmer which could released nifedipine from the maximum to the minimum in the period of 12 hours were following: PVA-PVP copolymer Pluronic$^{(R)}$F 127, Methocel$^{(R)}$A 4M, Methocel$^{(R)}$K 100M, Methocel$^{(R)}$K 4M, and PEG 4000 : PEG 400 copolymer.

3.2 In-Vivo Diffusion Studies

3.2.1 Application of Nifedipine TDDS Preparations

In this study, the serum concentration-time profiles of TDDS preparations appeared to vary widely. This may be due to an individual variation of the rabbit and the number of rabbit uesd for the study was not enough. It was noticed that the observed maximum serum concentration may not be the actual value and no serum sample was taken after 12 hours of administration. Thus, the sampling time interval should be taken more frequently in order to solve these problems. However, it may be said that the amount of penetrated drug had tendency to relate the amount of drug application. The drug release pattern of the preparation formulated from PVA-PVP copolymers was somewhat constant and intended to control

the release of drug more than that from Pluronic$^{(R)}$F 127 in the period of 24 hours.

3.2.2 Intravenous Administration

The nifedipine serum concentration-time profile from intravenous administration was not used as the reference for the TDDS preparations due to the error of drug administration. Since the nifedipine solution prepared as 30% v/v in PEG 400 was not clear, it seemed as if a suspenion. Thus, it is possible that when the drug suspension was injected into the ear vein of rabbit, all of the drug might not immediatly dissolved into the blood circulation. This caused the pattern of drug concentration time profile following IV administration appeared to be quite different to the usual profile.

Conclusion

1. Nifedipine TDDS preparation could be developed via matrix diffusion using the hydrophilic polymers for controlling drug release in the period of time as required.

2. From this *in-vitro* diffusion studies, it was found that the different release mechanism of nifedipine TDDS depended on the polymer.

3. The only certain range concentration of the polymer affected the percentage of drug release. The increasing concentration of polymer decresed the percentage of drug released.

4. PVA-PVP copolymer and Pluronic$^{(R)}$F 127 could possibly use for formulation nifedipine TDDS preparation because they could sustain drug release for 12 hours as required and gave much more the percentage of nifedipine released than the other polymers.

5. From the *in-vivo* diffusion studies, it was indicated that nifedipine from TDDS preparation containing either PVA-PVP copolymers or Pluronic$^{(R)}$F 127 could be penetrate through the skin into the blood circulation. The amount of drug *in-vitro* release and *in-vivo* penetration seemed to be related.

Suggestion

In the future study it could be suggested that for the *in-vivo* evaluation, the freshly prepared IV preparation should be used, a number of animal used should be increased to decrease the intervariation of the results, the sampling time interval should be more frequent and also the analytical method for drug determination in plasma or serum by HPLC technique must be improved.

For the *in-vitro* diffusion study, the excised skin should be used in stead of the synthetic membrane as a barrier and the medium solution must not be the pure organic solvent.