CHAPTER IV

DISCUSSION AND CONCLUSION

1. Discussion

1.1 Solubility of Nifedipine

Owing to NFP-solubility data in Table 10, the solubility of NFP in aqueous solution was found very poor. Its solubilities in water and PBS were almost equal and were identified as practically insoluble. The reasons for these results dued to its lipophilic property. The highest solubility of NFP was found from its solubility in ethanol. Organic modifiers, Glycerol and PG, and co-solvent, PEG 400, could increase NFP-solubility in aqueous solution, especially PG. The solubilities of NFP in PG, PG and water (1:1), 20% v/v PEG 400 in PBS and glycerol and water (1:1) were found increasing as, approximatly, 68, 55, 11, 4 folds, respectively when compared to its solubility in water. Thus, it could be concluded that NFP was practically insoluble drug, organic modifier and co-solvent could improve its solubility in aqueous solution.

1.2 Physical Appearance of Nifedipine TDDs

The desired NFP-TDDs using PF-127 gel and Ae-200 gel as drug carriers for this reserch studies exhibited a good physical appearance. Owing to the result of drug preparing and the obtained physical appearance of each preparation, Tables 11-16 and 19, 20, the addition of organic modifiers and thickening agent could exhibit a more appreciate physical appearance. Although, 50% w/w PF-127 gel, solely exhibited a high viscous, clear gel but its consistency was not suitable to be used as matrix for TDDs because of it provided a large amount of residue on the surface of skin after removed the disc of gel matrix off. Besides, a long term therapy required separated using TDDs this defects might be not compliance to the patient. For this affects, the addition of thickening agent could solve them and improved the consistency of the gel as same as HPMC in Ae-200 gel matrix.

The organic modifiers and co-solvent could improve the physical appearance of gel matrices by reduce the stiffness of the gel. In addition they could reduce the difficultly in preaparing and homogeneity of the gel. However, high concentration of organic modifier and co-solvent might decrease the gel consistency, especially in the Ae-200 gel. Because of it very difficult in exactly indicated the consistency of the gel between the degree +4 and +5, it might due to the inditification of the gel

consistency by impressing was not suitable for high consistency gel matrix, so the results form desired preparation were similary. However, the desired preparations could exhibited overall presant physical appearance.

1.3. **Evaluation of the Nifedipine TDDs preparations**

The slow release of NFP obtained from NFP saturated solution and its profile related to Higuchi´s model kinetic indicated that the amount of drug released from donor receptor would be directly proportional to the square root of time and the permeation of NFP could be suggested to be controlled by diffusion process through pig´s skin. Because of lipophilic properties of NFP, poor solubility in water play an important role on the skin permeation of NFP from saturated solution, thus, the maximum skin permeation of was quite low of 0.1058 mcg/cm^2 after 24 hour.

The structural property of gel matrix is an important effect to the mechanical modelling of drug release rate and the expected performance of the controlled release drug devices fabricate from the gel. The release of drugs from monolithic devices has been investigated extensively. The release rate from matrix system containing suspened drug has been discuss on diffusion control (Wood, Attwood and Gollett, 1984;

Gollett, Attwood, Wood, 1983), and dissolution control which for release medium uptake was addapted to solute release (Huglin and Sloan, 1983). However, the formulation and gel properties were the factors to determine the drug release mechanism.

PF-127 is a copolymer blocking surfactant and can be used as gelling agent which can form gel as the concentration is over 20% w/w. PF-127 gel are to be formed by H-bonding in aqueous system, caused by the attraction of the surfactant ether oxygen atoms with water proton (Schmolka, 1991; BASF, 1987; Chen-Chow and Frank, 1981). Owing to the properties of PF-127, non-ionic surface active agent, it can form non-ionic micells in aqueous solution (Rassing and Attwood, 1983) and in gel (Chen-Chow and Frank, 1981) which are assumed to consist of large population of micelles. The characteristics and shape of micelles are dependent on temperature. At low temperature PF-127 can form unimicelle, single molecule of PF-127 per micelle, and when the temperature up to $10^{o}C$ and over, PF-127 will form micelles of polymolecule as sixmolecules per micelle (Schmolka, 1991). Due to its properties in micelle formation, PF-127 can improve solubility of poorly water soluble drug by micellar interaction, this is a behavior of typical micellar solubilization (Tomida, Kuwada and Kiryu, 1988). Thus, NFP might increased its solubility in PF-127 aqueous gel

matrices and it must be held into the micelles of the gel matrices.

The release of drug from PF-127 gel matrix was purposed by several investigators. Chen-Chow and Frank (1981) and Hadgraft and Howard (1982) indicated that the release of drug from PF-127 gel matrix was diffusion process which took place at water channels of the matrix. They suggested that the release profile of drug from this matrix might followed Higuchi's model. The release rate was depended on solubility and distribution of drug between the micellar phase and the aquous contineous phase and the distribution should depend on the nature of solute and the properties of the aquous phase. The increasing or decreasing in release rate of drug might be dued to the size and number of extramicellar water channels within the matrix. The increasing solubilization of drug in the gel matrix resulted in a reduction of free water concentration, therefore reduced the rate of drug release. So, the release rate of drug from gel matrix was mainly depended on the micro-viscosity of the fluid phase of the gel rather than the macro-viscosity. It could be suggested that the drug release from gel matrix of PF-127 could be determined by the micro-viscosity of the extramicellare fluid, the dimensions of the aqueous channels and the equilibium relationship of drug between the micelles and the external aqueous phase.

Other suggestion was reported from Fults and Jonhston (1990) that the matrix erosion was the predoninant mechanism geverning *in-vitro* release of drug from the semisolid, PF-127 gel matrix, and the polymer might act as a viscosity enhancing vehicle which prolong the diffusion of the drug form the matrix. The release of drug was dued to matrix solubilization and dissolution not diffusion of drug and the profile was of zero-order kinetic with a constant release rate.

From the permeation profile, the mechanism of NFP permeation from PF-127 gel matrix was further analysed following the suggestions of Peppas (1985), $M_t/M_\infty = kt^n$, and computerized with the mechanism analysis program created by Leesawat (1991). The exponential value (n) of drug permeation from PF-127 gel matrix (Table 27), which was used to analysed the drug release mechanism in Appendix XXVI, the results indicated that the mechanism of NFP release from P01, P02 and P03 was case II transportation, zero order release mechanism and all others were non-Fickian transportation. Moreover, because of co-solvent properties, PG and PEG 400 could increase NFP aqueous solubility more than glycerol. From the NFP-solubility result data (Table 10), it was found that PG and mixture of PBS and PEG 400 (20% v/v) could increase the NFP solubility approximately 68 and 11 folds while the solubility of NFP in glycerol was almost equal to water. So the decreasing in permeation rate of NFP detected from

P04, P05, P06, P07, P08, P09 and P10 might be apparent that PG and PEG 400 in these preparations might increase the solubilization of NFP in gel matrix, the increased the interaction of drug and micelles, resulting in an increment of viscosity of water channel. Therefore the diffusion of drug from micelles through extramicellar fluid was retarded and the amount of free drug in the channel may be reduced. These phenomena might cause in decreasing the rate of permeation of NFP through PF-127 gel matrices.

For the preparation P03, the increasing in permeation of NFP might be dued to the large amount of dissolved drug in extramicelle water channel, thus, exhibit more permeation of NFP through the PF-gel matrix. The other discussion for the increasing in permeation of NFP from P03 was related to its release mechanism, zero order transportation. It was purposed that P03 exhibited constant permeation rate by the dissolution process of matrix eroxsion as in P01 and P02 but the erosion of matrix was faster because of the influence of glycerol.

Pluronic F-127, the block copolymer, could be used as a drug carrier for transdermal delivery system with the improvement for physical appearance of gel matrix. The used of this hydrophilic gel matrix could achieved the prolong release of drug over peroid of designed time and with the better designed formulation, it

could be achieved the designed constant release rate at therapeutic level.

Owing to the NFP release data and profiles of Ae-200 gel matrix, it was found that the release profiles of NFP prefer rarely be first order or zero order kinetic rather than Higuchi's model except A03, A10. Although the overall released profile from A03, A10 is rather be diffusion controlled but with further analysis, it was found that the release mechanism of NFP from Ae-200 gel matrix were non-diffusion mechanism. Thus, the dominant mechanism for NFP-released from all preparations of Ae-200 gel matrix was non-diffusion mechanism, zero or first order kinetic.

For the effects of both concentration and organic modifiers, glycerol and PG, it was found that the permeation rates from A01, A07 composed low concentration of glycerol and PG, respectively, were greater than those from A02 and A08, composed high concentration. To explain this phenonema, hydrogen bonding between silanol group sling on the surface of silica and hydroxyl groups of organic vehicle might be considered in addition to the different in solubility of NFP in water and organic solvent.

Ae-200, fumed silicon dioxide, gelled when dispersed in organic vehicles due to the formation of a network structure of the silica particle, silanol groups on the particle surfaces have a tendency to form hydrogen bond together (Marshall and Rochester, 1975). In polyol organic vehicle, excess of hydroxyl groups, the intermolecular hydrogen bonding between hydroxyl group and silanol group on the surface of silica more preferably occured than intramolecular hydrogen bonding of silanol group. This phenomena could influence the rheological properties of the gel and drug release from the gel. Sherriff and Enever (1979) indicated that the gel produced with high quantities of hydroxyl organic vehicle might be weaker or had looser lattice than the gel produced with a lower one. Therefore, higher amount of hydroxyl group or high concentration of vehicle produced weaker or looser gel structure than lower amount of hydroxyl group or low concentration of vehicle. In addition, the affinity of NFP to dissolved in organic solvent was higher than permeation medium. Therefore, the permeation rate of NFP into permeation medium was so slow in the Ae-200 gel matrix produced with high concentration of used vehicle.

The results of NFP-permeation rate from A03-A06, A09-A12 showed that the high concentration of co-solvent, PEG 400, produced higher release rate of NFP from gel matrix in order of using high centration of PEG 400 could be explained by the aforemention concept. In addition,

the high concentration of PEG 400 can retard the rate of drug dissolution in aqueous due to PEG 400 has critical micelle concentration whereat this concentration, PEG 400 can form micelle or gel which entrap the drug in its micelle (Vormans and Moollennaar, 1985; Calwell and Livegood, 1962). So, PEG 400 at high concentration could be retard the rate of NFP dissolution that occured in A04 and the results was relatively slower permeation rate of NFP than A03.

The reason for the slow permeation rate of NFP achieved from A05, A06 and A11, A12 with effect of thickening agent, HPMC, was the ability of HPMC in gel forming in aqueous solution (Wan, Heng and Wong, 1990). The gel of HPMC occured in Ae-200 gel matrix was futher retard the release of NFP that produced the slow release rate of NFP throughout the Ae-200 gel matrix.

By the conclusion from the overall results from the *in-vitro* skin permeation experiment of NFP-Ae-200 gel matrix, it was found that the preparation of Ae-200 gel matrix as NFP carrier produced by using PG as vehicle and PEG 400 as co-solvent exhibited the superior permeation rate to others preparations.

2. Conclusion

In summary, the results reported in this reserch study indicated that *in-vitro* skin permeation of NFP from PF-127 gel matrices and Ae-200 gel matrices showed a good performance in terms of permeation rate and permeation profile, especially the preparation which composed of additive, organic modifier and/or co-solvent. Estimating of NFP permeation rates *in-vitro* from a such preparation showed a high concentration of NFP over the lowest therapeutically effective level of NFP, 20-30 ng/ml, and could sustained NFP permeation over 24 hours with a constant rate. The most interested preparation of these gel matrix was gel matrix composed of PF-127 50% w/w and glycerine 10% w/w, for hydrophilic gel and gel matrix composed of Ae-200 30% w/w, PG 27% w/w and PEG 400 25%, for hydrophobic gel and the highest *in-vitro* skin permeation rate of NFP was achieved from the former preparation. Accordingly, it was concluded that Pluronic F-127 was the useful gelling agent as matrix-carrier for Nifedipine transdermal delivery system that could be further developed for once-a-day medication of angina pectoris or hypertension.

3. Suggestion for further study

For further studies, such as *in-vivo* experiment, improvement in the formulation of these gel matrix has to performed in order to achieve suitable permeation rate which provides optimal therapeutic level of NFP. The package of NFP-TDDs has also to be developed. For this research study, an aluminum mold, which obtained by moled-pressed machine, was used to produce a unit dosage of NFP-TDD_s with a defined surface area and controlled thickness and to perform the occlusive effect when intacted to the surface of skin. However, this mold is not suitable for an *in-vivo* experiment and stability studies because its adhesive layer does not suitable for long contact to skin. It can not intimately contact to skin, easy loose and induced skin irritation reaction. The foil cover cannot prevent the loss of water and/or additive solvent caused instability of products. Thus, more suitable material should be investigated to construct a suitable backing substate and protective pel strip for NFP-TDDs.

The variations of the NFP permeation from the same preparation between skin-permeation diffusion cell also occurred because of the variations of use pig's skins in different parts of the bodies. It is very difficult to have the same part of pig's bodies due to a large number of experiment. To reduced these variations a more suitable diffusion cell which consume very small area of animal or cadaver skin must be used instead.