CHAPTER IV

DISCUSSION AND CONCLUSION

DISCUSSION

The presence study intends to develop and evaluate diltiazem hydrochloride (DTZ HCl) transdermal drug delivery systems, hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) were chosen as hydrophilic and hydrophobic film formers, respectively. Moreover, dibutyl phthalate (DBP), diethyl phthalate (DEP), and triethyl citrate (TEC) were chosen as organic ester plasticizers. The effects of polymer ratios and plasticizer types on the physical characteristics of free films were evaluated.

An evaluation of polymer ratio effects on film thickness and mechanical properties were conducted for formulations *F1* (10:0), *F2* (8:2), *F5* (6:4), and *F8* (4:6). They show the differences in film thickness ($p<0.05$); it might come from the film preparation step. Since the evaporation rate of mix solvent in film casting is very fast, the glass plate should be carefully covered. The addition of EC in HPMC film produced lower UTS, percent elongation at break, Young's modulus, and toughness, as may be seen in Figures 21 - 24. The presence of EC might have been responsible for the lower strength and elongation (when compared to HPMC alone) because the EC molecular structure composed of the interchain hydrogen bonding and the bulkiness of the glucose subunits. This could explain the weak and soft character of the polymer films. The increasing of EC ratio from 20 to 60% of total polymer weight resulted the increasing of film strength (higher UTS, percentage of elongation and Young's modulus). According to Table 2, EC has a lower T_g (131.5°C) as compared to HPMC (153.5°C), the increasing of EC ratio resulted the increasing T_g of films and tensile strength.

The evaluation of plasticizer effects on film thickness and mechanical properties were conducted for the HPMC:EC films at the ratio of 8:2 and 6:4. Dibutyl phthalate (DBP) and diethyl phthalate (DEP) were used as hydrophobic plasticizers, while, triethyl citrate (TEC) was used as hydrophilic plasticizer. The solubility in water at 20°C of DBP, DEP, and TEC are 0.04, 0.15, and 6.90 %, respectively (Frohoff-Hülsmann, et al., 1999). The 8:2, HPMC:EC films plasticized with the water-soluble plasticizers, TEC, had higher elongation and lower strength values (correspondent to a lower modulus), while films prepared with the water-insoluble plasticizers, had lower elongation and higher strength values (higher modulus). It can be concluded that the mechanical properties of HPMC-EC films were affected by the type of plasticizer. Plasticization results in a decrease in the inter-molecular forces between polymer chains, generally causing a decrease in the glass transition temperature and tensile strength. It is well known that different plasticizers will affect the glass transition temperature and hence the mechanical properties to a different extent (Bodmeier and Paeratakul, 1994; Saettone, et al., 1995). In this study, the water-soluble plasticizers probably reduced the glass transition temperature more than the water-insoluble plasticizers, thus explaining the lower moduli.

Differences of the film thickness were found ($p<0.05$) at the ratio of 4:6. The effect of the water-soluble plasticizers, TEC and of the water-insoluble plasticizers, DBP and DEP, on the mechanical properties of HPMC-EC films are shown in Figures 24 - 28. The differences in the mechanical properties of films could be explained with the different plasticizing efficiencies of the plasticizers on the polymer.

DTZ HCl is a water-soluble drug. Okumura and others (1989) reported that DTZ HCl solubility in water at 37°C is 557.06 mg/ml. Since the skin temperature is approximately 32°C, the solubilities of DTZ HCl in various solvents were examined at this temperature. These solvents were classified into three groups according to their dielectric constant values (ε), including non-polar ($\varepsilon \approx 2$-3), semi-polar ($\varepsilon \approx$ 12-46), and polar ($\varepsilon \approx 80$) solvents (Martin, 1993). However, there are no sharp boundaries between polar, semi-polar, and polar solvents. The rank order of solubilities (mg/ml) of DTZ HCl in various solvent systems according to Table 9, is:

DI water (486.4) > PBS (461.9) > PG (86.0) > ethyl alcohol (52.0) > PEG (20.5) > IPP (19.0) > IPM (14.3), respectively. This is almost the same order as dielectric constant values of these solvents which is DI water (80.4) > PBS (less than 80.4) > PG (32.0) > ethyl alcohol (24.3) > PEG (12.4) > IPM (3.3) > IPP (less than 3.3), respectively.

The methods to demonstrate the compatibility include scanning electron microscopic observation, thermal analysis, and solubility parameter analysis (Lin, Lee, and Lin, 1991). In the presence, compatibility of the drug-free HPMC-EC film was evaluated using scanning electron photomicrograph (SEM) observation. It was found from Figures 36 – 39 that the surface topography of the HPMC:EC free films at the ratio of 10:0 appeared porous, whereas the surface topography of the free films at the ratios of 8:2 and 6:4 were uniform and smooth. In the case of the free film at the ratio of 4:6, it was the separation of EC appeared. Scott (1949, cited in Lin, Lee, and Lin, 1991) has suggested that a solution of two polymers in a common solvent will separate into two phases if the total concentration is increased a few percent. Thus, in this study, the HPMC-EC film at the ratio of 4:6 should not be used. Furthermore, compatibility of the drug-contained HPMC-EC film was done in the same way. Figures 40 – 41 demonstrates the rod shape DTZ HCl crystal stuck on the film surface. However, the flower-like DTZ HCl crystal was investigated on the surface topography of HPMC:EC films at the ratio of 6:4 and 4:6 in Figures 42-43.

Then, the surface topography of the drug-contained HPMC-EC films at the ratio of 8:2 with different enhancers was observed. It was found in Figures 44 – 45 that the traces of oil drop (IPM and IPP, respectively) appeared on the film surface. The film with IPM (Figure 44) shows the porous surface like HPMC film containing DTZ HCl (Figure 40). Surprisingly, there is a lot of DTZ HCl crystals spread almost the surface topographies of films in Figures 46 – 49 (contained NMP, OA, PEG and PG, respectively). These surfaces seemed to be the same as films without enhancers. However, the DTZ HCl crystals covered all the film with Tw (Figure 49). Thus, the changing in surface topography can not be investigated.

In addition to determine the transparency of the drug-contained plasticized films, the spectrophotometry was used to investigate the compatibility. The decreasing of HPMC ratio resulted in the more transparent films. In this case, decreasing of HPMC ratio resulted increasing of EC ratio. The film formulations were plasticized with DBP (hydrophobic); as a result the film became more transparent. However, at the 100% of EC ratio, the film became hazier. This might occur from the limit of DTZ HCl solubility in EC and DBP.

The effect of enhancers on the transparency of the plasticized films was also evaluated. According to Figures 35, it was found that the addition of enhancers resulted in the haziness of the films. The worst transparent was found from the films with Tween 80. Allen et al. (1959, cited in Lin, Lee, and Lin, 1991) have reported that the extent of phase separation increases with the molecular weight of the polymer. Therefore, the phase separation by the higher molecular weight could account for the haziness of the film. The presence of Tween 80 (MW 1,310) might have bee responsible for the phase separation (resulted in the haziness of the film). Hildebrand and Scott (1950) have defined the solubility parameter (δ) of a substance as the square root of its cohesive energy density. Thus, heat of mixing (ΔH) is represented by Eq. (15):

$$\Delta H = V(\delta_1 - \delta_2)\,\phi_1\,\phi_2 \qquad (15)$$

where V is the total volume of the mixture,

ϕ_1 and ϕ_2 are the volume fraction of components 1 and 2 in the mixture, and

δ_1 and δ_2 are the solubility parameters of components 1 and 2, respectively.

If the values of these two components are nearly equal, the heat of mixing approaches zero and the substances will be miscible. The addition of enhancers which have lower solubility parameters (compared to HPMC and EC), for example IPM, IPP and OA, increased the heat of mixing, thus, the phase separation occurred.

The water uptake or absorption behavior of the polymeric film plays an important role at the beginning stage of drug release from dosage form (Golomb,

Fisher, and Rahamim, 1990). It is clearly indicates that the moisture uptake is dependent on the polymer ratio, as seen in Figure 32. HPMC has a high affinity for water, therefore it induced higher moisture uptake as the HPMC ratio in the films increased.

Furthermore, the effect of enhancers on the moisture uptake of the film was evaluated. The percentage of moisture uptake of films are in the order of A47 (Tw, 37.8%) > A41 (IPM, 35.9%) > A45 (PEG, 34.9%) > A44 (OA, 33.2%) > A43 (NMP, 30.9%) > A46 (PG, 29.6%) > A42 (IPP, 23.8%), respectively. It can be seen from Figure 33 that the two highest formulations were composed of Tw and IPM. In contrast, the formulation A42 which composed of IPP gave the lowest moisture uptake. Although, IPM solubility in water is very low, it produced the porous surface of the film, according to the surface topography in Figure 44. The appeared porosity could explain the higher moisture uptake of the film with IPM as compared to the film with IPP.

Formulations for skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin. DTZ HCl is classified as calcium channel blocker. It has a mean plasma half-life of 3.5 hr and only 40% of the orally administered drug reaches the circulation due to hepatic metabolism (Mazzo, Obetz, and Shuster, 1994). The *in vitro* release and *in vitro* permeation of DTZ HCl from polymeric have been evaluated. The pig ear skin was used in the permeation study. Analysis of drug-release kinetics through skin is important in the assessment of transdermal drug-delivery system, and in vitro skin permeation experiments are valuable and necessary for studying the rate and mechanisms of percutaneous absorption of drugs (Gupta and Mukherjee, 2003).

The *in vitro* release study was to investigate the effects of polymer ratios on the release-time profiles of DTZ HCl from the film formulations. The increasing of EC ratios produced the lowering of the initial rates of DTZ HCl released (the slopes of 0-1 hour) from the film formulations. At 12 hours of the release study, DTZ HCl

almost not released from the EC films. The presence of EC might have been responsible for the lower of the initial rates of DTZ HCl released from the film formulations because of the hydrophobic property of EC. However, there is not a statistically significant difference (P = 0.201) between each release-time profiles of the films containing EC ratios from 0 to 80% of total polymer weight.

The effect of plasticizers on the *in vitro* release-time profiles of DTZ HCl from the film formulations was investigated. It was found that various types of plasticizers only affected on to the initial release rate of drug from HPMC films. There is not a statistically significant difference (P = 0.400) between each permeation-time profiles of the HPMC films plasticized with different plasticizers. In the same way, there is not a statistically significant difference (P = 0.247) between each permeation-time profiles of the 6:4, HPMC:EC films plasticized with different plasticizers.

There were three film formulations chosen for further *in vitro* permeation study. They are the film formulations of HPMC:EC polymers at the ratios of 10:0, 8:2, and 6:4, respectively. As may seen in Figure 54, the permeation-time profiles of the prior two formulations are almost the same, while that of the 6:4, HPMC:EC film formulation is lower. According to Table 18, the fluxes of DTZ HCl from the HPMC film and the 8:2, HPMC:EC film were not different, 97 $\mu g/cm^2.h$. The lag times (intercept) from both formulations were also similar (0.75 and 0.73 hr.). Thus, the film formulation composed of HPMC:EC at the ratio of 8:2, plasticized with DBP, was selected to add the enhancers and evaluate the skin permeation parameter from the in vitro permeation study.

Although the orders of slopes and cumulative percent of drug release of film with 8:2 are lower than 10:0, its content was higher (higher ΔC). The permeation kinetic of the HPMC films and the 8:2, HPMC:EC films seemed to follow the Higuchi's equation with the higher correlation values from Higuchi's plot as compare to the zero's order plot.

The film formulations with IPM, IPP, and Tw gave higher permeation-time profiles as depicted in Figure 56. The fluxes from these formulations increased approximately 1.5 – 2 times of the formulation without the enhancer. However, there was only the formulation with Tw showed the lower lag time (0.03 hour) as compared to the formulation without the enhancer (0.73 hour). Lag times from the formulations with IPM and IPP were 1.67 and 1.9 hr, respectively.

Many solvents enter the SC, change its solution properties by altering the chemical environment, and thus increase partitioning of the drug into the horny layer (i.e. rise K in Eq.(12)). Isopropyl myristate (IPM) and isopropyl palmitate (IPP) may have the different mode of action in enhancing the permeation of drug from TDDS. These could be seen from the difference in surface topography. IPM gave higher drug content and higher moisture uptake as compared to IPP. Furthermore, IPM gave higher lag time (lower diffusivity), but lower flux (lower Kp). In contrast, IPP may improve partitioning between the formulation and the SC (perhaps by altering the solvent nature of the skin to improve partitioning into the inner tissue).

Surfactants are added to formulations in order to solubilise lipophilic active ingredients, and so they have potential to solubilise lipids within the SC. They typically composed of a lipophilic alkyl or aryl fatty chain, together with a hydrophilic head group; surfactants are often described in terms of the nature of the hydrophilic moiety. Anionic and cationic surfactants have potential to damage human skin; by swelling the SC and interact with intercellular keratin. Non-ionic surfactants tend to be widely regarded as safe. Surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes (William and Barry, 2004). Rejendran and others (1997) studied the effect of non-ionic surfactants (Spans and Tweens) on the transdermal delivery of prazosin HCl across guinea pig skin *in vitro*. They found that Tweens produced higher permeation than Spans; Teen 80 was found to produce the highest permeation of the drug. Shokri, et al. (2001) and Nokhodchi, et al. (2003) reported that Tween 80 increased the permeation rate of lorazepam through rat skin.

There are two possible mechanisms by which the rate of transport is enhanced using nonionic surfactants. The surfactants may initially penetrate into the intercellular region of SC, increase fluidity and eventually solubilise and extract lipid components. Secondly, penetration of the surfactant into the intercellular matrix followed by interaction and binding with keratin filaments may results in a disruption within the corneocyte (Breuer, 1979, cited in Nokhodchi, et al., 2003; Walters, et al., 1987). Tween 80 is thought to enhance the DTZ HCl via both the lipophilic and the hydrophilic molecular mechanisms, and to disrupt the lipid arrangements in the SC and to increase the water content of the proteins in the barrier. Tween 80 contains the ethylene oxide and a long hydrocarbon chain. This structure imparts both lipophilic and hydrophilic characteristics to enhancer, allowing it to partition between lipophilic mortar substance and the hydrophilic protein domains. It may interact with the polar head groups of the lipids and the modification of H-bonding and ionic forces may occur.

CONCLUSION

1. To develop diltiazem hydrochloride transdermal drug delivery systems, hydroxypropyl methylcellulose and ethylcellulose could be appropriated as hydrophilic and hydrophobic film formers, respectively.
2. Dibutyl phthalate as organic esters plasticizers gave the good the physical characteristics of free films.
3. The plasticizer types were not affected to the release time profiles of the film formulations.
4. Isopropyl myristate, isopropyl palmitate, and Tween 80 could be used as the enhancers for the 8:2, HPMC:EC film formulations.
5. The fluxes from 8:2, HPMC:EC film formulations with isopropyl myristate or isopropyl palmitate reached the target flux of this study

Suggestion for further study:

The co-enhancer between isopropyl myristate or isopropyl palmitate with Tween 80 might increase the enhancing effect of diltiazem hydrochloride permeation from the transdermal delivery systems. Finally, the loading dose of diltiazem hydrochloride in the transdermal delivery system might also be decreased.