CHAPTER IV

DISCUSSION AND CONCLUSION

DISCUSSION

According to the poor solublity of DD in water, it is important to use co-solvent in the formulations to solubilize the drug. Although, benzyl alcohol, N,N-dimethyl acetamide, and isopropyl alcohol showed the higher solubilities for DD, they could not employed in the formulations because of unstability properties to the drug (Table 4 and Figure 14). DD in propylene glycol and ethyl alcohol exhibited higher stability than other solvents, however, after transferring the formulation into a patch, the evaporation of ethyl alcohol caused leakage and resulted in changing in the release and permeation profile of the drug. Therefore, propylene glycol was used as a solvent for DD formulations.

Sorensen phosphate buffer system was utilized in order to decrease the effect of buffer species on the degradation of DD (Connors, 1981; Flynn, 1980). Since lower the pH value of not less than 7 showed higher stability (aggregation occur at pH 6), phosphate buffer at pH 7 was used in almost all of the formulations to minimize drug instability (Figure 15).

Stability data of DD for 4 months revealed that drug stability in poloxamer F-127 and hydroxypropyl methylcellulose were higher than other gelling agents (Table 4 and Figures 16-19). Therefore, both poloxamer F-127

and hydroxypropyl methylcellulose were selected for further evaluation in *in-vitro* skin permeation study.

For *in-vitro* evaluation of diclofenac diethylamine-TDS formulations, the drug release-time profiles from Voltaren® emulgel in patch indicated that the initial release kinetic of DD seemed to follow the Higuchi's model (Figure 20).

The influence of the drug and polymer concentrations on the release characteristic of the preparation were evaluated. Higher concentration of the drug produced higher release rate. In contrast, the higher concentration of polymer will produced an opposite effect for all polymers. Poloxamer F-127 is a gelling agent with a nonionic surfactant and a solubilizing properties which can form micelles in an appropriate medium (Tomida et. al., 1987). The effect of this polymer concentration on the release rate was noted. The increasing in the polymer concentration, decreased the release rate of the drug. This may be due to the reduction in size and number of water channels within the gel matrix and increasing the micro-viscosity channels of the gel (Chen-Chow and Frank, 1981; Hadgraft and Howard, 1982). For sodium alginate and hydrophilic cellulose derivatives (hydroxypropyl methylcellulose and sodium carboxymethylcellulose), increasing concentration in the formulation resulted in a decrease in the release rate. The reason may be due to an increase in the polymer concentrations increased the viscosity which directly affect the gel strength and this viscous gel acts as a barrier preventing the diffusional movement of the drug across the membrane or the medium (Dawid, 1984). Furthermore, these evens may explain by Stokes-Einstein equation,

$$D = kT/6\eta r \quad \ldots\ldots(1)$$

where D is diffusion coefficient of the drug molecule, k is Boltzmann constant, T is absolute temperature, η is vehicle viscosity, and r is molecular radius.

By increasing the gel viscosity, the drug diffusion coefficient will decrease as well as the dissolution.

All of the formulations (Formulas #1-23) seemed to follow the Higuchi's model.

According to stability study as indicated in Figures 16-19 and Table 5, it was concluded that DD was not stable in sodium carboxymethylcellulose and sodium alginate, thus, these two polymers could not be employed for drug reservoir. The six designed formulations (Formulas #6-8 and #11-13), which could exhibit higher release when compared to Voltaren® emulgel patch, were selected to further evaluation the skin permeation study.

From skin permeation study, the high relationship between cumulative skin permeation as a function of time of Voltaren® emulgel patch and all other 6 formulations were investigated, these indicated zero-order permeation of drug through the skin (Tables 12-13 and Figures 32-37). Formula #6 which contained 10% poloxamer F-127 was most suitable to employ in *in-vivo* study.because of the highest permeation rate than the other formulas. In the case of other formulas, they presented lower permeation rate than that of Voltaren® emulgel patch, thus, they were not utilized for further study in *in-vivo* study.

The diffusion of the drug molecules from the donor to the receptor is illustrated in the Figure 38. It was found that the multi-laminated layer controlled the total permeation rate.

This system could possible be applied to the laminate barrier of drug release from reservoir to receptor. The well developed equation from absolute rate theory for the flux of a drug through the barrier is given in equation 2 (Flynn, Yalkowsky, and Roseman, 1974).

$$J \propto P(C_0-C_n) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

where J is equal to flux; P is transition state partition coefficient (P = D/l); D is diffusion coefficient in a specific boundary; l is the thickness of the boundary; C_0 is the concentration at the donor cell; C_n is concentration at the receptor cell.

Equation 2 can be rewritten as,

$$J = \frac{D}{l}.k_d.(C_0-C_n) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where D, l, C_0, and C_n are previoulsy mentioned; k_d is partition coefficient.

From the system, drug in the reservoir was released through the membrane, the adhesive, and the skin before reaching the receptor site, respectively. A diagram representing the transport is as follows.

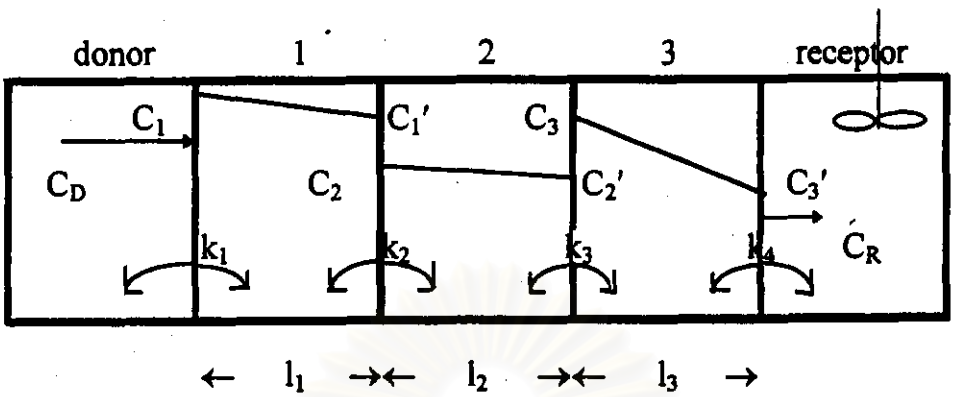

Figure 38 Schematic diagram of the rate determining barrier.

Remark : $k_1 = C_1/C_D$; $k_2 = C_2/C_1'$; $k_3 = C_3/C_2'$; $k_4 = C_3'/C_R$ (k = partition coefficient), 1 = membrane; 2 = adhesive, and 3 = skin

Two assumption assumptions must be made in order to use this model. First, no concentration gradients occurred within the donor or the receptor cell (i.e. the drug in the donor cell is released continuously and the receptor side is well agitated). Second, the transport is assumed to reach a steady state and flux in each layer, also, equal.

According to steady state approximation, the flux across all three barriers are in the same manner. The following equations will be obtained.

$$J_1 = \frac{D_1}{l_1}(k_1C_D - C_1') \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

$$J_2 = \frac{D_2}{l_2}(k_2C_1' - C_2') \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$$J_3 = \frac{D_3}{l_3}(k_3C_2' - k_4C_R) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Solve Equation 4 to obtain C_1' and Equation 6 to obtain C_2' and substitute these in to Equation 5.

$$J_1 = \frac{D_1k_1C_D}{l_1} - \frac{D_1C_1'}{l_1} \quad \text{.....(7)}$$

$$C_1' = \left[\frac{D_1k_1C_D}{l_1} - J_1\right]\frac{l_1}{D_1} \quad \text{.....(8)}$$

$$C_1' = k_1C_D - \frac{J_1l_1}{D_1} \quad \text{.....9)}$$

$$J_3 = \frac{D_3k_3C_2'}{l_3} - \frac{D_3k_4C_R}{l_3} \quad \text{.....(10)}$$

$$C_2' = \left[J_3 + \frac{D_3k_4C_R}{l_3}\right]\frac{l_3}{D_3k_3} \quad \text{.....(11)}$$

$$C_2' = \frac{J_3l_3}{D_3k_3} + \frac{k_4C_R}{k_3} \quad \text{.....(12)}$$

From the previous assumption that the steady state flux are equal, Equation 5 becomes

$$J_2 = \frac{D_2}{l_2}\left[(k_2k_1C_D - \frac{k_2J_1l_1}{D_1}) - (\frac{J_3l_3}{D_3k_3} + \frac{k_4C_R}{k_3})\right] \quad \text{..(13)}$$

[All flux are equal; $J = J_1 = J_2 = J_3$]

The following equation will be obtained.

$$J + \frac{D_2k_2l_1J}{l_2D_1} + \frac{D_2l_3J}{l_2D_3k_3} = \frac{D_2k_2k_1C_D}{l_2} - \frac{D_2k_4C_R}{l_2k_3} \quad \text{.....(14)}$$

Multiply Equation 14 by l_2/D_2 and factor J out,

$$J\left[\frac{l_2}{D_2} + \frac{k_2l_1}{D_1} + \frac{l_3}{D_3k_3}\right] = k_2k_1C_D - \frac{k_4C_R}{k_3} \quad \text{.....(15)}$$

$$J\left(\frac{l_2D_1D_3k_3 + k_2l_1D_2D_3k_3 + l_3D_1D_2}{D_1D_2D_3k_3}\right) = k_2k_1C_D - \frac{k_4C_R}{k_3} \quad \text{.....(16)}$$

Rearrange the equation to get equation 17,

$$J = \frac{D_1D_2D_3k_3\left[k_1k_2C_D - k_4C_R/k_3\right]}{D_1D_3k_3l_2 + D_2D_3k_2k_3l_1 + D_1D_2l_3} \quad \text{.....(17)}$$

$$J = \frac{D_1D_2D_3k_1k_2k_3C_D - D_1D_2D_3k_4C_R}{D_1D_3k_3l_2 + D_2D_3k_2k_3l_1 + D_1D_2l_3} \quad \ldots(18)$$

At sink condition, $C_R \cong 0$.

$$J = \frac{C_D}{\frac{l_2}{D_2k_1k_2} + \frac{l_1}{D_1k_1} + \frac{l_3}{D_3k_1k_2k_3}} \quad \ldots\ldots\ldots\ldots\ldots(19)$$

$$J = \frac{C_D}{\frac{1}{P_1} + \frac{1}{P_2} + \frac{1}{P_3}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots(20)$$

where $P_1 = D_1k_1/l_1$; $P_2 = D_2k_1k_2/l_2$; $P_3 = D_3k_1k_2k_3/l_3$ (P = permeability coefficient)

Substitute permeability coefficient in Equation 20,

$$J = \frac{P_1P_2P_3C_D}{P_2P_3 + P_1P_3 + P_1P_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots(21)$$

$$J = P_TC_D \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(22)$$

where P_T represents complex permeability coefficient.

It can be concluded that for any diffusional experiments perform on multi-laminate layers, the flux is dependent only on the P_T value. Thus the overall permeation rate is mainly controlled by the laminate layers which is considered to be the rate determining barrier.

The anti-inflammatory activity on carrageenan-induced paw edema in rat was applied to the *in-vivo* evaluation of selected patch. Formula #6 containing 2.32 %w/w DD in 10 %w/w poloxamer F-127 was exhibited no significant difference anti-inflammatory activity as compared to Voltaren® emulgel after 3 hours of application ($p \geq 0.05$) (Table 14). Since the patch was placed on the rat dorsal skin whereas carrageenan was injected into right hind paw of the rat, the decreasing in paw edema volume indicated systemic effect of the patch on anti-

inflammatory activity. Moreover, after applied patch for 12 hours and then removed it off, Formula #6 was shown significant higher anti-inflammatory activity as compared to Voltaren® emulgel ($p<0.05$). These may indicate for prolonged release of the patch upto 12 hours, while Voltaren® emulgel did not indicate any anti-inflammatory activity.

CONCLUSION

1. The various solvents, pH values of buffer solutions, and polymers could affect DD stability.
2. The higher drug concentrations produced higher release rate, in contrast, the higher polymer concentrations produced the opposite effect.
3. A membrane-controlled type transdermal DD delivery system could be developed using 10% poloxamer F-127 as a gelling agent and 14% propylene glycol as a co-solvent.
4. For any diffusional experiments perform on multi-laminate layers, the flux is dependent on the complex permeability coefficient (P_T) and the laminate layers is considered to be the rate determining barrier.
5. The anti-inflammatory activity and the duration of the activity of the formulated patch (Formula #6) was sustained upto 12 hours.