# CHAPTER III

# RESULTS AND DISCUSSION

## Approximation of Piroxicam Solubilities in pH 7.4 Phosphate Buffer Solution and Normal Saline Solution at Ambient Temperature.

Reported receptor fluids used for in-vitro percutaneous absorption experiments include normal saline solution, pH 7.4 buffer, isotonic pH 7.4 buffer, 50 % aqueous ethanol, polyethylene glycol 400, volpo N 20, and water. Of all the receptor fluids, normal saline solution, pH 7.4 buffer and 50 % aqueous ethanol appear to be the most widely used (Jones, Greenway, and Orr, 1989). Because 50 % of aqueous ethanol does not really represent biological fluid, it was not considered in this study.

The approximate solubilities of piroxicam in pH 7.4 phosphate buffer solution and normal saline solution were determined in order to choose a suitable receptor fluid for diffusion studies. A prime objective of a receptor fluid is to provide sink condition for the penetrating molecule during the diffusion studies. It is generally accepted that sink condition is maintained when the concentration of penetrant in the receptor phase does not exceed 5 % of the donor concentration.

The approximate solubilities of piroxicam in pH 7.4 phosphate buffer solution and in normal saline solution at ambient temperature are shown in Table 4. It can be seen that the approximate solubility of piroxicam in pH 7.4 phosphate buffer solution (0.7670 mg/ml) was higher than that in normal saline solution (0.0293 mg/ml). Thus, pH 7.4 phosphate buffer solution was chosen to be the receptor fluid for in-vitro diffusion studies.

## Preparation of Piroxicam Gels.

In general 0.5% piroxicam is the strength of commercial piroxicam gel preparations. However, 2% piroxicam was used in this study because its slow penetration rate made the analysis impossible.

Table 4 : Approximate solubilities of piroxicam in pH 7.4 phosphate buffer solution and in normal saline solution at ambient temperature.

| Sample No. | Solubility (mg/ml) | |
|---|---|---|
| | pH 7.4 Phosphate Buffer Solution | Normal Saline Solution |
| 1 | 0.7625 | 0.0325 |
| 2 | 0.7635 | 0.0313 |
| 3 | 0.7885 | 0.0282 |
| 4 | 0.7635 | 0.0280 |
| 5 | 0.7570 | 0.0263 |
| mean ± SD | 0.7670 ± 0.0123 | 0.0293 ± 0.0026 |

Piroxicam is very slightly soluble in water therefore, an increase in its solubility is essential in preparing a 2 % piroxicam gel. The solubility of piroxicam may be increased tremendously by having the pH of a formulation of more than seven as shown by Tsai, 1985. Triethanolamine was used as an alkalinizing agent to promote the solubility of piroxicam. It was also used as an alkali titrant of carbopol to form gel structure.

Various synthetic gelling agents used in different concentrations had been preliminary studied as gel bases. And the following gelling agents were selected : 20 % pluronic F-127, 1 % carbopol - 940, 3.5 % hydroxypropyl methylcellulose, and 2.5 % hydroxyethyl cellulose. Reasons for choosing the gelling agents were their good physical appearances, their ease of spreadabilities, and their pleasances to the skin after applications. The concentrations of the gelling agents selected would give gel bases with about the same viscosities as shown in Table 5 except pluronic F-127. A stable pluronic F-127 gel base would form at the concentration of at least 20 % which was more viscous than the others. Pluronic F-127 was found to promote the solubility of piroxicam (result obtained from preliminary study) because of its surfactant property. However, triethanolamine was also incorporated to adjust the pH of this preparation.

The additives used were 10 % and 20 % isopropyl alcohol, 5 % and 10 % propylene glycol, 0.5 % and 1.0 % Tween 20, and 0.5 % and 1.0 % Brij 30. Isopropyl alcohol and propylene glycol have been widely used as solvents for topical preparations. Isopropyl alcohol is also used in the formulas to give a cooling effect as it evaporates upon application and propylene glycol is also used as a humectant. Tween 20 and Brij 30 are nonionic surfactants which can promote the solubility of piroxicam and they also have some effects on the penetrating rates of some substances.

The appearance of all piroxicam gel preparations is yellowish transparent because piroxicam itself is yellow. Not surprisingly, pluronic F-127 gel was much stickier than the others when it was applied to the skin because of its highest viscosity.

The pH and viscosity of a formulation were important factors in determining skin penetration rates. The skin permeation of ionizable drugs will be sensitive to the vehicle pH since the relative portions of charged and uncharged species are different in different pH's and the charged and uncharged species diffuse with different rates (Zatz and Sarpotdar, 1987). The viscosity of preparation influences the diffusivity of penetrant. A viscous preparation may retard permeation rate. So, in this study an attempt to adjust all preparations without any additives to about the same pH and viscosity was

Table 5 : Concentrations and viscosities of gelling agents used in piroxicam gel formulations.

| Formulation | Gelling Agents | Concentration (% W/W) | Viscosity (cps) |
|---|---|---|---|
| I | Pluronic F-127 | 20.0 | 9,945 |
| II | Carbopol - 940 | 1.0 | 6,846 |
| III | Hydroxypropyl methylcellulose | 3.5 | 7,140 |
| IV | Hydroxyethyl cellulose | 2.5 | 6,924 |

made. Table 6 shows the pH's and viscosities of all formulations. The pH of all formulations were adjusted to about eight. This pH of eight corresponded with the highest pH value of the carbopol gel base in the preliminary study.

The results in Table 6 showed drops of viscosity from 6,846 cps. (Formulation II) to 5,772 and 5,769 cps., respectively when 10 % and 20 % isopropyl alcohol (Formulation V and VI) were included in the preparations. Although carbopol can be used in gel formulations with a large proportion of alcohol, the dehydration effects of alcohol on the polymer are still substantial (Pena, 1990). Increasing isopropyl alcohol content would reduce solvent affinity for carbopol and therefore, the polymer contracts with a consequential increase in the interparticle distance and subsequent decreased in the number of entanglements and crosslinks.

The viscosities of the preparations containing 5 % and 10 % propylene glycol (Formulation VII and VIII) were 6,471 and 6,645 cps., respectively. They were not significantly different from that of Formulation II. This might suggest that propylene glycol does not affect the carbopol gel structure.

When the nonionic surfactants were included in the preparations, the viscosity dropped but in different degrees. The preparations containing 0.5 % and 1.0 % Tween 20 (Formulation IX and X) had the viscosities of 6,303 and 5,922 cps., respectively. While the preparations containing 0.5 % and 1.0 % Brij 30 (Formulation XI and XII) had the viscosities of 5,210 and 4,736 cps., respectively. This indicates the physical instability of carbopol gel structure when it is exposed to a nonionic surface active agent. The more the surfactants in the formulations, the less stable it becomes. When the drops in viscosities were compared, it was found that Tween 20 had less effect on carbopol gel structure than Brij 30 had.

**In-Vitro Diffusion Studies.**

Data of individual diffusion runs are given in Appendix II through V. In each study, the permeation process was characterized in terms of permeability rate. The steady-state diffusion rate divided by the diffusional area of the membrane yielded the penetration flux. Each experiment was performed in triplicate. The values of penetration flux were averaged, and the mean was utilized as an index of absorption for that formulation. An example of permeation profiles of piroxicam is shown in Figure 7.

Table 6 : pH's and viscosities of piroxicam gel preparations.

| Formulation | pH | Viscosity (cps.) |
|---|---|---|
| I | 7.98 | 9,945 |
| II | 7.94 | 6,846 |
| III | 8.00 | 7,140 |
| IV | 8.03 | 6,924 |
| V | 7.96 | 5,772 |
| VI | 8.01 | 5,769 |
| VII | 8.00 | 6,471 |
| VIII | 8.00 | 6,645 |
| IX | 8.04 | 6,303 |
| X | 7.98 | 5,922 |
| XI | 8.01 | 5,210 |
| XII | 8.05 | 4,736 |

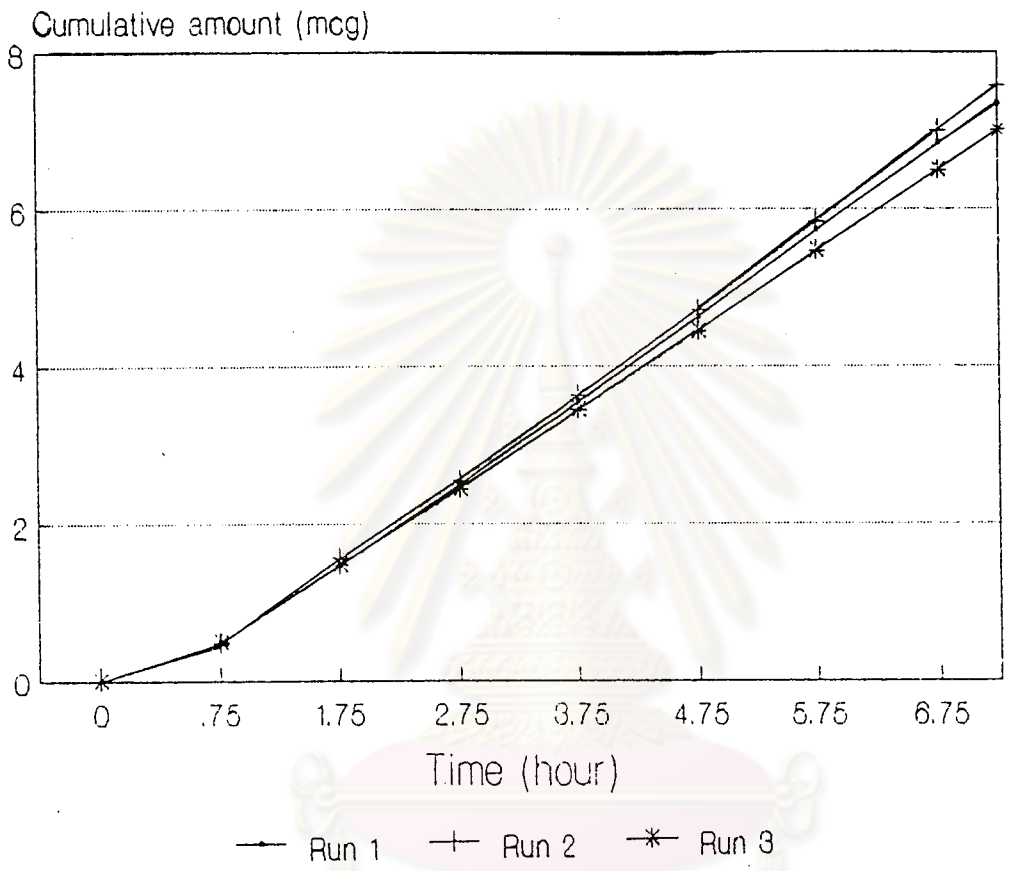


Figure 7 : Permeation profile of piroxicam from carbopol –940 gel base through silastic®.

1. Effect of Gelling Agents on Piroxicam Flux through Silastic® and Pig Skin.

Table 7 shows steady-state fluxes of piroxicam and their variations from four gel bases through silastic®. The piroxicam flux from pluronic F-127 gel base (Formulation I) yielded the slowest flux. Whereas the carbopol gel (Formulation II) was found to yield the highest piroxicam flux (0.7193 ± 0.0292 mcg/hr $cm^2$). Both the cellulose derivatives (Formulation III and IV) gave intermediate and comparable fluxes.

Table 8 shows piroxicam fluxes from those selected gel bases through pig skin. The highest piroxicam flux (0.5772 ± 0.2185 mg/hr.$cm^2$) was also obtained from the carbopol gel base. Hydroxypropyl methylcellulose and hydroxyethyl cellulose gels yielded comparable fluxes. No piroxicam was detected in the receptor phase when pluronic F-127 was employed.

The diffusivities of any drugs through different gel bases depend on the nature and composition of the individual bases and any changes in the nature and/or composition of the bases will affect the permeation rates of the active ingredients. The diffusion coefficient, D, is inversely proportional to the viscosity of the vehicle. From Stokes-Einstein equation, the diffusion coefficient of colloidal particles is related to the viscosity as follow :

$$D = \frac{RT}{6\pi r \eta N} \qquad \text{eq. 7}$$

where R is the gas constant, T is the absolute temperature, r is the mean radius of particle, $\eta$ is the viscosity of the vehicle, and N is the Avogadro's number. According to this equation, the decrease in viscosity of the vehicle would increase the diffusion coefficient of the drug and thus, increase the release rate. As far as the viscosity is concerned, the diffusivity of piroxicam in pluronic F-127 gel should be the lowest because of the highest viscosity of the gel. And it is reasonable to assume that the diffusivity of piroxicam in carbopol and cellulose derivatives bases are comparable.

The changes in piroxicam flux from different gel bases may also result from changes in the partition coefficient. In other words, the affinity of piroxicam for these gel bases are different. When the partition coefficient is large, or when the affinity of piroxicam for a base is small, there is a greater tendency for transfer of piroxicam to the membrane. And this should be the case of carbopol gel. The stronger binding force between piroxicam and the gel base (low partition coefficient) as in the cases of hydroxypropyl methylcellulose and hydroxyethyl cellulose gels would reduce the drug

Table 7 : Steady-state fluxes of piroxicam from various gel bases through silastic®.

| Formulation | Gelling Agents | Steady-state Flux* (mcg/hr. $cm^2$) | % CV |
|---|---|---|---|
| I | Pluronic F-127 | 0.1788 ± 0.0093 | 5.23 |
| II | Carbopol - 940 | 0.7193 ± 0.0292 | 4.07 |
| III | Hydroxypropyl methylcellulose | 0.4913 ± 0.0247 | 5.04 |
| IV | Hydroxyethyl cellulose | 0.4238 ± 0.0289 | 6.83 |

* Mean ± SD, average of three experiments.

Table 8 : Steady-state fluxes of piroxicam from various gel bases through pig skin.

| Formulation | Gelling Agents | Steady-state Flux* (mcg/hr. $cm^2$) | % CV |
|---|---|---|---|
| I | Pluronic F-127 | - | - |
| II | Carbopol - 940 | 0.5772 ± 0.2185 | 37.86 |
| III | Hydroxypropyl methylcellulose | 0.2458 ± 0.0667 | 27.14 |
| IV | Hydroxyethyl cellulose | 0.2711 ± 0.0869 | 32.05 |

* Mean ± SD, average of three experiments.

permeation rate. Since pluronic F-127 gel is believed to consist of large populations of micelles (Chen-Chow and Frank, 1981; Rassing and Attwood, 1983), the high ability to solubilize piroxicam by the micelles should result in a low partition coefficient of the drug. And this may be another reason of the very low steady-state flux of piroxicam from this gel.

The general rank order of the in-vitro permeation of piroxicam through silastic® was found to be correlated with that through pig skin ($r^2 = 0.9631$) as shown in Figure 8. The regression line is

$$\bar{J}ss, \text{silastic} = 0.20 + 0.92 \; \bar{J}ss, \text{pig skin} \qquad \text{eq. 8}$$

which indicates that the steady-state flux of piroxicam through silastic® is greater than the steady-state flux of piroxicam through pig skin about 0.2 mcg/hr.cm$^2$. In other words, the silastic® sheet was more permeable to piroxicam than the pig skin. The difference in the steady-state fluxes through the two membranes is due to significant differences between a simple synthetic membrane of silastic® and a structurally highly complex pig skin. The silastic® was shown to be selectively permeable to unionized species (Garrett and Chemburkar, 1968; Touitou and Abed, 1985). While the pig skin behaved as a heterogeneous phase system which ionized species diffuse across aqueous shunt pathway and unionized species penetrate the lipophilic barrier (Touitou and Abed, 1985). The lag time ($t_L$), which is obtained by extrapolating the steady-state portion of piroxicam permeation profile to the time axis (data are shown in Table 9, of the permeation through pig skin is more than that through silastic® sheet. Thus, the unionized species seemed to be the more important permeant through both membranes even though the ionized species was dominant at this pH (pKa's of piroxicam = 1.8 and 5.1).

Consequently, the silastic® sheet can be used for comparison of piroxicam permeation rates from various gel bases not containing any additives. The silastic® has an obvious advantage over the pig skin in that it is more reproducible than the pig skin as its % CV's are much less.

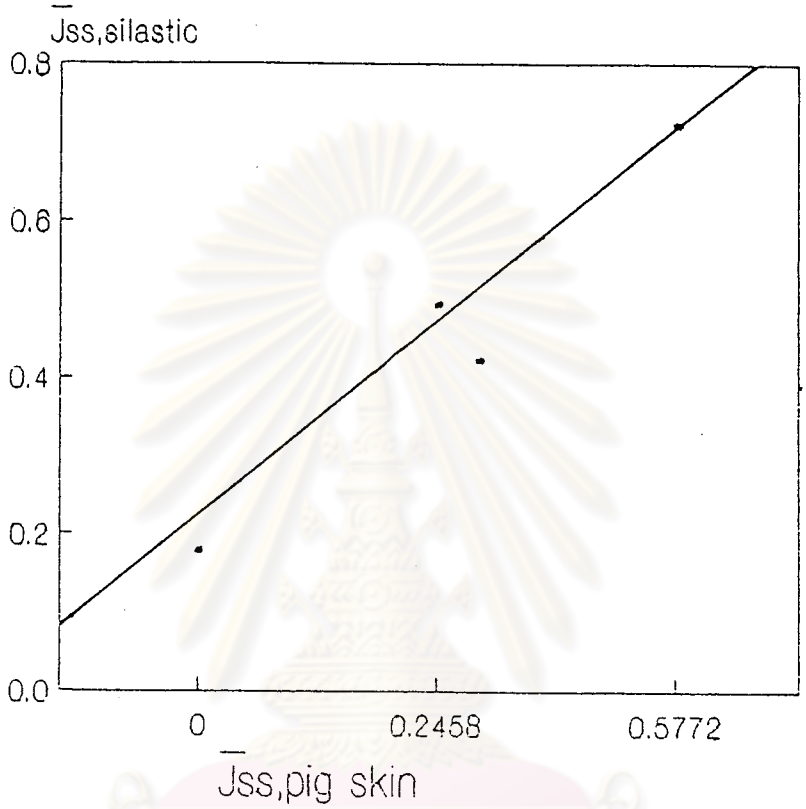


Figure 8 : Correlation of the permeation flux of piroxicam from four gel bases through silastic® and pig skin.

Table 9 : Lag times obtained from piroxicam permeation profiles using silastic® and pig skin.

| Formulation | Gelling Agents | lag time (hr)* | |
|---|---|---|---|
| | | silastic® | pig skin |
| I | Pluronic F-127 | 0.45 | - |
| II | Carbopol - 940 | 0.61 | 1.57 |
| III | Hydroxypropyl methylcellulose | 0.61 | 1.99 |
| IV | Hydroxyethyl cellulose | -0.43 | 1.61 |

* Mean, average from three experiments.

2. Effect of Various Additives on Piroxicam Flux through Silastic® and Pig Skin.

The viscosity of a preparation influences the steady-state flux according to the Stoke-Einstein equation (equation 7) as previously described. Other parameters also have some effects on the flux.

For drugs in a relatively fluid vehicle such as gel, the transport across membrane is the rate-limiting step. Under these conditions, steady-state flux is described by equation 5 ($J = DKC_d / h$).

The product of K and $C_d$ represents the concentration gradient across the membrane which provides the driving force for diffusion. Higuchi, 1960 had derived an alternative form of equation 5 that is sometimes easier to apply :

$$J = \frac{Da_V}{h\ \gamma_S} \qquad \text{eq. 9}$$

where $a_V$ is the thermodynamic activity of the drug in the vehicle and $\gamma_S$ is the activity coefficient of the drug in the membrane. The value of $\gamma_S$ is usually taken to be constant when the same drug is applied in the same concentration in all of the vehicles. So changes in penetration rate are attributed to alterations in the thermodynamic activity of the drug in the vehicle (equation 9) and/or the membrane/vehicle partition coefficient according to equation 5. The thermodynamic activity of a drug in a saturated vehicle is assumed to be unity as being the reference state. If the drug concentration was less than that required for saturated solution, the activity would be reduced. Theoretically, then, the penetration is fastest from a vehicle that is just able to dissolve the drug completely. Vehicles that have higher solubility should have lower penetration rate if the drug concentration is kept constant.

The results obtained from previous studies demonstrated that piroxicam in 1 % carbopol gel base yielded the highest flux through both silastic® and pig skin. Therefore, 1 % carbopol gel base was selected for study of the effect of various additives on the piroxicam flux though silastic® (Table 10) and pig skin (Table 11).

Table 10 : Piroxicam fluxes from carbopol-940 gel bases containing various additives through silastic®.

| Formulation | Additives | Viscosity (cps.) | Steady-state Flux* (mcg/hr. $cm^2$) | % CV |
|---|---|---|---|---|
| II | none | 6,846 | 0.7193 ± 0.0292 | 4.07 |
| V | Isopropyl Alcohol, 10 % | 5,772 | 0.8687 ± 0.0684 | 7.87 |
| VI | Isopropyl Alcohol, 20 % | 5,769 | 0.5651 ± 0.0170 | 3.02 |
| VII | Propylene Glycol, 5 % | 6,471 | 0.9085 ± 0.0371 | 4.08 |
| VIII | Propylene Glycol, 10 % | 6,645 | 0.6107 ± 0.0169 | 2.78 |
| IX | Tween 20, 0.5 % | 6,303 | 1.1526 ± 0.0428 | 3.72 |
| X | Tween 20, 1.0 % | 5,922 | 1.1697 ± 0.0505 | 4.32 |
| XI | Brij 30, 0.5 % | 5,210 | 1.9933 ± 0.1211 | 6.07 |
| XII | Brij 30, 1.0 % | 4,736 | 1.7762 ± 0.0494 | 2.78 |

* Mean ± SD, average of three experiments.

Table 11 : Piroxicam fluxes from carbopol - 940 gel bases containing various additive through pig skin.

| Formulation | Additives | Viscosity (cps.) | Steady-state Flux* (mcg/hr. $cm^2$) | % CV |
|---|---|---|---|---|
| II | none | 6,846 | 0.5772 ± 0.2185 | 37.86 |
| V | Isopropyl Alcohol 10 % | 5,772 | 2.1869 ± 0.3542 | 16.20 |
| VI | Isopropyl Alcohol 20 % | 5,769 | 2.8255 ± 0.4666 | 16.52 |
| VII | Propylene Glycol 5 % | 6,471 | 0.4434 ± 0.1655 | 37.32 |
| VIII | Propylene Glycol 10 % | 6,645 | 2.3781 ± 0.8995 | 37.82 |
| IX | Tween 20, 0.5 % | 6,303 | 1.0638 ± 0.2291 | 21.54 |
| X | Tween 20, 1.0 % | 5,922 | 1.2539 ± 0.2237 | 17.84 |
| XI | Brij 30, 0.5 % | 5,210 | 1.2180 ± 0.0652 | 5.35 |
| XII | Brij 30, 1.0 % | 4,736 | 3.6808 ± 1.1432 | 31.06 |

* Mean ± SD, average of three experiments.

2.1 Effect of Isopropyl Alcohol on Piroxicam Flux.

The influence of isopropyl alcohol concentrations on piroxicam penetration rate from carbopol gel through silastic® are summarized in Table 10. The piroxicam concentration was kept constant at 2 %. The addition of 10 % isopropyl alcohol (Formulation V) increased the steady-state flux from 0.7193 ± 0.0292 mcg./hr.cm$^2$ (Formulation II ) to 0.8687 ± 0.0684 mcg./hr.cm$^2$. This might be due to the decrease in viscosity which resulted in the increase in diffusivity of the drug. In contrary, when the percentage of isopropyl alcohol was increased from 10 % (Formulation V) to 20 % (Formulation VI), the steady-state flux was reduced from 0.8687 ± 0.0684 mcg./hr.cm$^2$ to 0.5651 ± 0.0170 mcg./hr.cm$^2$. The viscosities of Formulation V (5,772 cps.) and Formulation VI (5,769 cps.) were comparable but they were less than that of Formulation II (6,846 cps.). Therefore, the viscosity of preparation must not be the only reason for changes in the steady-state flux. Increasing the amount of isopropyl alcohol also increased the piroxicam solubility in the preparation and therefore, decreased the membrane/vehicle partition coefficient. In conclusion, increasing the percentage of isopropyl alcohol in a gel preparation would decrease both the viscosity of the gel and the partition coefficient of the drug providing that the drug solubility in the membrane was the same. In other words, isopropyl alcohol exerted its effect on the piroxicam flux through silastic® sheet in both directions, i.e., increased and decreased the flux. In a small amount of isopropyl alcohol, the effect on viscosity was more than the effect on solubility (or partition coefficient) and therefore, the flux was increased. An increase in solubility in the gel preparation (or decrease in the partition coefficient) outcomed the effect on viscosity when the amount of alcohol became larger and thus, the flux was now decreased.

The piroxicam flux from carbopol gel base (Formulation II) through pig skin was 0.5772 ± 0.2185 mcg./hr.cm$^2$ (Table11). When 10 % (Formulation V) and 20 % (Formulation VI) of isopropyl alcohol were added to the preparations, the steady-state fluxes were increased to 2.1869 ± 0.3542 mcg./hr.cm$^2$ and 2.8255 ± 0.4666 mcg./hr.cm$^2$, respectively (Table 11). In the case of pig skin, the increase in the amount of isopropyl alcohol to 10 % or 20 % increased the flux and the flux values were much higher than those obtained in the case of silastic®.

The results obtained in the present study seem to be in agreement with the recent studies (Ghanem, et. al., 1987; Ghanem et al., 1988). They demonstrated that 30 % ethanol, 10 % n-propanol, 10 % isopropanol, and 3 % n-butanol resulted in a ten fold enhancement of the permeation of ß-estradiol and hydrocortisone through hairless mouse skin.

This change in piroxicam flux was quite complex mechanisms. Isopropyl alcohol might have several effects on the penetration of piroxicam from the gel base to the skin. The reduction in viscosity of carbopol gel containing isopropyl alcohol increased the diffusivity of the drug and thus, the penetration rate. But increasing isopropyl alcohol concentration also increased the piroxicam solubility in the vehicle which resulted in a reduction of the skin/vehicle partition coefficient and thus, decreased the penetration rate. Apart from the effects on the gel preparation, isopropyl alcohol also affected the pig skin directly. Isopropyl alcohol had the dehydration action on the skin, resulting in the decrease of the percutaneous absorption of the drug. But this effect should be negligible. The considerable change in piroxicam flux could only be explained by considering the interaction between the isopropyl alcohol and the skin membrane. The stratum corneum represents the most important barrier to penetration. Isopropyl alcohol migration from the gel base into the stratum corneum might alter the effective resistance of the barrier. It was suggested that the enhancing ability of alcohols appeared to be related to their capability of extracting stratum corneum lipids (Walters, 1983). Knutson et al., 1990 studied the influence of short-chain alcohols (ethanol, n-propanol, isopropanol, n-butanol) on the thermotropic phase behavior of stratum corneum lipid. They found that the alcohols disrupted the lipid polar head groups and increased the interfacial area of the lipids thus, increased the "fluidity" in liquid crystalline lipids. The reduction in diffusional resistance of the barrier leaded to the ease of drug molecule to traverse.

2.2 Effect of Propylene Glycol on Piroxicam Flux.

Table 10 shows the effect of increasing propylene glycol concentrations on piroxicam flux through silastic®. The gel containing 5 % propylene glycol (Formulation VII) yielded a higher flux (0.9085 ± 0.0371 mcg./hr.cm$^2$) than the gel containing 10 % propylene glycol (Formulation VIII, 0.6107 ± 0.0169 mcg./hr.cm$^2$). The results were similar to those obtained in the case of isopropyl alcohol through silastic® except that the values obtained were higher than those obtained from the study on the effect of isopropyl alcohol. The viscosities of gel preparations containing propylene glycol (Formulation VII and VIII) were comparable to that of gel preparation not containing propylene glycol (Formulation II). Thus, the diffusivity of the drug in these gel bases would be comparable. Poulsen et al., 1968 indicated that the maximum release of fluocinolone acetonide was obtained from the vehicles containing the minimum amount of propylene glycol required to dissolve the steroid. Increasing the concentration of the effective solvent might, in fact, result in a reduction of the amount released. He concluded that an excess of propylene glycol lowered the thermodynamic activity of the drug in the vehicle, so partitioning into a membrane was reduced and the penetration rate went

down. The results in this study also support such a conclusion. That is, an optimum concentration of propylene glycol was required for maximum penetration rate of piroxicam. A higher concentration of propylene glycol would lower the diffusion rate of piroxicam.

The effect of propylene glycol concentrations on piroxicam flux through pig skin are displayed in Table 11. The piroxicam fluxes from the gels containing 5 %, and 10 % propylene glycol (Formulation VII and VIII) were 0.4434 ± 0.1655 mcg./hr.cm$^2$ and 2.3781 ± 0.8995 mcg./hr.cm$^2$, respectively. The values obtained were opposite to those obtained using silastic®. This suggested that the effect of solubility on the penetration rate might be ignored. Propylene glycol could dehydrate the pig skin because of its hygroscopicity and thus, lowed the steady-state flux. However, the decrease in flux was negligible when there was 5 % propylene glycol in the piroxicam gel. At higher concentration of propylene glycol (10 %), there was a marked increase in piroxicam flux. Although the diffusion rate could be reduced by the lower partition coefficient or the dehydration effect, 10 % propylene glycol might enhance penetration by disrupting the normal structure of stratum corneum. The mechanism of action was probably by solvating alpha-keratin and occupying hydrogen-bonding sites thus, reducing drug/tissue binding (Barry, 1987). However, it did not appear to influence horny layer lipid structure. These changes in intracellular channel usually leaded to an increase in the effective diffusion coefficient through the stratum corneum.

### 2.3 Effect of Tween 20 and Brij 30 on Piroxicam Flux.

The addition of Tween 20 and Brij 30 to carbopol gel containing 2 % piroxicam increased the penetration rates through both silastic® (Table 10) and pig skin (Table 11). The steady-state fluxes through silastic® when 0.5 % and 1.0 % Tween 20 were included were comparable. So were the case of 0.5 % and 1.0 % Brij 30 inclusion. The addition of 0.5 % Tween 20, 1.0 % Tween 20 and 0.5 % Brij 30 yielded comparable fluxes through pig skin. Whereas a marked increase in the steady-state flux was resulted when 1.0 % Brij 30 was included.

In general, the effect of surfactants on diffusion rates varies widely depending on type of surfactants and membranes studied. A specific result cannot be concluded. The ability of a surfactant to alter penetration is a function of its polar head group and hydrocarbon chain length. In this case of nonionic surfactants, the hydrocarbon chain length is the more prominent criterion for permeation alteration. The optimal chain length is required for a balance between sufficient lipophilicity to partition into the stratum corneum and sufficient water solubility which decreases with increasing alkyl chain

length. Monomeric surfactant molecules may enhance the adsorption of drug on to the donor side of the membrane (thus, increasing the membrane/vehicle partition coefficient), possibly by reducing the surface tension between the membrane and the vehicle (Barry, 1983). The surfactants may act as carriers of drug to traverse through the membranes. Finally, the surfactants may alter protein conformations or may solubilize or fluidize lipids of the stratum corneum and thus, enhance the permeation rate (Dominguez et al., 1977; Breuer, 1979).

Tween 20 and Brij 30 should be good carriers for piroxicam permeation since their nonionic nature could shield the anionic piroxicam and resulted in a faster permeation. Brij 30 enhanced the diffusion rate through silastic® more than Tween 20 did. This might be due to the more lipophilicity of Brij 30. Brij 30 has the HLB (hydrophile - lipophile balance) of 9.5 which is much less than that of Tween 20 (HLB = 16.7). Brij 30 also reduced the viscosity of the preparation more than Tween 20 did.

The flux alteration by different concentrations of surfactant is also another subject (Walters, 1989). Some surfactants may increase the diffusion rate as their concentrations increase and some have plateau regions after their critical micelle concentrations (CMC) have been reached. In contrary, increasing the surfactant concentration may decrease the diffusion rate of permeant. Sometimes the diffusion rate is not altered by changing surfactant concentration. The concentrations of Tween 20 and Brij 30 used in this study were over their CMC. The CMC's of Tween 20 and Brij 30 are 0.0044 % w/v (Sarpotdar and Zatz, 1986b) and 0.006 % w/v (Walters et al., 1982), respectively. The results suggested that the flux enhancement by Tween 20 was saturated when its concentration exceeded the CMC. The effect of Brij 30 concentration on silastic® and pig skin were different. Increasing Brij 30 concentration from 0.5 to 1.0 % lowered the steady-state flux through silastic® just a little. While the flux from formulation XII through pig skin was about three times as much as the flux from formulation XI. Consequently, Brij 30 affected the pig skin dramatically even after its CMC had been reached.