CHAPTER IV

DISCUSSION AND CONCLUSIONS

Preliminary Investigation on Drug-free Transdermal Patch

In this study, one of proposed objectives was to prepare self-adhesive transdermal patch. Preliminary study was focused on selection of an appropriate amount of chitosan and polyvinyl derivatives (PVA and PVP K-90) to obtain flexible and adhesive film.

The casting solution of chitosan and polyvinyl derivatives did not show any phase separation, since PVA and PVP K-90 were nonionic polymer. Therefore, the blending showed good compatibility.

Lin, Lee and Lin (1991) studied the use of plasticizers to improve the transparency, flexibility and adhesion of Eudragit E-100 film. In this experiment propylene glycol and glycerin were chosen as plasticizers for chitosan and polyvinyl derivatives because their highly hydrophilic property and molecular structure were easily compatible with the property of chitosan and polyvinyl derivatives. Films prepared by using chitosan and PVA did not show adhesive property for all concentrations of plasticizers used whereas those prepared by using chitosan and PVP K-90 showed adhesive property in some formulations. This might be due to very hygroscopic property of PVP K-90 (Walkling, 1994). The absorbed moisture led the film to become adhesive on hydration, since PVP K-90 contained numerous hydrogen bond forming groups.

It was found that glycerin increased adhesive property of film whereas propylene glycol in the same concentration did not improve adhesive property of film. It might be due to glycerin had three hydroxyl groups per molecule whereas propylene glycol had two hydroxyl groups per molecule. Therefore glycerin was capable of forming more hydrogen bonds with moisture, actually increased adhesive property.

Due to the yellowish color of chitosan, the obtained casting solutions were in yellowish color. Thus, increasing amount of chitosan in formulation produced yellower film.

Physicochemical Properties of Terbutaline Sulfate Transdermal Patches

Physical Characteristics

The physical characteristics of the obtained terbutaline sulfate transdermal patches depended on the chemical compositions in the formulation. The obtained terbutaline sulfate transdermal patch was flexible and did not show phase separation and precipitation. The solubility of terbutaline sulfate was very high. A 1 g of terbutaline sulfate could soluble in 4 ml of water (Reynolds et al., 1989). Thus, terbutaline sulfate could completely dissolve in polymer matrix to form a transparent film after casting.

Moisture Absorption/Loss

Bhalla and Bhate (1994) studied the effect of moisture absorption on drug diffusion across the skin. It was found that films stored at 20 %RH showed a decrease in the rate of diffusion while films stored at 85 %RH showed a higher diffusion rate.

It might be due to higher moisture content at 85 %RH led to higher dissolved drug in the film. Thus, film at 85 %RH showed a higher diffusion rate than film at 20 %RH. This indicated that the moisture content of the film played an important role in diffusion across the skin. So, in this experiment moisture absorption/loss of films were investigated. The effect of chitosan concentration on degree of moisture loss of films could illustrate that, the degree of moisture loss increased with the increasing concentration of chitosan probably due to intermolecular and intramolecular bonding of the polymer chain. The formation of film by evaporation of solvent from a polymer solution could be explained by the following discussion. As the solvent evaporation, the polymer content was increasing. Since the number of molecules of solvent per molecule of polymer was decreasing as evaporation proceeded, desolvation of the polymer was continuously effected. At some point during the evaporation, three or more active centers per macromolecule were bared by desolvation, thereby, a three-dimensional gel structure could form and the solution went through a semigel phase. The dry film therefore represented the final stage of gel-like aggregation resulting form the progressive evaporation of the volatile solvent (Doolittle, 1954). In the dry state, the polymer chain was restricted and intermolecular and intramolecular bonding might be formed when the active centers of the polymer chain became closer. The higher amount of polymer led to the higher number of polymer molecules to form intermolecular and intramolecular bonding. Thus, films became less capable H-bonding with water molecules because of intermolecular and intramolecular bonding, resulting in an increase degree of water loss.

The effect of molecular weight of chitosan on moisture sorption/loss was also investigated. Film prepared by using SEACURE 243 exhibited the lowest moisture loss. From the IR spectrum of SEACURE 243, it could be seen that SEACURE 243 had the highest degree of acetylation. Increasing degree of acetylation led to decrease

moisture loss. These results appeared to agree with those of Blair et al. (1987) who reported that chitosan samples with a high amino group content showed lower moisture regain than samples with a lower amino group content. It was possible that conversion of acetyl groups to amino groups resulted in closer packing of the polymer chains and a decrease in hydrophilicity. However, in some formulations the results were not the same as previously noted. It might be due to there were several parameters influencing the moisture absorption/loss of film.

When concentration of PVP K-90 increased it was found that moisture absorption of film decreased. It might be due to increased PVP K-90 able to form intermolecular and intramolecular bonding thus less free hydroxyl group to form H-bond with water.

From the result of films stored at 93 %RH for 4 weeks, it was found that film prepared by using 10 %w/w PVP K-90 and 0.1 %w/w of all grades of chitosan tended to be viscous liquid and could not maintain integrity of films. Thus, terbutaline sulfate transdermal patch required a special storage condition. It should not be stored in a high relative humidity.

Mechanical Properties

The mechanical properties of a polymer might be characterized as follows: A soft and weak polymer was characterized by a low ultimate tensile strength and low elongation, a hard and brittle polymer was defined by moderate ultimate tensile strength and low elongation, a soft and tough polymer was characterized by a moderate ultimate tensile strength and high elongation, whereas a hard and tough polymer was characterized by a high ultimate tensile strength and high elongation

(Aulton, 1982). The ideal film for a transdermal delivery system should be soft and tough. The effects of chitosan and PVP K-90 concentrations on mechanical properties of film indicated that increasing polymer concentration increased ultimate tensile strength of film. It might be due to an increase in a number of polymer molecules produced more interchain attraction, resulting in an increase ultimate tensile strength (Keith, 1983; Martin, Swarbrick and Arthur, 1983). The effects of chitosan and PVP K-90 concentrations on elongation at break revealed different result. The higher PVP K-90 concentration tended to produce higher elongation at break whereas the higher chitosan concentration tended to produce lower elongation at break. It might be due to the different in the property and structure of chitosan and PVP K-90.

Blair et al. (1987) studied the effect of molecular weight of chitosan on mechanical properties. High molecular weight of chitosan tended to increase ultimate tensile strength and elongation at break of film. The effect of molecular weight of chitosan in this experiment agreed with those results. Rowe and Forse (1980) reported that the ultimate tensile strength was generally increased as the molecular weight of the polymer increased. This was probably due to an increase in the intermolecular forces along the polymer.

Peel Adhesion Property

Glycerin could improve adhesiveness of terbutaline sulfate transdermal patches. This might be due to plasticizer prevented crystallization of the polymer. Lim and Wan (1994) reported that glycerin and propylene glycol prevented crystallite formation in the PVA films. In the plasticized films, crosslinking of PVA molecules could occur via hydrogen bonding with the plasticizer molecules. Such structural modification may hinder the formation of PVA crystallites in the plasticized films, the

extent of hindrance being influenced by the size of the plasticizer molecule. The molecular weights of propylene glycol and glycerin were 76 and 92 respectively. Small molecules like propylene glycol could prevent the formation of PVA crystallites in the films to a small extent. Propylene glycol also slightly lowered the melting temperature of PVA crystallites, possibly by introducing defects into the crystal lattice. Glycerin showed higher decrease in melting temperature of PVA. It might be due to more defective PVP crystallites were formed in the PVA films plasticized with glycerin. Thus, the more prevention of crystallite formation of glycerin led to the more increasing adhesiveness of film. Lin et al, (1991 and 1995) reported that the added plasticizer decreased the aggregate force of the intermolecular attraction of the polymer, thus resulting in an increase in the adhesion strength of the film.

Moreover, it might be due to hygroscopic property of glycerin. In case of propylene glycol, low molecular weight plasticizer, could not improve adhesiveness of film. It might be due to propylene glycol had two hydroxyl groups per molecule whereas glycerin had three hydroxyl groups per molecule. Therefore glycerin was capable of forming more hydrogen bonds with moisture, actually increased adhesive property.

Higher molecular weight chitosan produced the more adhesiveness of film. It was probably due to high molecular weight chitosan that had more NH_3^+ groups per molecule to react with negatively charged mucopolysaccharides and proteins of skin. Lower (1984) reported the adhesiveness of chitosan to natural polymers such as skin and hair, which composed of negatively charged mucopolysaccharides and proteins.

Surface Morphology

The surface topography of terbutaline sulfate transdermal patches was uniform, smooth and nonporous. It could be possible that polymers and plasticizers used in this study were the same hydrophilic type, so there was no phase separation. The obtained films showed uniform and nonporous surface. Lin et al. (1991) studied the surface topography of the Eudragit E-100 (hydrophobic polymer) film plasticized with the higher concentration of hydrophilic plasticizers such as polyethylene glycol 1000, polyethylene glycol 4000, PVP K-90 or glycerin it was found that films appeared porous, whereas the surface topography of the films plasticized with hydrophobic plasticizers such as triacetin or diethyl phthalate was uniform and smooth. The porous structure of the former films might be due to the phase separation that occurred between polymer and plasticizer. These results agreed with Lim and Wan (1994) who studied polyvinyl alcohol (hydrophilic polymer) films plasticized with hydrophilic plasticizer. The surface of these films had a smooth and nonporous morphology. In addition, the surface morphology of ethyl cellulose film plasticized with dibutyl sebacate also showed smooth surface (Hyppola, Husson and Sundholm, 1996).

Another reason might be due to the low drying temperature used in this experiment. The drying temperature was 40 °C. Guo, Robertson and Amidon (1993) reported that many voids or pin holes were found in the films formed at 140 °C, but not in those formed at 100 °C. It might be due to vapor pressure and rate of water evaporation increased with film forming temperature and, when the film forming temperature was above 100 °C.

Microscopic observation revealed that all the matrix systems prepared by using 10 %w/w PVP K-90 were transparent gels and did not reveal the presence of a

dispersed solid particle in the adhesive matrix. Whereas the matrix system prepared by using 15 %w/w PVP K-90 showed the presence of needle-shaped crystals on the surface of films. Although, terbutaline sulfate completely dissolved when mixed to form the casting solution. Some of it might separately precipitate from the matrix during the subsequent process of solvent evaporation. It was probably due to the solubility of terbutaline sulfate in water was higher than its solubility in PVP K-90. Increasing the amount of PVP K-90 to 15 %w/w required higher amount of water to dissolve this polymer. Thus the less water remained to dissolve terbutaline sulfate and solubility of drug in polymer matrix was decreased. The results in this study indicated that the films using lower concentration of chitosan exhibited higher amount of crystals than those using higher concentration of chitosan did. It might be due to higher concentration of chitosan decreased free volume for polymer chain mobility and disturbed the rearrangement of crystals.

In this study chitosan and PVP K-90 were hydrophilic polymers. In scanning electron photomicrographic process, the high-energy electron beam used for cross-section photomicrography directly attacked on the surface of the films led the film to swell especially at the higher magnification.

Infrared Spectrometry

Infrared spectra of polymer-polymer blend and drug-polymers blends were examined to study the interaction in the formulation.

IR spectra of polymers blend and drug-polymers blends exhibited the combination of the characteristic band of those blends. From the results, it could be concluded that the interactions between polymers, drug and polymers were hardly

seen. The terbutaline sulfate transdermal patches could not be directly ground with finely powder of potassium bromide. Since, films tended to adhere with potassium bromide and could not be tabletted into disc. Thus, in this study the terbutaline sulfate transdermal film was directly used for observation in IR study. However, Infrared spectra of terbutaline sulfate transdermal patches did not reveal any peak of IR spectra. It might be due to sample was directly scanned in FT-IR case and concentration and thickness of sample were not appropriate that might affect the absorption of IR.

Powder X-ray Diffraction Analysis

The crystallinity of chitosan powder and film was investigated by X-ray diffraction analysis. Chitosan was in amorphous form because there was no prominent peak. The crystallinity of salt form chitosan film was less than neutral form of chitosan powder. This observation showed that the film formation altered the lattice structure of chitosan. The reflection of anhydrous crystalline at 15° 2θ could not be observed so the intensity of hydrated crystalline at 10.4° 2θ of different grades chitosan was used to estimate their moisture sorption. The higher intensity of hydrated crystalline could be attributed to higher crystallinity. The higher crystallinity could absorb lower moisture content. The result from this study indicated that shorter chain length chitosan powder showed the higher intensity of hydrated crystalline. It could be estimated that shorter chain length chitosan powder absorbed lower moisture content. This estimation from chitosan powder did not agree with the result of moisture absorption/loss of terbutaline sulfate transdermal patches. It might be due to chitosan in transdermal patches was in the form of chitosan salt and had the structural change due to film forming. On the other hand, no difference in the peak intensity of hydrated crystalline of chitosan film was evident but the results from different grades chitosan transdermal patches showed the different moisture absorption/loss data. It

might be because there were several parameters influencing on the moisture absorption/loss of transdermal patch. The difference in degree of moisture sorption possibly depended on crystallinity, chain length and degree of acetylation (Sawayanagi, Nambu and Nagai, 1982c).

Differential Scanning Calorimetry

The endothermic peak temperature of pure polymers in this experiment differed from the reported value because of a difference in either a given condition to scan or a molecular weight of polymer itself. The various endothermic peak temperatures of pure substances, polymer-polymer blend, drug-polymers blends and terbutaline sulfate transdermal patches indicated differences in molecular weight, chemical structure and structural arrangement.

Thermal property of the patches indicated that in the dry state different amount of polymer helped the film to acquire different structural arrangements and chain conformations. This was also reflected in inconsistent enthalpy changes.

From the endothermic peak temperature of plasticized and unplasticized SEACURE 243 films, it was found that lactic acid and glycerin affected the structural arrangement of film. Whereas, endothermic peak temperature of plasticized PVP K-90 film did not show significant difference from pure PVP K-90.

The DSC thermogram of SEACURE 243 and PVP K-90 blend film did not show peak separation. The peak temperature of these polymers blend was higher than the peak temperatures of SEACURE 243 film and PVP K-90 film. Qurashi et al. (1992a) prepared modified chitosan membranes by blending with PVP. Those

membranes were characterized by differential scanning calorimetry. It was found that increasing the amount of PVP in the blends led the DSC peak temperature shifted toward higher values. This suggested that the blends in the dry state were made up of stiff polymer chains and their stiffness increased as the amount of PVP in the blend was increased. The addition of PVP in chitosan membrane facilitated intermolecular hydrogen bonding and bound the two biopolymer chains together, therefore further restricting chain mobility in the dry state.

The DSC peak temperatures of terbutaline sulfate from drug-polymers blends and terbutaline sulfate transdermal patches were different from peak temperature of pure terbutaline sulfate. It was possible that preparing drug-polymers blends and terbutaline sulfate transdermal patches led to the change of terbutaline sulfate lattice structure. It might be present of new polymorph or combination of two polymorphs of terbutaline sulfate.

In-vitro Skin Permeation Study

The skin permeation-time profiles of all terbutaline sulfate transdermal patches indicated that the skin permeation kinetic pattern seemed to follow the zero order, Higuchi's or first order kinetic. The results had no significant difference. It might be due to the small flux of drug permeated through shed snake skin. Form microscopic observation, it could be seen that surface topography of these terbutaline sulfate transdermal patches was smooth and nonporous. Thus the process of drug delivery from terbutaline sulfate transdermal patch could be due to diffusion of drug through polymer matrix.

The effect of molecular weight of chitosan on the skin permeation of terbutaline sulfate indicated that higher molecular weight led to lower skin permeation. This observation could be attributed to the higher degree of chain length, which required a high energy of activation for the motion of polymer chain and also a greater frequency factor in response to the increase in the entropy of activation (Chien, 1992).

The skin permeation rate from system using higher amount of chitosan was lower than that from system using lower amount of chitosan. It could be due to the more chitosan content produced less polymer chain mobility and hence decreased diffusion of drug in the polymer matrix. However, there was no difference in the skin permeation rate of films prepared by using 15 %w/w PVP K-90 and different amounts of chitosan (Formulations BB_1-BB_4). It could be because the amount of chitosan was slightly low when compared to that of PVP K-90, thus the higher amount of PVP K-90 shadowed the effect of the amount of chitosan. Increasing PVP K-90 concentration in the system prepared using the same chitosan concentration also decreased the skin permeation rate of transdermal patches. The reason for the effect of PVP K-90 concentration on skin permeation rate was also the same as that of chitosan concentration. The viscosity of polymer matrix also affected the diffusion coefficient of drug in the matrix (Baker, 1987). It could be seen that viscosity of prepared casting mixture increased when chitosan and PVP K-90 concentrations in the formulation were increased.

The crystallites introduced regions of very low diffusion relative to the diffusion in the surrounding amorphous structure, which led to a significant reduction in gross polymer diffusivity (Chien, 1992). However, the result from X-ray diffraction analysis of chitosan films revealed that there was no obvious difference in

the crystallinity of three grades of chitosan films. So, the other parameters should be concerned in the diffusion of terbutaline sulfate from transdermal patch.

On the basis of pharmacokinetic parameters, the drug delivery rate through the skin required to achieve an effective plasma concentration was calculated to be 40.5 μg/hr, using an equation described by Guy and Hadgraft (1986). Terbutaline sulfate transdermal patch that gave the fastest skin permeation was formulation A_1. The skin permeation rate was 1.202 μg/hr/cm^2. Films of terbutaline sulfate as 1.77 cm^2 showed a lower skin permeation and used of 35 cm^2 patch was required to provide the adequate amount of drug into the systemic circulation.

CONCLUSIONS

Chitosan could blend with PVA and PVP K-90 to form transparent and flexible film. Variation on amount and molecular weight of chitosan and amount of polyvinyl derivatives affected to chemical structure of the obtained transdermal patches, thereby influencing the physical characteristics, mechanical properties and finally the skin permeation of drug.

From this study, it was concluded that the self-adhesive terbutaline sulfate transdermal patch could act as controlled delivery device for 24 hours period. The addition of glycerin tended to improve adhesiveness of the transdermal patch prepared by using chitosan and PVP K-90 blend.

From the *in vitro* skin permeation study, films of terbutaline sulfate as 1.77 cm^2 showed a lower skin permeation and used of higher surface area was required to provide the adequate amount of drug into the systemic circulation.