CHAPTER IV

Discussion and Conclusions

Film casting formulation

In acidic evironment, chitosan presents positive charge therefore it is good compatibility with the solution of non-ionic polymers including PVA, PVP K 90, HPMC 15, MC 15 and corn starch. Apparently, all casting solutions showed no sign of phrase separation during the preparation. Due to the yellowish color of chitosan, the obtained casting solutions were in yellowish color. Therefore, all casting solutions yielded yellowish cast films.

Free film characteristics and mechanical properties

Surface photomicrographs indicated that all free films obtained in this study were microporous membranes.Those of the membranes were charactrized to be soft and tough films with the low to moderate ultimate tensile strength and very high percent elongation at break (>20%).

Both the moderate ultimate tensile strength and percent elongation at break of membranes H15 and H18 indicated that these two membranes were strong membranes.

Membrane C17 having the low ultimate tensile strength and moderate percent elongation at break was characterized to be the soft and weak membrane.The physical characteristics of the obtained free films were depended on the chemical compositions in the casting solution to form film. The chemical compositions as one of the important factor could determine the molecular order and morphologic characteristics of free film objects, specially,

the crystallinity, the degree of chain orientation or alignment. The difference in the membrane structure mainly due to the difference interaction involving type and quantities of components in each crosslinked chitosan-polymer system influenced on the polymer free film characteristics and properties. The course of events leading to the formation of a film by evaporation of solvent from a polymer solution might be inferred from the following discussion. As the solvent evaporates, the polymer content is increasing. Since the number of molecules of solvent per molecule of polymer is decreasing as evaporation proceeds, desolvation of the polymer is continuously effected. At some point during the evaporation, three or more active centers per macromolecule are bared by desolvation, thereby, a three-dimensional gel structure can form and the solution goes through a semigel phase. The dry film therefore represents the final stage of gel-like aggregation resulting from the progressive evaporation of the volatile solvent. If a plasticizer is present in the fluid composition, it remains in the final film because it is not volatile. Being a solvent, it is bound, in a statistical sense, to a certain fraction of the active centers on the polymer macromolecules. The plasticizer prevents more complete aggregation of the polymer macromolecules to an extent by reducing the relative number of polymer-polymer contacts, determined by its amount and solvent strength and thereby relieving the rigidity of the trusslike three-dimensional structure to form a soft and flexible film. Considered in the morphology aspect, crystallization starts when nuclei develop here. The nuclei form as a few chain segments in the randomly coiled and entangled mass line up and arrange themselves into an orderly lattice. Crystallization proceeds as these nuclei grow into crystallites until all the solvent has evaporated. When neighboring crystallites grow, quite a few segments of chains forming these crystallites cannot be incorporated into them but remain outside in a disordered state. Being trapped between crystallites immobilizes such segments and

prevents them from aligning and fitting into a lattice, therby, these segments are into their disodered conformations as amorphous regions. Overall, each crosslinked chitosan-polymer system could provide its individual structure arrangements and chain conformations resulting in the individual polymer free film characteristics and properties. (Doolittle, 1954, Martin, 1993)

The presence of plasticizers not only changed free film characteristics in a more softer and ductile form but they also resulted in a decrease in the ultimated tensile strength and an increase in the elongation at break of free films. In addition, plasticizers could reduce tackiness of free films to the glass surface. At the molecular level, plasticizers caused an increase in free volume of polymer network due to interposing themselve between the polymer chains and interacting with the forces with hold the chains together thereby extending and softening the polymer matrix. However, the degree of such effects could be vaired in given system by the amount of plasticizer used. PEG 1450 and triacetin had individual degree of compatibility in a given system, thereby producing various free film characteristics and mechanical properties. Plasticizer effect on the mechaincal parameters may not be the same of each plasticizer and hence unpredictable.

As the more concentration of crosslinking agent, the tensile strength of membranes increased. The reason was that the more crosslinking reaction via the more intermolecular and intramolecular crosslinking maked a contribution to enhancing the tensile strength. Unfortunately, the more crosslinking could promote rigidity to the polymer network, thereby resulting in the more brittleness free films. However, extensive crosslinking in a crystalline polymer might cause loss of crystallinity with accompanying deterioration of the mechanical properties. When this occurs, the initial trend of mechanical properties might be toward either enhancement or deterioration, depending on

the degree of crystallinity of the given system (Billmeyer, 1971). These reasons were in agreement with the mechanical results of membranes containing PEG1450. Because of the long chain polymer and film-forming property of PEG 1450, it could be crosslinked via hydrogen bond with crosslinking agent and/or others polymer so that membranes containing PEG 1450 could exhibit tensile strength in higher or lower than unplasticized membranes. Triacetin, being smaller in size than PEG 1450, could interpose itself between polymer chains to act as barrier to interrupt the crosslinking, thereby causing in lower tensile strength of plasticized membranes in comparison with unplasticized membranes.

Water sorption

Generally, membrane readily swelled or dissolved when immersed in aqueous environment. Wet membranes became rupture after exposure to water at 37°C might be discussed that these membranes had lower water resistance and/or high sensitivity to temperature changes. The lower water resistance was due to the uncounterbalance between the elastric forces in the network structure acting to hold them together and the ability of the solvent to move the chains apart. Under equilibrium conditions, the swelling might be regarded as the expanion of the network structure by the solvent molecules up to point where the elastric forces in the network counterbalance the ability of the solvent to pry the chain apart. The interaction of solvent with polymers might be critical in the cases (Winding and Hiatt, 1961, Florence,1984).

With the lower amount of crosslinking agent in the given systems, when the membranes were immersed in aqueous environment, PEG 1450 might leach out from the membranes due to the hydrophilic nature of PEG 1450. These void volumes would be expected to be occupied by external

solvent diffusing into the membranes, thereby raising the water sorption ability. On the other hand, with the higher amount of crosslinking agent in the given systems, the presence of PEG 1450 possibly encouraged the crosslinking to take place, thereby resulting in the more continuous network structure. Thereafter, the amount of water absorbed could reach a limit beyond which no furthur swelling occured so that the water sorption decreased. In addition, these reasons were in agreement with the surface morphology of the membranes containing PEG1450 as compared to the unplasticized membranes. The surface photomicrographs of the membranes with PEG 1450 exhibited less porosity and narrower pore-size than the unplasticized membranes.

The membranes with triacetin exhibited lower water sorption ability might be attributed to the interstitials filling of triacetin, being small in size, into the polymer network. Again, water sorption which closely related to degree of swelling had been reported to indicate that the degree of swelling was governed by crosslinking density, temperature, molar volume of the solvent and the polymer-solvent interactions (Thacharodi and Rao, 1993).

Infrared spectra

Chitosan and cellulose had linear structures due to β-1,4 glycosidic bonds. The difference between infrared spectra of chitosan and cellulose around 3520-3400- cm^{-1} possibly be due to N-H stretching of chitosan. The disappearance of the 3451-, 1094-, 665 cm^{-1} bands, all of which were reported to be related to crystallization of chitosan, and the 1598 cm^{-1} band in the crosslinked chitosan-polymer membranes indicated that there were structural changes in the crosslinked chitosan-polymer membranes. The changes of the band shape and the lower frequency shift of the band in the O-H

stretching region in the crosslinked chitosan-polymer membranes indicated that there might occur stronger hydrogen bonding interactions in the crosslinked chitosan-polymer membranes since hydrogen bonding caused the stretching vibration to shift to a lower frequency (Miya, Iwamoto and Mima, 1984). In addition, the IR spectra clearly indicated the presence of a Schiff base type (RCH=NR) of crosslink in the crosslinked chitosan-polymer membranes.

Differential scanning calorimetry

By DSC method, the difference in endothermic peak temperature of pure polymers in this observation from those of reports might be due to a difference in either a given condition to scan or a molecular weight of polymer itself. The various endothermic peak temperatures of the crosslinked chitosan-polymer membranes clearly indicated that the membranes had different structural arrangements. In addition, the membrane thermograms also indicated that the membranes had structural changes which were due to the blending and crosslinking in the membrane systems.

For crosslinked chitosan-PVA membranes, the results could be discussed on the basis of the effect of plasticizers. Again, the molecular weight of triacetin was 218. Small molecule like triacetin could interpose itself to introduce defects into the crystal lattice and prevent to a small extent the formation of crystallites in the membrane, thereby lowering the melting temperature of the membrane. On the other hand, the incorporation of PEG1450, being larger in size than triacetin, into the membrane did not significantly affect the crystalline melting temperature, indicating that PEG1450 did not cause defects into the crystal lattice. Thus, it was reasonable to conclude that the observed differences between the DSC thermograms were due to changes in the crystal structure of these samples.

Porosity

The difference in the membrane porosity could be attributed to the influence of the formulation components including the type and concentration ratio of the blend polymer, type of plasticizer and the concentration of the crosslinking agent. This means that both the type and concentration ratio of the blend polymer which was crosslinked and blended in the membrane preparation could offer the difference in the membrane structure. PVA, PVP K-90, HPMC15, MC15 and corn starch are compounds that illustrate the marked difference in chemical nature, configuration and the rigidity of the molecule (Winding and Hiatt, 1961). The chemical structure of PVA consisting of a carbon-chain backbone with alternating hydroxy groups favors the formation of crystalline aggregates whereas cellulose including HPMC15 has the rigid molecules. Starch and cellulose approach each other in rigidity but differ in the shape of the molecules which cause widely different packing of the polymer chains. Because of the nature of the blend polymer itself, it could generate various pore characteristics when interact with other components. Due to the intrinsic chemical structure of PVP K-90, HPMC15, MC15, and corn starch, their crosslinked chitosan-polymer membrane structure might be loosen but the presence of plasticizer, triacetin or PEG1450, could be interpose itself to the interstices, resulting in either the narrower pore size or the less porosity (Guo, 1993). The incorporation of PEG1450 into the membranes resulting in various pore characteristics could attribute to its plasticizing and film forming properties which could simultaneously occur(Samuelov, Danbrow and Friedman, 1979, Jain, Vyas and Dixit, 1990). However, the higher porosity the membranes, the more the cumulative ISDN permeated, and the larger the pore size, the more the cumulative ISDN permeated. This was in general agreement with the

observations of several workers (Samuelov, Danbow and Friedman, 1979, Jain, Vyas and Dixit, 1990).

Characteristics of ISDN transdermal patch

The ISDN transdermal patches prepared in this work showed satisfactory transdermal patches of light, thin dosage forms characteristics. Drug reservoir was the uniform suspension of unleachable viscous liquid. However, the patch was difficult in preparing in the process of mounting the membrane on the drug reservoir. Industrially, free films can be made by several suitable techniques. The operation of manufacturing process for the production of this ISDN transdermal patches are also easy to achieved.

Permeation studies

The maximum correlation coefficient in the relationship between cumulative drug permeated against time of all membrane-moderated transdermal patches in the studies could indicate that the ISDN permeated was predominantly controlled by pore mechanism. By the means, ISDN was presumed to diffuse through microchannels within the membrane structure. Thereby, the permeability could be determined by the average pore size in relation to the molecular volume of ISDN. This reason was in agreement with the surface photomicrographs of the membranes used as rate-controlling membranes in the transdermal patches.

The sequence of drug permeation in the in vitro skin permeation studies could be described in two consecutive steps: The release of drug delivered from the transdermal patch and the permeation through the skin barrier by the passive process to the receptor medium. The first phase, showing the lower permeation rate of each cumulative ISDN permeated

profile of each ISDN transdermal patch could attribute to the effect of skin uptake on the permeation of drug through shed snake skin (Chien, 1987). By the means, over a ten-hour period, the rate of ISDN delivery seemed to be controlled in part by the shed snake skin. After the shed snake skin was saturated with the drug molecules, the rate of ISDN delivery did not alter by the effect of skin uptake. This was contribution to the higher permeation rate of drug delivery of the second phase (10-24 hours) than the first phase.

Membrane-moderated transdermal patches containing unplasticized membranes A14 and A15 as rate-controlling membranes showing higher cumulative ISDN permeated through shed snake skin as compared to transdermal patches containing membranes A11, A12, A17, or A18 as rate-controlling membranes were attributed to either higher porosity or larger pore size in the rate-controlling membrane structure.

Within the plasticized membranes obtained from crosslinked chitosan-PVA blended which were used as rate-controlling membranes in the transdermal patches, their morphological characteristics showing the difference in both porosity and pore size in the membrane structure were contributory to the difference in the cumulative drug permeated.

Crosslinked chitosan-corn starch membrane C2 plasticized with PEG1450 showed more porosity so that it was reasonable in agreement with the high cumulative ISDN permeation result of transdermal patch containing C2 as rate-controlling membrane.

Both the less and the porosity and narrower pore size of membrane H18 could contributed to the less cumulative ISDN permeated through shed snake skin of membrane H18 transdermal patch.

Conclusions

For the application of chitosan as membrane in TDDs, it was found that chitosan not only enabled to form a transparent crosslinked chitosan-polymer membrane with other polymers and crosslinking agent but the obtained membrane also presented good mechanical properties.

Variation of the membrane components had a marked influenced on the obtained membrane structure which mainly influenced on the physical and mechanical properties of the membranes. Finally, these changes in turn affected the permeation of drug.

The incorporation of plasticizers into the membranes generally increased film flexibility whereas increasing the amount of crosslinking agent generally resulted in a decrease in water sorption ability, percent elongation at break and an increase in the ultimate tensile strength of the membranes.

The porous morphology of the obtained crosslinked chitosan-polymer membranes were also in agreement with the permeation study to conclude that ISDN could be transported through crosslinked chitosan-polymer membranes mainly via microchannels within the membrane structure.

From this investigation, it was indicated that crosslinked chitosan-polymer membranes could be used as release rate-controlling membrane in isosorbide dinitrate transdermal patch.