CHAPTER I

General Background

Introduction

In the management of angina pectoris , vasodilators such as nitrates have been found to be important chemicals available. The nitrates are originally throught to act as coronary vasodilators with no effect on total coronary blood flow.

Isosorbide dinitrate (ISDN), an organic nitrate, is one of the nitrate agents for the acute treatment of angina pectoris and for long-term prophylactic management of angina pectoris. ISDN shows poor bioavailability after oral administration and short plasma half life about 0.5 to 1.5 hours (Reynolds, 1989, Moffat, 1986, Cleveland et al., 1992). Absorption of ISDN through the skin is also noted (Bhalla and Khanolkar, 1985, Reynolds, 1989, Gilman et al., 1990).

The design of controlled-release dosage form for transdermal drug delivery is a subject for interest. It can offer many advantages such as avoidance of the variables associated with gastrointestinal absorption, avoidance of first-pass metabolism in the liver, ease to administer and allowance rapid termination of treatment, if required, by removal of the device from the skin surface, etc(Parikh, Babar, and Plakogiannis, 1984, Livingstone, and Livingstone,1988, O'Neill and Deasy,1988).

Recently, several researches have been studied the use of biocompatible polymers as film-forming materials to control the release and administration of drugs. Greater attention is likely to be paid to the use of biopolymer. In this case, chitosan is a biopolymer, which is a linear polysaccharide formed by β-1,4 linkage of D-glucosamine and N-acetylglucosamine residues. Chitosan is unique with a polyamine character which makes it a water-soluble polymer at acidic pH, positively charged and easily modified chemically (Lower, 1984, Skaugrud, 1989, Pelletier et al.,1990).

Chitosan is biocompatible with living tissue such that there is substantially no adverse tissue reaction. Chitosan solution can be cast to form film. Chitosan free film is a polymer network containing contiguous channels throughout the network.

Not only did the applications of chitosan on sustained release of drug were investigated in many studies but the mechanical properties of its free film were also studied and noted as well (Miyazaki,Ishii, and Nadi,1981, Miyazaki et al., 1988, Candinal et al.,1990, Averbach, 1977, Kienzle-sterzer, Sanchez, Karalekaset al., n.d., Kienzle-sterzer, Sanchez and Rha, n.d.).

In the past, drug containing film so called "matrix" were studied in many investigations by using various film-forming materials. According to unique film-forming properties of chitosan and its production from chitin contributes to the development of useful by-products from the shellfish transformation industry, chitosan was used in many applications, but no such application used chitosan free film as a rate-controlling membrane to regulate drug release in pharmaceutical dosage form. Therefore, this study was aimed to stydy with a view to evaluate the feasibility of chitosan membrane for use as

a rate-controlling membrane in the design of ISDN transdermal drug delivery system.

Objectives of this study

1. To design and develop a controlled release transdermal drug delivery system of ISDN using chitosan as release rate-controlling membrane.

2. To study the effect of types and concentration of blend polymer on the physical and mechanical properties of free films of crosslinked chitosan-polymer blend membrane.

3. To study the effect of concentration of crosslinking agent (glutaraldehyde) on the physical and mechanical properties of free films of crosslinked chitosan-polymer blend membrane.

4. To obtain information on the effect of various plasticizers (PEG 1450,triacetin) on the physical and mechanical properties of free films of crosslinked chitosan-polymer blend membrane.

5. To investigate and compare the amount and mechanism of drug permeation from the designed dosage form by in-vitro skin-permeation study.

Literature Reviews

Membrane-Moderated Transdermal Drug Delivery Systems.

(Parikh, Babar and Plakogiannis, 1985, Chien, 1987, Hadgraft and Guy, 1989)

A. Formulation

This system represents five elements as follow:

1. Backing substrate

It is an impermeable film or membrane as backing support of the system. It must be flexible and provide a good bond to the drug reservoir in order to prevent drug from leaving the dosage form through the top. The most commonly used backing materials are polyester (Mylar)-polyethylene coextruded films.

2. Drug reservoir

The drug solids are either dispersed homogeneously in a solid polymer matrix such as polyisobutylene adhesive or suspended in an unbleachable, viscous liquid medium like silicone fluid to form a pastelike suspension. The system's reservoir must contain a constant activity level of drug and in the required amount for the prescribed drug program.

3. Rate-controlling membrane

It can be either a microporous or a nonporous polymeric membrane with a defined drug permeability. For example, ethylene-vinyl acetate copolymer or microporous polypropylene films have been used as membranes in transdermal devices.

4. Contact adhesive layer

This layer is a thin layer of drug compatible, hypoallergenic, pressure-sensitive adhesive polymer which is placed on the external surface of

the polymeric membrane and may be applied to provide intimate contact of the transdermal therapeutic system with the skin surface. Generally, the materials must provide desired the adhesive-cohesive properties, peel strength, tack, creep qualities of adhesives and provide greater TDDs and skin compatibility. For example, Alza uses polyisobutylene as adhesive in most devices.

5. Protective peel strip

The peel strip is a sheet that serves as a protectant for TDDs from the environment until use and carrier for an adhesive layer. It prevents the loss of drug that has migrated into the adhesive layer during storage and protects the finish device against contanination. The peel strip must be easily removed from the adhesive layer before use. The commonly used peel strip materials are fluorocarbon polyester film, silicone foil and paper foil combination.

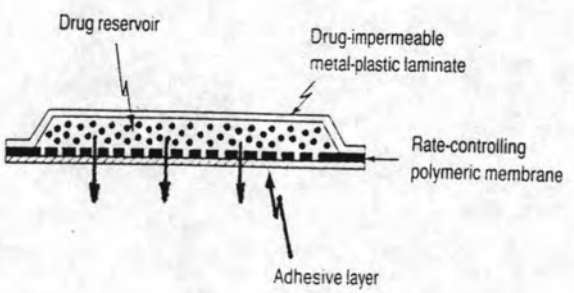

Figure 1 Cross-section view of the structural components of a transdermal drug delivery system in which drug release is controlled by membrane permeation.

B. Mechanism

For simplicity,the drug in the reservoir is formulated in excess so as to maintain constant thermodynamic activity whilst the device is releasing drug.

A molecule diffusing from the reservoir can explain as following steps:

a. Dissolution into the dispersion medium of the reservoir.

b. Diffusion within the dispersion medium

c. Partitioning into the membrane

d. Diffusion across the membrane

e. Partitioning into the receptor medium

f. Diffusion across the stagnant diffusion layer.

Diffusion across the membrane is the most important transfer process and the one which ultimately controls the effectiveness of the device (Illum and Davis, 1987).

Generally, the release must involve the initial burst effect and boundary conditions. Therefore, the release of drug can be described by the appropriate equation of Fick's second law of diffusion (Berner, 1985). This equation is also used to describe the movement of drug either from the dosage form or through skin.

$$\frac{\partial c}{\partial t} = \frac{D(\partial^2 c)}{\partial x^2}$$

Under this device, rate-controlling membrane is the film that controls the rate of drug flux from the device. The release rate can be modified by varying the polymer composition, the permeability coefficient, and the thickness of the rate-controlling membrane and adhesive. Theoretically, the

release rate is controlled by diffusion process and defined as follows (Chien,1985).

$$\text{Release rate} \quad \frac{dQ}{dt} = \frac{[K_{m/r}K_{a/m}D_aD_m]C_r}{[K_{m/r}D_mh_a + K_{a/m}D_ah_m]}$$

where Q = the amount of drug release at time t

C_r = the drug concentration in the reservoir

D_m, D_a = diffusion coefficients in the rate-controlling membrane and in the adhesive layer respectively

h_m, h_a = the thickness of the rate-controlling membrane and adhesive layer, respectively

$K_{m/r}, K_{a/m}$ = the partition coefficients for the interfacial partition of the drug from the reservoir to the membrane and from the membrane to the adhesive respectively.

C. Kinetic evaluation

(Robinson and Lee, 1987, Chien 1987, Hadgraft and Guy, 1989, Bronaugh and Maibach,1989)

In consideration, the transdemal patch evaluation must be run step by step. Primarily, in vitro evaluation is based on either drug release kinetics or skin permeation kinetic studies. Both kinetic studies can be evaluated using the same diffusion cell assembly, under identical condifions. For skin permeation kinetics studies. it is carried out by mounting the skin used as a model membrane on permeation cell. The drug delivery systems are then applied with their drug-releaseing surface in intimate contact with the outer surface of the skin. The skin permeation profile of drug is followd by sampling

the receptor solution at predetermined intervals and assaying drug concentration in the sample by a sensitive analytical method.

Again, the in-vitro release profiles of drug from transdermal patches are also studied following the same procedure, except that no skin sample is used.

1. Skin model

A varity of model membrane has been used for transdermal research such as human cadaver skin, animal skin and synthetic membrane. Human skin is the best model membrane. The use of human skin for in vitro penetration studies is limited because human skin is often difficult to obtain, expensive, difficult to store and variable in penetration properties depending on the body site (Hadgraft and Guy,1989,Itoh, Magavi et al.,1990).

Excised animal skins also have variable properties depending on preparation method, skin area and animal species. The skin of common laboratory animals including rabbit, rat, mice, guinea pigs is usually more permeable than human skin, partly because of the greater number of hair follicles (Kligman, 1983).

So, there is no animal skin that completely mimics the penetration characteristics of human skin.

As a third alternative, artificial membranes designed to mimic the barrier properties of the skin have been used with some success in many investigations. However,a suitable synthetic membrane presents no significant diffusion barrier effects on the transport of a test compound from a formulation into the receptor fluid. Thereby, the use of artificial membranes in transdermal research is limited because they lack keratinized proteins and lipids which are primary components in the stratum corneum of mammalian skins. So, certain

sunthetic membranes may be unsatisfactory for the permeation studies (Wu et al., 1992).

Recently, many investigations have placed attention to use shed snake skin of *Elaphe obsoleta* (black rat snake) as a model membrane of transdermal research (Itoh, Wasinger et al.,1992).

Shed snake skin is a nonliving pure stratum corneum with no hair follicles. Itoh, Wasinger et al. (1992) reported that there were similarities between human skin and shed snake skin of this species in terms of structure composition, permeability of several compounds and the functional group contribution to the permeability.

Comparison between human skin and shed snake skin were shown in Table 1 (Itoh,Xia et al.,1990).

Table 1 Comparison of Thickness, Lipid Content, and Water Evaporation Rate Between Human Stratum Corneum and Shed Snake Skin

	Human stratum corneum	Shed snake skin (*Elaphe obsoleta*)
Thickness	13-15 μm	10-20 μm
Lipid content	2.0-6.5 %	6%
Water evaporation rate	0.1-0.8 mg/cm^2 hr	0.15-0.22 mg/cm^2 hr

The potential of shed snake skin as a model membrane had been reported by several workers (Akazawa et al.,1989, Itoh, Xia et al.,1990, Itoh, Magavi et al.,1990, Bhattachar et al.,1992, Itoh, Wasinger et al., 1992).

Shed snake skin appears to be a useful alternative to animal skin in assessing the potential for transdermal drug delivery that it has many properties similar to those of the human stratum corneum, and is comparable to some other membrane that have been used for in-vitro evaluation. It is also easy to obtain, store and use.

2. Apparatus used for in-vitro permeation study

In recent years, interest in the development of transdermal dosage forms has grown exponentially. Specialized diffusion cell are still popular during the development stages to study transfer kinetics. These cells are available in various types and volumes and use with associated accessories. One of the most widely used diffusion cells is the Franz diffusion cell. However, because of differences in cell design, it is difficult to compare the results reported from different laboratiories using defferent diffusion cell systems. Several diffusion cell designs and its drawback had been summarized, described and addressed by several workers (Bronaugh and Maibach, 1989, Arom Tattawasart,1992).

On review of the diffusion cell designs, it was found that a two-compartment diffusion cell design was the common features to many of the designs.

Nowadays, the USPXXII addresses that standard apparatus for the determination of release rate from TDDs present in three different types.

The first type is a modified USP apparatus I,where the basket is replaced with a hollow stainless steel cylinder. TDDs is attached to the surface of the cylinder and immersed in the dissolution medium.

The second type is the USP apparatus II, paddle method, where an appropricate disk or cell TDDs attached at the bottom of dissolution vessel containing the dissolution medium.

The third type, a reciprocation or rotating disk, where the TDDs is attached to the bottom of the disk, which is placed in a 25x150 cm testtube containing the dissolution medium.

In consideration, official system used for evaluation of TDDs has many advantages that it is to allow a laboratory that has existing dissolution equipment to conduct diffusion studies. In addition, it also reduces investment in new equipment.

The later step evaluation is the in-vivo study of drug bioavailability in human volunteers using the optimal formulation developed in the in-vitro study. Systemic bioavailability is indicated by the plasma drug concentration after a long time transtermal application.

Free Film

A. Formulation

Typically, casting solution formulation comprises as following (Lachman, Lieberman and Kanig, 1976, Aulton,1988, Pillai, Babar and Plakogiannis, 1988).

1. Polymer as film-former
2. Solvent
3. Plasticizer
4. Other additives

1. Polymer

A wide variety of materials to act as film-former have been investigated for film casting. The characteristics of the polymer are governed by the structure, properties of its macromolecules.

Ideally, the film-forming polymer should have the following qualities:

1. Sufficiently soluble in solvents convenient for the casting operation intended.
2. Capable of producing a strong continuous film that is smooth and elegant.
3. Stable in the presence of heat,moisture,air.
4. Nontoxic,inert and requiring no complicated casting procedures.

Polymer as film former used in pharmaceutical industries were broadly classified into three groups as cellulose derivative, polyvinyl derivative and acrylic resin.Most commonly used are the derivates of cellulose

such as hydroxypropylmethylcellulose, methylcellulose and ethylcellulose. These have the advantages of forming clear,non-tacky, mechanically strokinilms from a wide variety of suitable solvents (Lachman, Lieberman and Kanig, 1976).Acrylic resin are also used extensively in the film formulations and widely prepared to be the polymeric colloidal dispersions which commercially available under various trade name, for example, Eudragit E, Eudragit L, Eudragit S and Eudragit NE.

According to the distinct characteristics of the polymer itself, casting solution is in consideration to be designed and used at high polymer concentration as possible in order to achieve rapid build-up of film thickness.

2. Solvents

In the past, the early polymer used as film forming were invariably dissolved in an organic solvent. Recently, modern technique have been interested to rely on water as a solvent in order to circumvent the restrictions imposed on the use of organic solvent.

The most solvents which have been employed in film-casting technique are water, ethanol, methanol, isopropanol, chloroform, acetone and methylene chloride, either alone or in combination. Water has been considered more seriously in recent years as a primary solvent.

The primary function of a solvent system is to convey the film-former uniformity. In addition to the distinct characteristics of the polymer itself, the degree of solvation influences the viscosity of the casting solution and the type of solvent used often influences the manner in which the film is formed. As solvent evaporates, a polymeric gel forms and the manner in which the polymer chains orient themselves is influenced by the type of solvent used as

well as the rate of the film formation. The influences affects on dried films properties such as permeability.

3. Plasticizers

Plasticizer is defined as relatively low molecular weight substances of low volatility. Plasticizer is generally added to film casting formula to modify the physical properties of the resulting film. At the molecular level, a plasticizer must interpose itself between the polymer chains and interact with the forces which hold the chain together thereby extending and softening the polymer matrix. Thus, such activity imparts flexibility and reduces brittleness by relieving molecular rigidity.

However, selection of a plasticizer can be considered on the basis of compatibility with the film-former and the other additive within the film. The other basic requirment is permanence which dictates that it has low vapor pressure and low diffusion rate within the polymeric film. The most effective plasticizer generally closely resemble in the structure the polymers they plasticize.

The concentration of plasticizer in the casting solution formula depends on many factors including the nature of the polymer and types of other additive present. Generally, plasticizer is normally used in lower concentration than the film-former. Most often, plasticizers are used at levels of 1 to 50% by weight of film-former.

Plasticizers commonly used in film formulation can be conveniently devided into three groups that was described below (Florence,1984).

3.1 Polyols

Plasticizers which are included in this group are glycerol, propylene glycol and the polyethylene glycols of molecular weight 200 to 6000. All plasticizers are used as plasticizers for the water soluble

polymer.All are miscible or freely soluble in water and,with the exception of the high molecular weight PEG, all are hygroscopic.

3.2 Organic esters

Included in this group are glycerol triacetate (triacetin), the citrate esters, the phthalate esters and dibutyl sebacate. All are liquids miscible with most organic solvents but of limited solubility in water. Of the group both triacetin and triethyl citrate have a high affinity for water.

3.3 Vegetable oils and glycerides

Castor oil and the acetylated monoglycerides are included in this group. Castor oil is liquid miscible with many organic solvents. The distilled acetylated monoglycerides are modified fats of high purity which are soluble in most common organic solvents.

Generally, it is found that plasticizers such as glycerol, propylene glycol, the polyethylene glycols and triacetin are often used with aqeuous formulations. On the other hand, the less water soluble polymers are best plasticized by organic esters.

Indeed, it was also noted that mechanical properties of plasticized films showed a decrease in the Young's modulus of elasticity, an increase in the elongation at break and decrease in both the yield strength and the ultimate tensile strength. However, the relative changes in each of these parameters is not the same for each plasticizer and hence unpredictable.

4. Additives

Film-casting solutions may contain a variety of ingredients in addition to the film-former, plasticizer and solvent system. A number of miscellaneous materials may be added to polymer solution when unique characteristics are desired. Theoretically, the additives has major effects on the

properties of the final free film. Some additive may even change the solubility characteristics of the film, either by direct chemical reactions or by physical means.

Surfactants can be added to improve spreading properties of some film-solution, to permit use of otherwise immiscible or insoluble ingredients.

Crosslinking agent have been used in film-casting formulae in order to modify the properties of free films. Crosslinking agents used here are small sized ones such as glutaraldehyde, glyoxal, epichlorohydrin etc., which they are capable of penetrating the pores of polymer matrix and affecting the release rate. Crosslinking takes place by contacting a solution of the crosslinking agent.

As a general rule, it is noted that the higher the degree of crosslinking, the harder the material and the lower the rate of drug release. In addition, it is also stated that the higher the concentration of the agent,the slower the release and the longer the treatment, the slower the release (Hadgraft and Guy, 1989, Cardinal et al., 1990).

B. Preparation of free films

Generally, free film can be cast from polymeric solutions or polymeric dispersions. Polymeric solutions were prepared by dissolving the film-former into the suitable solvent system at the desired concentration. Then plasticizer, if required, and other additive are also added. The solution is mixed thoroughly using continuous agitation to ensure homogeneity. For polymeric dispersions,preparing technique must be devised to ensure suspension uniformity.

There are three methods which are commonly employed for preparing free films. The first method is a solvent-casting technique.Free films are

prepared by casting polymeric solution onto a suitable flat surface substrates such as glass, mercury, aluminium, stainless steel or Teflon plate. By this technique, an adjustable spreading edge, doctor blade, casting knife or the Gardner applicator can be used to control the thickness of solution applied to the casting surface (Kaning and Goodman, 1962). Thus, the thickness of free film is controlled. The solvent is subsequently evaporated by drying at room temperature or in an oven. After drying, the free film is obtained and peeled off.

The mercury substrate technique, the second method is accomplished by pouring a predetermined volume of polymeric solution on a pool of mercury. After drying, the film is removed (Lachman, Lieberman and Kanig, 1976, Patel, Treki and Vasavada, 1988).

The third method is carried out by spray casting technique. This technique has been used by several workers in preparation of free film (Allen, De Marco and Kwan, 1972, Okhamafe and York, 1983, Gordon et al., 1986, Lindstedt Ragnarsson and Hjartstam, 1989,Hjartstan, Borg and Lindstedt, 1990).

Free film is obtained by spraying polymeric solutions or polymeric dispersion mixture onto a rotating cylinder or Teflon rotating plate. While being sprayed, the polymeric solution or dispersion must be continuously stirred. After drying, the film is peeled off the cylinder or plate. This method favors latex and pseudolatex to form film.

For those methods mentioned above, the temperature and rate of drying are important to avoid the introduction of asymmetry in the membrane as the solvent is removed. Clean room conditions may be required to prevent pin-holing caused by particles of dust (Florence, 1984).

In addition to the method described above, polymer free film could be produced by melt-pressing where the polymer was placed between two metal plates and the plates then placed between two heated platens in a press. In this procedure, the polymer was squeezed into a thin film (Robinson and Lee, 1987).

For example, Nakatsuka and Andrady (1992) prepared chitosan free film by dissolving chitosan in aqueous acetic acid solution at ambient temperature and stirring. Then the solution was cast on a clean glass plate. Drying of the cast film was carried out in an air oven at 60^{o}C for 20 hours. After drying, the chitosan free film was easily separated from the glass surface.

Gordon et al., (1986) prepared Eudragit E30D free film by mixing Eudragit E30D with solution of other water soluble ingredients to provide colloidal aqueous dispersions. Then, the mixture was continuously stirred while being sprayed on a Teflon coated rotating plate. Warm air was directed at the plate to evaporate the water. After drying, the films were removed.

C. Free film evaluation

The evaluation tests designed to study the characteristics and final properties of free film are varied by many utilizing laboratory techniques including termal analysis, mechanical measurements, microscopic examination and diffusion experiments (McGinity, 1989). The most commonly used methods are thermal analysis and mechanical property evaluations. With crosslinked polymers, both evaluation tests will provide useful information (Robinson and Lee, 1987, Bhalla and Toddywala, 1988). Other test procedures are considered on the basis of needful information in that investigation.

For thermal analysis, two sensitive techniques commonly used are differential scanning calorimetry (DSC) and differential thermal analysis (DTA).DSC test reveals the glass-transition temperature (T_g)whereas the crystalline-melting temperature (T_m) is obtained by DTA method.

Mechanical properties of a free film are most conveniently determined by measuring their stress-strain relationship. Stress is the stretching force applied to the sample and strain is the elongation of sample under a given stress. Stress-strain measurements in free film are usually performed on dumbell-shaped specimens.

To ascertain reproducibity of the test, care must be taken during cutting to avoid jagged edges. The specimen is clamped in a tester such as an Instron tester that is capable of extending the specimen at a chosen constant rate and measuring the force that the specimen exerts on a load cell. Percent elongation at break is also obtained from an examination. The tensile properties may vary with sample thickness, rate of grip separation, type of grips used and the method used to measure the extension. Generally, a suitable free film or membrane required adequate strength to avoid failure in use.

Scanning electron microscopy is the microscopic examination used to study the homogeneity of a film. Free film was mounted on a metal stub, coated with gold and examined using a scanning electron microscope.

Diffusion test can be useful method for free film intended to use as a release rate-controlling membrane. This test can be utilized to compare the diffusivity of the solute through film. Two compartment glass permeation cells are useful apparatus for this study.

In addition to the evaluation methods described above, other characterization methods were stated in many testing procedures for the useful

information for free film evaluation including the determination of moisture sorption, water vapor and gas transmission, swelling measurements and solvent uptake, water sorption and the study of stability under accelerated temperature, light and humidity conditions (Lachman,Lieberman and Kaning,1976,Gordon et al., 1986, Yuk et al., 1991).

Chitosan

The occurrence, isolation and chemistry have been reviewed by Murzzarrell (1977). Chitosan is soluble in many dilute aqueous organic acids at pH levels below 6. These acids include citric, formic, lactic and tartaric acid etc (Skaugrud, 1989,1991). In acid environment, chitosan is an excellent viscosifier. It behaves as a pseudoplastic material showing decreasing viscosity at increased shear (Skaugrud, 1989). In addition,chitosan can react with dialdehyde to form hydrogels.

Averbach (1977) investigated the film-forming capacity of chitosan.He found that chitosan films were tough, clear and very flexible. This results were in agreement with the studies of Blair et al (1987).

Sawayangi, Nambu and Nagai (1982) studied the permeation of a series of drugs through chitosan hydrogel membrane. They noted that the permeation rates to decrease with increasing molecular volume of the drug. The decrease was linear in the range of molecular volume of 270 to 350 ml/mol.

Kim et al. (1992) studied the permeation of riboflavin and insulin through crosslinked PVA - chitosan blend membranes. In addition, membrane properties and swell characteristic were also investigated. The results were discussed and concluded that the permeability of both solutes through the hydrophilic membranes were controlled by a change in water content in the

swollen membrane. Crosslinking not only reduced the swelling capacity of the membrane due to the discounted ability of hydrogen bonding between water molecules and hydroxyl and amino group in the PVA and chitosan blend but also made a contribution to enhancing the tensile strength in both dry and wet states of the blend. The tensile strength increased with the amount of crosslinking agent.

Due to the same β-1,4 glycosidic bonds between chitosan and cellulose, characterization of cellulose-chitosan blend films were studied by Hasegawa et al (1992). They found that crystallinity of cellulose in the blend decreased with an increase in chitosan content. In addition, Raman spectra of the blend films showed that most of cellulose and chitosan molecules in the blend films had the same secondary structure as those in 100% cellulose and 100% chitosan films, respectively. The results also indicated the presence of interactions in the interfacial region between small domains of cellulose and chitosan.

Qurashi, Blair and Allen (1992a,1992 b) studied on preparation and characterization of PVP-chitosan blend membrane. It was found that the membranes appeared tough and flexible in dried state but softened in wet state. The stress-strain curves of the blends resumbled tough and brittle polymers. Later, they studied the permeability of low molecular weight metabolites through the membranes using a diaphram-type test cell. The results indicated that dialysis rates of all the metabolites increased as the amount of PVP in the blends was raised.

Thacharodi and Rao (1993) studied the permeability characteristics of nifedipine through crosslinked chitosan membranes. Chitosan membranes were crosslinked with different concentration of glutaraldehyde. The results showed that a definite decrease in the diffusion coefficient equilibrium

swelling, partition coefficient and permeability coefficient was observed with increasing degree of crosslinking. In addition, the data also supported the involvement of the both pore and partition mechanisms in the transport through the membranes.

Polyvinylalcohol (PVA)

PVA $(C_2H_4O)_n$ is odorless, white to cream-colored powder or granules. PVA is essentially soluble in hot and cold water. Pure aqueous solution are neutral or faintly acid. It is stable to light. It has no irritating effect up to 10% and it is non-toxic when applied to eye or skin. Acceptable in cosmetics up to 7%.PVA can be used as a pharmaceutic aid such as suspending agent, emulsifying agent. PVA can be easily prepared by evaporation to dryness an aqueous solution of the polymer. PVA film is clear, insoluble in solvents and impermeate to oils, solvents, chemicals and gases. It has high tear resistance and tensile strength. Furthermore, it has potential for use in membrane-controlled drug delivery system (Winding and Hiatt, 1961, The American Pharmaceutical Association,1986, Budavari, 1989, Gennaro,1990, Lim and Wan, 1994).

Novel PVA hydrogel prepared by low temperature crystallization method was a non-erodible, non-dissolving and fully swollen matrix. It was used as controlled transdermal delivery system of bunitrolol-HCl for hypertension therapy. This hydrogel had porous and three-dimensional network structure with high mechanical strength and high water contents. The release of bunitrolol from hydrogel preparation followed the Fickian diffusion (Morimoto et al., 1990).

Polyvinylpyrrolidone (PVP)

PVP $(C_6H_9NO)_n$ an odorless, hygroscopic, white to creamy white powder. It is soluble in water giving a colloidal solution. It also soluble in a wide range of organic solvent systems as well as in gastric and intestinal fluids. It is produced as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. PVP is inert and non-toxic agent. It has no irritant effect on the skin and causes no sensitization. PVP is a well known material commonly used for film coating and for other pharmaceutical and non pharmaceutical applications. PVP films when dry are clear, glossy and hard. It is extremely tacky while drying. Excellent adhesive qualities warrant combining it with other film-formers to keep the film from flaking and rubbing off during coating. Although soluble in both acidic and basic fluids, it can be crosslinked with tannic acid and other to produce films with enteric properties(Lachman, Lieberman and Kaning, 1976, The American Pharmaceutical Association, 1986, Budavari, 1989, Gennaro, 1990).

Hydroxypropylmethylcellulose (HPMC)

HPMC is an odorless, tasteless, white to slightly off white fibrous or granular, free flowing powder. It swells in water producing a clear to apalescent, viscous colloidal solution and undergoes reversible transformation from sol to gel on heating and cooling, respectively, but insoluble in anhydrous alcohol, ether or chloroform. It very stable in dry conditions. Solutions of HPMC exhibit pseudoplastic rheology and there is no yield point. In addition, that permits its use in usual amounts without interfering drug availability. The HPMC solutions are stable at pH 3.0-11.0. HPMC, a nonionic cellulose ether, is a safety material and presents one of the most popular film former employed

for tablet coating. Films of HPMC are tasteless, odorless, flexible and chip resistant. HPMC is available in a wide range of grades that provides solutions viscosities required for coating solutions, suspension and gels. Their particular designations reflect viscosity obtained from 2% aqueous solutions. Type 50 cps is commonly used for coating solution in concentrations of 2 to 4% w/v. Low viscosity types (approximately 3 to 15 cps) are used in aqueous film coating in concentration of approximately 5 to 10% w/v whereas high viscosity grades are used in solvent film coating. HPMC satisfies most of the criteria established for idea film-formers. It is used alone or in combination with other film-formers, depending on desired film characteristics. HPMC may be used as binder, emulsifier, protective colloid stabilizer, suspending and thicking agent.

Okhamafe and York (1983) studied on moisture permeability and mechanical properties of aqueous-based free film of HPMC-PVA blend film compared to hydroxypropylmethylcellulose film plasticized with polyethylene glycols.It was found that polyethylene glycol increased the moisture permeability of HPMC films while PVA decreased it. Both polyvinylalcohol and polyethylene glycols lowered tensile strength at break and Young's modulus.

Methylcellulose (MC)

Methylcellulose is a nonionic long-chain-substituted cellulose ether of 50-1,500 anhydroglucose unit containing 26-32% methoxyl groups. It is white to slightly off-white, essentially odorless and tasteless powder or granules. It is soluble and swells in cold water producing a clear to opalescent, viscous colloidal solution but insoluble in hot water, alcohol, ether and chloroform. Its solubility is dependent upon degree of substitution providing

variation in viscosity. The solution is stable to alkalis and dilute acid over a pH range of 2-12 at room temperature. The rheology of aqueous methylcellulose solutions is pseudoplastic and there is no yield point. Methylcellulose mucilage is incompatible with large amounts of electrolyte owing to the salting out of methycellulose. Methycellulose aqueous solution can be cast to clear films. Highly substituted, low viscosity grade are preferred to film coating. The usual concentration of methylcellulose is in concentrations of 1-5% w/v (The American Pharmaceutical Association, 1986, Budavari, 1989, Gennaro, 1990).

Triacetin

Triacetin is soluble in water at 25^{o}C approximately 6.1 percent. It also soluble in organic solvents and aromatic hydrocarbons. It is compatible with cellulose esters and ethers, acrylic resins and polyvinyl acetate but incompatible with resins of vinyl chloride type, polystyrene and rubber chloride. Triacetin finds some market as specialty plasticizer for cellulose acetate and nitrocellulose compositions. It is also employed as a solvent and fixative in the compounding of flavors and essences (Doolittle, 1954).

Guo (1993, 1994) studied the effects of plasticizers including triacetin,PEG 600,PEG 4000 and PEG 8000 on water permeation and mechanical properties of cellulose acetate films. It was found that water permeability of cellulose acetate films decreased to a minimum value at low plasticizer concentration and then increased with higher concentration of plasticizer. This results were interpreted by the antiplasticization effect of low plasticizer concentration. This effect was confirmed by mechanical measurements of polymer free film.

Polyethylene glycols

They are classified by average molecular weight in various forms. Those designated as 200 to 600 are liquid at room temperature and are excellent plasticizers. Types 1000 to 6000 are white solids at room temperature and have waxy characteristics and film-froming ability. The polyethylene glycols are soluble in water.In addition to their uses in pharmacy, polyethylene glycols are polymers of ethylene oxide which have found a popular place in film coating. Coats produced with polyethylene glycol waxes are hard, smooth, tastless and nontoxic. Polyethylene glycol films, at reasonable thickness levels, are continuous and provide good gas barriers for controlling drug odors. These polymers are being use in combination with other film formers to modify film characteristics. The hygroscopicity of the waxy forms can be controlled by proper formulation with additives (Lachman, Liemberman, and Kanig, 1776).