CHAPTER I

GENERAL BACKGROUND

Introduction

In the present, the design of controlled-release dosage form transdermal drug delivery is a subject of 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 of administration and allowance of rapid termination of treatment, if required, by removal of the device from the skin surface, etc. (Parkish, Babar and Plakogiannis, 1988, Neil and Deasy, 1988).

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 biological half life i.e., 3.8 $\pm$ 0.5 hours (Harvey, 1980). Therefore 5 to 20 mg of drug is recommended to be administered thrice a day (Vyas et al., 1994). The production of ISDN in transdermal dosage form is a good way to solve these problems because ISDN can absorb through skin (Bhalla and Khanolkar, 1985, Renolds, 1989, Gilman et al., 1990).

There are two concepts in the design of transdermal delivery, namely, the reservoir type and the matrix type. In the reservoir type, the most interesting design, the drug is stored in a reservoir form and diffuses through a rate-limiting membrane to the site of absorption. One of the advantages of such system is the near constant release rate of drug dosage form the device (Hadgraft and Guy, 1989). A major component of the membrane is polymer. In the recent years a great deal of effort has gone into the use of biocompatible polymers as film-forming materials to control the release and administration of drugs. After cellulose, the most abundant biocompatible polymer is chitin, which is the natural structure component of shellfish skeleton. Chitin of poly-beta (1,4) linked N-acetyl-D-glucosamine is an acetylated polyamine, which is biodegradable and non-toxic. It can also be produced in a deacylated form known as"chitosan", where the degree of deacetylation can be varied according to the intended use. Chitosan has been examined extensively by the pharmaceutical industry in Japan and the US for its potential in controlled drug delivery systems (Miyazaki et al., 1988, Shiraishi, Imai and Otagiri, 1993, Luessen et al., 1994). The polymeric cationic character together with its potential reactive groups give chitosan unique properties for utilization in controlled release technologies and make it a water-soluble polymer at acidic pH. In dilute acidic solution of chitosan can be cast to form tough, flexible, water soluble film or crosslinked with glutaraldehyde to form hydrogels. In addition, both the biocompatibility and biodegradability of chitosan have been will established (Karlsen and Skaugrud, 1991).

Studies of chitosan as release rate-controlling membrane were subject of a number of investigations (Nakatsuka and Andrady, 1992, Thacharodi and Rao, 1993, Leesajakul, 1995). Almost all studies demonstrated that chitosan membrane with different permeability characteristics in the release of bioactive materials could be prepared by crosslinking and the release of drug through chitosan membrane could be regulated as required, based on the degree of crosslinking. The mechanical properties of membrane also could be improved by crosslinking.

From the above reasons, the crosslinking chitosan generally led to a reduction in water sorption and permeability of drug. Then the study of effect of blending with a hydroplilic polymer such as polyvinyl alcohol and various type of starches is interesting. These polymers are miscible readily with chitosan. In general, increasing in weight of hydrophilic polymer in the blend membranes tends to increase the ability to absorb water and drug permeability. Moreover, the blend membranes also change in their physicochemical properties.

In addition to the parameters described in the previous sections, molecular weight of the polymers blending with chitosan is also an interesting parameter. The effect of molecular weight of polymer on drug release control was studied in several workers (Saettone et al., 1991, Bhagat et al.,1994, Merkli et al., 1994, Park 1994, Durrani, Farr and Kellaway 1995). They found that the change in molecular weight of polymer underwent variation in physicochemical properties and drug release. Generally, a higher molecular weight polymer led to a slower

hydration and a lesser permeability of drug through polymer. Therefore, the purpose of this study are to point out the effect of molecular weight and type of polymer blending with chitosan on permeability and physicochemical properties of membrane. Effect of amount of crosslinking agent on characteristics of membrane and interaction occurred from blending polymer are also investigated for use as rate-controlling membrane in development of ISDN transdermal patch. In addition, the prepared ISDN transdermal patch is compared with commercial ISDN transdermal patch in amount and mechanism of drug permeation.

Objectives of this study

1. To develop ISDN transdermal patch using crosslinked-chitosan as rate-controlling membrane.

2. To study the effect of molecular weight of polyvinyl alcohol on physicochemical properties of crosslinked chitosan-polyvinyl alcohol blend membranes.

3. To study the effect of type of starch on physicochemical properties of crosslinked chitosan-starch blend membranes.

4. To study the amount of crosslinking agent on physicochemical properties of crosslinked chitosan-polymer blend membranes.

5. To study interactions occurred from blending polymer and crosslinking.

6. To study and compare the amount and mechanism of drug permeation between commercial ISDN transdermal patch and various prepared membranes by in vitro skin-permeation study.

Literature Review

A. General Informations of Reservoir-Type Device with Rate Limiting Membrane (Parkish, Babar and Plakogiannis, 1985, Hadgraft and Guy, 1989, Chien, 1992)

Essential component

This transdermal drug delivery system (TDDS) is essentially a multilayer laminate hosing a steady-state reservoir of drug sandwiched between an impermeable backing and rate-controlling membrane of precisely controlled composition, morphology and dimension.

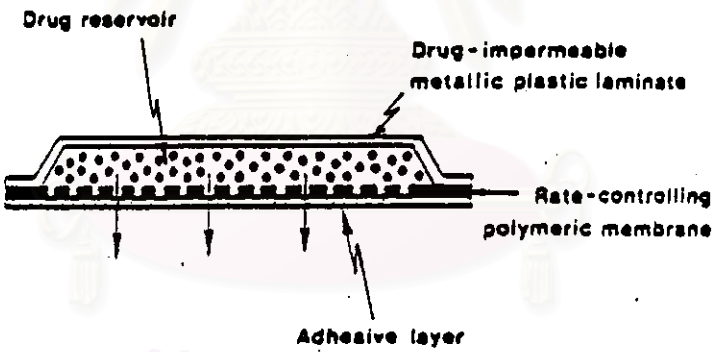


Figure 1. Basic elements of TDDS in which drug release is controlled by membrane permeation.

The system represents five functional elements as follow:

1. Impermeable backing

The backing layer must be impermeable to the drugs and enhancers, if used, and as a result, it is usually impermeable to water vapor. The most commonly use backing materials are polyester

polyethylene coextruded films. Other nonporous plastics could equally well be used.

2. Drug reservoir

This is a single or multicomponent element in which the drug is stored in a stable form and in the required amount for the execution of the prescribed drug program. In the drug reservoir compartment the drug solids are dispersed homogeneously in a solid polymer matrix(e.g., polyisobutylene), suspended in a unleachable, viscous liquid medium (e.g., silicone fluid) to form a pastelike suspension, or dissolved in a releasable solvent (e.g., alkyl alcohol) to form a clear drug solution.

3. Rate-controlling membrane

The rate-controlling membrane can be either a microporous or nonporous polymeric membrane, e.g., ethylene-vinyl acetate copolymer, with a specific drug permeability. The rate-controlling element establishes and maintains the prescribed rate of drug administration through the operational life of the system.

4. Adhesive layer

This layer is on the external surface of the polymeric membrane. It is a thin layer of drug-compatible, hypoallergenic pressure sensitive polymer and is applied to provide intimate contact of the transdermal drug delivery system with the skin surface. There are three types of adhesives commonly used in transdermal delivery devices: acrylic based, silicone based and polyisobutylene.

5. Peel strip

The peel strip prevents lost of drug that has migrated into the adhesive layer during storage, and protects the finished device against contamination. As such, the impermeable material described as appropriate for the backing also would be suitable for the peel strip, and it is often convenient and easy to use. Polyester, foil, and other metallized laminates are typical devices.

In addition, a membrane of other design criteria must be taken in account;

1. the system had to occlude the skin to ensure one-way flux of drug;

2. the system should exert a bacteriostatic effect, to curtail the proliferation of skin flora likely to occur beneath on occlusion.

Mechanism

A membrane transdermal device with a reservoir is shown in Figure 2. As can be seen from the schematic representation given in Figure 2, the predominant events involve partition and diffusion. Beginning with the delivery systems, and assuming a membrane-modulated devices, the following steps can be indentified. First, the drug will partition from the reservoir into the polymer matrix that comprises the rate-controlling membrane. Once in the membrane, diffusion will occur down a concentration gradient at a rate which will be controlled by the diffusion coefficient of the drug in the polymer. Once the drug has

diffused through the rate-limiting membrane it will partition into the adhesive layer. Drug contained in this area will be released relatively rapidly to the skin and will act as a loading dose (Hadgraft and Guy, 1989).

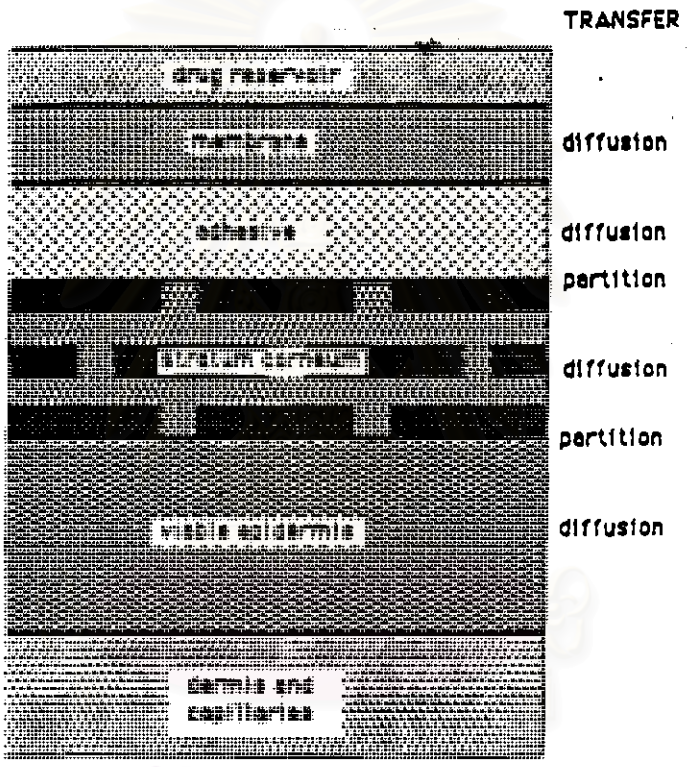


Figure 2. The schematic of transdermal device with a reservoir

In this type of device, the rate of drug release (dQ/dt) is theoretically constant, and is defined as follows:

$$\frac{dQ}{dt} = \frac{C_R}{1/P_m + 1/P_d} \qquad (1)$$

where

C_R = the drug concentration in the reservoir

P_m = the permeability coefficient of the rate-controlling membrane

P_d = the permeability coefficient of the hydrodynamic diffusion layer existing on the membrane surface.

The permeability coefficients P_m and P_d are defined as follows:

$$P_m = \frac{K_{m/r} D_m}{h_m} \qquad (2)$$

$$P_d = \frac{K_{a/m} D_a}{h_d} \qquad (3)$$

where

$K_{m/r}$ = the partition coefficient for the interfacial partitioning of drug molecules from the reservoir to the membrane

$K_{a/m}$ = the partition coefficient for the interfacial partitioning of drug molecules from the membrane to the aqueous diffusion layer

D_m = the diffusion coefficient in the rate-controlling membrane

D_a = the diffusion coefficient in the aqueous diffusion layer

h_m = the thickness of the rate-controlling membrane

h_d = the thickness of the aqueous diffusion layer

A substitution of equations (2) and (3) for P_m and P_d in equation (1), followed by integration of the resultant equation, give the following:

$$\frac{Q}{t} = \frac{K_{m/r}\, K_{a/m}\, D_a\, D_m}{K_{m/r}\, D_m\, h_d + K_{a/m}\, D_a\, h_m}\, C_r \qquad (4)$$

This equation defines the rate of drug release at steady state from drug delivery device in which release is controlled by permeation through a membrane (Chien, 1985).

In vitro evaluation of transdermal delivery (Chien, 1987, Guy and Hadgraft, 1989)

The aim of in vitro experiment in transdermal delivery is to understand and/or predict the delivery and penetration of drug from the skin surface into the body via the skin of a living animal. Ideally, an in vitro system for transdermal drug delivery studies should de designed in such a way that the intrinsic rate of release or permeation, which is theoretically independent of the in vitro design, can be accurately determined. The release and skin permeation kinetics of drug from transdermal drug delivery system can be evaluated using a two compartment diffusion cell assembly under identical conditions. This is carried out by individually mounting a skin specimen on a vertical or horizontal diffusion cell. Each unit of transdermal drug delivery system is then applied with its drug-releasing surface in intimate contact with the skin specimen. The skin permeation profile of drug is followed by

sampling the receptor solution at predetermined time and assaying drug concentrations in the samples by a sensitive analytical method, such as high-performance liquid chromatography (HPLC). The release profiles of drug from these transdermal drug delivery systems can also be investigated in the same diffusion cell assembly without a skin specimen. Then the importance elements for in vitro evaluation of transdermal delivery are diffusion cell apparatus and skin model.

Diffusion cell apparatus

For transdermal drug delivery, it is well known that the main resistance to drug transport resides in the skin, that is, diffusion through the stratum corneum. If an in vitro apparatus has poor mixing condition, the release rate from transdermal drug delivery system, which is usually much greater than the skin permeation rate, may be strongly distorted by the diffusion boundary layer. In the case, the in vitro release rate may become relatively close to the in vivo permeation rate, and it will be believed erroneously that the rate of drug delivery is controlled by the transdermal drug delivery system, not by the skin permeation. On the other hand, a well-designed in vitro apparatus can assure that the mechanism of drug delivery is truly from the transdermal drug delivery system.

Various type of in vitro apparatus for measuring drug permeation profiles across the skin can be broadly classified into two categories as shown in Table 1.

Table 1. Classification of In vitro Membrane Permeation Systems

Physical design of diffusion cell
Horizontal type
Vertical type
Flow-through type
Method of sampling and measurement
Continuing system
Fluid circulation system
Noncirculation system
Intermittent system: rotating agitation system

The horizontal-type skin permeation system is developed by Vilia and Chien. This cell design has a solution compartment of relatively small volume in each half-cell for maximal analytical sensitivity, and a rather small membrane area to accommodate the skin specimen available. Both the donor and receptor solutions are agitated, under a totally enclosed system. The temperature of the system can be controlled isothermal or nonisothermal condition by circulating thermostated water through the water jacket surrounding the solution compartment.

The vertical-type skin permeation system developed by Franz, and Keshary and Chien have been frequently used for studying the kinetics of percutaneous absorption. The cell has a receptor compartment with an effective volume and effective surface area. The solution in the

receptor compartment is stirred by a rod-shaped magnet. The temperature in the bulk of solution can be maintained a constant level by circulating thermostated water through the water jacket surrounding the receptor compartment.

Recently, the USP XXIII has defined three types of apparatus for drug release test. First, a use of paddle and vessel assembly from apparatus II which consists of the following: a convered vessel made of glass or other inert, transparent material; a motor; a paddle formed from a blade and a shaft is used as the stirring element; a stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel. The vessel is partially immersed in a suitable water bath of any convenient size that permit holding the temperature inside the vessel at constant during the test and keeping the bath fluid in constant, smooth motion. A distance of 25 $\pm$ 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any 'dead' volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.

Second, a use of vessel assembly from apparatus I except to replace the basket and shaft with a stainless steel cylinder stirring element and maintain the temperature during the test.

Third, a use of reciprocating disk, the assembly, consists of a set of volumetrically calibrated or a tared solution containers made of glass or other suitable inert material, a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of disk shaped sample holders.

Effect of diffusion cell apparatus on skin permeation was investigated by Keshary and Chien (1984). In the study, the release and skin permeation rates from four nitroglycerin transdermal therapeutic systems were evaluated in Franz and Keshary-Chien diffusion cell. The obtained result indicated that using the Keshary-Chien cell increase in the release and skin permeation rates comparative with Franz cell. These increases from the systems releasing nitroglycerin could be attributed to the improvements in the hydrodynamic conditions in the Keshary-Chien cell. These improvements result in a thinner hydrodynamic boundary layer, more efficient solution mixing, and better temperature control in the cell.

Thereby, in selection of diffusion cell apparatus, not only available dissolution equipment in laboratory is applied to reduce cost of experiment, but solution hydrodynamic, mixing efficiency, and temperature control are also considered to highest efficiency in in vitro permeation study.

Skin model

The vast majority of in vitro experiments are conducted on animal skin. The use of human skin in vitro penetration studies is limited because human skin is often difficult to obtain, expensive, difficult to store, and full of variable in permeation properties. A variety of model membranes has been used for transdermal research such as hairless mouse skin, rabbit, rat and guinea pigs (Kligman, 1983). However, the time for experimental of some animal skin in in vitro penetration studies is limited because of deterioration of membrane integrity after a prolonged use. Moreover, most animal skin are more permeable than human skin partly because of a larger number of hair follicles. Excised animal skin also have variable properties depending on preparation method and animal species.

Besides animal skin, the artificial membranes have been used for transdermal research, but the use of artificial membranes is limited because they lack keratinized properties and lipid which are primary component in the stratum corneum of mammalian skins (Wu et al., 1992).

Nowadays, shed snake skin appears to be a useful alternative to animal skin in assessing the potential for transdermal drug delivery. Shed snake skin is nonliving, pure stratum corneum with no hair follicles. The permeability of several compounds through shed snake skin was found to be similar to, but often slightly less than, that through human skin, which may make shed snake skin a better model membrane than other animal skins because most animal skins are much more permeable than human

skin (Itoh, Xia et al., 1990, Itoh, Magavi et al., 1990, Bhattachar, et al., 1992).

Shed snake skins of ***Elaphe obsoleta*** have been used in in vitro percutaneous permeation studies, and the similarities between the shed snake skin of this species and the human stratum corneum in terms of thickness, lipid contents and water evaporation rate are summarized in Table 2.

Table 2. Comparison of Thickness, Lipid Content, and Water Evaporation Rate Between Human Stratum Corneum and Shed Snake

	Human stratum corneum	Shed snake skin *(Elaphe obsoleta)*
Thickness	13-15 μm	10-20 μm
Lipid content	3.0-6.8 %	6%
Water evaporation rate	0.1-0.8 mg/cm^{2}hr	0.15-0.22 mg/cm^{2}hr

The data in Table 2., suggests that shed snake skin of this species may offer a good model membrane for transdermal research.

B. Membrane

A membrane used in reservoir-type transdermal drug delivery can be dense membrane structure (nonporous) or microporous structure (Robin and Lee 1987). In nonporous, homogeneous membrane, transport of the drug in the reservoir through membrane occurs by dissolution at one

interface of the membrane and then diffusion down a gradient in drug concentration. For membranes show a well-defined pores connecting the two sides of the membrane; this pore can be used to immobilize a liquid that is different from the external environment. Diffusion of a drug then occurs principally by diffusion through the liquid-filled pores.

The importance element of reservoir-type device with rate-controlling membrane is inert material that controls rate of drug-release to the skin. This material is polymer. Variations in characteristics of the membrane due to composition of the polymeric membrane affect release rates (Illum and Davis, 1987). Besides polymer, in general, a membrane formulation is composed of solvent for dissolving or dispersing polymer and other additives such as plasticizer, crossliking agent etc. for approving characteristics of membrane.

Polymers

Criteria of polymers suitable for use as rate-controlling membranes are:

- Solubility in solvent of choice as rate controlling membrane preparation.
- Capacity to produce an elegant looking product.
- Stability in the presence of heat, light, moisture, air and the other substrate. The film properties should not change with aging.
- Essentially no color, taste or odor.
- Compatibility with common additives.

- Nontoxicity with no pharmacological activity, and acceptability for medical devices.

No commercially available material fulfills all requirements of an ideal film material. A pharmaceutical scientist usually formulates a membrane solution to achieve certain desired properties for the film product (Lachman, 1986).

Polymers, which are also known as macromolecules, are very large molecules consisting of many repeating units (monomers) and are formed by a process called polymerization. The monomers can be linked together in various ways to give linear polymers or branched polymers. Because polymerization is a random process, molecules within a given polymers mass will have different molecular weights, and for this reason molecular weights of polymers are described in terms of average molecular weights.

A knowledge of molecular weight and molecular weight distribution of polymers is important because there is a definite relationship between polymer molecular weight and polymer properties. McCormick, Brower and Kin (1987) studied tensile strength of various molecular weight polystyrene. The increasing number average molecular weight of polymer tend to increase its tensile strength. This relationship is analogous to glass transition temperature.

Influence of molecular weight on release rate of drug interested several workers. Merkli et al. (1994) studied the release of 5 fluorouracil (5-FU) from poly(ortho ester) with 3,500, 5,800, 10,100, 15,200 and 33,300 Da molecular weight. The obtained data showed that, 5-FU was released from poly (ortho ester) in with one day for the lowest molecular weight polymer and in about 7 days for the highest molecular weight polymer. Thus, it is possible to modulate the release from one day to up to one week by using polymer having increasing molecular weight.

Bhagat et al. (1994) used three different molecular weight calcium alginates (low, medium and high molecular weight) for studying release rate of guaifenesin compressed tablets. A higher molecular weight polymer produced membrane with lower permeability for guaifenesin and decreased in release rate.

Effect of molecular weight on degradation of polymer was also studied by Park (1994) and Durrani, Farr and Kellaway (1995). The obtained result concluded that the lower molecular weight polymers exhibited a significant degradation with reduced glass transition temperature while the higher molecular weight polymer show a slower change in the degradation.

Polymers most commonly used in pharmaceutical industry were cellulose derivatives, acrylate polymers and polyvinyl derivatives. For the reservoir-type device, the used polymers have capacity to form film.

Examples of polymers used in reservoir-type devices with rate-limiting membranes are as follows:

Microporous membrane	:	polypropylene
		cellulose acetate nitrate
		polyacrylonitrile
		ethylene vinyl acetate copolymer
Nonporous, homogeneous	:	silicone
membrane		polyethylene
		polyvinyl chloride

(Parikh, Balar and Plakogiannis, 1985, Tyle, 1988)

Solvent

The primary function of a solvent system is to dissolve or disperse the polymer and other additives and convey them to the substrate surface. Some important considerations for an ideal solvent system are as follows:

1. It should either dissolve or disperse the polymer system.
2. It should easily dissolve or disperse other additive components into the solvent system.
3. Small concentrations of polymers (2-10%) should not result in extremely viscous solution system, creating system.
4. It should be colorless, tasteless, odorless, inexpensive, nontoxic, inert and nonflammable.
5. It should have a rapid drying rate.
6. It should have no environmental impact.

The most widely used solvents, either alone or in combination are water, ethanol, methanol, isopropranol, chloroform, acetone, methylethyl ketone, and methylene chloride. Because of environmental and economic considerations, water is the solvent of choice.

Other additives

Because it is rare to find a commercial polymer that has exactly the properties required for a particular systems, some form of approving will almost in variable be necessary. A number of techniques can be used to improve polymer properties (Hadgraft and Guy, 1989).

1. Addition of plasticizer.
2. Crosslinking.

1. Addition of plasticizer

Most often, a formulator uses additives to the film solution formula so that the desired effects are achieved for the film. A plasticizer can be a nonvolatile liquid of another polymer, which when incorporated with the primary polymeric film former, changes the flexibility, tensile strength or adhesion properties of the resulting film.

As the solvent is removed, most polymeric materials tend to pack together in three dimensional honeycomb arrangements. The choice of plasticizer material to solvate the polymer and alter the polymer-polymer interactions when used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity. So that membranes with higher plasticizer loading normally give a higher release rate than those with low plasticizer content. The type of plasticizers and its

ratio to the polymer can be optimized to achieve the desired film properties. In the selection of a plasticizer, as with the polymer itself, care must be taken to select a material that is acceptable for use in medical application, and it is clearly advantageous to choose one that has already been used in pharmaceutical devices.

The type of plasticizers to be used in pharmaceutical can be divided into three groups that are polyols, organic esters, and vegetable oils and glycerides.

Polyols

The plasticizers of this group are glycerol, propylene glycol, and polyethylene glycol of 200-4000 series. These plasticizers can dissolve or miscible with water except polyethylene glycol with high molecular weight and be used for water soluble cellulose polymer. They are nonvolatile, stable in wide range of temperature, and hygroscopic.

Organic acid esters

The plasticizers of this group are glycerol triacetate (triacetin), citrate ester, phthalate ester, and dibutyl sebacate. They are used as plasticizers for ethycellulose. The properties of this group are liquid, miscible with organic solvents, and hydrophobicity except glycerol triacetate and triethyl citrate which are hydrophilic.

Vegetable oils and glycerides

The plasticizers of this group are castor oil and acetylated monoglycerides. Castor oil is composed of a large number of glycerides. The characteristic of this oil is liquid which is miscible with organic solvents. Acetylated monoglyceride, which is a wax or liquid, can dissolve in organic solvent and is a good plasticizer for ethylcellulose and cellulose acetate phthalate.

Besides above, surfactants, such as polysorbates (Tweens) and sorbitan esters (Spans) are also used as plasticizers.

2. Crosslinking

The use of crosslinking agents to modify property of membrane is found in a number of controlled-release studies (Cardinal et al., 1990, Kim et al., 1992, Nakatsuka and Andrady, 1992, Thacharodi, and Rao, 1993). In conclusion of these studies, the higher the degree of crosslinking, the harder the material, and the slower in the diffusion of drug from the device.

Examples of the crosslinking agents used in the present are as follows (Maruhashi et al., 1992):

1. Polyaldehyde : glyoxol, succindialdehyde, malonaldehyde, maleic dialdehyde, phthalic dialdehyde, glutaraldehyde, and the like.

2. Polyepoxy compounds : ethylene glycol diglycidyl ether, polyethylene glycol diglycidyl ether, glycerol diglycidyl ether, glycerol triglycidyl ether, and the like.

3. Polyamine compounds : urea, melamine, methylol melamine, triethanol amine, and the like.

4. Compounds capable of producing a radical : hydrogen peroxide, benzoyl peroxide, and the like.

5. Oxidizing agent : potassium dichromate, ammonium dichromate, and the like.

The amount of the crosslinking agent is preferable 0.1 to 50 parts by weight, more preferable from 0.5 to 30 parts by weight, based on 100 parts by weight of the polymer. The crosslinking takes place by contacting between a solution of the polymer and all polymer chains then are interconnected by covalent crosslinks.

In addition to crosslinking and addition of plasticizer, blending polymers was used to tailor polymer properties. For example, the blending of chitosan and polyvinyl alcohol was occurred to produce controlled-release membrane (Kim et al., 1992, Nakatsuka and Andrady, 1992). In these studies, the blending of polyvinyl alcohol with chitosan tends to increase water uptake and permeability because polyvinyl alcohol is a water-soluble polymer.

Membranes preparation

After the polymeric solutions or polymeric dispersions was prepared. The methods, which are commonly used for preparing the free films or membranes are casting and spraying technique (Kanig and Goodman, 1961, Allen, DeMarco and Kwan, 1972).

For film casting technique, the polymeric solution or polymeric dispersion is spread on a flat, nonadhesive surface; glass, mercury, aluminium stainless steel or Teflon plate, then the solvent slowly evaporates (Robinson and Lee; 1987). The solvent is evaporated by drying at room temperature or in the hot air oven. The resultant polymer film is then peeled from the surface. On a laboratory scale, the thickness of the polymer solution is usually controlled with a "Gardener knife". It is composed of two parts, a block and a blade. When used, the blade position is adjusted for the desired wet film thickness and the block is placed over a small pool of the solution of the film former on a smooth surface. The entire application is then drawn downward on the pool to spread it evenly over the surface. The resultant wet films are then dried and removed for evaluation. Industrially, rotating metal drums or moving belts systems are used.

The last method, spraying technique has been used by several workers is preparing of free films. The apparatus are reciprocating spray nozzle and a revolving cylinder which is coated with Teflon of other inert substrates. While spraying, the polymeric solution or polymeric dispersion must be continuously stirred. After drying, the films were separated from the substrate.

For these methods, the rate of drying are important to avoid the asymmetry in the membrane as the solvent is removed.

Film can also be produced by melt-pressing, the polymer is placed between two metal plates and the plates then place between two heated platens in a press.

Another process known as calendering, in this procedure the polymer is squeezed into a thin film between heated roller.

Membranes evaluation

The potential utilization of films or membranes as specialized coating on medication or as controlled-release has prompted several studies within recent years which evaluated various film for these application. In this evaluation, thermal and mechanical properties were studied.

Thermal properties of the membrane were examined by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and thermomechanical analysis (TMA) (Robinson and Lee, 1987, Thacharodi and Panduranga, 1993).

Thermogravimetric analysis is used to determine thermal stability of membranes and the upper limit of thermal stability is usually taken as the temperature at which weight loss of the sample begins.

Differential scanning calorimetry is an extremely useful technique for measuring glass transition temperature (Tg).

Thermomechanical analysis measures deformation of a substance under a non oscillatory load and can also conveniently measure transition from a glassy to a rubbery polymer.

Mechanical properties of a polymer are most conveniently determined by measuring their stress-strain relationship. Stress is the stretching force applied to the sample, and the strain is the elongation of the sample under a given stress. Because stress-strain relationship in membrane are time-dependent, the speed at which stress is applied is an important experimental parameter.

Stress-strain measurements in polymers are usually performed on dumbell-shaped specimens as show in Figure 3. The specimens 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. A typical stress-strain curve for a thermoplastic material is shown in Figure 4.

Figure 3. Typical shape of a flat polymer sample used for stress strain tests

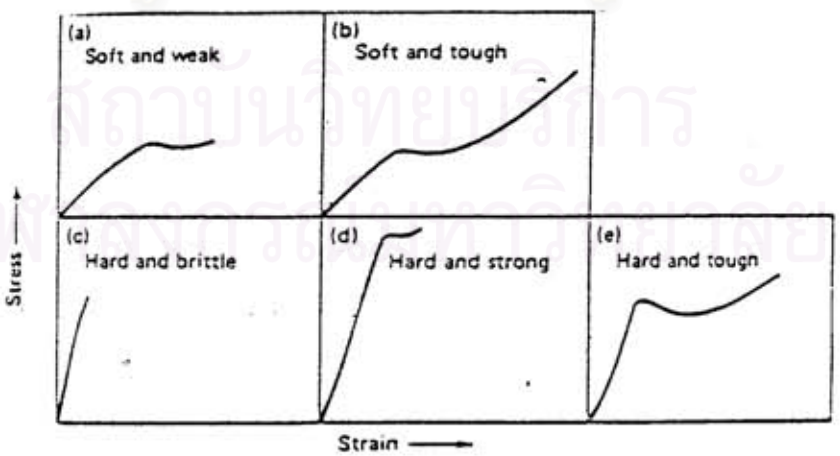


Figure 4. Characteristic stress-strain curves for five different types of polymeric materials

Besides, scanning electron microscope used to examine the homogeneity of membrane. The small amount of membrane was mounted on a metal stub, coated with gold and examined using a scanning electron microscope.

Permeability study was used for release-controlling membrane. This study is used to examine the permeation of most solutes through a polymeric membrane. The apparatus of this study is static glass diffusion cell which composes of two compartments.

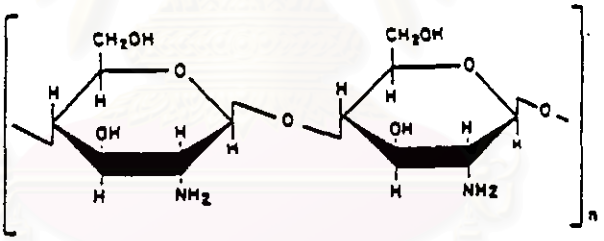
Degree of swelling and water sorption study are of considerable importance. When a membrane is placed in an aqueous environment, it will gradually absorb water, and the amount of absorbed water is determined by the polymer structure. Because use of a membrane controlled release device exposes the membrane to an aqueous environment is importance.

In addition to noted as above, other methods such as gas transmission, water vapor transmission and the study of stability of membrane under controlled temperature and humidity conditions are also used in evaluation (Kanig and Goodman, 1962, Lachman, Liberman and Kaning, 1976, Gordon et al., 1981, Yuk et al., 1991).

C. Polymers used in this experiment

Chitosan

Chitosan was first prepared by Hoppe Seyler and is a macromolecular material, obtained by the substantial or complete deacetylation of chitin, which is one of the main constituents in the shell of crustaceans, but without the destruction of its polymeric chain (Lowee, 1984). Chitosan is a cationic polymer and a cationic polyelectrolyte (Skaugrud, 1989, Karlsan and Skaugrud, 1991). Similar to cellulose, chitosan are long linear chained molecules of (1-4) linked glycans. Chemical structure for chitosan is shown as below.



The molecular weight of chitosan will, for commercial products, depend on the processing conditions, and more grades within the range of 10,000-1,000,000 Dalton are available.

Standard grades of chitosan requires the addition of acid to solubilized in water. Acetic acid is commonly used as a reference, but other organic acids such as citric acid, formic acid, lactic acid, tartaric acid etc., as well as mineral acids, can be used successfully. For practical purposes chitosan is regarded as insoluble in sulphuric acid and

phosphoric acid, while a certain solubility exists for other mineral acids like hydrochloric, nitric and perchloric acid.

The advantage of using chitosan in such products is firstly based on its ability to form tough, clear and very flexible film, more stable at high humidity and nontoxic (Averbach, 1977, Blair et al., 1987). Increasingly over the last few years, chitosan has been used in the cosmetic and the pharmaceutical industries for its potential use in controlled drug delivery systems (Miyazaki et al., 1988, Cardinal et al., 1990, Skaugrud, 1991, Thanoo, Sunny and Jayakrishnan, 1991).

Chitosan is capable to form complexes with polyanionic substances as carboxymethylcellulose, sodium alginate, pectin, acacia and poly (acrylic acid) (Dutkiewicz and Tuora, 1993, Mireles et al., 1993). Meshali and Gabr (1992) investigated and characterized the possible interaction between chitosan and pectin / acacia. It was also intended to prepare sustained release tablets of chlorpromazine hydrochloride. Shiraishi, Imai and Otagiri (1993) also studied controlled release of indomethacin by chitosan-polyelectrolyte complex.

Chitosan are also useful for the preparation of gels that exhibit sustained release of drugs. Miyazaki, Ishii, and Nadai (1981) examined the sustained release of indomethacin and papaverine hydrochloride when chitosan gel was used as vehicle. The results suggest that chitosan gel might be useful as a vehicle for a sustained release preparation of indomethacin and papaverine hydrochloride.

In addition to the advantage of chitosan described above, the film-forming property of chitosan finds many applications in various fields. For example, Sawayanagi, Nambu and Nagai (1981) prepared chitosan membrane and studied permeation of several drugs, such as promethazine hydrochloride, chlorpromazine hydrochloride, diethazine hydrochloride, trifluprομazine hydrochloride, fluflenamic acid, ketoprofen, indomethacin and tolbutamide, through a chitosan membrane. Some studies have been performed on the usefulness of chitosan films as drug delivery systems (Miyazaki et al., 1988, Nakatsuka and Andrady, 1992, Thacharodi and Rao, 1992, Thacharodi and Rao, 1993). These studies were focused towards the development of chitosan membranes with different permeability characteristics by blending with other polymers as polyvinyl alcohol, cellulose and crosslinking with crosslinking agent and its utilization in controlled drug delivery systems. From these studies, the results were discussed and concluded that the permeability through the hydrophilic membranes were controlled by a change in the swollen membrane. The blending of polyvinyl alcohol with chitosan tend to increase the water uptake. When crosslinking agent was raised, not only the swelling capacity was reduced due to the discounted ability of hydrogen bonding between water molecules and hydroxy and amino groups in the polyvinyl alcohol and chitosan blend, but also the tensile strength was increased with the amount of crosslinking agent.

Polyvinyl alcohol

Polyvinyl alcohol is a white, powdered synthetic resin which is manufactured by the hydrolysis of polyvinyl acetate. Chemically polyvinyl alcohol can be described as a polyhydric alcohol with secondary hydroxyl groups on alternate carbon atoms. It is represented structurally as follows:

$$[\text{-}CH_2\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_2\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}]_n$$

All grades of polyvinyl alcohol are hygroscopic. Polyvinyl alcohol is readily soluble in water. However, the temperature at which complete solution occurs various with the grade, depending on percent hydrolysis and all grades of polyvinyl alcohol remain in solution when cooled. The viscosity of water solution of polyvinyl alcohol varies with the grade, molecular weight, concentration and temperature. The molecular weight, which is reflected in its solution viscosity, is a direct function of the molecular weight of the precursor polyvinyl acetate resin. The average molecular weights of four types of polyvinyl alcohol are commercially characterized as:

Super-high viscosity	250,000-300,000
High viscosity	170,000-220,000
Medium viscosity	100,000-150,000
Low viscosity	25,000-35,000

Polyvinyl alcohol is cast into film from water solutions and form exceptionally transparent, puncture-resistant films with good abrasion resistant. Tensile strength of polyvinyl alcohol film increases when molecular weight of polymer increases. In comparing commercial grades of polyvinyl alcohol, there is a greater difference in strength between low and medium molecular weight grades than between medium and high molecular weight grades in the same hydrolysis range.

Elongation at break for films of polyvinyl alcohol may vary from less than 10% to more than 600%, depending on molecular weight and humidity. Tear resistant varies with the grade of polyvinyl alcohol in the same manner as does tensile strength.

Polyvinyl alcohol is not a primary skin irritant and does not produce skin sensitization. Use of polyvinyl alcohol in pharmaceutical is worldwide.

Polyvinyl alcohol hydrogel prepared by low temperature crystallization was used as controlled transdermal delivery system of bunitrolol hydrochloride for hypertension therapy. This hydrogel had porous and three-dimensional network structure with high mechanical strength and high water contents (Morimoto et al., 1990).

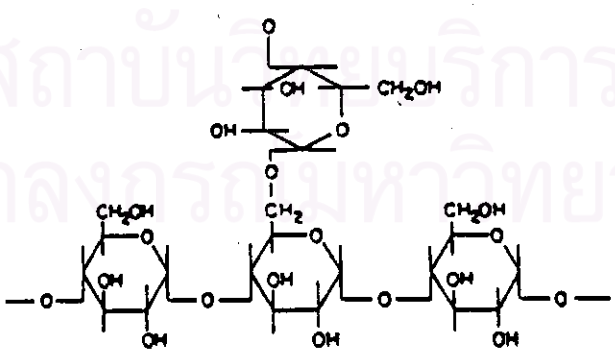
A release of miconazole from topical polyvinyl alcohol matrices with different molecular weigh (26,000, 49,000 and 84,000), with the same degree of hydrolysis, was examined. The in vitro release data

showed that the lowest molecular weight of polyvinyl alcohol gave a highest release rate. This result enclosed to the result of microbiological study (Saettone et al., 1991).

Kim and Lee (1992) developed a new method of preparing composite polyvinyl alcohol beads with double-layer structure. Thanoo, Sunny and Jayakrishnan (1993) prepared controlled release of oral drugs from crosslinked polyvinyl alcohol microspheres.

Starch

Starch is composed of carbon, hydrogen and oxygen in the ratio of 6:10:5 ($C_6H_{10}O_5$), placing it in the class of carbohydrate organic compounds. Most starches consist of a mixture of two polysaccharide types: amylose, an essentially linear polymer, and amylopectin, a highly branched polymer. The structure is shown as below (Davidson, 1980).



The amylose polymer fraction of a starch will show a distribution of molecular sizes, and the average degree of polymerization will vary with the plant variety from which the starch is obtained. Depending upon the type of starch, the degree of polymerization will range from about 250-4000 anhydroglucose units per amylose, corresponding to a molecular weight of approximately 40,000 to 650,000. The amylose from potato and tapioca starches has a higher molecular weight than that from corn starch. As noted earlier, starch molecules have a multitude of hydroxyl groups which impart hydrophilic, properties to the starch. These hydroxyl groups also tend to attach each other, forming hydrogen bonds. Since amylose is linear polymer containing hydroxyl groups, it shows special properties when it is dispersed or dissolved in water. The linear amylose molecules can readily align themselves next to each other and form interaction hydrogen bonds through the hydroxyl groups. When sufficient interchain hydrogen bonds are formed, the individual amylose molecule are associated to form molecular aggregates with reduced hydration capacity and hence, lower solubility.

In dilute solutions (less than 1%) the amylose precipitates. In more concentrated dispersion, the aggregated amylose entraps the aqueous fluid in a network of partially associated amylose molecules,forming a gel. The process of alignment, association and precipitation is essentially a crystallization process and is known to starch chemist as "retrogradation". The process takes place at room temperature. The rate of retrogradation depends upon the molecular size, concentration of the amylose, the temperature and the pH. Large amylose molecules have a slower rate of

retrogradation (as for potato and tapioca amylose), presumably because the alignment process is more difficult. As the molecular size decreases, the retrogradation rate increases (as for corn amylose). Because amylose is a linear molecule with a marked tendency to associate, it can form strong, unsupported films similar to that of cellulose.

Amylopectin is a very large molecule and highly branched. It cannot readily undergo the retrogradation or crystallization phenomenon that amylose so easily does. It is also noted that amylopectin does not form strong, unsupported films because the highly branched molecule cannot readily orient itself in parallel alignment with other amylopectin molecules to form the multitude of associate hydrogen bonds necessary to produce strong films.

The amylose and amylopectin molecules are organized and packed into granules, which are insoluble in water at room temperature. Plants synthesize starch and accumulate it in the form of granules which are distinctive to the plant in which they are formed, varying in size, shape and relative proportion of amylose and amylopectin (Table 3). Thus the source of starch can be determined by microscopic examination of the granule. Photomicrographs of starch granules are shown in Figure 5.

When the aqueous slurry of starch is heated to temperature (about 55 to 80°C) where, depending on the type of starch and concentration, the intermolecular hydrogen bonds holding the granule together are weakened and the granule undergoes a rapid, irreversible swelling. The critical

Table 3. Starch Granule Properties

starch	type	size (diameter) μm	shape (light microscope)	gelatinization temperature °C	amylose content
corn	cereal	5-26	round polygonal	62-72	22-28
tapioca	root	5-25	truncated round, oval	62-73	17-22
potato	root	15-100	oval spherical	59-68	23
wheat	cereal	2-35	round lenticular	58-64	17-27
rice	cereal	3-8	polygonal angular	68-78	16-17

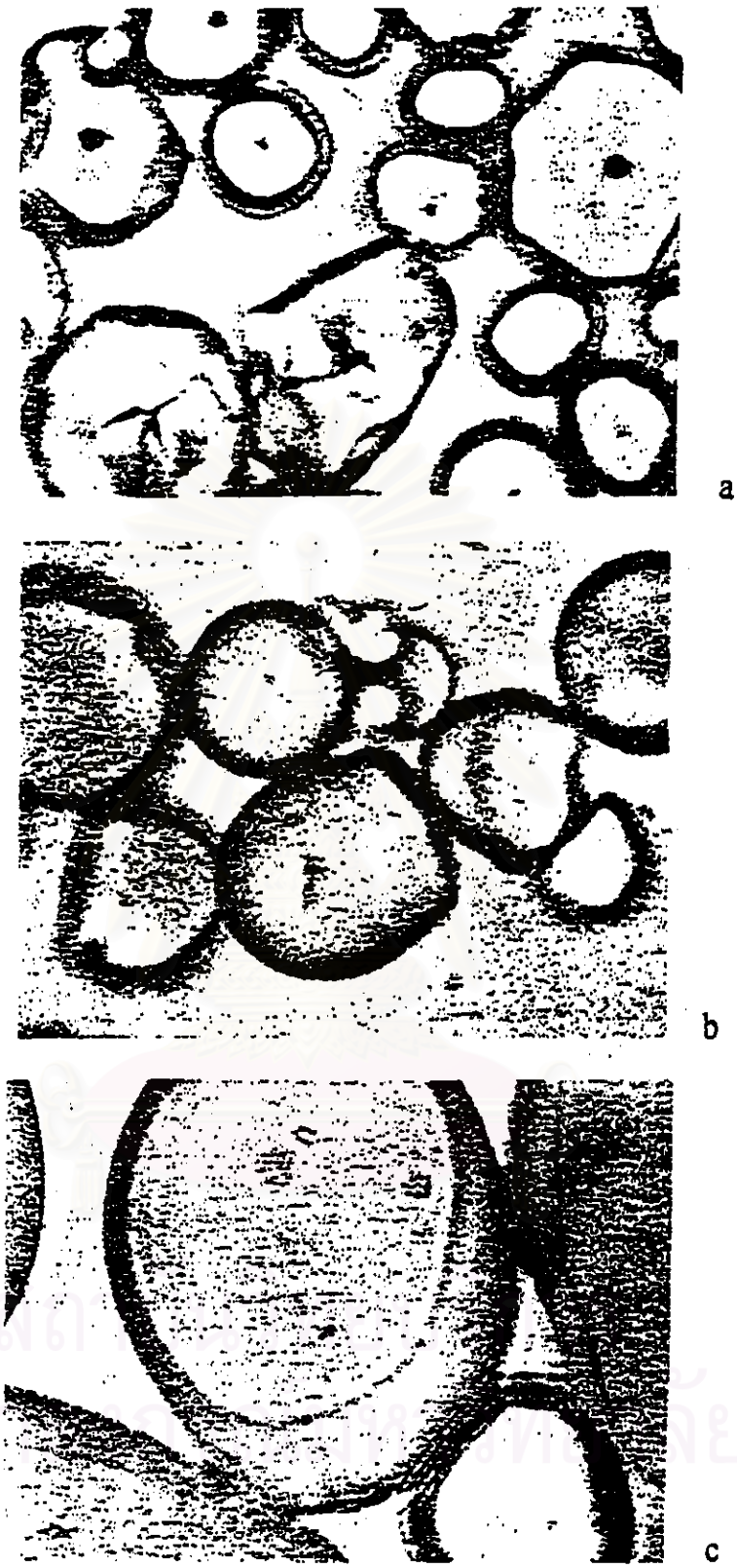


Figure 5. Photomicrographs of starch granules.

(a) Corn starch

(b) Tapioca starch

(c) Potato starch

temperature at which this occurs is known as the gelatinization temperature which is shown in Table 3. The granules take up the water, swelling to many times their original volumes, rupturing and collapsing as the heating and agitation of the mixture continues, and releasing concurrently some of the starch molecules, particularly amylose, into solution. The result is a viscous colloidal dispersion which is a complex mixture of residual, swollen granule masses, hydrated molecule aggregates and dissolved molecules.

Although the starch granule is insoluble in water below the gelatinization temperature, there is a limited absorption of water when the granule is wetted or exposed to high humidity. This results in a slight swelling of the granule which is reversible on drying. Capacity of water sorption and granule swelling are shown in Table 4.

Table 4. Water Sorption and Granule Swelling as A Function of Relative Humidity

starch	Percent relative humidity			
	100%		75%	
	water sorption (%)	diameter increase (%)	water sorption (%)	diameter increase (%)
corn	39.9	9.1	17.4	5.4
potato	50.9	12.7	19.4	10.3
tapioca	42.9	28.4	17.6	12.5

Corn, potato and tapioca starch can be made into fluid, stable glues giving films of good clarity. Variation in properties of starch film due to difference in type of starch. High amylose content in starch (50-75%), which confers strong gelling tendencies, makes forming strong film. In addition, bonding strengths in the starch granules conducts to varying in gelatinization temperature, rate of swelling, and solubility.

Gelatinization temperature of starch granules varies with the particular starch type. However, not all the granules of a given starch start to swell at the same temperature ; rather, there is a temperature range. Since the granules are held together by intermolecular hydrogen bonding and gelatinization results from a weakening and disruption of these bonds, the gelatinization temperature and the rate of swelling can be considered a measure of the strength and character of the associative bonds. As starch granule swell, there is a corresponding increase in clarity, starch solubility and viscosity. Each species of starch has a characteristic swelling and solubility pattern.

Potato starch undergoes a very rapid and unrestricted swelling at relatively low temperature, indicative of weak bonding forces of approximately uniform strength. Tapioca starch starts to swell at about the same temperature as potato starch, but the swelling continues at a much slower rate. This suggests that the internal bonding forces in the tapioca granule have a wider range of bonding strengths than those in potato granules. Corn starch show a characteristic two-stage swelling pattern as related to temperature, presumably indicative of two types of internal

bonding forces. Even though the potato starch granule swells much more readily than even the corn starch, it gives much less soluble at any given degree of swelling than the corn starch. This suggests that the potato starch has a more extensive and uniform molecular network.

Starch is used in pharmaceutical tablets as a binder, filler and disintegrant. Levy and Andry (1989) used hydrosoluble starch derivatives: hydroxyethyl starch (HES) and carboxymethyl starch (CMS) to preparing microcapsules. Shukla et al. (1990) prepared a hydrophilic matrix for encapsulation by crosslinked starch-urea formaldehyde.

Application of crosslinked chitosan-polymer as release rate controlling membrane in isosorbide dinitrate transdermal patch was investigated by Leesajakul (1995). She found that the obtained crosslinked chitosan-corn starch membrane showed a porous film and it was reasonable in agreement with the high cumulative amount of permeated isosorbide dinitrate.

D. Plasticizer

Triacetin

Triacetin is soluble in organic solvents, aromatic hydrocarbons and also soluble approximately 7.1 percent in water at 25°C (Phuapradit et al., 1995). Triacetin finds some market as speciality plasticizer for cellulose acetate and nitrocellulose composition. It is compatible with cellulose esters and ethers, acrylic resins and polyvinyl acetate (Shah and Zatz, 1992) but incompatible with vinyl chloride, polystylene and rubber chloride resins (Doolittle, 1954).

The effect of triacetin on water permeation and mechanical properties of cellulose were investigated by Guo (1993). He found that, the water permeability of cellulose acetate was decreased with increasing plasticizer to a minimum and then increased with higher concentration of plasticizer.