CHAPTER I
INTRODUCTION

Control release technologies are becoming more and more important in modern medication and pharmaceuticals. All controlled release systems aim to improve the effectiveness of drug therapy. This improvement can take the form of increasing therapeutic activity comparing to the intensity of side effect, reducing the number of drug administration required during treatment, or eliminating the need for specialized drug administration.

One of the possible routes of introducing controlled release medication into the body, the oral administration of single dose medication is one of the simplest and safest. However, this traditional administration have some disadvantages for example it bypasses a gastrointestinal (GI) absorption which changes can occur in pH as a molecule passes from gastric acid with a pH as low as 1 to the intestine with a pH of up to 8 and problems of absorption in the stomach which often contains food resulting in erratic and pulsed delivery of drugs into the intestine and variability in plasma concentration-time profiles. The development of transdermal delivery system is one of approaches to eliminate some of the problems of traditional administration. Transdermal delivery systems are specifically designed to obtain systemic blood levels. They facilitate the passage of a drug from the outside of the skin through its various layers into the bloodstream (Ranade and Hollinger, 1995). The delivery of drugs transdermally (through the skin) provides several important advantages over traditional oral and intravenous delivery routes. Transdermally delivered drugs avoid the risk and inconvenience of intravenous therapy, bypass the liver in terms of first pass elimination, usually provide less chance of an overdose or underdose, allow for easy termination, and permit both local and systemic treatments.

Hydrogels are currently being studied as controlled release carriers of drugs and proteins because of their good tissue compatibility, easy manipulation under swelling conditions, and control of solute permeability. Hydrogels are three-dimensional hydrophilic polymeric networks capable of entrapping large amounts of water without changing their shapes. Hydrogels have been developed from hydrophilic polymers which were water-soluble substances such as polyvinyl

alcohol, polyethylene oxide, and polyvinyl pyrrolidone. Extensive studies have been conducted into synthesis and characterization of hydrogesl as a matrix for entrapment of drugs in controlled release systems, because of their ability to release an entrapped drug into aqueous media and to regulate the release of such drug by control of swelling. Because of the many other advantages of hydrogels such as biocompatibility, and stimuli-responsiveness, especially for the water retention which allows control of the drug diffusion pathway (Yin *et al.*, 2002), hydrogels have found various applications such as soft contacts, cosmetic and reconstructive surgery, artificial organs, drying agents, intelligent stimuli-sensitive materials, as well as in drug delivery systems. The pH-sensitive swelling of covalently and non-covalently crosslinked hydrogels appears to be a useful route to localized antibiotic delivery in the acidic environment of the gastric fluid (Torre *et al.*, 2003)

In the meantime the use of biopolymers such as proteins and polysaccharides for the preparation of delivery systems has also attracted investigators. Such materials have the added advantage that they are susceptible to enzymatic digestion inside the body (Yao *et al., 1994*). Furthermore, the natural macromolecules are of interest because of their biocompatibility and the fact that they are obtained from renewable natural mass. Certain biopolymers can form hydrogels suitable for used as a matrix for entrapment of drugs in controlled release systems, e.g. carboxymethyl-cellulose (Zhang *et al.*, 2001), chitosan (Yao *et al.*, 1994; Thacharodi and Rao, 1996), carboxymethyl-chitin (Song *et al.*, 1992; Watanabe *et al.*, 1992), alginate (Gonzalez-Rodruguez *et al.*, 2002), fibroin (Katayama *et al.*, 2000). Biodegradable polymers have found applications in the medical field, such as surgical sutures, surgical implants, and in drug delivery systems (Katayama *et al., 2000*).

Chitin, a naturally abundant biopolymer next to cellulose and the supporting material of the shell of crustacea, the cuticle of insects and in the cell wall of fungi and microorganisms, is substantially composed of 2-acetamido-2-decxy-D-glucopyranose (*N*-acetyl-D-glucosamine, GlcNAc) unit linked by β-(1,4-) linkage. Although the insolubility of chitin has been suggested to be due to its rigid crystalline structure through intra- and intermolecular hydrogen bonds. The soluble chitin derivatives have been prepare by chemical modifications such as acylation or alkylation (Tokura *et al*, 1983).

Carboxymethyl-chitin (CM-chitin), a water soluble chitin derivative, is a polyelectrolyte with properties resembling those of carboxymethyl-cellulose (CMC). CM-chitin has a high susceptibility to lysozyme, high water solubility, a reactive functional group, chelating ability with calcium ions, and forms a gel-like matrix in the presence of ferric ions. Furthermore, it has been found that CM-chitin and its lysozymic hydrolysate showed little immunogenicity except for a slight mitogenic activity. These properties make it a very suitable material for a drug carrier (Tokura *et al*, 1994). CM-chitin has been used to form gels containing neocarzinostatin (NCS), a peptidic anticancer drug, in the presence of iron (III) chloride and in the co-presence of calcium chloride. These gels con be digested by lysozyme and were demonstrated to prolong the plasma concentration of NCS after subcutaneous injection (Watanabe *et al*, 1992). CM-chitin has been considered to be one of advanced carriers for the polymeric drug, since Because of its highly biodegradable and non-toxic character, and the ability of CM-chitin to form hydrogels by crosslinking reaction, so that drug molecules can be conveniently trapped within the polymer network, CM-chitin has been considered to be an attractive candidate for use as a polymeric drug delivery vehicle. It is therefore of interest to investigate CM-chitin as a matrix to entrap drugs for application in a transdermal drug delivery system.

Chitosan, poly-β(1→4)-D-glucopyranosamine composed of glucosamine and a N-acetyl glucosamine unit, is normally obtained by alkaline deacetylation of chitin. Chitosan is a natural poly cationic polymer that possesses valuable properties as a biomaterial for biomedical application such as nontoxicity, biocompatibility, and biodegradability. It is known that chitosan can form hydrogels and that crosslinked chitosan hydrogels can swell extensively due to the positive charges on the network.

Poly(vinyl pyrrolidone)(PVP) is a synthetic polymer with biocompatibility and has wide applications as a biomaterial. UV-cured films of *N*-vinyl pyrrolidone copolymers have been proposed as a bioadhesive wound dressing matrix (Kao *et al,* 1997). Due to its lubricity and viscous properties, PVP has been used to coat tissue contacting surfaces (Howard 1998) and as a vitreous humor substitute (Hong *et al,* 1998). PVP possesses a good gas permselectivity (Li *et al,* 2001). PVP adhesive has

been designed to serve as a skin contact adhesive and as a drug reservoir in transdermal patches for controlled drug delivery (Novikov *et al,* 2003).

Poly(vinyl alcohol)(PVA) is a nontoxic, water-soluble, biocompatible, and biodegradable synthetic polymer, which is widely used in biochemical and biomedical applications. PVA has good film-forming and highly hydrophilic properties which enable it to form hydrogels.

In this study, films of CM-chitin, chitosan, and their blends with PVA and PVP, were prepared and cross-linked, using glutaraldehyde as the crosslinking agent. Salicylic acid and theophylline were used as a model drugs. Drug release characteristics of the films were studied using a modified Franz diffusion cell. The amount of released drug was analyzed by UV-Visible spectrophotometry. Effects of drug concentration, drug type, drug release time, crosslinking concentration and the blend composition were investigated.

1.1 Theoretical Background

1.1.1 Transdermal Drug Delivery System

Transdermal Drug Delivery (TDD) involves the application of a drug to the skin to achieve systemically active levels of the drug to treat diseases remote from the application site. Transdermal delivery is an important delivery route that delivers precise amounts of drug through the skin for systemic action. Transdermal Drug Delivery is a non-invasive means for providing continuous transcutaneous drug infusion to a patient, similar to intravenous administration, except that the drug is delivered from patches applied to the skin, which eliminates the need for vascular access and syringes or pumps.

It is customary to compare the percutaneous route with oral delivery since the latter provides the most popular way for delivering drugs. Transdermal delivery of a drug may eliminate several variables associated with oral intake, since it bypasses GI absorption. It is know that in the GI tract, changes occur in pH as a molecule passes from gastric acid with a pH as low as 1 to the intestine with a pH of up to 8. Other variables that are important include gastric emptying, intestinal motility and transit times, the activity of human and bacterial enzymes, and the influence of food.

In transdermal delivery, the drug enters the systemic circulation without first passing into the hepatic portal system and traversing the liver. This route, therefore, avoids the "first pass" phenomenon by which the liver can significantly reduce the amount of intact drug. Additionally, the drug avoids the enzymes present in the gut wall. However, as has been emphasized earlier, the skin itself possesses some metabolic capability for biotransformation.

Percutaneous administration of a drug can control administration and limit pharmacological action, while the corresponding oral or injectable formulation may well elicit several effects, including toxic reactions. Patient compliance may be achieved by the continuity of delivery of drugs with short half-lives

Transdermal administration, under suitable rate control, may minimize pulse entry of a drug into the bloodstream. However, it is difficult to deliberately provide a controlled on/off action because intact skin membranes are known to be intrinsically slow-response systems with prolonged lag times, at least when shunt diffusion via the appendageal route is negligible.

Several designs of *in vitro* membrane permeation apparatus, whose hydrodynamic characteristics have been fully investigated, are discussed in the sections that follow.

(a) Horizontal-Type Skin Permeation System, Small Cell Volume

The skin permeation system (Figure 1.1) has been extensively used for studying the skin permeation kinetics of drugs, using either human cadaver skin or freshly excised animal skin. This cell design has a solution compartment of relative small volume in each half-cell for maximal analytical sensitivity, and rather small membrane area (0.64 cm2) to accommodate the skin specimen available. Both the donor and receptor solutions are agitated, under a totally enclosed system, by a mateched set of star-head magnets (diameter, 8 mm), which are rotates at a synchronous sped of 600 rpm at a fixed position in the stirring platforms by a specially designed driving unit positioned directly underneath the cells. The temperature of the system can be controlled at isothermal or nonisothermal conditions by circulating thermostated water through the water jacket surrounding the solution compartment.

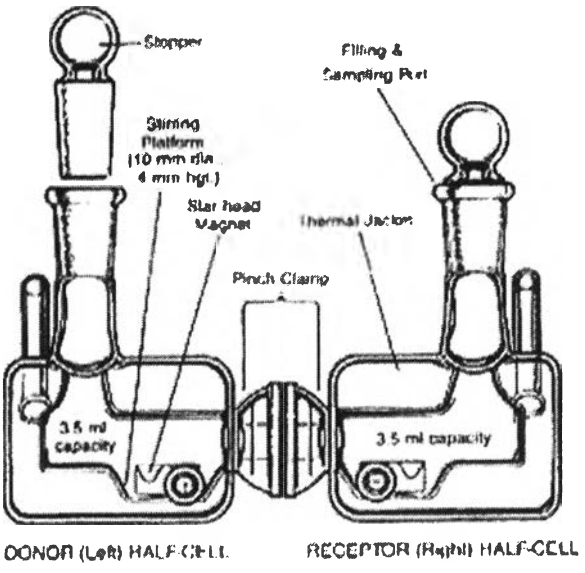


Figure 1.1 Horizontal-type skin permeation system, small cell volume.

(b) Horizontal-Type Membrane Permeation System, Large Solution Volume

The second horizontal membrane permeation system is also composed of one pair of donor and receptor compartments in mirror image (Figure 1.2), in which the fluid is agitated by a matched set of bar-shaped magnets (2.54 com long). The magnets are driven by a pair of synchronous motors located directly underneath the cells to rotate at a synchronous but variable rate in a specially designed stirring platform. Each pair of half-cells has a large effective membrane area for permeation (13.9 cm^2). Each compartment can hold a volume of 140-250 ml of solution. The rotation speed of the magnets can be controlled at a constant level of 60-100 rpm. Samples may be withdrawn for analysis from a sampling port at various intervals. The donor and receptor compartments are both jacketed and thermostated by an external circulating bath to maintain isothermal conditions, or if designed, the temperature in either donor or receptor compartment can be programmed to simulate any environment variations.

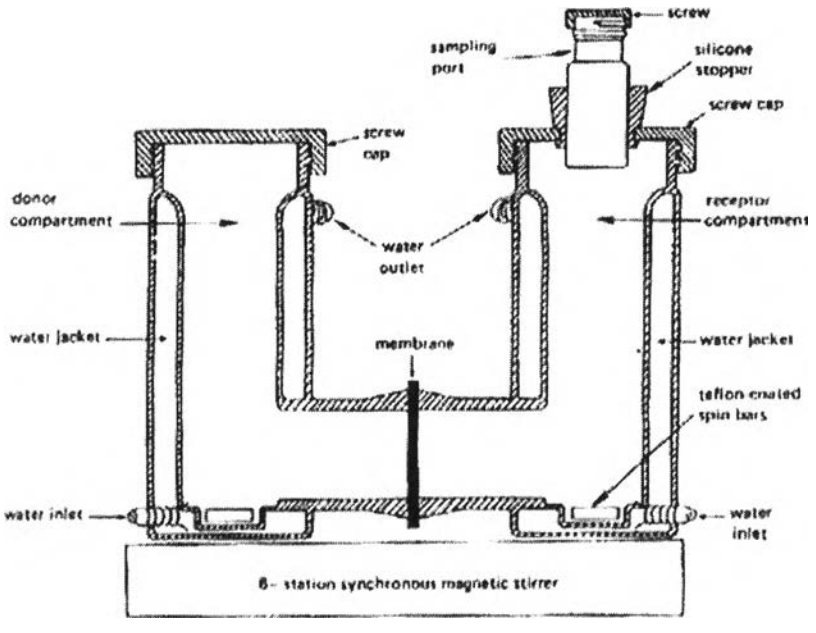


Figure 1.2 Horizontal-type membrane permeation system, large solution volume.

(c) Franz Diffusion Cell

The vertical-type skin permeation system (Figure 1.3) developed by Franz and commercialized by Crown Glass has been frequently used for studying the kinetics of percutaneous absorption. The cell has a receptor compartment with an effective volume of approximately 10-12 ml and an effective surface area for permeation varying from 1.57 to 4.71 cm^2. The solution in the receptor compartment is stirred by a rod-shaped magnet driven by a 3-w synchronous motor. The stirring magnet rotates at a speed of 600 rpm in a low viscosity receptor solution such as saline solution. The temperature in the bulk of the solution can be maintained at a constant level by circulating thermostated water through the water jacket surrounding the receptor compartment. However, the temperature near the upper opening, at which the skin will be positioned, varies as the surrounding temperature varies. The observed variation in receptor solution temperature results because the donor compartment is not thermally controlled. The hydrodynamic characteristics of the Franz diffusion cell recently were established.

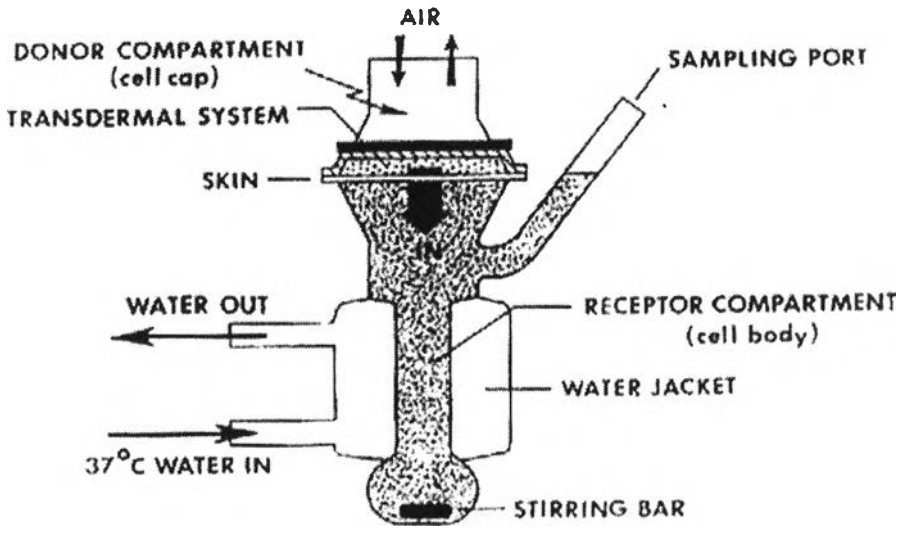


Figure 1.3 Franz diffusion cell.

(d) Modified Franz Diffusion Cell

Another vertical-type skin permeation cell was recently developed in response to the observation that the Franz cell has rather poor solution hydrodynamics as a result of inefficient mixing. The results are a significant temperature gradient in the diffusion. The Franz diffusion cell (Figure 1.4) improve efficiency of fluid mixing. The modified cell has an effective receptor solution volume of 12 ml and a skin surface area of 3.14 cm^2. The receptor solution is stirred by a star-head magnet rotating at a constant speed of 600 rpm by the same driving unit originally designed for Franz diffusion cell. The hydrodynamic characteristics of the modified Franz cell were recently investigated.

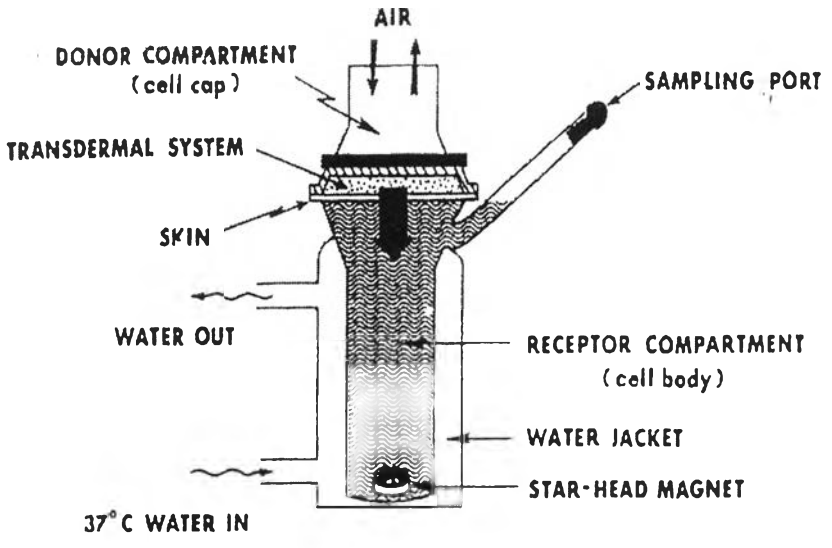


Figure 1.4 Modified franz diffusion cell.

(e) Rotating-Disc-Type Membrane Permeation Cell

One of the advantages of the rotating-disc cell is that the hydrodynamic diffusion boundary layer on the surface of the rotating disc has been well established theoretically (Figure 1.5).

If the rotating disc is assumed to be sufficiently large that the edge effects are negligible, the thickness of the diffusion boundary layer is given by :

$$\delta = 1.61\ (D_f\ \rho/\mu)^{1/3}\ \{\mu/(\rho\omega)\}^{1/2}$$

Where D_f is the drug diffusivity in the fluid,

ρ is the density of the fluid,

μ is the viscosity of the fluid,

ω is the angular velocity (= ¶Nd).

In the rotating-disc diffusion cell, if the disc is not large enough the flow pattern in the cell is easily influenced by the wall of the vessel. Then the diffusion layer determined experimentally is usually thicker than that calculated from equation 1.1 due to the dissipation of additional energy on the vessel wall. Therefore, equation 1.1 should not be used a priori for estimating the diffusion boundary layer thickness existing on the surface of the rotating disc.

Recently, a rotating-disc-type membrane permeation cell for studying the release of drug from suppositories was developed. The rotating disc has an effective membrane area of 12.6 cm^2 and can be used together with the one-liter USP dissolution vessel as the receptor compartment. The hydrodynamic characteristics of the diffusion cell were recently investigated (Chien, 1987).

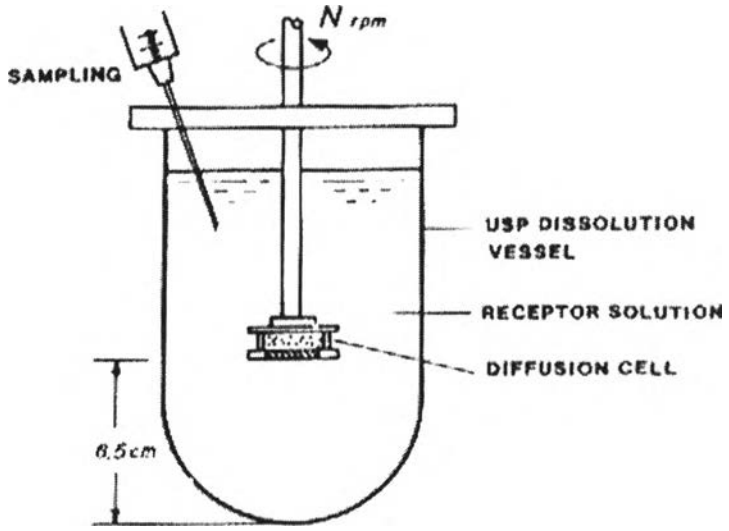


Figure 1.5 Rotating-disc-type membrane permeation cell.

1.1.2 Hydrogels

Hydrogels are currently being studied as controlled release carrier of drugs and proteins because of their good tissue compatibility, easy manipulation under swelling condetion and solute permeability. There are two general methods for loading into hydrogels as drug carriers. In one method, a hydrogel monomer is mixed with drug, initiator, and crosslinker and is polymerized to entrap the drug within the matrix. In another method, a preformed hydrogel (in most case lyophilized) is allowed to swell to equilibrium in a suitable drug solution. The release of these drugs from the hydrogel delivery system involves absorption of water into the polymer matrix and subsequent diffusion of the drugs as determined by Fick's law. Kim *et al.* reviewed the detailed consideration of swelling, drug loading, and drug release. They reported that factors that affect the drug release from hydrogels include the drug

loading method, the local partition of drugs, the overall hydrophilic/hydrophobic balance, the osmotic effect of dissolved drugs, and the polymer chain elasticity. The preparation of hydrogel matrix for a specific drug carrier should be tailored considering the aforementioned effects as well as the physical properties of drugs, loading level, and release kinetics.

1.1.3 Carboxymethyl-chitin

Carboxymethyl-chitin (CM-chitin), a negatively charged ether derivative of chitin, is a polyelectrolyte with properties resembling those of carboxymethyl-cellulose (CMC). CM-chitin is soluble in water and any pH media. The water solubility of CM-chitin becomes apparent when the fraction of substitution is more than 0.6 (Tokura *et al.*, 1983).

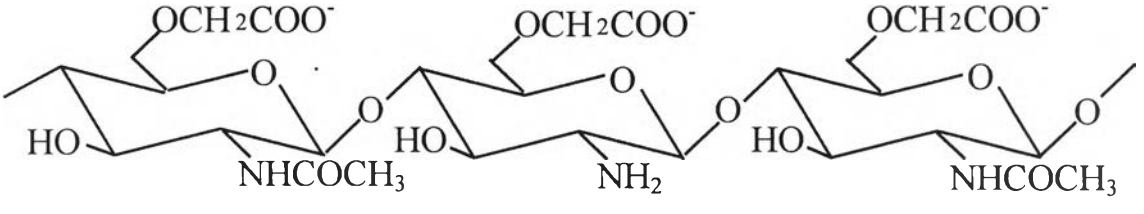
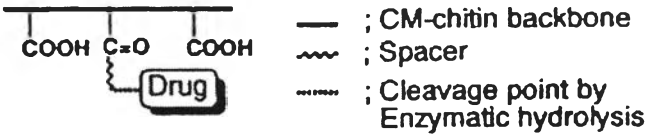


Figure1.6 Chemical structure of CM-chitin.

CM-chitin have been considered to be one of advanced carriers for the polymeric drug, since CM-chitin were reported as highly biodegradable and non toxic mucopolysaccharide in animal body. CM-chitin is thought much easier to load drugs either through chemical reaction or physical interactions due to its sophisticated properties.

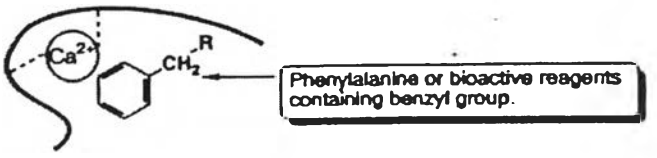
There are several purposed types of CM-chitin drug carrier

1. *Pendant type*



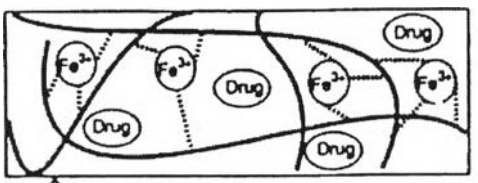
CM-chitin backbone, spacer and drug can be bonded covalently.

2. *Absorption type*



Calcium ion can chelate with CM-chitin and chelate surface was also flavored to adsorb several neutral amino acid especially phynylalanine or bioactive reagents containing benzyl group.

3. *Entrapping type*



CM-chitin gel formed by the addition of Fe^{3+} .

4. *Mixed type*

Composed of adsorption type and entrapping type using calcium and ferric ion.

1.1.4 Chitosan

Chitosan, poly-β(1→4)-D-glucopyranosamine composed of glucosamine and a N-acetyl glucosamine unit, is normally obtained by alkaline deacetylation of chitin, which is the major constituent of the exoskeleton of crustaceous water animals, the cuticles of insects and the cell walls of fungi.

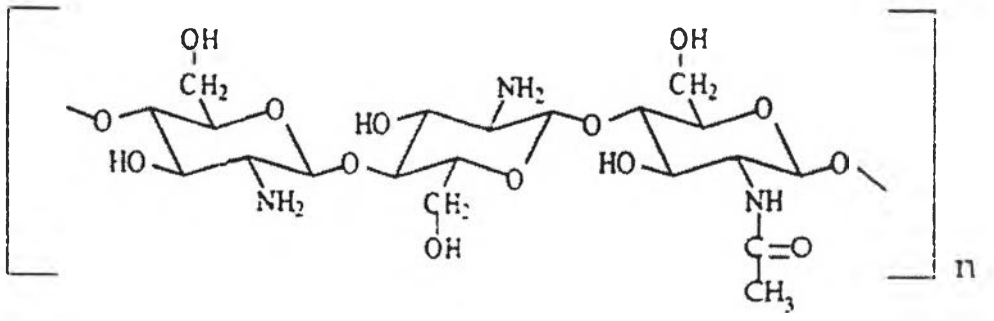


Figure 1.7 Chemical structure of chitosan.

Chitosan is biocompatible with its degradation products being know natural metabolites and can produced in powder, film, bead, fiber, and fabric formats. It was evaluated in a number of medical applications including as a potential wound dressing where it was shown that if it could enhance wound healing and blood clot formation. Many of chitosan properties depend upon its cationic nature. Chitosan is a good cationic polymer for membrane formation. In early research it was shown that membranes formed from the polymer could be exploited for the water clarification, filtration, fruit coating, surgical dressing, and controlled release.

In addition, another property of chitosan is for chelation. Chitosan can selectively bind desired materials such as chloreaterol, fats, metal ions, protein, and tumor cells. Chelation has been applied to areas of food preparation, health care, water improvement, and pharmaceutics. Therefore, chitosan is very useful for inhibition of tumor cells, antifungal effects, accelelation of wound healing, stimulation of the immune system, acceleration of plant germination. Moreover, the other applications are waste water treatment for heavy metal and radioisotope removal metal recovery, potable water purification for reduction of unwanted metals, complex binding of iron in precooked to reduce warmed-over flavour.

1.1.5 Poly(vinyl pyrrolidone)

PVP (polyvinyl pyrrolidone) is made from the monomer *n*-vinyl pyrrolidone:

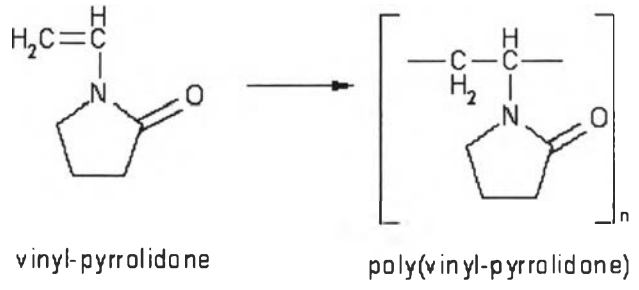


Figure 1.8 Chemical structure of vinyl pyrrolidone and Poly(vinyl pyrrolidone).

The monomer is carcinogenic and is extremely toxic to aquatic life. However its polymer PVP in its pure form is so safe that not only it is edible by humans, it is used as a blood plasma expander for trauma victims.

PVP is soluble in water and other polar solvents. In water it has the useful property of Newtonian viscosity. When dry it is a light flaky powder, which readily absorbs up to 18% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

The uses to which PVP has been put are very wide. For example, it is used as a binder in many pharmaceutical tablets; being completely inert to humans, it simply passes through. PVP binds to polar molecules exceptionally well, owing to its polarity. This has led to its application in coatings for photo-quality ink-jet papers and transparencies, as well as in inks for ink-jet printers.

PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives that you have to moisten, such as old-style postage stamps and envelopes. It has also been used in contact lens solutions and in steel-quenching solutions.

In the aspect of biochemical, PVP has been widely used as plasma expander. The excretion of PVP is inversely related to increasing molecular weight.

Low molecular weight PVP adsorbs various substances, e.g. bacterial toxins, inorganic poisons, barbiturates, vitamins and hormones in the blood, either reducing their toxicity or prolonging their activity (Weese, 1944). In the PVP-storing cells it is surrounded by proteins, carbohydrates and lipids in a capsule-like manner, perhaps due to coacervation processes (Hübner, 1960). The problem of whether the extremely long storage of PVP in the body produces toxic effects is open to discussion (Altemeir et al., 1954; Ammon & Miller, 1949).

1.1.6 Poly(vinyl alcohol)

Poly(vinyl alcohol) (PVA) is a water-soluble polymer. PVA can be prepared by hydrolysis or alcoholysis of poly(vinyl esters). PVA cannot be made directly because vinyl alcohol is simply unstable enol form of acetaldehyde.

Its solubility in water depends on its degree of polymerization and degree of hydrolysis; the effect of the latter is especially significant. The many hydroxyl groups cause it to have a high affinity to water, with strong hydrogen bond between intra- and intermolecular hydroxyl groups, greatly impeding its solubility in water. In case of partially hydrolysed PVA, there are the residual acetate groups which are essentially hydrophilic, and weaken the intra- and intermolecular hydrogen bonding of adjoining hydroxyl groups. The presence of an adequate amount of acetate groups increases the water solubility.

PVA is the only carbon-carbon backbone polymer that is biodegradeble. PVA has attracted attention as a biodegradable segment for the design of biodegradable water-soluble funtional polymers.

There are many application of PVA such asmedical device, packaging, and hydrogel for drug delivery system. In general, fully hydrolysed grades of PVA are used mainly in paper coating, in textile warp sizing of hydrophilic fibers, such as cotton and rayon staple yarns, and in laminating film in safety glass.