Chapter I

General Background

Introduction

Chitosan is a deacetylated polyamine which is biodegradable and biocompatible. Chitosan, a water soluble product, is transformed from chitin which is commercially extracted from shrimp and crab shells. A variety of pharmaceutical applications of chitosan have been proposed. It can be applied into tablets, beads, membranes, microcapsules, gels and so on. Over the years, there have been a number of references to the use of chitosan as pharmaceutical excipients in formulation (Bodmeier and Paeratakul, 1989; Lin and Lin, 1992; Knapczyk, 1993; Thacharodi and Rao,1993 a; b; Kristl et al. , 1993).

In Thailand, shrimp farming has been extensively popular especially in the southern area along the shorelines. Being one of the major export products, the processing of this industry nowadays results in enormous amount of by-products especially the shells that become industrial wastes and eventually can create an environmental problem. By converting this by-products to chitosan as a highly valuable material will reduce this polution problem from seafood industry (Yoawapha Waiprib, 1991).

Tablet film coating is a process which involves the deposition of a thin plastic-like material consisting of polymer, plasticizer, colorant and / or other additives upon the surface of tablets. The reasons for film coateng include improvement of the product appearance, protection of the active ingredient against the environment (heat, light, air and moisture), identification and decrease the risk of confusion, separation of the incompatible active ingredients, prevention of the dust formation and / or control of the release of an active ingredient.

The polymers that are widely used in film coating are the cellulose derivatives such as hydroxypropyl methylcellulose,

cellulose acetate phthalate, sodium carboxymethyl cellulose and ethylcellulose. Chitosan which has a close chemical relative of cellulose and like cellulose should have film forming capacity and should probably be applied as film former in tablet film coating.

Chitosan can be dissolved in many acid solutions which acetic acid solution is most often used (Lower, 1984 a). Chitosan solution can be prepared to the cast film having a good mechanical properties (Averbach, 1978; Kienzle-sterzer,nd.) and chitosan films are used in dosage form for controlled drug release (Kanke et al. , 1989; Miyazaki, Yamaguche and Takada, 1990).

However, no studies have been published on the effect of the molecular weight of chitosan, plasticizer and color in film coating formulations on the properties of cast films and coated tablets. In this study, the aqueous-based coating solution and the pan spray method were used to prepare film coated tablets by using chitosan as film former, and the effect of variables in coating formulations on the cast film and coated tablet properties was evaluated. The model drug used in the experiment was propranolol hydrochloride, a water soluble drug generally used as antihypertensive agent. The USP requires propranolol hydrochloride preparations to be protected from light and should be preserved in well-closed container, and commercial tablet dosage forms are film coated (John,1990; Lund,1994; The United States Pharmacopeial Convention,1994).

Objectives of the study

The aims of this study are :

1. To study the effect of molecular weight of chitosan on chitosan free films and propranolol hydrochloride coated tablets.
2. To study the effect of type and amount of plasticizer on chitosan free films and propranolol hydrochloride coated tablets
3. To study the properties of propranolol hydrochloride coated tablets after exposure to the accelerated condition.

Literature Review

Pharmaceutical Film Coating

Film coatings are an integral part of the dosage form development process. The process of film coating involves the application of a thin plastic-like material onto the surface of a solid substrate. The substrate can be tablets, capsules, pellets, granules, or particles. Typically, the coating is approximately 25 to 100 μm in thickness. The film coating is applied to improve the physical and chemical properties of the substrate.

Film coating, in contrast to sugar coating, has minimal impact on the substrate, and final product size and weight. The film coating process is a faster and can be automated. The advantages of the film coating technique compared to the sugar coating are listed in Table 1.

Table 1 The advanges of the film coating compared to the sugar coating(Ansel and Popovich, 1990).

Considerable reduction in application time
Lower material cost
Allow monogramming identification at no additional cost
Durable and resistant to chipping and cracking
Stable to light, air, heat and moisture
Water permeable and permeable to gastrointestinal juices
No undercoat or protective precoating required
Odourless and tasteless
Simple procedure to learn and reproduce
No dusting
No separate wax or polish coat necessary
No more adverse effect on disintegration time.

The initial tablet film coatings applied in 1953 used organic solvents, and the equipment and coating processes were those used in sugar coating. The coating compositions were ladled onto the tablets, resulting in coatings that were thicker, had more variable film thickness, and were less pharmaceutically elegant than the current coating. Significant improvements have been made over the part 30 years in the equipment, the coating process, the coating composition, and the quality of the film coatings. However. aqueous-based film coatings did not replace the organic solvent-based systems for almost 20 years. This evolution was primarily encouraged by stricter Environmental Protection Agency (EPA) laws limiting the quantity of organic solvents that could be discharged by an industrial plant into the environment, and by Qccupational safety and Health Act (OSHA) concerned about the health and safety of the operators. During the petroleum crisis in the 1970s, the cost of organic solvents increased dramatically, so aqueous-based coatings also had potential cost saving.(Ansel and Popovich,1990; Seitz,1990).

Due to the expense of the organic solvents, the problem of the release of these potentially toxic agents into the atmosphere, the high cost of solvent recovery systems and their explosiveness, pharmaceutical manufacturers are flavoring the use of aqueous-based film coating (Ansel and Popovich, 1990)

The Tablet Coating Process

The coating process can be described by initially discussing the key factors that it comprises and then showing their complex interaction. There are two primary components involved in tablet coating including coating process and materials used in film coating.

1. Coating process

Tablet are film coated by the application or spraying of the film coating solution upon the tablets. The volatility of the solvent enables the film to adhere quickly to the surface of the tablets. The equipment and other coating variables are important factors in coating proces.

1.1 Equipment

Most equipment currently used for film coating has

evolved from standard panning equipment that was prevalent in the sugar coating.

Although conventional equipment can be practically used for film coating, it does not represent an ideal choice,partly because of the relatively low efficiency in air exchange, and also because it does not usually represent a closed system in which the hazards of using organic solvents can be kept to a minimum. Thus, the trend has been to increases greatly the ability of the equipment to remove solvent from the coating environment and also to improve tablet mixing efficiency within the pan. This has been achieved with the development of the horizontally rotating, baffled, perforated pan such as the Accela-Cota, Hi-Coater or Driacoater and air suspension system (Porter,1982). The general types of the equipment for tablet coating may be categorised as shown in Table 2.

Table 2 Types of the equipment for tablet coating (Porter,1982; Seager et al.,1985).

Type	Modification
1. Conventional pan system.	
- Standard coating pan	A pear,hexagonal or spherical metal pan
- Pellegrini pan	A integral baffled pan containing a drying air diffuser (an angular pan)
- Glatt immersion-sword system	A pan containing a perforated metal sword
- Immersion-tube system	A pan containing a tube delivering the heated air and a spray nozzle

Type	Modification
2. Perforated pan system.	
- Acela-Cota	An angular pan with the completely perforated flat portion of the pan periphery
- Hi-Coater	An anqular pan with the four perforated flat portion of the pan periphery
- Driacoater	An angular pan with the inside periphery having a hollow perforated ribs for introducing drying air
3. Air suspension system	
- Wurster fluidized bed coater	Tablets continuously pass up the central column
- Glatt fluidized bed coater	Tablets continuously pass up the central column
- Aeromatic fluidized bed coater	Lack the inner coating portion
- Freund Flo-coater	Lack the inner coating portion and locate the spray guns in column wall air angle downwards

1.2 Variables

The coating of tablets in a coating pan involves spraying the coating compositions through one or more spray guns onto a rotating bed of tablets. The applied coating must be dried before it touches the coating pan or receives its next application. To attain a continuous coating operation, the rate of water evaporation from the coated tablets must equal the rate of water applied in the coating liquid. At equilibrium, there is a balance between the input and the exhaust variables. The input variables include temperature and humidity if the drying air, rate of application of the coating liquid, and surface area of the tablets. The exhaust variables include the exhaust air, the capacity of the exhaust air to carry the evaporated water at that temperature, the rate of evaporation of water from the coated tablets at the tablet bed temperature and the

coated tablet surface area from which the water must evaporate.

The numerous variables involved in the film coating process need to be controlled to ensure consistent product quality. These variables may be classified into following categories (Kulvanich, 1993) :

Variables	Comment and Discussion
1. Equipment	
- Pan design / baffling	Pan speed, baffling and loading affect the mixing of the tablet bed
- Speed	Speed that are too slow may cause localized overwetting, tablets sticking to each other or to the pan
2. Spray system	
- Spraying rate/degree of atomization/spray pattern	In the airless, high pressure system, the spray rate, the spray pattern and degree of atomization are directly affected by fluid pressure and nozzle design. In the air system, the rate of solution flow is most directly affected by the liquid pressure and liquid orifice size The degree of atomization and spray pattern are affected by air pressure, air volume, the orifice size, nozzle configuration, fluid pressure,and fluid viscosity
- Nozzle-to-bed distance and angle/number of spray gun / pumping system	The spray width can be adjusted by moving the nozzle close or futher away from the tablet bed, but not too wide which could result in application of the solution directly on the pan surface or localized overwetting may result by to narrow of spray pattern. More spray guns can be used to apply the coating

	solution The pumping of the solution should be also adjusted to obtain a suitable condition
3. Process air system - Temperature, volume and quality/balance between supply and exhaust air flow	Supply air should have some degree of dehumidification in order to minimize seasonal fluctuation in the moisture content of incoming air. An alternative procedure is to compensate for variation in humidity of inlet air by optimizing one or more of : air volume,inlet air temperature and spraying rate

2. Materials used in film coating

The typical film formulation consists of polymer, plasticizer, solvent, colorant, opaquant-extender, and miscellaneous. An ideal film coating material should have the following attributes :

1. Solubility in solvent of choice for coating preparation
2. Solubility required for the intended use, eg., free water-solubility, slow water-solubility or pH-dependent solubility
3. Capacity to produce an elegant looking product
4. Stability in the presence of heat, light, moisture, air and the substrate being coated
5. Essentially no color, taste or odor
6. Compatibility with common coating solution additives
7. Nontoxicity with no pharmacologic activity, and ease of application to the particles or tablets
8. Resistance to cracking, and provision of adequate moisture, light, odor, or drug sublimation barrier when desired
9. No bridging or filling of the debossed tablet surfaces by the film former
10. Ease of printing procedure on high-speed equipment.

No commercially available material fulfills all requirement of an ideal coating material. A pharmaceutical scientist usually formulates a coating solution to achieve certain desired properties

for the film coating product. The availabed film former can be classified into nonenteric materials (hydroxypropylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, ethylcellulose, povidone. polyethylene glycol and acrylate polymer) and enteric materials (cellulose acetate phthalate, acrylate polymer, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate) (Rowe, 1984).

Some pharmaceutical investigators found that some materials such as maltodextrin (Porter and Woznicki, 1989), cereal solid hydrolysate (Small and Jeffries, 1973) and substance isolated from roots of *Salacia macrosperma* (Venkateswarlu et al., 1993) could be used as film forming material.

Theory of film formation

In pharmaceutical film coating process, when a coating solution is applied upon the surface of tablets, sets of force occur between the film forming polymer molecules (cohesion), and between film and substrate (adhesion)(Banker, 1966).

Cohesion refers to the ability of contiguous surfaces of the same material, at a molecular or at a supermolecular level, to form a strong bond which prevents or resists separation at the point of contact. To obtain high levels of cohesion the two phenomena are necessary :

1. The cohesive strength of the material, molecule to molecule, must be relative high.
2. The coalescence sufficiently occurs to disappeare the boundary layers between adjacent polymer molecular layers.

The individual or segments of macromolecules between and within film layers may diffuse under a variety of conditions including gelation, when polymers are deposited in solution over a previous polymer layer or at elevated temperatures corresponding to a semisolid state. The result, if there is adequate cohesive attraction between the molecules and sufficient diffusion and coalescence, will be a restoration of the polymer structure to a uniform nonlaminated matrix at the contact zone (Honeywill, 1986). There are some factors

affecting a cohesion in film coatings which can be briefly mentioned (Banker, 1966) :

1. Processing factors

The factors which may increase film cohesion include : increase contact temperature, surface contact time and coat thickness, and use a suitable coating solution concentration, degree of polymer solvation and viscosity.

2. Formulation factors

The formulation factors affecting cohesion include polymer chemistry and polymer structure properties, solvent effects, the dispersed solids, and plasticization.

Both processing and formulation factors affecting cohesion in film coating can be adjusted to achieve a desired film coating product (Banker, 1966).

Fundamental Properties of Polymeric Materials and Their Application in Film Coating Formulations

The technology of film coating is not new; it has precedents in both paints and adhesives technology. It is a field of applied science where specfic disciplines such as polymer science, material science, surface science, mechanics, physical chemistry and pharmacy meet. It is safe to say that when problems occur the solution will never be found in one discipline.

The fundamental properties of polymer, i.e. their molecular weight and molecular weight distribution, interaction with plasticizers and solubility in solvents can be used in optimising the formulation, especially in the solution of such problems as film cracking, edge splitting and bridging found during the film coating. These three problems are thought to be caused by the buid up of stresses within the film coating during shrinkage on evaporation of the solvent. This will result in either cracking or edge splitting if the stresses are greater than the tensile stress required to rupture the film or bridging if the stresses greatly exceed the forces of adhesion holding the film into the intagliation (Rowe, 1982 c). These problems are shown in Figure 1.

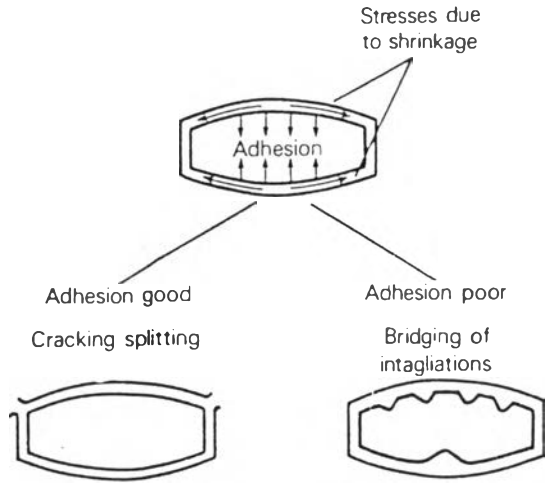

Figure 1 Film cracking, edge splitting and bridging of the intagliation.

During the coating process polymer chain mobility is an important factor in influencing the magnitude of the stresses developed. When the polymer chains are mobile, as in the case of the polymer solution and, to a certain extent, the gel, they orientate themselves so as to relieve any stresses formed. However, as solvent, and hence the free volume, is lost from the gel structure, the chain mobility becomes progressively restricted and any developed stresses become in (Rowe, 1982 c).

The solution of these problems has at least two courses of action; to attack the root cause of the problem and to formulate so as to minimise the incidence of the defect. The various aspects of the film coating formulation will be controlled, i.e. the choice of the grade of polymer, the plasticizer and the other additves.

1. The grade of polymer

Some properties of polymeric materials for film coating may be mentioned to a molecular weight and molecular weight destribution, a polymer chemistry, and a crystallinity.

1.1 Molecular weight and molecular weight distribution

In film coating, the suitable mechanical strength is required. One way to increase the strength of a polymer is to increase its molecular weight. Low molecular weight polymers are usually relativelly weak but as the molecular weight is increased the strength also increase until at some critical molecular weight there

is no further increase in strength (Radebaugh,1988; Rowe, 1982 a). However, for smooth coating operation, the coating material should be sufficiently low molecular weight, low viscosity and should have good film-forming ability. Therefore, its molecular weight and molecular weight distribution are important factors in determining the efficiency as a coating material (Nagai, Sekigawa and Hoshi, 1989).

All the polymers used in film coating are controlled by means of an apparent viscosity representing the viscosity of a specific concentration of the polymer dissolved in a specific solvent at a specific temperature. Since viscosity control is achieved by controlling the chain length during the production process, the viscosity can be regarded as an indirect measure of the molecular weight of the polymer (Florence and Attwood , 1981; Rowe, 1984).

It is possible to determine the molecular weight by using the Mark-Houwink equation :-

$$[\eta] = KM_v^a$$

which relates the intrinsic viscosity of the polymer [η] to its molecular weight (M_v) using the constant (K) and (a). These constants are usually determined empirically by applying the equation to sample of known molecular weight and with very narrow molecular weight distribution and are dependent on the solvent and the temperature used (Rowe, 1982 b).

The low viscosity grade polymer is preferred as it is possible to prepare with a higher concentration which permits the formation of a coating more quickly and with economy of solvents (Johnson and Mich, 1970). It is also known that the addition of high molecular weight components to a distribution e.g. as a consequence of blending high and low molecular weight grades of a polymer can increase the effective strength of that polymer. This effect has been shown to be beneficial in the case of film coated tablets prone to edge splitting in that the incidence of this defect was significantly reduced when blends of high and low molecular weight grades of hydroxypropyl methylcellulose were used (Rowe, 1982 b). Blending may be carried out using the formula :

$$\log \eta_S = \frac{N \log \eta_1 + (100\text{-}N) \log \eta_2}{100}$$

Where η_S is the apparent viscosity sought, η_1 and η_2 are the apparent viscosities of the first and second components of the blend, and N is the weight percent of the first component (Rowe, 1984).

1.2 Polymer chemistry

The shape of polymeric molecules exerts a strong influence on cohesion in film, since molecular shape largely determines both the diffusibility of a macromolecule or its individual branches or segments, and the strength of its interlacing areas. Branched molecules in which the branches do not greatly hinder diffusion may have a greater cohesive strength than nonbranched equally noncrystalling polymers, based on a firmer anchoring of such macromolecules in the diffusion layer. Macromolecules with a regular structure and not in a strongly crystalline state should be more diffusible than molecules with a highly irregular stereochemical structure. In a homologous series, lower molecular weight fractions exibit a greater cohesion, and show a greater change in cohesive strength with temperature changes. In strongly polar polymers, self-adhesion by diffusion is insignificant, due to the minimal flexibility and fixed order of the macromolecules caused by the intermolecular forces holding the polymer chains in a fixed form (Banker, 1966).

1.3 Crystallinity of polymer

A high ordered, crystalline polymer represents a polymer system of maximum compactness and cohesive strength. The intermolecular forces which promote cohesion, particularly hydrogen bonding, also premote crystallinity. The closer the polar groups are to one another along the chain and the better their lateral fit, the more crystallinity is promoted crystallinity is related to film stiffness and yield point, and also affects film permeability,

flexibility, and brittleness. Modulus increases with increase in crystallinity (Banker, 1966; Radebaugh, 1988).

2. The plasticizer

The plasticizer is defined as a substantially nonvolatile, high boiling and nonseparating substance. plasticizer is often added to polymers in order to change the physical properties and enhance the film forming characteristics of polymers

Mechanism of Plasticization

Attempts at explanation of the mechanism of plasticization may be grouped under three concepts called the lubricity, the gel and the free volume theories (Doolittle, 1954; Seara and Darby, 1982).

1. The lubricity theory, which is proposed the function of the plasticizer is to reduce the intermolecular friction. The underlying thought is that when a plastic is fixed the macronolecules must work back and forth over each other. The plasticizer is thought of as lubricating this movement and thereby reducing the internal resistance.

2. The gel theory viewes the plasticization as disgregation with subsequent more or less oriented aggregation by the possibility of the formation of the three-dimensional network by many unions of macromolecules at a few places along their chain lengths and to increased tendency toward gel formation in more concentrated solutions because of the greater likelihood of polymer-ploymer contacts.

The gel theory differs from the lubricity theory in several important aspects. The proponents of the gel theory consider rigidity in an unplasticized mass to be caused by an internal three-dimentional honeycomb structure and gel formed by loose attachments between the macromolecules which occur at intervals along the molecular chains. The plasticizer masks the centers of force by selectively solvating the polymer chains. At the same time there are free molecules of plasticizer unattached to polymer to be particularly effective in swelling of the gel and to facilitate the

movement of the polymer molecules, that is, increasing flexibility.

3. The free volume theory started simultaneously with the atomic and molecular theories and the inevitable question, what lies between the atoms and molecules. The free volume or free space of a crystal, glass, or liquid may be defined as the difference between the volune observed at absolute zero temperature and the volume measured for the real crystal, glass, or liquid at a given use temperature. This may be expressed by the equation :

$$V_f = V_t - V^o$$

where V_f is the free volume. V_t is the specific volume at temperature t, and V^o the specific volume at some reference point.

The glass transition temperature is reached at which the material becomes glassy. At this point the decrease in volume continues, but the amount of change is smaller. The decrease must represent the decrease in space between the atoms and molecules (Sears and Darby, 1982). Because an increase of hole free volume permits increased motion of polymer molecules, a study of plasticization is a study of ways to increase free volume. The motion and there fore the free volume of a system may be increase by :

1. Increasing the number of end groups (lower the molecular weight of polymer).

2. Increasing the number or length of side chain (internal plasticization).

3. Increasing the chance of main chain movement by inclusion of segments of low steric hindrance and low intermolecular attraction , low polarity and H-bonding,(internal plasticization).

4. Inclusion of a compatible compound of low molecular weight (external plasticization).

5. Raising the temperature.

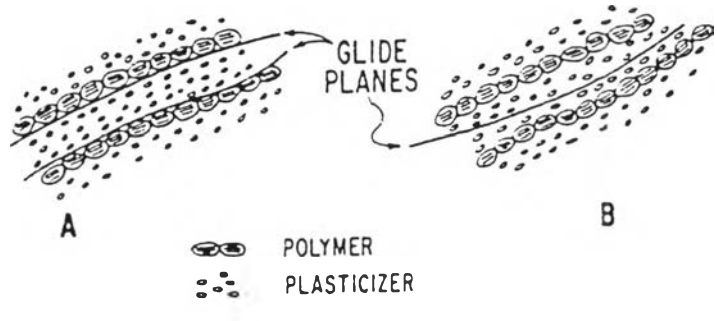

Figure 2 The lubricity theory of plasticization. A. polymer-polymer bonds and plasticizer -plasticizer bonds are preferred over polymer- plasticizer bonds: B. polymer-plasticizer bonds are preferred.

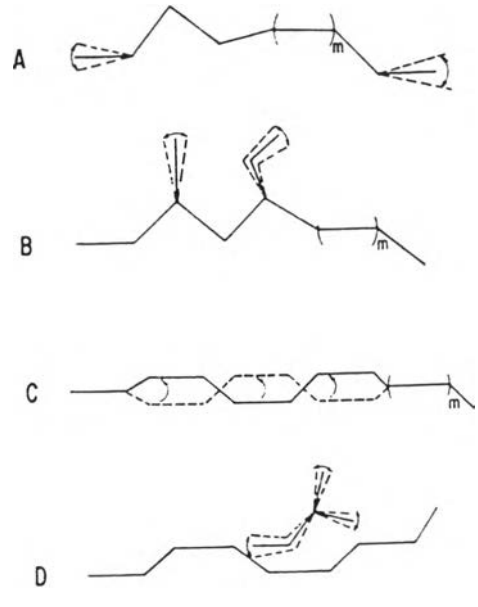

Figure 3 Sources of free volume for plasticization; A, chain end motion ; B, side chain motion; C, main chain "crankshaft" motion; D, external plasticizer motion.

The plasticizer and polymer are generally thought to be held together by intermolecular secondary valence forces forming a complex or molecular aggregate. The lowering of the glass

transition temperature below room temperature by plasticization changes a hard, brittle, glass-like material at room temperature to a soft, flexible and tough material (Banker, 1966).

Plasticizers commonly used in pharmaceutical applications include: (a) glycol derivatives which are useful for cellulosics and polyvinyl alcohol; (b) phthalate esters, which account for over half of all the plasticizers used industrially; (c) phosphate esters; (d) adipates, azelates, oleates, and sebacates, especially useful for vinyls; (e) epoxy plasticizers; and (f) fatty acid esters from natural sources (Edgren and Theeuwes, 1990).

The basic requirements of any plasticizers in a polymer system are compatibility and permanence. The most effective plasticizers will generally resembly most closely in structure the polymer they plasticized. Thus, water soluble cellulose ethers are best plasticizer by hydroxyl containing compounds. Substantially aliphatic nonpolar polymers are best plasticized by esters and nonsolvent oils. (Banker, 1966; Aulton, Houghton and Wells, 1985; Radebaugh,1988).

Some interesting effects of plasticizers related to the film coating are :

1. The relationship between intrinsic viscosity of polymer solution and film properties.

A convenient way of assessing the degree of polymer / plasticizer interaction is to measure the intrinsic viscosity of the polymer dissolved in the plasticizer. A liquid with high solvent power for the polymer is expected to cause chains to expand, whereas a liquid with low solvent power would be less effective or possibly cause the chains to coil up. Therefore the resulting solution has high viscosity where interaction between polymer segments and solvent molecules is prefered (Radebaugh, 1988).

Entwistle and Rowe (1978) found a correlation between the intrinsic viscosity of the polymer/plasticizer solutions and the tensile strength, elongation at rupture of cast film. The mechanical properties were at a minimum when the intrinsic viscosity was at a maximum. A relationship was found between the lowering of a calculated glass transition temperature of hydroxypropyl

methylcellulose in the presence of the propylene glycol, PEG 200 and glycerol, and the higher of the intrinsic viscosity. Shah and Zatz (1992) found that the high values for reciprocal of modulus of elasticity and low tensile strength correlated with high intrinsic viscosity values. Among the plasticizers tested dimetyl phthalate and glyceryl triacetate were most efficient plasticizers for cellulose esters.

2. The effect of plasticizer type and amount

The degrees of lowering in softening point and glass transition temperature depend on the types and levels of plasticizer used.

Effect of plasticizer concentration on certain film properties : swelling, porosity and permeability has been studied in films of two acrylate-methacrylate copolymers. It was found that glycerol triacetate or glycerol tributyrate content in both films cannot be varied beyond 16 $\pm$ 5 % w/w of film weight because of the bleeding occurrence. Mixing of the two plasticizers offered of means of varying the content of individual plasticizer in the film. Increase in the fraction of the more hydrophilic glycerol triacetate in the mixed plasticizer coupled with a decrease in the less hydrophilic glycerol tributyrate increase the urea permeability of the less hydrophilic films of methacrylate film; this was related to the leaching of glycerol triacetate with also resulted in enhancement of film porosity. In the more hydrophilic film of acrylate, urea permeability increased as the more hydrophilic glycerol triacetate fraction decrease and the less hydrophilic glycerol tributyrate fraction increased, a finding which was attributed to the potential of glycerol tributyrate for promoting film swelling and porosity. Permeability is therefore dependent on the hydrophilicity of both the plasticizer and polymer considered together (Okor, 1982).

Free films produced using ethylcellulose pseudolatex were prepared by a spraying method. The effect of 10 different plasticizers repersenting three chemical classes (citrate esters, di-acid esters and fatty acids/alcohols) on free film mechanical properties was determined. Increasing the amount of plasticizer led to an increase in free film elongation and a decrease in modulus and stress and the results indicated that type, amount, elevated storage temperature and humidity influenced free film mechanical

behaviour. These changes by temperature probably arised from further gradual coalescence of ethycellulose pseudolatex particles (Hutchings, Clarson and Sakr, 1994).

Plasticized hydroxypropyl methylcellulose free films was used to study the effect of two plasticizers with different aqueous solubilities, triacetin and PEG 400 on the water vapor permeability of free films. PEG 400 was found to enhance water vapor permeability while triacetin slightly decreased water vapor permeability (Okhamafe and York, 1983; Johnson et al., 1991).

3. The effect of molecular weight and size of the plasticizer

The effect of the addition of various grades of PEG to HPMC film has been studied. The ultimate tensile strength and elongation at break were reduced. However, in the case of higher molecular weight grades of PEG , this was without a corresponding large increase in elongation. Only the lower molecular weight grades of PEG had a significant effect on elongation and a marked reduction in strength (Aulton and Abdul-Razzak. 1981). Lim and Wan (1994) observed the bleeding of PVA films plasticized with PEG. The reason could be that the PEG molecules, being seven times larger in size than glycerol molecules, were rejected from the crystal lattice of PVA films. Sakellariou, Hassan and Rowe (1994) have been studied the plasticization by PEG 6000 on hydroxypropyl methylcellulose and polyvinyl alcohol films. PEG 6000 was a poor plasticizer for the two polymers. It segregated into a separate due to its thermodynamic incompatibility.

4. Antiplasticization

Antiplasticization arises from an interaction between the polymer and the plasticizer molecules and decreases the molecular mobility of the polymer. However, when the temperature is raised above the glass transition temperature, the polymer films contain enough energy to overcome the interaction between the polymer and plasticizer molecules, and the antiplasticization effect is disappeared (Guo, 1993; 1994). Poor plasticization by propylene glycol on HPMC film has been studied. The result may be due to hydrogen bonding which would reduce the movement of the chain molecule. Also, because propylene glycol is a relatively small molecule, when interspersed in the large polymer structure, it may not adequately reduce the rigidity of the polymer (Masilungan and Lordi, 1984).

Antiplasticization decreases the free volume and accompanies with a decrease in the water transport. The free volume in the polymer is affected by annealing and the other by antiplasticization (Guo, 1994 a).

3. The other additives

Frequently adding other ingredients to a coating composition is necessary to stabilize or improve the product. These some materials are colorant, opaquant and others.

3.1 Colorant and lake

Often a distinctive color is desired to give the product a unique identity. The colorant can be either solubilized or suspended in the solvent system. The addition of these materials provides distinctive color and elegance to the coated tablet. The most brilliant colorants are provided by certified Food, Drug and Cosmetic (FD&C) or Drug and Cosmetic (D&C) dyes and lakes (Goldemberg. 1983; Seitz. 1990).

Prillig (1969) has studied the effect of colorants on the solubility characteristics of cellulose polymers (HPMC,HPC and sodium ethycellulose sulfate). Coatings containing FD&C Red No.3,FD&C Red No.4, D&C Red No.17, D&C Red No.18, D&C Red No.21 and D&C Red No.22 were shown to have a retardation effect on disintegration and dissolution rate of riboflavin coated tablet.

3.2 Opaquant

Insoluble particulate materials in film coatings provide color and opacity to improve appearance or stability. Occasionally they are used to reduce tackiness or stickiness. Opacifiers are usually inorganic materials that provide hinding power. (Radibaugh, 1988). The incorporation of opaquants into the polymer film was also affected the mechanical properties and water transmission. Talcum created more stress in the film owing to its platelike shape when compared with the spherical shape of titanium dioxide (Akhamafe and York, 1985 b). The rate of water vapor transmission is decreased but defferent extents as solid-loading content is increased for both talcum and titanium dioxide (Parker, Peck sand Banker, 1974).

3.3 The others

To provide a dosage form with a unique characteristic, special materials may be incorporated into the coating solution. Flavors or sweeteners are added to mask objectionable odors or to enhance a desired taste. Waxes are used in small amount to lend a finish touch. Surfactants are used to solubilize immiscible or insoluble ingredients, or to facilitate faster dissolution of the coating. Antioxidant or sunscreening agent are incorporated to stabilize a dye system to oxidation and color change. Antimicrobials are added to prevent microbial growth in the coating composition (Hajratwala, 1974; Seitz, Mehta and Yeager, 1986; Carroll, Bradley and Kalmikoff, 1994).

Mechanical Properties of Film(Aulton and Abdul-Razzak, 1982; Radebaugh, 1988).

The elasticity and tensile strength of the various films can be evaluated by a tensile-strength tester. The test is particularly appropriate to obtain the optimum ratio of plasticizer to polymer and to determine the effect of colorants and opaquants on the film properties.

The tensile testing process is to apply increasing tensile load at a constant rate to a film strip which know dimensions in the dimension perpendicular to the cross-section of the film strip until the failure takes place. The load at film failure will be measured in term of force per unit cross-sectional area of the film.

A typical stress-strain curve is shown in Figure 4. The ultimate tensile strength is the maximum applied stress at which the film breaks. Stress is calculated by dividing force by original cross-sectional area and elongation at break is calculated by dividing the increase in length by original length. Elastic modulus is a measure of the stiffness and rigidity of the film. It is calculated as applied stress divided by the corresponding strain in the region of linear elastic deformation. Yield point in the figure is a limit of elasticity. Area under curve is a function of the work done in breaking the film and is representative of the film's toughhness. The energy to break per unit area is calculated by dividing the area under curve by the volume of the specimen between the clamps.

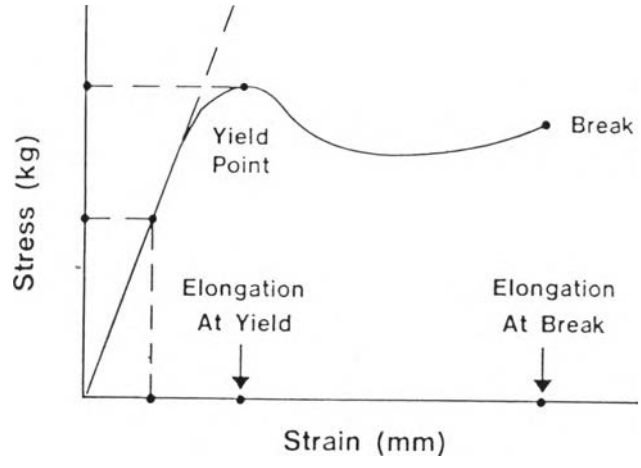

Figure 4 The stress-strain curve of a polymer film.

In addition, the film can be submitted for the following tests shown in Table 3 and the evaluation of the quality of coating on a tablet can be determined by many methods as shown in Table 4.

Table 3 The polymeric film evaluation.

Test	Method
Film hardness	- The microindentation apparatus (Rowe,1992 b)
Puncture and shear	- Using the force-detecting and drive mechanism (Radebaugh,1988)
Moisture sorption	- Periodic weighing of film after exposure to elevated humidity
Water vopor permeability	- Sealing film across the transmission cell and periodic weighing of cell (Prater, Meakin and Wilde, 1982) - A mass spectrometric technique (Porter,1982)
Thermal properties	- Differential scanning calorimetry (DSC)and Thermal mechanical analysis (TMA) (Misev,nd;Radebaugh,1988)
Chemical analysis	- Using static secondary ion mass spectrometry(Davies et al.,1990)

Table4 The coated tablet evaluation (Mehta,Yeager,1986 Redebaugh,1988; Rowe,1992 b).

Test	Method
1. Visual inspection and counting of defects	Simple and rapid method for assessing the incidence of defects
2. Color measurement	The tristimulus colorimeter is used to assiss color uniformity
3. Opacity measurement	The tristimulus colorimeter is used to assiss color uniformity
4. Roughness	Using a stylus-type analyzer
5. Gloss measurement	Photodetector is used to measure light reflection
6. Film continuity	A mercury intrusion method
7. Film hardness / elasticity	Using microindentation
8. Crushing strength	Using tablet hardness tester
9. Film adhesion	The tablet-filmadhesion tester
10.Disintegration and dissolution rate	Using disintegrater and dissolution apparatus
11.Stability	Exposure the coated tablet to stress condition and determine the drug content and list 1-10 again

Film Coated Tablet Defects

Variations in the coating formulation or a poorly controlled coating process may result in unacceptable quality defects in the film coating such as cracking, splitting, picking, roughness, bridging and filling, blistering, hazing, mottling and pitting. For this experiment there are three interesting film defects (cracking, splitting and picking) included in the assessments.

1. Cracking. Cracking occurs if internal stresses in the film exceed the tensile strength of the film. The film cracks across the crown of the tablet. The addition of higher molecular weight polymer, use of polymer blends, and/or addition of some plasticizers can relieve the internal strain to avoid film cracking (Rowe, 1982 a; Okhamafe and York,1985 c; Rowe and Roberts, 1992).

2. Splitting. The edges of coated tablets are a weak point. When internal stresses in the film exceed the tensile strength, the film splits around the edges of the tablets. The use of higher molecular weight polymer and/or adding plasticizers is the best way to solve this problem (Rowe, 1992 c).

3. Picking. Picking occurs under the overwetting where tablets can stick together or the coating pan and then break a part giving a picked appearance to the tablets surface and resulting in a small exposed area of the core. A reduction in the liquid application rate or increase in the drying air temperature and air volume usually solve this problem (Seitz, Mehta and Yeager, 1986).

Chistosan (Knarczyk, Krowczynski and Krzek, 1988)

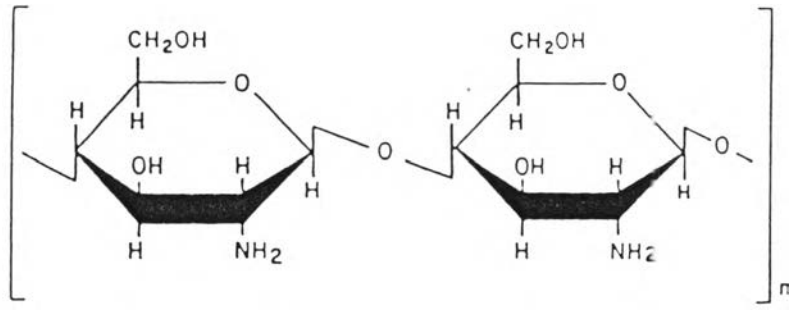

Figure 5 Structure formula of chitosan.

Chemical name : Poly - 2 deoxy - 2 amino glucose

Chitosan is a linear cationic biopolymer combined by beta 1 - 4 glycosidic linkage. It is produced by deacetylation of chitin. The empirical structure is $(C_6 H_{11} O_4 N)n$ with molecular weight 161 for monomer and 10,000 - 1,000,000 for polymer Chitosan is tasteless, odorless, white to cream flake or powder. It has pKa 6.3-7. Chitosan is incompatible with anionics and substances with aldehydes groups. It is hygroscopic and should thus be kept in well-closed container.

Characteristics of Chitosan

Some important characteristics of chitosan can be briefly mentioned as the following :

1. Molecular weight

The average molecular weight of chitosan is certainly the most difficult parameter to obtain with precision. This is not only the strong interactions of various origins occuring with this polysaccharide but also to the difficulty to determine precisely the exact value of the concentration of the polymer used, especially if chitosan is not fully deacetylated. Various methods to determine

the molecular the molecular weight of chitosan are listed in Table 5(Muzzarelli, Lough and Emanuelli,1987; Knapczyk, Krowczynski and Krzek,1988; Tokura, 1994).

Table 5 The method of determining the molecular weight of chitosan.

Method	Average weight determination	Related equation
Direct determination		
1. Osmotic pressure method - Membrane osmotic pressure - Vapor-pressure osmotic pressure	Mn	$\pi/C = RT\ (1/Mn + A_2C+...)$ π/C VS.C $(\pi/C)c \rightarrow o = RT/Mn$ π = osmotic pressure, A_2 = second virial coefficient
2. Light scattering method	Mw	$Kc/R\theta = 1/Mwp\ (\theta) + 2A_2\ C+..$ $Kc/R\theta$ VS $\sin^2(\theta/2) + Kc$ (zimm plot) $(Kc/R\theta)\ c \rightarrow o = 1/Mw$ $\theta \rightarrow o$ $R\theta$ = Reduced light scattering intensity
3. Sedimentation equilbrium method	Mw,Mz	$M = RT/(1-V\rho)\omega^2$ ✳ $((dc/d\chi)\ /\chi c)$ ω = Angular velocity, χ = Distance from rotation axis
Indirect determination		
1. GPC method	M,Mw,Mw/M	log M VS.Ve , Ve = Elution volume
2. Viscosity method	Mv	$[\eta] = KM^a$, $[\eta]$ = intrinsic viscosity η_{sp}/c , $\ln \eta_r/c$) VS. C $[\eta] = (\eta_{sp}/C\ )\ c \rightarrow o = (\ln \eta_r/c)$ $c \rightarrow o$ η_{sp} = specific viscosity , η_r = relative viscosity

Mn : Number-average molecular weight
Mw : Weight-average molecrlar weight
Mz : Z-Average molecular weight
Mv : Viscosity-average molecular weight

2. Degree of deacetylation

Chitosan does not refer to a specific compound but to two ranges of copolymers, containing the two monomer residue, anhydro-N-acetyl-D-glucosamine and anhydro-D-glucosamine. The former is the predominant component in chitin and the latter is the predominant conponent in chitosan. Usually, chitosan has degree of deacetylation between 70 and 90 % . The molecular structure and properties of chitosan are affected by the degree of deacetylation. As a consequence of the influence of this parameter on the properties of chitosan and thus numerous methods of determination the degree of deacetylation were proposed in many literatures. These methods are given in Table 6. Unfortunately, a large discrepancy exists between the values obtained with some of them. For example, the titration methods are imprecise and uneasy to use. Spectroscopic determinations have been prefered. NMR and IR were proposed, but the first is limited to values of degree a acetylation > 5 % and the second depends on the choice of the standardization method allowing a correlation between degree of deacetylation and a given absorbance to be established, but also on the choice of the two bands required for the calculations as shown in Table 6. Thus if the IR spectroscopic determination remains an easy and fast determination, a low of difficulties and imprecision must be avoided and the other methods can be used to confirm the IR spectroscopic test (Rinaudo and Domard,1989; Tokura,1994).

Table 6 Method of determining the degree of deacetylation.

Method	Description	Ref.
Colloidal titration	Amino residue analysis	Terayama,1952
Elemental analysis	Carbon,hydrogen and nitrogen determination	Tokura,1994
Enzymatic method	Colorimetric or HPLC assays of hydrolyzed chitosan	Nanjo, Katsumi and Sakai,1991
First derivative ultraviolet spectro-photometry	Absorption determination at 199 nm by first derivative UV spectrophotometry	Muzzarelli et al., 1985
Gas chromatography	Retention time of methanol in a chitosan column	Muzzarelli et al., 1980
Infrared spectrometry	Absorption band ratios a. 1655^{-1} cm / 2867^{-1} cm b. 1655^{-1} cm / 3450^{-1} cm	Miya et al.,1980 Baxter et al,1992
Mass spectrometry	NH_2 / NHCO CH_3 ratio	Hayes,1978
NMR spectroscopy	Chemical shift	Tokura,1994
Thermal analysis	Empirical calibration technique	Alonso,Peniche-Covas and Nieto, 1983

3. Solubility

Since chitosan is a cationic polymer having a pKa of about 6.3, its solubility depends on the presence of the free amine groups capable of being protonated by the acid medium. It might be expected that these would be a specific level of deacetylation above which solubility in acid solution would be exhibited. Certainly there would appear to be no need for the high level of deacetylation in order to induce solubility in acid solution. For example, chitosan having degree of deacetylation about 64 % can be completely soluble (Robert, 1994).

Thus the exact degree of deacetylation required to render a polymer soluble is not readily determined, and undoubtedly varied with such factors as chitosan molecular weight, concentration and impurity, and nature of the acid used.

The acid species which can solubilize and insolubilize the chitosan are listed in Table 7. Miscibilitly of chitosan solution with acetone, ethanol and methanol depends on a concentration of the organic solvent. At concentration as high as 50 % of

organic solvent, chitosan solution still functions without any precipitation (Lower,1984).

Table 7 Solubility of chitosan in various acids.

Type	Soluble in	Insoluble in
Inorganic acid Organic acid	HCl and $HClO_4$ Acetic, adipic, citric, formic, lactic, malic, malonic, oxalic, propionic, pyruvic succinic and tartaric acid	H_2SO_4 and H_3PO_4

4. Viscosity

The apparent viscosity of chitosan solution is dependent on the molecular weight, the concentration, the added salt concentration and the temperature. The viscosity increases with an increase in molecular weight and concentration of chitosan, while it decreases the viscosity with an increase in temperature. The addition of salts will reduce the repelling effect of each positively

charged deacetylated unit on neighboring glucosamine unit and will reduce in an extended conformation of the polymer in solution. This effect resulting in a more random coil like conformation of the molecule will decrease the viscosity of chitosan solution (Muzzarelli,1976).

Filar and Wirich (1978) defined the molecular weight ranges of chitosan in terms of solution viscosity. These viscosity types were selected as representatives of readily be produced on a commercial scale from shrimp shell. The viscosity ranges are :

High : > 1000 cps., 1 % polymer in 1 % acetic acid.
Medium : > 100 - 250 cps.,1 % polymer in 1 % acetic acid.
Low : 25 - 70 cps., 2 % polymer in 2 % acetic acid.

Knapezyk, Krowczynski and Krzek (1988 b.) defined the molecular weight ranges of chitosan by determining the viscosity of the chitosan solution at concentration 1 % using acetic acid 1 %

of the solution. The viscosity ranges are low-below 200, medium-between 200-800 and high-above 800 mPa.s.

Rheology of chitosan solution behaves as a pseudoplastic material showing decreasing viscosity at increased shear (Muzzarelli,1976).

5. Chelating property

Contrary to other polysaccharides that give gels when they interact with multivalent cations, especially with divalent cations, chitosan solution does not follow this behaviour. This material can form complexs with many metals, such as Ag, Au, Cd, Cr, Cu, Fe, Hg, Mn, Ni and Pt, even though the mechanism probably is not completely understood. Rinaudo and Domard (1989) used the potentiometry method for understanding of the chelation process assuming that two vicinal NH_2 functions on the same chain are too far to interact with the same Cu and that only small variations of viscosity were observed during complex formation. Their predicted structure is depicted in Figure 6.

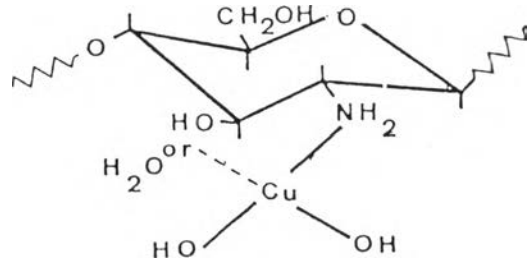

Figure 6 The predicted structure of cu-chitosan complex (Rinaudu and Domard, 1989).

6. Adsorption property

Chitosan was found to adsorb on some substrates such as cellulose and kaolin. With cellulose as the substrate the amount of chitosan adsorbed at equilibrium decreased with increase in the molecular weight of chitosan and with decrease in the degree of acetylation while with kaolin as the substrate there was the reverse dependence on the structural parameters with the equilibrium adsorption of chitosan increasing with increase in its motecular weight and with decrease in the degree of acetylation. The different dependencies on the molecular weight of the sorbate may be explained as due to the porous nature of cellulose while kaolin is nonporous. The low molecular

weight chains will be able to penetrate the small pores of cellulose. Contrary to the adsorption on kaolin which is dominated by electrostatic interactions. An increase in the adsorption on kaolin occured with increase in the charge on the chitosan molecule by decreasing degree of acetylation (Domszy, Moore and Robert, 1985; Robert, 1994).

The adsorption of cellulose-like biopolymers such as chitin, chitosan and microcrystalline cellulose on indomethacin was also investigated. The adsorptive capacity was ranked in the order : chitosan > chitin > microcrystalline cellulose and the adsorption isotherms were found to follow Langmuir and Freundlich equations (Lin and Perng, 1992).

7. Crosslinking (Lower, 1984 a; Skaugrud, 1989; Mireles et al., 1991)

Many multivalent anions can be reacted with the chitosan molecules giving the crosslinking products. Crosslinking can be done in acid, neutral or basic environment, depending on methods applied. Several gelling counter ions are available such as alginate,carboxymethyl cellulose, carrageenan, epichlorohydrin heparin, glutaraldehyde, molybdate, oxo acid and pectin.

8. Susceptibility to enzymatic hydrolysis

The susceptibility of chitosan to hydrolysis by a series of commercial enzyme, including lipases,proteases,carbohydrases, tannase and several glycanases has been explored. The large number of these enzymes were found to result in varying degrees of chitosan hydrolysis based on viscosity determinations (Pantateone, Yalpani and Scollar, 1991).

9. Toxicity

Chitosan is not expected to be digested or absorbed from the human gastrointestinal tract. The ingested chitosan would be excreted unchanged in the feces without significant absorption. This expected lack of absorption would preclude significant systemic toxicity. An oral LD50 of chitosan > 10 g / Kg was reported, indicating a lack of acute oral toxicity. In addition, the glucosamine backbone of chitosan can be considered

innocuous. Glucosamines are natural aminosugars found in large concentrations in certain foods, i.e. milk, egg, liver, yeast, molasse and tripe. They exist naturally in the body as components of mucopolysaccharides, mucoproteins and mucolipids (McCurdy, 1991). Another important aspect is that chitosan does not contain harmful mononers from any polymerization step and is regarded as physiological safe (Skaugrud, 1989).

Applications of Chitosan

Chitosan has been reported to have useful applications in the agricultural, biotechnology, clarification and waste management, cosmetic and personal care, dental, food, medical, pharmaceutical and other areas.The lists of them are given here:

1. Agricultural application

Use	*Ref.*
- Coat seeds (wheat, rice and peas)	Sandford, 1989
- Postharvest preservation of fruits and vegetables (bell pepper, cucumber, lime, strawberry and tomato)	Ghaouth, Aruland Assilin, 1991; Benjakul,1990
- teat-sealant in cow	Carolan et al., 1991
- Animal feed	Sandford, 1989

2. Biotechnological application

Use	*Ref.*
- Immobilization of enzymes	Sandford,1989; Leuba, Renken and Flaschel, 1990
- Immobilization of living cell	Skaugrud, 1989
- Encapsulation of DNA	Theodora, 1993
- Encapsulation of mammalian cell	Kim and Rha, 1989
- Purification and recovery	Sandford, 1989

3. Clarification and waste management application

Use	*Ref.*
- Water treatment - Petroleum sorbent - Amino acid recovery	Lower,1984 b; Struszczyk and Kivekas,1991
- Sewage effluent treatment - Radioactive waste treatment - Recovery microalgae	Lower,1984 a; Tony,1984; Sandford,1989

- Metal recovery	Kurita, Koyama and Taniguchi,1986

4. Cosmetic and personal care application

Use	*Ref.*
- Hair care (hair spray, shampoo, hair conditioner, setting lotion, blow-dry lotion	Lang and Clausen,1989
- Skin care (moisturizer, liptic, eye shadow, soap and cosmetic pack	Sandford,1989; Kokai and Koho ,1992 b; c
- Nail (nail varnish)	Lang and Clausen;1989
- Thickening agent and foam enhancer	Poole,1989; Lang and Clausen,1989

5. Dental application

Use	*Ref.*
- Gel for the treatment of periodontitis	Muzzarelli, 1993
- Prevention the formation of parodontal pocket	
- Filling paste	
- Toothpaste, chewing gum and mouth wash	Lang and Clausen,1989

6. Food application

Use	*Ref.*
- Anticholesterol and fat-binding substance	Fukada, Kimura and Ayaki, 1991;Ikeda,1993; Le Houx and Grondin,1993
- Inhibition of lactose intolerance	Laochariyakul, nd
- Recovery the flavour from seafood processing stream	
- Control the food additives release	
- Thickening agent	
- Dehumidifying and clarifying beverage	Averbach,1978; Imeri and Knorr,1988;Laochariyakul, nd
- Packaging of food	Nishiyama,1992; Kokai and Koho, 1992 a; d ; Wei et al., 1992

7. Medical application

Use	*Ref.*
- Wound healing accelerator	Jackson, 1984; Sparkes and Murray, 1986; Mosbey, 1988; Schmidt et al., 1993
- Plastic surgery	Muzzarelli, 1993
- Orthopedic (The cartilaginous tissue promotion)	Muzzarelli, 1993
- Urology (hemostatic effect and wound healing)	Bartone and Adickes, 1988; Muzzarelli, 1993
- Contact lenes	Markey, Bowman and Bergamini, 1989
- Antimicrobial activity	Muzzarelli, et al., 1990; Muzzarelli, 1993
- Antimycotic	Knapczyk, 1992; Lnapczyk, Macura and Pawlik, 1992
- Contraceptive	Smith, 1984

8. Pharmaceutical application

Use	*Ref.*
Tablet excipient	
- Direct compression diluent	Sawayanagi, Nambu and Nagai, 1982 a; b; Inouye et al., 1988; Knapczyk, 1993
- Wet granulation diluent	Brine, 1991
- Disintegrant	Ritthidej et al., 1994
- Binder	Upadrashta, Katikaneni and Nuessle, 1992
Matrix	
- Bead and pellet	Bodmeier, Oh and Pramar, 1989; Bodmeier and Pacratakul, 1989; Tapia, Goskonda and Upadrashta, 1993; Buckton and Newton, 1993
- Granule	Chandy and Sharma, 1992; Miyazaki et al., 1983
- Tablet	Nigalaye Adusumilli and Bolton, 1990; Adusumilli and Bolton, 1991; Akbuga, 1993
- Porous matrix for the controlled release of macromolecule	Cardinal and Curntolo, 1990

Dissolution enhancement of insoluble drug

- Dissolution enhancer	Sawayanagi, Nambu and Nagai,1982 c; Shiraishi et al., 1990; Imai et al.,1991

Film

- Polyelectrolyte complex film	Kawashima et al.,1985
- Film dosage form for coating granule	Kanke et al.,1989; Miyazaki, Yamaguchi and Takada,1990

Membrane

- Control drug permeation	Sawayanagi, Nambu and Nagai,1982 d;Nakatsuka and Andrady,1992; Thacharodi and Rao,1993 a; b
- Dialysis or filtration	Chandy and Sharma,1990; Gurashi, Blair and Allen, 1992
- Pervaporation process	Yisong, Wenjun and Tongyin, 1990; Uragami,1991
- Control some substances transport	Uragami,1994
- Reverse osmotic membrane	Shigeru and Fumio,1978; Yang and Zall,1984

Microcapsule or microsphere

- Microcapsule or microsphere	Gallo and Hassan,1988; Meshali et al.,1989; Nishioka, et al.,1989 a,b; Thanoo, Sunny and Jayakrishnan,1992; Ohya et al.,1993; Lin and lin,1992; Akbuga and Kurmaz,1994; Polk, et al.,1994

Bioadhesive

- Bioadhesive	Takayama, et al.,1990; Lehr, et al.,1992

Liposome

- Liposome stabilizer	Ohsoyen,1991; Henriksen, Smistad and Karlsin,1994

Gel

- Gel preparation	Roberts,1989; Tomoko,1992; Kristl,1993; Kubota,1993

9. Others : Antifouling, concrete processing, detergent ingredient, fabric for clothing, paper coating, photography and textile treatment (Brzeski,1987; Laochariyakul,nd)

Plasticizers

1. Propylene glycol (American Pharmaceutical Association and the Pharmaceutical Society of Great Britain,1986; John,1990; Reynolds,1993)

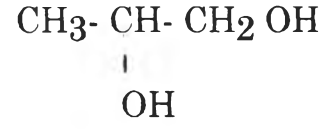

Figure 7 Structure formula of propylene glycol.

Chemical name : ($\pm$) - Propane -1,2 - diol

The empirical structure is $CH_3.CHOH.CH_2OH$ with molecular weight 76.10. Propylene glycol is clear, colorless, viscous and practically odorless liquid having a sweet, slighthy acrid taste. It has boiling point at 188 °c and flash point at 99 °c. It is miscible with water, acetone, alcohol, glycerin and chloroform, and immiscible with light mineral oil and fixed oils.

Use : Propylene glycol is a solvent or co-solvent used in solutions, parenterals, topical preparations and aerosol solutions and used as humectant in topical preparations.

Incompatibility : It is incompatible with oxidizing reagents such as potassium permanganate.

Stability and storage condition : It is stable in well-closed containers, but at high temperature in the open it trends to oxidise, giving the products such as propionaldehyde, lactic acid, pyruvic acid and acetic acid. It absorbs moisture when is exposed to moist air. This material should be stored in well-closed container and protected from light.

2. Polyethyene glycol 400 (PEG 400) (John,1990; Reynolds, 1993)

Chemical name : α - hydro - ω - hydroxypoly - (oxy-1,2-ethanediyl) glycol

The empirical structure is $HOCH_2(CH_2OCH_2)_nCH_2OH$ with molecular weight 380-420. PEG 400 is clear, colorless or slightly yellowish, viscous liquid having hygroscopic properties. The odor is slight but characteristic, and the taste is bitter and slightly burning. It has flash point at 238 °c and solidification point at 4-8 °c. PEG 400 is soluble in water, alcohols, glycols, acetone and benzene.

Use : PEG 400 can be used to be a solvent, solubilizer, suspending agent, emulsion stabilizer and lubricant. It is widely used as plasticizer in conjunction with film-former. It is useful as plasticizers in micro-encapsulated products to avoid rupture of the coating film when microcapsules are compressed into tablet.

Incompatibility : The two terminal hydroxyl groups can be esterified or eterified. Chemical incompatibilities occur with aspirin, carbonic acid, bismuth, mercury and silver salt, iodine, theophylline derivatives and some preservatives. It is incompatible with FD&C Red No.3 and FD&C Yellow No.5.

Stability and storage condition : It is chemically stable in air and in solution. PEG 400 do not support microbial growth nor become rancid. Oxidation may occur if PEG 400 is exposed for long periods to temperatures exceeding 50 °c. This material should be stored in well-closed container.

3. Glyceryl triacetate (Triacetin) (Doolittle,1954; Budavari,1989)

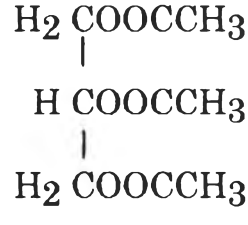

Figure 8 Structure formula of triacetin.

The empirical structure is C_3H_5 $(OCOCH_3)_3$ with molecular weight 248.20. Triacetin is colorless, somewhat oily liquid having a slight fatty odor and a bitter taste. It has melting point at -78 °c and boiling point at 258-260 °c. Triacetin is soluble in 14 parts of water, slightly soluble in carbon disulfide, insoluble in mineral oil and miscible with alcohol, ether and chloroform.

Use : Triacetin is used as fixative in perfumery, solvent for basic dyes and tanning in dyeing and plasticizer for cellulose acetate and nitrocellulose compositions.

Incompatibity : It is compatible with cellulose esters and ethers, acrylic resin, and polyvinyl acetate but incompatible with resins of vinyl chloride type, polystyrene and rubber chloride.

Stability and storage condition : It should be stored in airtight container.

Propranolol hydrochloride (John,1990; Gerber and Lotter, 1993; Lund,1994 Reynold,1994).

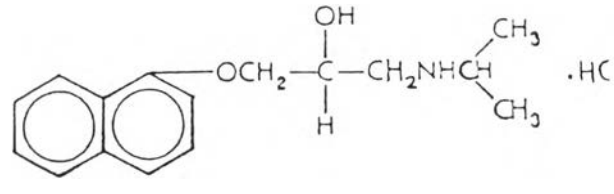

Figure 9 Structure formula of propranolol hydrochloride.

Chemical name:(±)1-Isopropylamino-3-(1-Naphthyloxy) propan-2-ol hydrochloride.

The empirical structure is $C_{16}H_{21}NO_2$, HCl with molecular weight 295.8. Propranolol hydrochloride is white or almost white crystalline powder, odourless, nonhygroscopic and bitter taste. It has melting point at 163-166 °c and pKa 5.0-6.0 .

It is soluble in 20 parts of water, in 20 parts of ethanol and slightly soluble in chloroform, and practically insoluble in ether.

Use : Propranolol is a beta blocker used in the treatment of hypertension and to improve the tolerance to exercise in patients with angina pectoris. It has been given for the prevention of re-infarction. It is also used in the treatment of cardiac arrhythmias and it is often effective in supraventricular tachyarrhythmias.

Pharmacokinetic : Propranolol is almost completely absorbed from the gastro-intestinal tract, but is subjected to considerable hepatic tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose, but vary greatly between individuals. It is metabolized in the liver, the metabolites being excreated in the urine together with only small amounts of unchanged propranolol. Propranolol crosses the placenta and traces are found in milk. It also crosses the blood-brain barrier. It is highly protein bound and reported not to be significantly dialysable.

Incompatibility : Propranolol HCl was found to be compatible with starch, Sta-Rx 1500®, Avicel PH 101, Elcema G 250® and Ac-Di-Sol®. Interactions between propranolol HCl and magnesium stearate, Emcompress®, calcium phosphate monohydrate, Primojel®, Steric acid, Avicel® and lactose were evident. This was achieved by comparing the DSC thermogram of propranolol HCl and each of the investigated excipients.

Stability and storage condition : Propranolol HCl is affected by light. In aqueous solutions, it decomposes with oxidation of the isopropylamine side chain, accompanied by reduction in the pH of the solution. Solution is most stable at pH 3.0 and decomposed rapidly under alkaline condition. Propranolol HCl is stable to heat. It should be preserved in well-closed containers and the USP requires preparations to be protected from light.