CHAPTER II
LITERATURES REVIEW

Capsule is a solid dosage form which the drug substance is filled inside a gelatin shell. There are 2 types of capsule shells in the market, namely "soft" and "hard" capsules according to its appearance. The "soft" capsule is an one-price, variable shape and seamed or seamless capsule while the "hard" capsule is a two separate semi-closed cylinder called "cap" and "body". The "cap" is slightly larger in diameter and shorter in length in comparison with the body. The cap fits tightly with the body to form a single sealed unit (Jones, 2004:1-22).

The gelatin capsule was invented as a result of the need to mask the obnoxious taste of many medicinal substances. The gelatin shell is smooth and becomes slippery in the mouth. Moreover, many colors are available to make the gelatin shell more pleasant dosage form. Additional advantages are rapid dissolution of the shell, which together with the lack of a compaction process comparable to tablet compression. Hard gelatin capsules are easier to formulate than tablets because there is no requirement that the powders be formed into a coherent compact that will stand up to handling (Augsburger, 1989).

Hard capsule shell compositions

Capsule shells contain small quantities of additives that enable either the capsule to be formed more easily or to improve their performances. The materials can be classified into six main categories which are gelatin, coloring agents, plasticizers, process and performance aids, preservatives and gelatin alternatives.

1. Gelatin

Gelatin is the major ingredient used to manufacture of hard shell capsule for a long time. It is readily soluble in biological fluids at body temperature (Podzeck, 2002). Gelatin is insoluble in cold water but it swells upon contact with water and forms large visible swollen particles know as "fish eye". The hydrated gelatin will go into solution when heated to about 160°F (King, 1969). Hard shell capsules made from gelatin showed strong temperature dependence, rapid shell dissolution in water and 0.1 M HCl which only occurred at temperature above 30°C (Chiwele, Jone, and Podezeck, 2000). Gelatin ability to form a thermally reversible gel makes it particularly suitable for the production of hard shell capsules. Its rapid gelling ability, excellent film forming properties and ability to impart oxygen impermeability. Films formed from gelatin set very quickly and have high film strength.They are also elastic with good clarity (Gilleland et al., 2002).

1.1 The structure of gelatin.

Gelatin is the water-soluble product from water-insoluble collagen fibers, which is the principal constituent of animal skin, bone, and connective tissue. Therefore, an understanding of the nature and structure of collagen and of its conversion to gelatin is a key element for understanding.

Collagen is a unique protein because of its unusual amino acid compositions. It contains large amount of the cyclic amino acids such as proline and hydroxyproline. In addition to these compounds, collagen also contains large quantities of glycine and alanine (the common nonpolar amino acids with short side chains). Collagen proteins consist of long chains of amino acids connected through peptide linkages between α-amino and α-carboxyl groups.

Water–insoluble collagen fiber is transformed from an infinite asymmetric network of link tropocollagen unit to a system of water-soluble, independent molecules with a much lower degree of internal organization. Since the original collagen structures are not all the same, and since there are many paths by which the structure may be broken down, there are obviously a many great varieties of gelatin formed by the destruction of

collagen (King, 1969). The triple helix structure of tropocollagen can be destroyed (denaturation) by the application of heat or by the use of compounds which destroy hydrogen bonds, with resultant conversion to gelatin. The tropocollagen-gelatin transformation has been extensively studied and reviewed. Denaturation involves breaking only the hydrogen bonds and those hydrophobic bonds that help to stabilise the collagen helix. This is followed by the disentanglement of the chains and dissociation into smaller components with a random coil configuration (Jones, 1987: 13-30). The disordered molecule falls apart in one of three ways as illustrated in figure 2.1 (King, 1969: 359 – 397).

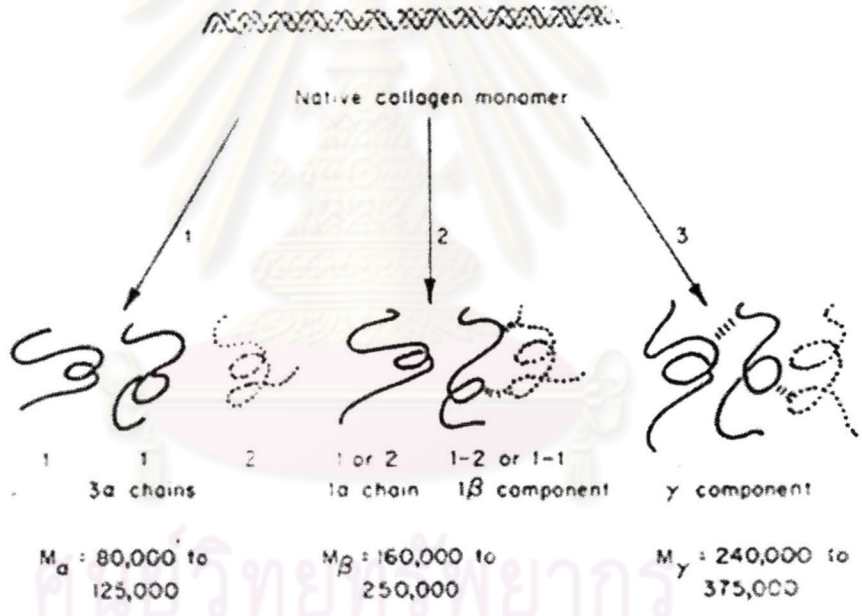

Figure 2.1 Possible paths for collagen conversion to gelatin (King, 1969)

1.2 Molecular weight of gelatin

The average molecular weight of commercial gelatin may vary from about 20,000 to 200,000 Daltons. However higher molecular weights (in excess of x 10^6 Daltons) have been reported for gelatin fractions separated by alcohol coacervation of gel electrophoresis (Jones, 2004: 23-60).

1.3 Chemical composition

The chemical composition of gelatin is well documented through research works carried out by several investigators. The chemical composition of gelatin consists of 18 amino acids. Gelatin is not a nutritional complete protein in that it is lacking the essential amino acid named tryptophan. However, it contains small amounts of a rare amino acid called hydroxylysine (Djagny, 2001; and Arvanitoyannis, 2002). Gelatin from different sources may exhibit small variation in amino acid compositions. For example, gelatin will have cystine in amino acid chain and consists of 19 amino acid; if it is made from cod skin or carp skin (King, 1969: 359 – 397; Eastor and Leach, 1977: 73 – 107; Jones, 2004: 23-60)

1.4 Physical and chemical properties

1.4.1) Acidic and basic properties

The acid–extracted gelatin is designated as "Type A" whereas the product of the alkaline method is referred as "Type B". The type A and type B gelatin have differences in the physical properties including the isoelectric and isoionic points. The isoionic point is the pH of a protein solution that contains no non-colloidal ions other than hydrogen or hydroxyl. In the absence of other ions, this pH corresponds to there being zero average net charge on the molecule and coincides with the isoelectric point for gelatin. The isoelectric point is the pH of a gelatin solution in which no net migration of the protein produced by the application of an electric filed. It is generally accepted that

the isoionic point of limed–processed gelatin falls within the pH range 4.8-5.2 while acid–processed gelatins exhibit the pH values of 6.0-9.4. Isoelectric focusing techniques applied to gelatin have shown that a distribution of isoelectric point value occurs not only in acid-processed gelatin but also in limed gelatins. For limed gelatins, the pH range was 0.5–0.7. A limed gelatin exhibits isoelectric point ranging from about 4.6 to 5.1. Acid–processed gelatins show a wider distribution about 2 pH units (Jones, 2004: 23 – 60).

1.4.2) Gel strength

Gelatin has the unique ability to form a thermally reversible gel. The sol / gel and gel / sol transformations occur very readily when the temperature is changed over a comparatively small range. Gel strength depends upon the gelatin concentration, pH, temperature and maturing time. When an aqueous solution of "gelling" gelatin above a certain minimum critical concentration is cooled below 40^0C, a three–dimensional gel network is formed. Gelation is accompanied by changes in optical rotation. The formation of the gelatin gel can therefore be considered as the production of a three–dimensional network of gelatin molecules with water entrapped in the meshes as shown in figure 2.2 (Jones, 1987: 31 – 48). Gel strength is usually measured with the Bloom geometer in bloom unit. Commercial gelatins vary from 50 to 300 bloom. Zero bloom gelatins have also been made for special applications (King, 1969: 359 – 397).

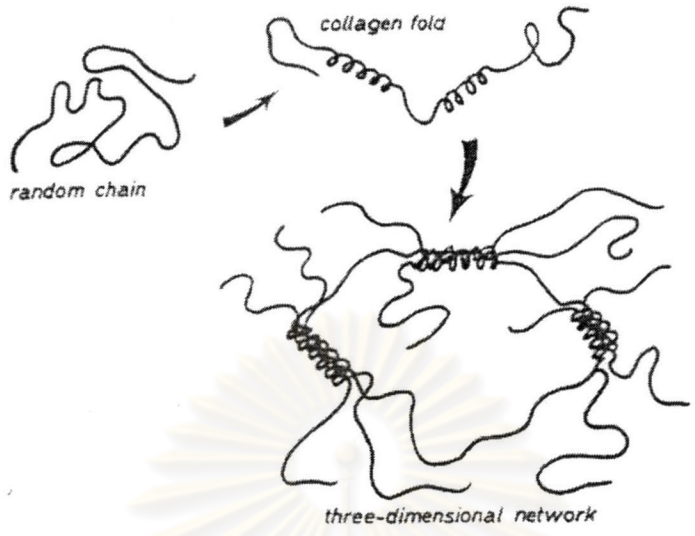

Figure 2.2 Schematic representation of the formation of three-dimentional network in gelatin gels (Jones, 1987: 31 – 48)

Prematuring the gel at a higher temperature than the final maturing temperature results in higher gel strength than if the gel has been chilled directly to the maturing temperature. Because of that rapid cooling of a gelatin solution results in a less ordered arrangement of gelatin molecules which have been "frozen" in the configuration that existed in the solution state and leads to only limited development of network junctions and is called a "fine" gel network. In contrast, slow cooling leads to the formation of a "coarse"network in which more highly organized links have had a chance to form (Stainsby, 1977: 179-207). The rigidity of a gelatin gel decreases with increasing maturing temperature. Different types of gelatin show varying dependencies of rigidity upon temperature. Moreover for similar gelatin types (i.e. similar raw material and processing), low bloom strength gelatins exhibit greater sensitive to temperature (Jones, 2004: 23 – 60).

The effect of added glycerol on gelatin rigidity has been quite widely studied. Addition of glycerol significantly increases gelatin gel rigidity for example gels containing 4-15% gelatin and up to 40% w/w of glycerol. A general relationship for rigidity modulus has been derived as followed:

$$G = a + bZ^2 + (c + dZ)g$$

Where Z is percentage gelatin concentration, g is percentage glycerol concentration and a, b, c and d are constants whose values depend upon the grade of gelatin (Nixon, Georgakopoulos, and Carless, 1966). Other polyhydric alcohols such as sorbitol and sugars (such as sucrose and maleadextrins) can increase gel strength. However, at high additive levels and high total of solids, the rigidity can start to fall again. (Jones, 2004: 23-60).

1.4.3) Viscosity

The viscosity produced by gelatin in water solution is one of its most important properties. Molecular weight distribution seems to be much more important in its effect on viscosity than on gel strength. Higher gel strength of gelatins may give lower viscosity than samples of lower gel strength, showing that gel strength and viscosity are not directly related (King, 1969: 359 – 397). The pH effect for dilute resembles that for the viscosity of solution is a minimum at the isoionic point and there are maxima at pH 3 and 10.5 approximately. However, the effect of pH becomes less significant particularly in acid solution as the gelatin concentration increasing (Stainsby, 1977: 109-136). The viscosity of a concentrated solution arises mainly from the hydrodynamic interactions between the gelatin molecules. In a concentrated solution, the charged sites on the gelatin molecules and their counter ions can provide a moderately substantial ionic strength. With increasing concentration, therefore, not only the macromolecules are brought into closer proximity but also the environment of each molecule is changed. As the temperature is raised above 40°C, the viscosity decreases exponentially. When aggregation occurs, the viscosity becomes time dependent and increases continuously. At

temperatures above the setting temperatures but below about 40°C, the viscosity can increase with time and then become non-Newtonian in character. This behavior is due to linking together of gelatin molecules to form aggregates. It varies in extent from one gelatin sample to another and also varies with pH, salt content, gelatin concentration, and temperature. At higher temperature, the viscosity falls continuously with time, however, thermal hydrolysis and degradation of this kind can be minimized by using neutral solutions (Stainsby, 1977: 109-136).

1.5 Degradation of gelatin

Gelatin in solution is susceptible to thermal or enzymatic hydrolysis leading to a reduction in average molecular weight and some changes, which may give useful properties (Jones, 1987: 31-48). The rate of thermal degradation of a gelatin solution is appreciable above 60°C and is rapid at 100°C. When a solution, which has been heated in this way, is cold to a gel again. The rigidity is found to decrease irreversibly (Finch and Jobling, 1977: 250-294). Dissolution temperature of 55-70°C can safely be used for gelatin that have pH values in the normal 'commercial range' of 5.0-6.5. Solution can be maintained at 45-60°C for several hours without significant changes in physical characteristics. At 40°C, the rate of thermal hydrolysis is negligible but the rate of bacterial or enzymatic degradation increase whenever contaminated by viable bacteria or existing of enzymes.

Regular specifications for hard capsule gelatins include a test for "degradation rate". For hard gelatin capsules industries, a test for "degradation rate" were used to ensure that the viscosity of solution can be stable at 45-60°C over a number of hours. The test is carried out by keeping a 12.5% w/w gelatin solution at 60°C over 17 hours. Under these conditions, if the viscosity drops more than 20% suggested that bacterial or extracellular enzymatic action does exist in the solution (Jones, 2004: 23-60).

1.6 Properties of gelatin film

Thin gelatin films are rich in colloid materials and behave similarly to rigid gels exhibiting elastic module and time-dependent phenomena. Commercially, gelatin is mainly characterized by Bloom strength and viscosity. However, tensile strength and elongation are equally important physical properties for edible film applications. The main parameter affecting film-forming properties of gelatin are raw material sources, extraction methods, molecular weight, film preparation methods (hot versus cold casting), degree of hydration or presence of plasticizers (Arvanitoyannis, 2002: 275-304).

The properties of cold-dried gelatin film are very important in the hard capsule production. These properties are intimately related to moisture content and may be affected by pH, additives, and relative humidity (RH). X-ray diffraction studies have shown that hot-films give only a broad, diffuse diffraction pattern typical of liquids or glassy materials, indicating a relatively simple random coil or amorphous structure. In contrast, cold-dried films give an X-ray pattern with a series of diffracted area and spots, indicating a high degree of ordering with triple-helix crystallites orientated in a direction parallel to the plane of the film. It has been estimated that up to 20% of the gelatin molecules in cold-dried films are in the triple-helix crystalline forms (Jones, 1987: 31-48).

Cold-dried at 20°C films have a greater tensile strength than hot-dried at 56-60°C films (i.e. 89.3 versus 64.2 MPa at 45% RH during testing). The greater tensile strength of cold-dried films was due to their higher crystallinity and degree of orientation of the crystallites. Tensile strength of both cold and hot-dried films decrease with increasing relative humidity because intermolecular bonds are weakened by absorbed water. Then, lower tension was required for rupturing the bonded regions within gelatin films. Also, cold-dried films had slightly greater extension at break than hot-dried films at 45-65% RH during testing. However, at higher RH (75-85%) during testing, hot-dried films had substantially greater extension at break, presumably due to an almost simultaneous failure of a high number of bonded regions (Arvanitoyannis, 2002: 275-304). Similar observations were reported for films from gelatin/modified or unmodified starch (Arvanitoyannis et al., 1997: Arvanitoyannis, Nakayama, and Alba, 1998b) and

gelatin/chitosan blends (Arvanitoyannis, Nakayama, and Alba, 1998a), where films were prepared by both hot and cold casting. The plasticizing effects of polyols/sugars on gelatin/starch films were also studied. The percentage of elongation at break showed proportional increases with increasing in plasticizer contents but sucrose showed an opposite effect (Arvanitoyannis et al., 1997; 1998a; 1998b). Cold-dried films swell without dissolving in cold water, whereas hot-dried films can dissolve spontaneously. Same gelling information from the individual molecules of amorphous gelatin are free to dissolve while the ordered structure of the molecules of the crystalline film prevents dissolution (Jones, 1987: 31-48, 49-60).

2. Coloring agent

The main reasons for coloring pharmaceutical products are the aesthetic effects, ease of identification, and the psychological effect on patients. Coloring agent may also be used for their light screening properties to protect photolabile substances. The colorants must be non-toxic, commonly used and stable under the conditions of capsule manufacture and storage. Food and Agriculture Organization of the United Nation and the World Health Organization (FAO/WHO) have classified food colors into a series of chemical group: anthraquinone, azo (mono- and bis-), carotenoid, flavone, indigoid, inorganic, intro, quinophthalone, phenylmethane, and xanthene (Jones, 1987: 49-67).

The colorants mainly used for colouring capsules are synthetic water-soluble dyes (azo, indigoid, quinophthalone, triphenylmethane, and xanthene), pigments (especially the opacifying agent; titanium dioxide) and certain dyes of nature origin (carotenoids). Pharmaceutical pigments are not certified, unlike soluble dyes. Specifications are published in the federal Registration-EU system presented in table 2.1 which contains the coloring agents used for the coloration of capsules (Jones, 2004: 61-77).

Table 2.1 Pharmaceutical colorants and water-soluble dyes (Jones, 2004: 61-77)

Common name	Chemical index number	EU number	USA number	Chemical class
Red				
Allura Red	16035	E129	FD&C Red No. 40	Azo
Amaranth	16185	E123		Azo
Azorubine	14720	E122		Azo
Ponceau 4R	16255	E124		Azo
Erytrosine	45430	E127	FD&C Red No. 3	Xanthene
Phloxine B	45410		D&C Red No. 28	Xanthene
Orange				
Sunset Yellow	15985	E110	FD&C Yellow No. 6	Azo
Yellows				
Tartrazine	19140	E102	FD&C Yellow No. 5	Azo
Quinoline Yellow	47005	E104	D&C Yellow No. 10	Quino-Phthalene
Blues				
Indigo Carmine	73105	E132	FD&C Blue No. 2	Indigoid
Brilliant Blue	42090	E133	FD&C Blue No. 1	Triphenylmethane
Patent blue V	42051	E131		Triphenylmethane

Pharmaceutical pigments

Name	Color Index number	EU number	Formula
Titanium Dioxide	77891	E171	TiO_2
Black Iron Dioxide	77499	E172	$FeO.\ Fe_2O_3$
Red Iron Dioxide	77491	E172	Fe_2O_3
Yellow iron dioxide	77492	E172	$FeO(OH).nH_2O$

Natural colorants used in pharmaceutical

Name	Hue	Color Index number	EU number
β-carotene	Orange	40800	E160a
Canthaxanthin	Orange	40850	E161g
Chlorophyll	Green	75810	E140, E141
Cochineal	Red	75740	E120

3. Plasticizers

The difference between hard and soft-gelatin capsule is that soft capsules contain appreciable quantities of plasticizer. On the contrary, hard gelatin capsules have been defined as having less than 5% by weight of plasticizer present (Jones, 1987: 49-60). The function of plasticizer in the capsule wall is to reduce the rigidity of the gelatin and make it soft and pliable.

A large variety of chemical materials have been suggested for this application. However, glycerol was the first true plasticizer and widely used in capsules until today (Jones, 1987: 49-60; Stroud and Norman, 1996; Gennadios and Aristippos, 2001; Hausmanns and Stephan, 2001; Oppenheim, Richarles, and Charles, 2003; Scott, Cade, and He, 2003). The other materials, which have been used, are some of the natural gum, sugar, and polyhydric alcohols such as sorbitol (Hausmanns and Stephan, 2001; Gennadios and Aristippos, 2001; Gilleland et al., 2002).

Plasticizer amount needed varies depending on the type of gelatin and gelatin alternatives. Hard gelatin capsules use glycerol or propylene glycol not more than 5% by weight of the dry gelatin (Bogin and Mich, 1949) and 15-30% by weight used in case of starch-extended gelatin formulations (hydroxypropylate and hydroxyethylated starch) (Stroud and Norman, 1996; Scott et al., 2003).

Classification of plasticizer (Sears, and Darby, 1982: 1-7)

1. External plasticizer: The plasticizer is a discrete material that is added to the polymer but for the most part never chemically combined with it.

2. Internal plasticizer: The original polymer can be modified chemically, or a related polymer can be synthesized that will have more flexibility or better low temperature properties. The development of the desired properties in the polymer itself is called internal plasticization. The final product is usually an internally plasticized resin that comes close to the desired properties but still requires an external plasticizer in small amounts to achieve the best performance.

General theories of plasticizers have 5 major theories (Sears, and Darby, 1982: 35-77).

1. The lubricity theory

The lubricity theory considers the resistance of a resin to deform or to result from intermolecular friction. Very much like oil, two moving parts acts as a lubricant. The plasticizer acts to facilitate movement of resin macromolecules over each others which give internal lubricity. The macromolecules must work back and forth over each other, and that a plasticizer lubricates these internal glide planes.

The lubricity theory is useful in conjunction with the other theories even when only segments of macromolecules must glide past other segments in a gel structure.

2. The gel theory

The gel theory considers the rigidity of a resin from an internal, three-dimensional honeycomb structure. This gel is formed by more or less loose attachments, which occur at interval along the polymer chains. The plasticizer acts on a resin that has many points of attachment along the polymer chain by breaking the attachment at places and masking the centers of force. It masks these centers of force by selectively solvating the polymer chains at these points. This produces much the same result as if fewer points of attachment had been provided on the macromolecules in the first place. This potential reduces the rigidity of the gel structure and this is enough to cause flexibility in the basic theory. At the same time, there are free molecules of plasticizer unattached to polymer anywhere except indirectly through other plasticizer molecules. These unattached molecules appear to be particularly effective in swelling the gel and in facilitating movement of the polymer molecules that is increasing flexibility.

3. The free volume theory

The free volume theory grew from less obvious characteristics of crystals, glasses and liquids. It depends to a large extent on mathematical corroboration for its strength. The free volume defined as the difference between the volume observed at absolute zero temperature and the volume measured for the real crystal, glass, or liquid at a given temperature.

$$V_f = V_t - V^\circ$$

Where V_f is free volume, V_t is the specific volume at temperature t, and V° is the specific volume at some reference point. Figure 2.3 illustrates the free volume concept. At absolute zero temperature, all atom or molecules perfectly compact (ideal crystal). But they are not this compact in reality because of nonharmonic vibrations and imperfections in the lattice structure, commonly called holes. In a liquid the number or volume of these holes has increased greatly. This theory is devided into two parts:

1. A continuous part that results from oscillations and that persists and increases slightly as the temperature is raised
2. A discontinuous part (holes part) which increases greatly with temperature

An increase of hole free volume permits increasing motion of polymer molecules so that a study of plasticization is a study of ways to increase free volume.

Free volume comes from three principle sources:

1. The motion of chain ends
2. The motion of side chains
3. The motion of the main chain

There are 5 methods to increase free volume.

1. Increasing the number of end groups
2. Increasing the number or length of side chains. (use internal plasticization)

3. Increasing the chance for main chain movement by inclusion of segments of low steric hindrance and low intermolecular at fraction.

4. Inclusion of a compatible compound of lower molecular weight that acts as though it does all of 1 through 3 above. (use external plasticization)

5. Raising the temperature

Figure 2.3 Free volume as a result of nonharmonic oscillation and holes. The large circles symbolize the volume of the molecule and the small circles symbolize the average oscillation points (Sears, and Darby, 1982: 35-77)

The basic weakness of the free volume theory as applied to external plasticization is the erroneous assumption that plasticization is synonymous with lowering to T_g.

The phenomenon of antiplasticization that occurs with many resins at low plasticizer content. Although the T_g value is lowered by the small amount of plasticizer, the modulus and tensile strength may increase appreciable before they begin to decrease. In the antiplasticization range of plasticizer concentration, the elongation to break is decreased. The concept of plasticization is equivalent to increase elongation which is certainly as valid as that of lowering T_g. Polymeric plasticizers have a large amount of free volume because of their special backbone structure and branching which permits them to act almost segment-by-segment as plasticizers.

4. Solvation- desolvation equilibrium or mechanistic theory

The action of a plasticizer on a resin having many points of attachment along the polymer chains appears to be to separate the chains, break the attachment, and mask the centers of force that have help these polymer chains together, perhaps by selectively solvating the polymer at these points. This produces much the same result as if fewer points for attachment had been provided on the macromolecules in the first place.

It seems probable external plasticizer and solvents has different classes are attracted to resin macromolecules by forces of different magnitudes and that none of them are bound permanently when they are attached. Insteads, there is a continuous exchange whereby one plasticizer molecule becomes attached to a given active group or force center only to be removed and replaced by another. This results in a dynamic equilibrium between solvation and desolvation in which a certain fraction of the force centers of the polymer chains is masked by solvent or plasticizer under a given set of conditions such as plasticizer concentration, temperature and pressure.

5. Generalized structures or fringed micelle theory

A visual concept of plasticization of a resin is attempted in Figure 2.4. Parts of some of the macromolecules line up together compactly as shown for four microregions to form the micelles. These may be ordered enough and large enough to be crystallites which are called bundles. The crystallites tend to make the resin rigid while the amorphous areas tend to be more flexible. The free volume of the amorphous material should be proportionately higher than that of the "crystalline" or ordered material. If a small amount of plasticizer is incorporated into the mass, perhaps by heating and cooling, it brings slightly more free volume and gives more opportunity for movement of the macromolecules. Many resins tend to become more order and compact as existing"crystallites" grow or new "crystallites" form at the expense of the more fluid parts of the amorphous material. As there are few plasticizer molecules, they may be almost totally immobilized by attachment to the resin (bound plasticizer) by various forces including hydrogen bonding. This tends to restrict the freedom of small portions

of the polymer molecules-sidechains and segment so necessary to absorption of mechanical energy. Therefore, it results in a more rigid resin with higher tensile strength and modulus than the base bolymer itself but with poorer impact reistance and less elongation. The mechanism is called antiplasticization.

When a larger amount of plasticizer is added to the resin-plasticizer system, again with heating and cooling, further" crystallite" formation may occur, but the amorphous regions are swollen until the whole mass becomes softer. This plasticized resin is more flexible, has better elongation, higher impact resistance, but lower tensile strength and modulus than the base polymer. If more plasticizer is added and its solvent power is great enough, more of the crystallites will disappear until a very soft gel is obtained or even a viscous liquid.

4. Process and performance aids

"Process aids" are materials that assist in the manufacturing process e.g. surfactants in enabling the polymer solution to take up the shape of the moulds. Sodium lauryl sulfate is one example used in the production of hard gelatin capsules with a suitable concentration as mentioned in the US Pharmacopoeia (Jones, 1987: 49-67). According to European patent (EP 1210939 A1), sodium lauryl sulfate was used in a range of 0.05 to 0.1% by weight of gelatin for the manufacture of hard gelatin capsule (Hwan, 2002). Sodium lauryl sulfate in solution is added to reduce the surface tension of the mixture and cause the mould pins to wet more uniformity. It is added to the gelatin solution during the preparation stage. An indication of a lack of sodium lauryl sulfate is the appearance of thin area on the capsule wall where the surface of the mould pins has not been sufficiently wetted (Jones, 1987: 49-67).

"Performance aids" are materials that help to improve the patient acceptable of the product, such as flavoring agents or to improve hard capsule performance on filling machines (Jones, 2004: 61-77).

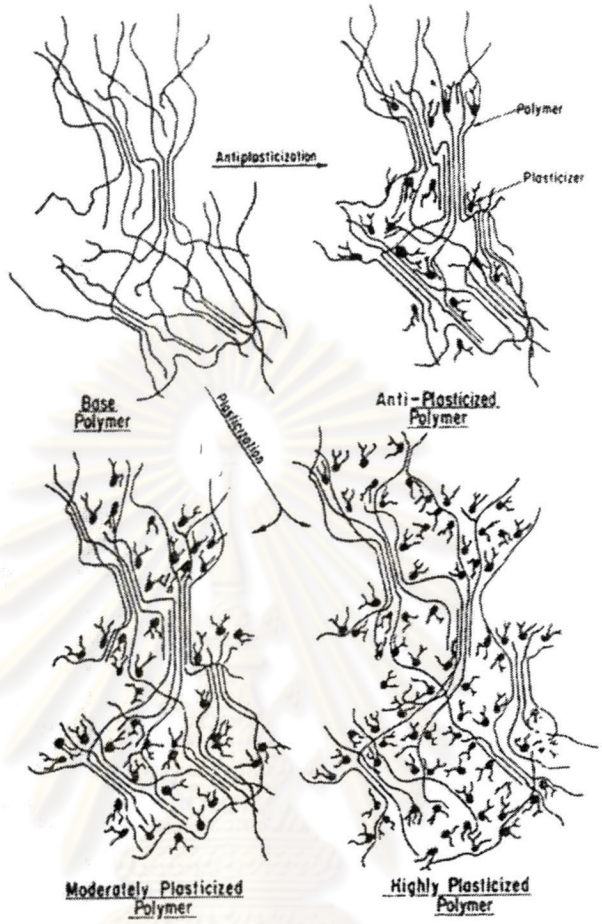

Figure 2.4 Stylized concept of plasticization of a resin, explaning antiplasticization and plasticization; plasticizer molecule are represented by relatively large frog-like symbols (Sears, and Darby, 1982: 35-77)

5. Preservatives

Gelatin is a good medium for bacterial and fungal growth, especially when sufficient moisture is available. During the capsule-manufacturing process, the gelatin is in solution and kept warm to prevent gelling which give almost ideal conditions for bacterial growth. Several esters of p-hydroxybenzoic acids have been used as preservative. They are used at a concentration up to 0.2% w/w in the finished capsule. Each ester effective againsts a different spectrum of organisms whereas ester combination is usually used. The most

commonly used combination is methyl hydroxybenzoate (methylparaben) with propyl hydroxybenzoate (propylparaben) in a 4:1 methyl to propyl ratio (Jones, 1987: 46-67).

The philosophy of modern good manufacturing practice (GMP) does not encourage the use of preservatives because they could cover up bad practices. The GMP way is to reduce the possibility of contamination during the manufacturing process. When the gelatin solution is being prepared, it should be heated to a temperature more than 50°C, at which bacterial growth will decline significantly. To prevent bacterial growth, gelatin solution should be maintained at this temperature with constantly stirring with no local cool spot thoughout the process. The normal moisture levels of both hard and soft capsules will be sufficient low to prevent the growth of any organisms during storage (Jones, 2004: 61-77).

6. Gelatin substitutes and extenders

The properties which are required of a gelatin alternative are, firstly, that it must be a good film former, film needs to be tough and flexible. Secondly, the capsule must rapidly dissolve in biological fluids at 37°C and, thirdly, it must exhibit a gelation property so that a capsule film can be cast or dipped (Jones, 2004: 61-77). One natural material, which is now comparative abundant, is starch. It is cheaper than gelatin and HPMC capsule and has film formation properties. Numerous studies have been done which study the properties of starch-based films obtained by casting from a solution or gel with addition of a plasticizer. The addition of glycerol (Lowton, 1996; Forsell et al., 2002; Myllarinen et al., 2002; Wilhelm et al., 2003) sorbitol (Gaudin et al., 2000) or glycerol and sorbitol (Krogars et al., 2002), considerably improves mechanical properties. National Starch and Chemical Corporation has obtained a patent for the use of modified starches in the production of capsule. The suggested material is a dextrin which modified either by acid-catalyzed hydrolysis of a waxy maize base. An extended gelatin composition 40 to 97 percent, by weight of gelatin and 3 to 60 percent, by weight of a dextrin. The capsules were prepared by dipping into the dextrin extended gelatin composition (Szymanski, Martinsville, and Helmstetter, 1973). Another modified starch product for substituted gelatin solution use to make capsule is hydroxyalkyl starch

(Christen and Cheng, 1977) and poly (1,4α-D-glucan) and starch based (Hausmanns and Stephan, 2001). This is both a gelatin replacement and an extender. However, none have succeeded in large-scale capsule manufacture with sufficient uniformity to be used on standard automatic filling machine.

Starch

Chemical Composition of starch

Starch is composed of carbon, hydrogen, and oxygen in the ratio of 6:10:5 $(C_6H_{10}O_5)_n$. It can be considered to be a condensation polymer of glucose and yields glucose when subjected to hydrolysis by acids and/or certain enzymes figure 2.5 The glucose units in the starch polymer are present as anhydroglucose unit (AGU) where the linkage between the glucose units is formed during a condensation polymerization, which water molecule is removed. The glucose units are connected by carbon-oxygen-carbon bonding between one glucose unit and the next glucose unit to form a long chain or polymer of interconnected glucose unit figure 2.5 This linkage of one glucose to another through the carbon atom number one and oxygen is known as a glucoside bond. Depending upon the variety, commercial starches contain small amounts of proteins, fatty materials, phosphorus-containing materials, or phosphate ester groups and traces of inorganic materials (Rutenberg, 1980).

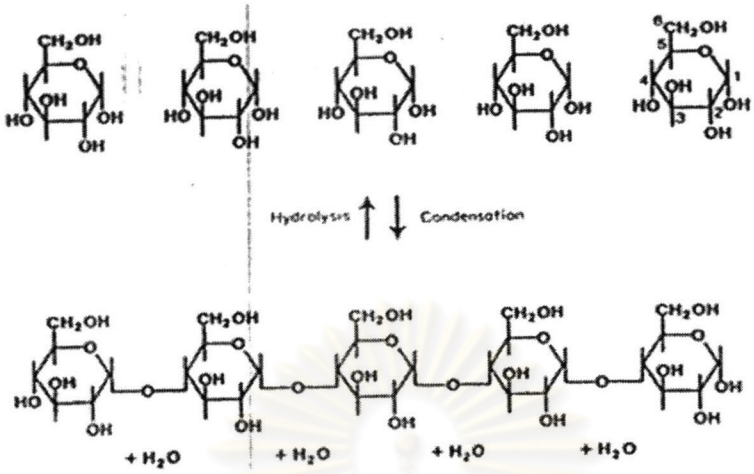

Figure 2.5 Starch considered as a condensation polymer of glucose (Rutenberg, 1980)
Note: numbering of carbon atom in the glucose and the spatial relationships of the hydroxyl groups with respect to the six numbered ring containing 5 carbon atoms and 1 oxygen atom

Molecular Structure

Most starches contain of a mixture of two polysaccharide types of polymer, amylose and amylopectin. The basic glucose building block is a ring shaped molecule with six atoms in the ring figure 2.6 (Chalmers, 1968).

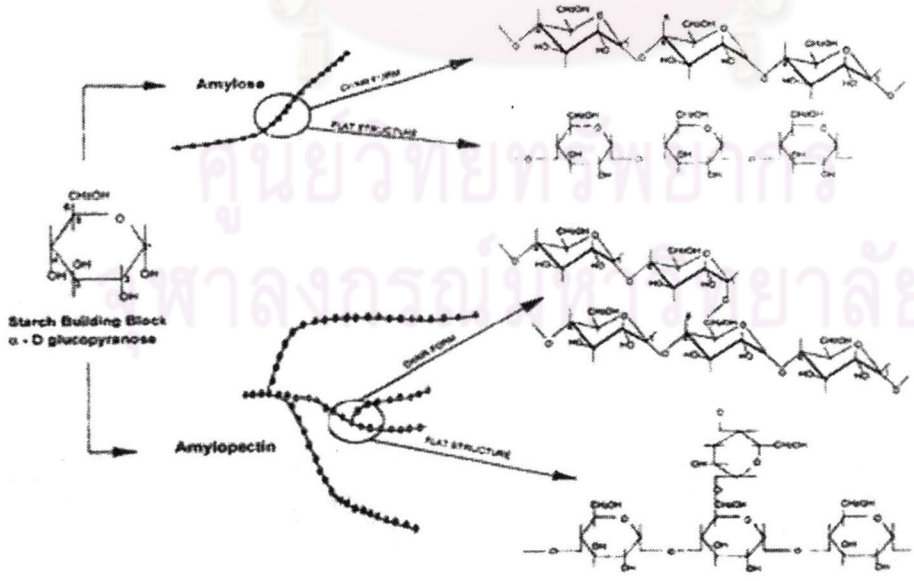

Figure 2.6 Linear and branched starch polymer (Chalmers, 1968)

Amylose is a linear polymer containing of a chain of glucose units connected to each other by 1-4 linkages. The glucose units are in the "alpha-D-glucopyranose" form or α-1,4 glycosidic bonds. Amylose molecules contain range from 200–4,000 AGU depending on the fraction as well as the plant source. Each of the monomeric unit contains two secondary and one primary hydroxyl group. The hydroxyl groups impart hydrophilic properties to the polymer leading to an affinity for moisture and dispersibility in water. However, the molecules are linear and contain hydroxyl groups. They have a tendency to be attracted to each other and to align themselves associating by hydrogen bonding through hydroxyl groups on neighboring molecules. Then, the water affinity of the polymers is reduced and polymer molecules tend to precipitate out of solution at dilute concentration (less than 1%). At higher concentration, gels made up of three dimensional polymeric networks held together by spot hydrogen bonding, which can be formed when the motion of the polymers and their ability to orient is more retricted. This phenomenon of hydrogen bond association or crystallisation from aqueous dispersions is commonly called retrogradation figure 2.7 The rate of retrogradation depends upon molecular size and concentration of amylose, temperature, and pH. More rapid the retrogradation rate occurs with lower temperature. Large amylose molecules have a slower rate of retrogradation because the alignment process is presumably more difficult. The retrogradation rate is the fastest at pH 5 to 7 and is decreasing at higher and lower pH. Calcium nitrate exhibits a very strong retardation effect on retrogradation. Other compounds such as formaldehyde, urea, and dimethylsulfoxide also act to retard retrogradation. The linearity of amylose molecules contributes towards film formation and it is possible to make strong moderately flexible free films from amylose dispersions. Lose amylose also has an affinity for iodine and large molecules containing hydrophilic and hydrophobic groups (such as fatty acids, fatty alcohol, etc). The mode of spatial configuration is for the amylose complex to form a helix around these molecules. The amylose complex also forms the characteristic blue color with iodine which is used in quantitative analysis to identify starch fractions and to quantitatively estimate the amylose content (Chalmers, 1968; Rutenberg, 1980).

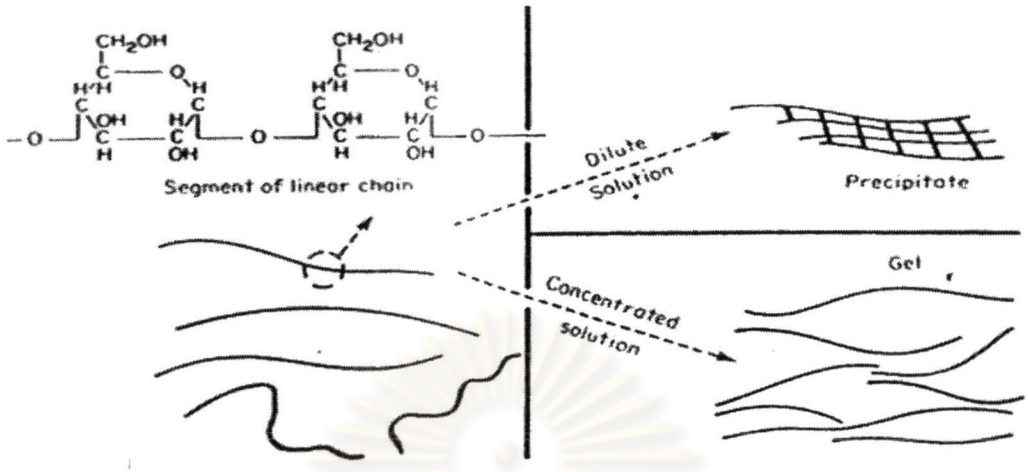

Figure 2.7. Mechanism of starch retrogradation (Rutenberg, 1980)

Amylopectin has a highly branched structure consisting of alpha-1,4-linked anhydroglucose unit in addition, there is a branch point from alpha-1,6-linkages at about very 15th unit as shown in figure 2.6 (Chalmers, 1968). Amylopectin presents a characteristic red to purple color with iodine because the outer chains available for complexing with iodine are not long enough to give the blue color as seen with amylose. The highly branched structure of amylopectin interferes molecule mobility and keeps molecules apart from approaching near enough to permit extensive hydrogen bonding necessary for retrogradation to occur. As a result, aqueous solution of amylopectin are characterized by good clarity and stability. They are resistant to gelling or changing with age, properties which are a major factor in the use of amylopectin starches as thickeners, or where stable solution are required. Amylopectin does not form strong, unsupported films because the highly branched molecule can not readily orient itself in parallel alignment with other amylopectin molecules to form the multitude of associative hydrogen bonds necessary to produce strong films (Chalmers, 1968).

Eight types of starches will be mentioned in the reviews, namely rice starch, glutineous rice starch, tapioca starch, Alpha® starch, Eragel®, Elastigel 1000J®, Elastigel 2000C® and Elastigel 3000M®.

Native starch

1. Rice starch

Rice starch consists of very small polygonal granules. The gelatinization temperature of a starch is the point at which the individual granules first commence to swell and simultaneously lose their interference crosses as viewed under the polarizing microscope. Not all granules of a particular sample gelatinize at the same temperature but rather over a normal range of 8°C – 12°C (Schoch, 1967). The gelatinization range of a commercial rice starch was 60–77°C. The molecular structure gave a 18-27% amylose content (Sriroth and Pipachomkwan, 2000).

2. Waxy or glutinous rice starch

Waxy rice was the first of the common starches to be identified by its red-straining reaction with iodine. The viscosity pattern of the milled flour is very similar to the refined starch, though, twice as much flour must be used to produce a given viscosity. Waxy rice starch has a branched structure. There is determined the average branched length of waxy rice starch is determined to be 20 DGU (Schoch, 1967).

3. Tapioca starch

A sample of tapioca starch will present a white appearance in the dry state. The molecular structure contains 18-23% of amylose content. The gelatinization temperature range is 58 – 70°C (Sriroth and Piyachomkwan, 2000). Viscosity and clarity of cooked tapioca starch are its most important characteristics. Viscosity development in a dilute slurry as recorded in the Brabender-Visco-graph is a means of determining the gelatinization temperature, the rate of viscosity development, the maximum viscosity, and the viscosity loss after the peak. In unmodified tapioca starch, these factors are influenced by variety and age of the roots at harvest time as well as the climate, soil, fertility and rainfall during the growing period (Shipman, 1967).

Starch Modifications

The modifications are designed to change the gelatinization characteristics, solids-viscosity relationships, gelling tendency of starch dispersions, hydrophilic character, moisture content, water-holding power of dispersions at low temperature, resistance of dispersions to breakdown in viscosity by acid and mechanical shear and to introduce ionic character. The modifications may involve merely a reduction in moisture content, a change in physical form, a controlled degradation, a change in the amount of amylose or amylopectin content, a molecular rearrangement, or the introduction of chemical groups not normally present in Table 2.2 (Rutenberg, 1980).

Table 2.2 Modification of starch (Rutenberg, 1980)

Type	Objectives	Treatment
1. Hybrid	Stability of sols (amylopectin) High gel strength (amylose) High film strength (amylose)	Plant breeding
2. Amylose Amylopectin	Same as 1	Fractionation
3. Acid fluidity	Lower viscosity High gel tendency	Acid hydrolysis
4. Oxidized	Lower viscosity with improved sol stability	Oxidation (hypochlorite)
5. Dextrins	Lower viscosity Range of sol stability Range of solubility in cold water	Heat treatment, dry (may be in presence of acid)
6. Inhibited	Modify cooking characteristics	Crosslinking
7. Stabilized	Improve sol stability (resistance to gelling) Lower gelatinization temperature	Esterification Etherification
8. Functional groups	Change colloidal, hydrophobic, hydrophilic, cationic, anionic character	Esterification Etherification
9. Changed physical character	Improve moisture absorption, molding flow characteristics, cold-water-dispersibility	Redrying to low moisture additives (oil, MgO) drum-drying

Modifications of native starches are carried out to provide products with the properties needed for specific uses. The range of modification types and manufacturing process is vast and extremely complex but it may be summarized under three heading:

1. Pregelatinised type, usually involves in feeding starch slurry onto a heated rotating drum.

2. Dextrin type, usually involves in chemical treatment in the dry state.

3. Other types, including thin-boiling and oxidized starch, usually involves in chemical treatment in the wet state. Other modifications involve the use of catalysts and cross-links and etherifying agents. An alternative classification is presented in Figure 2.8 (Jones, 1983).

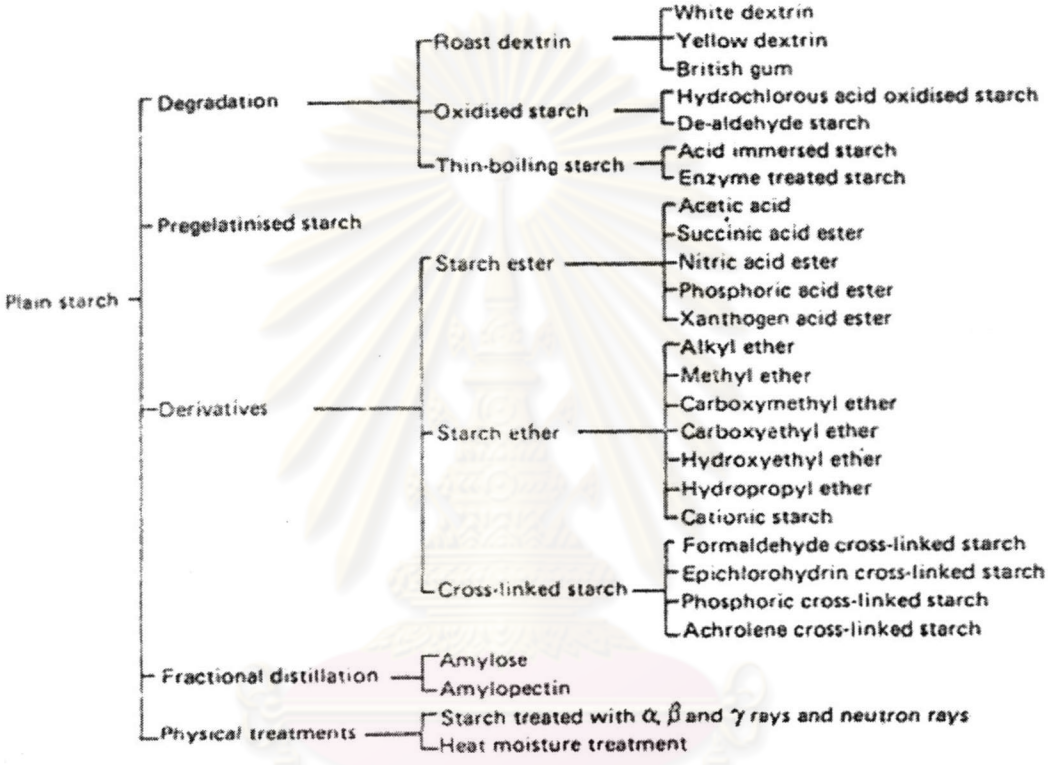

Figure 2.8 Classification of various kinds of modified starches (Jones, 1983)

1. Pregelatinized starches

Pregelatinized starches are swellable in cold water without cooking. These starches are prepared by cooking and drying starch slurries on heated drums. Since the granule structure has been disrupted by this process, the pulverized dried film from the drum dryer will hydrate and thicken in water.

1.1 Eragel® or pregelatinized rice starch.

Eragel® is entirely pregelatinized starch NF., BP. It has been heated to rupture all of the granules in the presence of water and subsequently dried. It may be classified as fully pregelatinized starch.

Eragel® is a physical modified rice starch. With the addition of water to Era-Gel , a vicous, slurry suspension, similar to starch paste is obtained. The advantage is that one can prepare starch paste from Eragel® at room temperature. It can also be dry mixed first with the other excipients, then with water. The amounts of dry binder as well as water can be easily controlled.

1.2. Alpha starch® or pregelatinized tapioca starch

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste. Examination of fully pregelatinized starch, as a slurry in cold water under a polarizing microscope, reveals no significant ungelatinized granules (Kibbe, 2000).

2. The other types of modified starches

2.1 Elastigel 1000J® (Food Product Division, 2004)

Elastigel 1000J® is a new, modified food starch designed specifically for confectionery applications where rapid gelling is required. It is recommended for use in food systems that require easy cooking along with the properties of low, hot viscosity and an elastic gel.

Physical Properties:

Color:	Off-white
Form:	Powder
Moisture:	Approximately 14%
pH:	Approximately 5

Features and Benefits:

Preparations of Elastigel 1000J® are low in viscosity when hot, and set quickly to elastic gels upon cooling. These characteristics enable Elastigel 1000J® to be used at higher starch solids than typical confectionery or native starches. These properties also impart the flexibility to obtain gels of various degrees of firmness.

Applications:

Elastigel 1000J® finds the widest application in confections. These include jelly gum, candies such as orange slices, mint leaves, and jelly beans.

Elastigel 1000J® is also suitable for use in the partial or total replacement of gelatin in products such as jelly candy. The level of usage can be varied to provide different textures. Gums and jellies produced with this starch have excellent sheen and a desirable short, elastic texture.

When Elastigel 1000J® is used as the sole gelling agent in a gum candy, 12-14% usage level on a dry solids basis (d.s.b.) is recommended. Candy preparations made with this starch can be kettle-cooked, static-cooked or continuously processed through jet cookers or tubular heat exchangers.

In addition to confections, Elastigel 1000J® can be used in other applications requiring improved gel strength such as desserts, dairy products and Asian foods. This starch also finds applications in chewy candy and pet foods.

Elastigel 1000J® provides the food formulator with the flexibility to develop products that can be labeled as "halal," "kosher," and "vegetarian."

Label Declaration:

"Food Starch-Modified"

2.2 Elastigel 2000C® (Food Product Division, 2004)

Elastigel 2000C® is a unique starch system that has been specifically designed for chewy candy applications (sometimes called soft candy, low boiled candy, or fruit caramel). This innovative ingredient can be used as a total replacement of gelatin and other hydrocolloids such as gum arabic or gum tragacanth, which may not be preferred in many confections. Therefore, the confection, which is prepared with Elastigel 2000C® ingredient system, can be declared as "halal", "kosher", and "vegetarian."

Physical Properties:

Color:	Off-white
Form:	Powder
Moisture:	Approximately 11%
pH:	Approximately 5

Features and Benefits:

Chewy candies can be prepared by using Elastigel 2000C® in most systems without changing the manufacturing process. It does not require high temperature activation. Elastigel 2000C® also has a viscosity allowing for easier processing. Chewy candies prepared with this product, exhibit a non-sticky, long lasting chewy texture similar to that imparted by gelatin. The level of Elastigel 2000C® used can be varied resulting in chewy candies with textures of differing degrees of hardness and chewiness.

Applications:

Elastigel 2000C® provides an excellent chewy texture without an undesirable stickiness. It also provides a long lasting chewiness similar to that of high bloom gelatin. Elastigel 2000C® exhibits excellent flavor release.

Elastigel 2000C® is suitable for complete or partial replacement of gelatin.

When Elastigel 2000C® is used as the sole texturizing agent in a chewy candy, 3-4% on a dry solids basis (d.s.b.) is recommended. Elastigel 2000C® can be processed with kettle-cookers, static-cookers, a continuous process with a jet cooker or tubular heat exchanger.

Elastigel 2000C® provides the food formulator with the flexibility to develop products that can be labeled as "halal", "kosher", and "vegetarian."

Label Declaration:

Food starch and dextrin

2.3 Elastigel 3000M® (Food Product Division, 2004)

Elastigel 3000M® is a specialty modified food starch developed to provide an elastic gelled texture to meat products. It has a smooth and short texture when hot and sets to a tender elastic gel upon cooling.

Physical Properties:

Color:	White to off-white
Form:	Powder
Moisture:	Approximately 11%
pH:	Approximately 6

Features and Benefits:

Elastigel 3000M® has been designed to have excellent water binding properties. It cooks easily in an aqueous system giving a smooth short texture with good clarity. On cooling, it will form a soft elastic gel.

Elastigel 3000M® is very bland in taste which will not mask the flavor profile of other ingredients in the formulation. It is an ideal thickener particularly for low acid foods.

Application:

Elastigel 3000M® is a flexible thickener with the ability to form an elastic gel at higher concentrations, making it suitable for a wide variety of applications.

Elastigel 3000M® is recommended for use in traditional Asian gelled desserts with or without the addition of gums. It is also used as a thickener for dry mixture, seasonings and fillings. The benefit of a bland tasting starch is to release the full flavor of the product.

The use of Elastigel 3000M® in processed fish and meat applications improve the firmness and bite of the product. In instant cup or bowl noodles, it helps to reduce the rate of the noodles softening on addition of hot water.

Elastigel 3000M® is also recommended for use in baby food products as a thickener because of its smooth texture and excellent taste profile.

Other applications include the use of Elastigel 3000M® as a thickener and binder in extruded pellet feeds and as a gelling agent in canned pet food.

Label Declaration:

Food Starch-Modified

Manufacturing process of hard gelatin capsule

The manufacturing process is started with the preparation of a 30-40% (w/w) gelatin solution by dissolving the gelatin directly into demineralised water at 60-70°C or by first hydrating the gelatin in cold demineralised water before dissolving. When the gelatin solution has matured, aliquots are withdrawn from the manufacturing vessel and are prepared for the requirement of each individual machine. Firstly the colorants are added. At the same time, other material such as preservatives may be incorporated into the mixture. The viscosity of the final solution is determined and adjusted to provide the desired capsule wall thickness. The gelatin solution is fed from the holding tanks into a "dip pan" which is maintained at 45-55°C (Jones, 2004: 79-100) The steps of capsule formation by dipping process are described as follows (Augsburger, 1989).

1. **Dipping**

Pairs of stainless steel pins are dipped into the dipping solution to form the caps and bodies simultaneously. The pins are lubricated with a proprietary mold-release agent. The pins are at ambient temperature, whereas the dipping solution is maintained at a temperature of about 50°C in a heated and jacketed dipping pan. The length of time to east the film has been reported to be about 12 seconds with a longer dipping time for larger capsule.

2. **Rotation**

After dipping, the pins are moved from the lower level to the upper level of the machine. As they do this, they are rotated horizontally to evenly spread the gelatin over the mold pins and are passed through a stream of cool air to harden the gelatin.

3. **Drying**

The pin bars are then passed through a series of drying kilns. In these, large volume of controlled humidity air are blown directly over the pins to dry the film. The air are blown directly over the pins to dry the film. The heated air is a few degrees above ambient (22-28°C) to prevent film from melting (Jones, 1987: 68-79). Drying also must

not be too rapid because excessive drying rate will cause splits to occur in the gelatin film or at least make them too brittle for the later trimming operation. Underdrying will leave the films too pliable or sticky for subsequent operations.

4. Stripping

A series of jaws strip the cap and body portions of the capsules from the pins.

5. Trimming

The stripped cap and body portions are delivered to collets, in which they are firmly held. As the collects rotate, knives are brought against the shells to trim them to the length required.

6. Joining

The cap and body portion are aligned concentrically in channels and the two portions are slowly pushed together.

The entire cycle takes about 45 min, however, about two-thirds of this time is required for the drying step alone.

7. Sorting

In the range 15 to 18% w/w the moisture content of the capsules as they are ejected from the machine. Additional adjustment of moisture content towards the final desired specification will occur during the sorting step. During sorting, capsules, passing on a lighted moving conveyor are examined visually inspectors. Any defective capsules or spotted capsules are removed manually. Defects are generally classified according to their nature and potential to cause problems in usage. The most serious are those that could cause stoppage of a filling machine such as imperfect cuts, dented capsules, or those with holes. Other defects may cause problems on usage such as capsules with splits, long bodies, or grease inside. Many less important, cosmetic faults, which only detract from appearance (small bubbles, specks in the film, marks on the cut edge, etc.) may also occur.

Packing and storage (Jones, 2004: 79-100)

The capsules are not placed directly in the boxes but they are put inside a liner. The liner which is adequate in temperate climates may be either a heat-sealed paper sack with saran lining or a polyethylthene bag sealed with a tie where proper warehouse facilities are available. However, multilaminate aluminium foil sacks, which are heat sealed, are required in severe climatic conditions or where the warehousing facilities cannot be maintained at uniform temperatures. The storage area preferable should have a temperature between 15 to 30°C and a relative humidity (RH) less than 70%.

Capsule standard

1. Pharmacopoeial standard

The official tests are designed to ensure that capsule products comply with a minimum acceptable standard. They fall into three groups: raw materials, product quality, which covers the content of active ingredient and uniformity of weight, and testes that measure the release of product from the capsule, e.g. disintegration and dissolution. Not all pharmacopoeias have a full set of tests. Most pharmacopoeias have testes for filled capsule products but most have none for the empty capsules themselves. The exception are the Chinese and Japanese pharmacopoeias. The entry in the Japanese pharmacopoeia (JP) in its capsule monograph has a test called "purity". This test uses a sample of five capsules. Each one is taken apart, placed in 100 ml. conical flask, 50 ml. of water is added and the flask is shaken repeatedly. During this test the water is maintained at 37±2°C. All the capsules must completely dissolve within 10 min. The resulting solutions must be odourless and neutral or slightly acidic. (Jones, 2004: 239-259).

2. Industrial standard

One official standard for quality control that can be applied to both hard and soft capsules is the American Federal Standard for capsules (for Medicinal purposes). It is frequently used as the basis for industrial quality control. However, since the defects may arise from the empty shells, the standards are applied in the industry to the quality control or empty capsules. Because defects may arise in the filling process. The Federal Standard includes references to pharmacopoeial standards but extends their scope to many other aspects of physical testing, packaging etc.

In Thailand, Thai industrial standard (TIS 913-2545) for hard gelatin capsule has been set Thai Industrial Standard Institute. The example of physical standard requirement are as follows (TIS 913-2545).

1. Definition: Hard Gelatin Capsule which called "capsule" in this standard means gelatin tube for filling drugs and foods. It contains body and cap which may be smooth or have the lock channel (see figure 2.9).

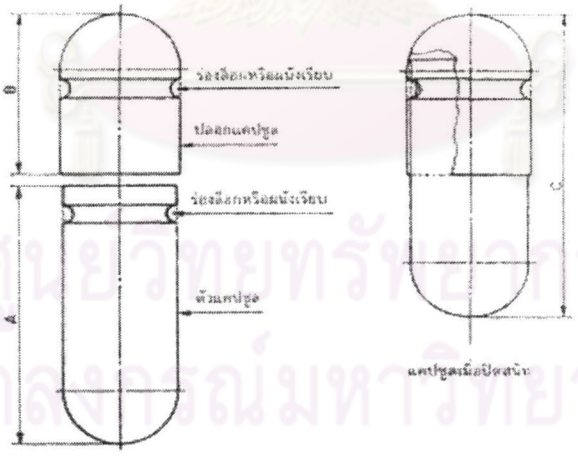

Figure 2.9 The hard gelatin capsule composition

2. size and standard deviation: The number of the size, dimension, capacity of the body, mass and standard deviation of the capsule should be follow the table 2.3

Table 2.3 Dimensions of hard gelatin capsule

Capsule size	Length (mm.)			Volume (ml.)	Weight (mg.)
	Cap	Body	Closed joined		
000	To agreed between the capsule producers and users ± 0.5			1.37±0.03	163±10
00				0.95±0.03	122±10
0				0.68±0.03	98±8
1				0.48±0.03	77±6
2				0.37±0.03	63±5
3				0.28±0.03	49±4
4				0.20±0.03	40±3
5				0.13±0.03	27±3

3. Water resistance: Gelatin capsules should remain undissolve or disintegrate in water at 25±1°C for 15 min. Cellulose capsules should dissolve in water at 25°C but gelatin capsule should swell and distort but should not dissolve (Chiwele et al., 2000).

4. Disintegration: The disintegration test for capsules follow USP 24 which have standardised on an apparatus with six tubes. The temperature of the fluid must be maintained between 35-39°C. A disc is added to the tube in order to keep capsules below the surface of the liquid. The end-point not more than 15 min. all of the capsules have disintegrated, there no residue or fragment of shell on mesh.

5. Ash: The ash should not more than below

5.1) 2.0 percent weight by weight for the transparent capsule

5.2) 5.0 percent weight by weight for the semi-transparent capsule

5.3) 7.0 percent weight by weight for the opaque capsule

6. Moisture content: The moisture content of gelatin capsule is normally 12.0 to 16.0 % by weight determined by drying at 105°C more than 17 hrs.

7. Capsule should not have more micro-organism than below

7.1) Total micro-organism not more than 1 x 10^3 colony per 1 gm of sample

7.2) *Escherichia coli* must not be found in 10 gm of sample

7.3) *Salmonella* must not be found in 10 gm of sample

7.4) *Staphylococcus aureus* must not be found in 10 gm of sample

7.5) *Pseudomonas aeruginosa* must not be found in 10 gm of sample

Mechanical and physical properties of polymeric films

1. Tensile properties

The properties of the various film forming materials have already been compared. Selection of the best film for any particular use is a matter of matching these film properties against the end-use performance required.

In order to carry out this matching of properties againsts requirement, it is necessary to know what the various properties actually mean in practice and to have some method of quantifying them. The testing of film properties is also necessary for other reasons. Traditionally, stress-strain testing in the tensile mode has been a popular and widely used mechanical test for the polymeric films. The tensile test gives an indication not only of the elasticity and strength, but also of the toughness of the film.

According to the ASTM guideline, the data for tensile properties may be acquired in the form of a load-time (elaped) profile instead of a typical load-displacement or stress-strain profile. The data collected to a load-time profile can be converted in the form of a load-displacement profile with the help of applied strain rate (O'Donnell and McGinity, 1997).

A tensile testing instrument such as an Instron-Model # 4200 or a Systems Corp. Model T 5002 mounted with a load cell may be used for the measurements. Three mechanical properties, namely, tensile strength, work of failure and elastic modulus are

computed from the load-time profile, cross-head speed, and film dimensions (Parikn, Porter, and Rohera, 1993). The theory behind the computation of these parameters is well documented. The final equations that define each of these parameters are present below.

1.1 Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks (Figure 2.10). Tensile strength can be computed from the applied load at rupture and the cross-sectional area of fractured film as described in Eq.(1):

$$\text{Tensile strength} = \frac{\text{load at failure}}{\text{film thickness x film width}} \qquad \text{Eq.(1)}$$

The determination of tensile strength alone is not very useful in predicting mechanical performance of the films; however, higher values of tensile strength of the films are desirable for abasion resistance.

1.2 Work of failure

Work of failure is a function of work done in breaking the film specimen and is representative of the film toughness. It can be calculate from the area under curve of the load-time profile, cross-head speed and film dimensions as described in Eq. (2):

$$\text{Work of failure} = \frac{\text{area under curve x cross – head speed}}{\text{film thickness x film width}} \qquad \text{Eq. (2)}$$

1.3 Elastic modulus

Elastic modulus is the most basic and structurally important of all mechanical properties and is a measure of stiffness of the film. It is the ratio of applied stress and corresponding strain in the region of approximately linear elastic deformation. It can be

computed from the slope of the linear portion of elastic deformation on the load-time profile, cross-head speed and film dimensions Eq.(3):

$$\text{Elastic modulus} = \frac{\text{slope}}{\text{film thickness x film width x cross-head speed}} \qquad \text{Eq.(3)}$$

1.4 Strain (Briston, 1990: 93-113)

This is a measure of change in the dimensions of the body when a force is applied to it and is calculated with reference to its original size. In tensile testing, strain is defined as :

$$\text{Strain} = \frac{\text{total elongation}}{\text{gauge length}}$$

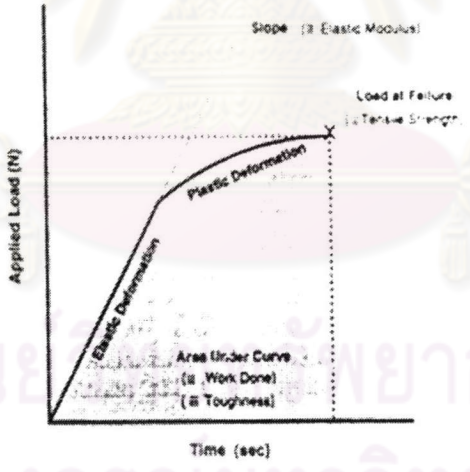

Figure 2.10 A typical load-time profile observed in the tensile testing of free films (Parikn, Porter, and Rohera, 1993).

The physical-mechanical properties of polymers will be influenced by both environmental factors and the chemical composition of the polymer.

Structural properties of the polymer will include molecular weight, crosslinking and branching, crystallinity and crystal morphology, type and amount of plasticizers and presence of additives or fillers. Environmental factors influencing polymer properties will include temperature, time and rate of stressing the polymer, pressure, stress and strain amplitude, type of deformation and the nature of the surrounding atmosphere. Most amorphous polymers behave as viscoelastic materials. Their mechanical properties will depend on the temperature and the application rates of stress and strain. The profile in Figure 2.11 shows the typical response from a plasticized polymer when evaluated with a tensile tester such as an Instron. In a typical stress-strain curve, there is a linear portion where the elongation is directly proportional to the applied stress. The slope of this straight line portion is used to calculate the elastic or Young's modulus. The greater the slope of the curve, the higher the elastic modulus and as the stiffness and the strength of the film increase. More stress will be required to produce a given amount of deformation. The elongation of the film will increase as the plasticizer levels are increased. For most polymeric films, physical aging will result in a stiffening of the film. The effect of aging and storage conditions on polymer properties can be predicted from physical-mechanical testing. Not all polymers behave in a typical manner and depending on the mechanical response of the polymer, a family of stress-strain profiles can be obtained to clearly define the modulus of elasticity, tensile strength and film elongation at break of the plasticized polymer (O'Donnell and McGinity, 1997).

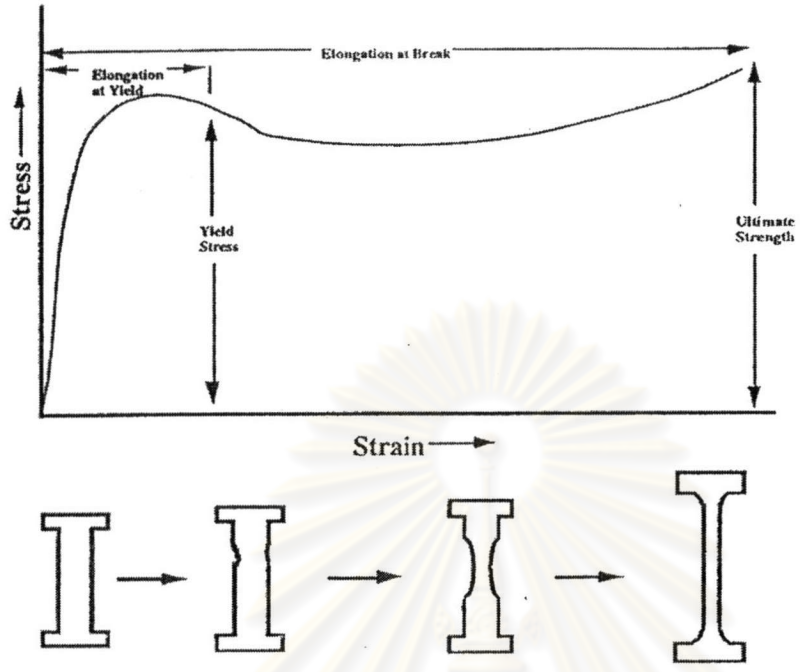

Figure 2.11 Stress-strain curve obtained from a free film of a plasticized polymer (O'Donnell and McGinity, 1997)

A great deal of information about the films can be obtained from tensile strength, Young's modulus, elongation or the shape of its stress/strain curve. Some typical curves and behaviours are shown in Figure 2.12 (a – e).

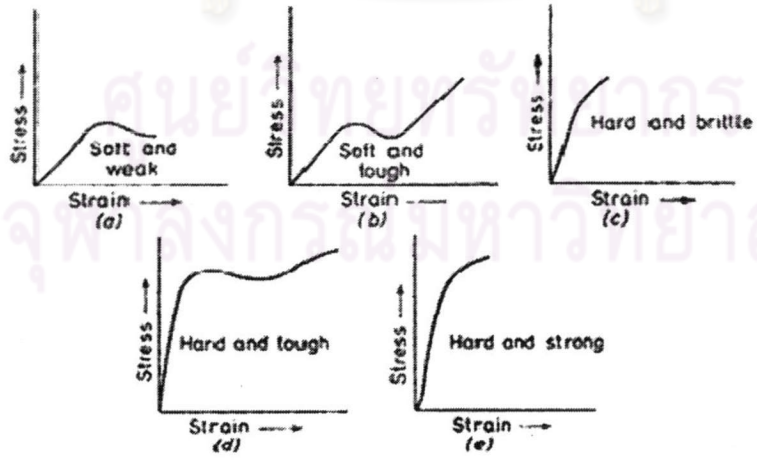

Figure 2.12 Typical stress/strain curves obtained with polymers (Briston, 1990).

A.) Soft and weak

Soft and weak films have a low value for Young's modulus, coupled with a low tensile strength. The elongation at break is only moderate. As illustrated the area under the curve is low.

B.) Soft and tough

These films have an appreciably higher area under the curve. The tensile strength is moderately high but Young's modulus is low as with soft and weak materials. The yield point is well marked and the elongation is high.

C.) Hard and brittle

As one would expect the tensile strength and Young's modulus are both high. Brittle materials have no distinct yield point, however, and the elongation is low.

D.) Hard and tough

The high tensile strength, Young's modulus and elongation combine to give the large area under the stress/strain curve, thus justifying the adjective, tough.

E.) Hard and strong

Such films are intermediate in character between the hard and brittle, and the hard and tough materials. Although there is still no clearly defined yield point, the elongation and tensile strengths are both greater than for hard and brittle materials (Briston, 1990: 93-113).

2. Gloss

Gloss is a measure of the ability of the film to reflect incident light. Usually, the incidence in a mirror-angle is equal to the angle of reflection. The mechanism of glossmeter are shown in figure 2.13 (Briston, 1990: 114-127).

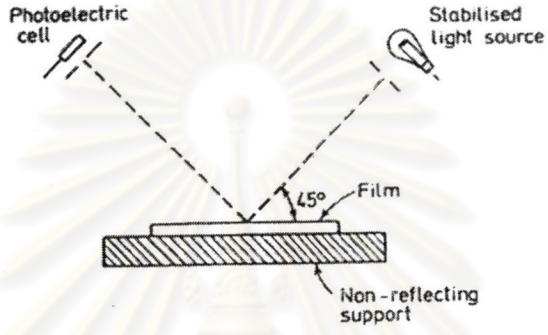

Figure 2.13 The mechanism of glossmeter (Briston, 1990: 114-127)

ProGloss 3™ is a portable measuring unit for determining the gloss of paint coatings, plastics, ceramics and similar materials. Light is directed onto the surface of the test specimen at a defined angle and the reflected light is measured photoelectrically. Depending on the typical gloss of the test specimens, you can use reflectometers with light beams directed onto the surface at different angles, which is called the "geometry" of the unit. This glossmeter provides the standard geometries 20°, 60° and 85° as shown in figure 2.14.

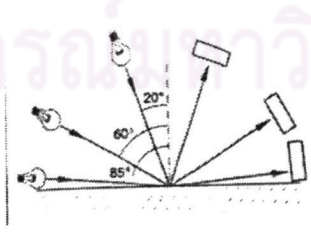

Figure 2.14 The gloss degree determines the selection of illumination and reflection angles

Dicloxacillin

Dicloxacillin is a semisynthetic penicillinase-resistant penicillin. Dicloxacillin, like cloxacillin and oxacillin, is an isoxazolyl penicillin. Figure 2.15 shows the chemical structure of dicloxacillin. The presence of two chloride ions on the phenyl group distinguishes this drug from cloxacillin. Dicloxacillin is commercially available as the monohydrate sodium salt. Dicloxacillin sodium occurs as a white to off-white crystalline powder. The drug is freely soluble in water and soluble in alcohol. Dicloxacillin sodium has a pK_a of 2.7-2.8 (Parfitt, 1999).

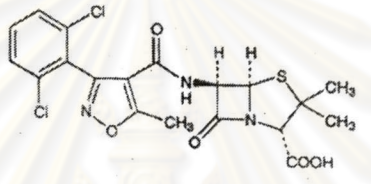

Figure 2.15 Chemical structure of dicloxacillin (O'Neil, 2001)

Chemical name	:	3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolylpenicillin
Empirical formula	:	$C_{19}H_{17}Cl_2N_3O_5S$
Molecular weight	:	470.33
Synonym	:	BRL-1702
Appearance	:	White crystalline powder