



CHAPTER I

GENERAL BACKGROUND

1. Introduction

In Thailand, Durian (*Durio zibethinus* L.) Mhontong cultivar is a famous fruit, which is available a large quantity every year especially on its season, enormous amount of durian fruit-hulls become waste products. Until 1988, Pongsamart *et al.* isolated heteropolysaccharide substance, polysaccharide gel (PG) from durian fruit-hulls has recently introduced as a natural water soluble polymer. The polysaccharide composed of repeating sugar unit of long or branch chain heteropolysaccharide, sugars component including arabinose, rhamnose, fructose, glucose and galacturonic acid was found to be a major component (Pongsamart and Panmuang, 1988; Gerddit, 2002). PG was found useful in pharmaceutical and food preparation such as tablet, suspension, jelly, emulsion, diet food and film coated tablet (Pongsamart *et al.*, 1989; Pongsamart, Dhumma-Upakorn and Panmaung, 1989; Umprayn, Kaitmonkong and Pongsamart, 1990; Umprayn, Chanpaparp and Pongsamart, 1990, Pongsamart *et al.*, 2001). Toxicity test of polysaccharide gel was determined using a high oral dose (2g/kg) did not induced severe toxicity in male mice and rats (Pongsamart, Sukrong and Tawatsin, 2001). No toxic effects were observed in subacute treatment in male mice (Pongsamart, Jesadanont and Markman, 1989) and subchronic studies in male and female mice confirmed the consumptive safety of PG (Pongsamart, Sukrong and Tawatsin, 2001). Polysaccharide gel showed inhibitory activity against 7 strains of bacteria. Minimal Inhibitory Concentration (MIC) of PG against *B. subtilis*, *M. luteus*, *S. epidermidis*, *E. coli* and *P. vulgaris* was 6.4 mg/ml and against *S. aureus* and *L. pentosus* were 12.8 and 25.6 mg/ml, respectively (Nantawanit, 2001). Polysaccharide gel at 2% concentration trapped up to 80-90% of cholesterol (Tippayakul, 2002) and sugars (glucose and sucrose), fat soluble vitamin(vitamin A) or water soluble vitamin(vitamin B1) (Piyasirananda, 2003) due to *in vitro* study. Film-forming property of polysaccharide gel was investigated to evaluate its application as a film patch for pharmaceuticals. Film of polysaccharide gel was prepared by casting/solvent evaporation method from mixture of aqueous solutions of polysaccharide gel with plasticizer. Satisfactory film products were obtained (Gerddit, 2002). PG dressing film can be satisfactory used for treatment of open wound better than the traditional treatment (Nakchat, 2002).

Some natural polysaccharides that are widely used in film former and gelling agent are chitosan used in the film coating of tablets (Phaechamud, 1995) and used as emulsion stabilizer and thickener (Dee, 2001), gelatin and pectin make suitable for use in the food and pharmaceutical aid, gellan gum is a gel-forming polysaccharide (Tang *et al.*, 2001). Many researchers reported other natural polysaccharide such as pectins, starch, gum and chitosan used as edible films (Conca and Yang, 1993; Nisperos-Carriedo, 1994; Krochta and Mulder-Johnston, 1997). The polymers of the cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose should be applied as film former in tablet film coating. The carbomer and carboxymethylcellulose (CMC) should be applied as a gelling agent in gel preparations (Actives C&T Formulary, 1999).

A novel natural polysaccharide from fruit-hulls of durian have gelling and film-forming properties and sugar component similar to those of polymers, which is an interesting substance for this study in order to discover of new gelling agent and film forming agent. Polysaccharide gel (PG) would possibly has advantage as a new type of water-soluble gelling agent and film forming agent to provide the satisfactory products for widely uses.

In this investigation, we have studied about the properties on gelling and film forming of polysaccharide gel (PG) from durian hull (*Durio zibethinus* L.) Mhontong cultivar, rheology, and compatibility of PG and each substance: chemical substances such as electrolytes, solvents, humectants, preservatives, including the studying of PG property at various temperatures. The result of the PG study, we have developed and produced vitamin gel by preparation of gel formula and vitamin E and C gel preparations and the stability of gel preparations were also studied.

In addition, the information of PG film from the study of Gerddit, W. (2002) found that we can develop PG as a mouth refreshing film, which composed of PG, menthol and peppermint oil, hydroxypropyl methylcellulose, fructose and food color. This gel formula was tested the properties of tensile, moisture sorption and swelling of film. In conclusion, we found the new polysaccharide is useful and is able to be developed pharmaceutical products.

2. Literature Review

Gels (Zatz and Kushla,1996)

Definitions

"Gel: a substance in a state between solid and liquid; jelly: hair gel"

(Longman Dictionary of Contemporary English 2nd Ed., 1987)

The United States Pharmacopeia (USP) defines gels as semisolids, being either suspension of small inorganic particles or large organic molecules interpenetrated with liquid. Gels are transparent or translucent semi-solid or solid preparations, consisting of solutions or dispersions of one or more active ingredients in suitable hydrophilic or hydrophobic bases. They are made with the aid of a suitable gelling agent. Usually gels exhibit pseudoplastic flow properties and those made with synthetic or semi-synthetic polymers with a high degree of cross-linking have relatively high yield values and low viscosity. Gels are often non-greasy and are generally applied externally. As vehicles for the presentation of water-soluble medicaments, gels are ideal because of their high water content. Products tend to be smooth, elegant, and produce cooling effects because of evaporation of water; they may also dry out to form films. Films adhere well to the skin and are usually easily removed by washing; gelatin containing films may be less readily removed. For the presentation of insoluble materials hydrophilic gels have the limitation that the resultant products may lack clarity and smoothness. Ideally, gelling agents for pharmaceutical and cosmetic use should be inert, safe, and nonreactive with other formulation components. A potential incompatibility is illustrated by the combination of a cationic drug, preservative, or surfactant with an anionic gel former. Inactivation or precipitation of the cationic substance is possible. Sodium alginate has been shown to reduce the concentration of cationic preservatives in solution, as well as complex with chlorpheniramine, reducing the drug release rate from gelled formulations. Polyethers have been shown to interact with phenols and carboxylic acids, leading to loss of potency. The inclusion of a gelling agent in a formulation should provide a reasonable solidlike nature during storage that can be broken easily when subjected to the shear forces generated in shaking a bottle, squeezing a tube, or during topical application. Cost considerations require a low concentration of gellant to produce the desired characteristics.

The gel should exhibit little viscosity change under the temperature variations of normal use and storage. For example, Plastibase exhibits a lesser decrease in

consistency than petrolatum over the same temperature range. This minimizes unacceptable changes in the product's characteristics. Many gels, particularly those of a polysaccharide nature are susceptible to microbial degradation. Incorporation of a suitable preservative may prevent contamination and subsequent loss of gel characteristics due to microbial attack. The gel characteristics should match the intended use. A topical gel should not be tacky. Too high a concentration of gel former or the use of an excessive molecular weight may produce a gel difficult to dispense or apply. An ophthalmic gel must be sterile. The aim is to produce a stable, elegant, economic gel product adequately suited for its intended use.

Swelling

Gels can swell absorbing liquid with an increase in volume. Swelling can be looked on as the initial phase of dissolution. Solvent penetrates the gel matrix. Gel-gel interactions are replaced by gel-solvent interactions. Limited swelling is usually the result of some degree of crosslinking in the gel matrix that prevents total dissolution. Such gels swell considerably when the solvent mixture possesses a solubility parameter comparable to that of the gellant.

Syneresis

Many gel systems undergo a contraction upon standing. The interstitial liquid is expressed, collecting at the surface of the gel. This process is referred to as syneresis. Syneresis is not limited to organic hydrogels but has been seen in organogels and inorganic hydrogels as well. Typically, syneresis becomes more pronounced as the concentration of polymer decreases.

The mechanism of concentration has been related to the relaxation of elastic stresses developed during the setting of the gel. As these stresses are relieved, the interstitial space available for solvent is reduced, forcing the expression of fluid. Osmotic effects have been implicated, as both pH and electrolyte concentration influence syneresis from gels composed of the ionic gel formers gelatin or psyllium seed gum.

Structure

The long chains of organic gel formers are extended in good solvents, as would be the case in aqueous gels, due to hydrogen bond formation between water and

hydroxyl groups of the gelling agent. In a poor solvent, the gel molecule would be more or less tightly coiled, preferring self-interaction to interaction with the solvent. Each segment of the dissolved molecules is in constant random motion, buffeted by the movement of solvent molecules through the bulk of the liquid. This random motion serves to entangle polymer strands. Molecular entanglement is responsible for the viscosity and structure of organic gels.

The organic polymers used in hydrogels tend to be sheathed with an envelope of water of hydration. This enables the polymer molecules to slip past each other at low concentrations due to the lubricity of the intervening water molecules. If the degree of hydration is low, then intermolecular attractive forces such as hydrogen bonding and Van der Waals forces form weak secondary bonds between polymer strands. At sufficiently high concentration, a continuous network of weakly interacting chains can be formed. The association may proceed far enough to produce small local regions of crystalline nature dispersed through a bed of randomly entangled polymer strands.

Salts may attract part of the water of hydration of the polymer, allowing the formation of more intermolecular secondary bonds, leading to gelation and precipitation. This is known as salting out. Multivalent cations have a strong effect on the solutions of anionic polymers. Bridging of the polymers by di- or trivalent cations, as in the addition of copper to solutions of sodium carboxymethyl cellulose or calcium to sodium alginate, leads to gel formation.

Alcohols have a similar effect. In addition, alcohols alter the solvent's characteristics, changing the solubility parameter. The addition of alcohol often brings about coacervation rather than gelation. Coacervation is the production of a viscous, solvated, polymer-rich phase, leaving behind a phase that is mostly solvent and therefore, polymer poor.

Many gel formers are more soluble in hot than cold water. If the temperature is reduced once the gel is in solution, the degree of hydration is reduced and gelation occurs. Some polymers exhibit thermal gelation. These polymers are more soluble in cold water; solution of these materials gel on heating. Examples include methylcellulose and poloxamer.

Gelation due to changes in hydration with changes in temperature tend to be reversible; gels liquefy and set again as the temperature is cycled. Gelation due to

chemical reactions as in salt bridging or cross linking is irreversible. These gels cannot be liquefied by dilution or temperature changes.

Molecular weight is an important consideration in gel formation. Very long polymers can entangle to a greater extent, leading to higher viscosity at a given concentration. Thus, lower concentration of a high molecular weight polymer may be required to gel the solvent. This can be a drawback exhibited as difficult spreading of a topical gel due to the high cohesive interactions between the gel strands. Likewise, low molecular weight polymers require a high concentration to build up viscosity and to set to a gel, possibly increasing the cost due to the amount of gellant used and overshadowing the desired properties of the formulation.

Viscosity & Rheology (Ramachandran, *et al.*, 1999, Tantry, *et al.*, 2001)

Viscosity

Viscosity is the measure of the internal friction of a fluid. This friction becomes apparent when a layer of fluid is made to move in relation to another layer. The greater the friction, the greater the amount of force required to cause this movement, which is called "Shear" Shearing occurs whenever the fluid is physically moved or distributed, as in pouring, spreading, spraying, mixing, etc. Highly viscous fluids, therefore, require more force to move than less viscous materials.

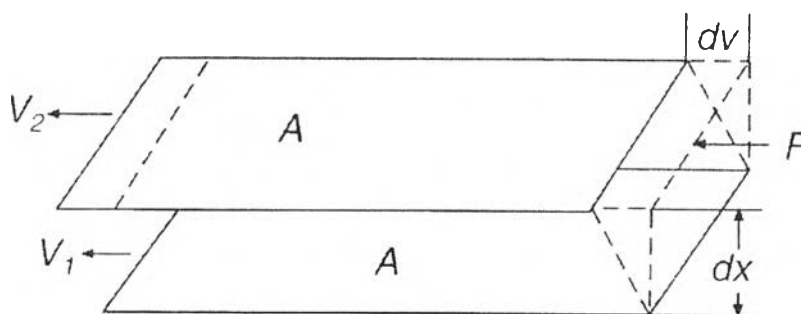


Figure 1 Viscosity model (Laba, D.. 2001)

Isaac Newton defined viscosity by considering the model represented in fig 1. Two parallel planes of fluid of equal area "A" are separated by a distance "dx" and are moving in the same direction at different velocities "V₁" and "V₂". Newton assumed that the force required to maintain this difference in speed was proportional to the difference in speed through the liquid, or the velocity gradient. To express this, Newton wrote:

$$\frac{F}{A} = \eta \frac{dv}{dx}$$

Where η is a constant for a given material and is called its "viscosity"

The velocity gradient, dv/dx , is a measure of the change in speed at which the intermediate layers move with respect to each other. It describes the shearing the liquid experiences and is thus called "shear rate." This will be symbolized as "S" in subsequent discussions. Its unit of measure is called the "reciprocal second" (sec^{-1}).

The term F/A indicates the force per unit area required to produce the shearing action. It is referred to as "Shear stress" and will be symbolized by "F". Its unit of measurement is "dynes per square centimeter" (dynes/cm^2).

Using these simplified terms, viscosity may be defined mathematically by this formula:

$$\eta = \text{Viscosity} = \frac{F}{S} = \frac{\text{shear stress}}{\text{shear rate}}$$

The fundamental unit of viscosity measurement is the "poise." A material requiring a shear stress of one dyne per square centimeter to produce a shear rate of one reciprocal second has a viscosity of one poise, or 100 centipoises. You will encounter viscosity measurements expressed in "Pascal-seconds" (Pa•s) or "millipascal-seconds" (mPa•s); these are units of the international system and are sometimes used in preference to the Metric designations. One Pascal-second is equal to ten poise; one milli-Pascal-second is equal to one centipoises (cps).

Newton assumed that all materials have, at a given temperature, a viscosity that is independent of the shear rate. In other words, twice the force would move the fluid twice as fast.

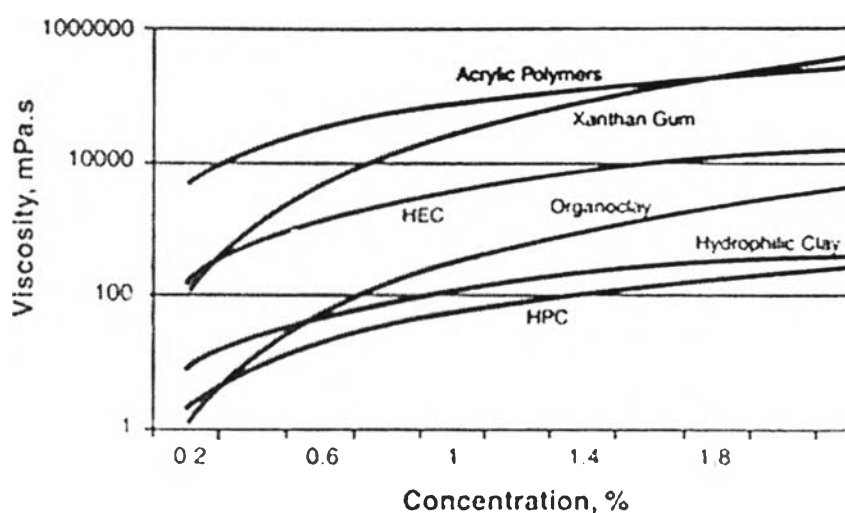


Figure 2 Typical viscosity profile (Laba, D. 2001)

The apparent viscosity of gelling agent solutions are dependent on the concentration. The viscosity increases with an increase in concentration of gelling agent as shown in figure 2.

Rheology

Rheology is defined by Webster's Dictionary as "the study of the change in form and the flow of matter, embracing elasticity, viscosity, and plasticity." Viscosity, further defined as "the internal friction of a fluid, caused by molecular attraction, which makes it resist a tendency to flow."

Solution of gelling agents and dispersions of flocculated solids are typically, pseudoplastic, exhibiting a non-Newtonian flow behavior characterized by a decreasing viscosity with increasing shear rate. Such behavior is due to progressive breakdown of the structure of the system.

The tenuous structure of inorganic particles dispersed in water is disrupted by an applied shear stress. As shear stress is increased, more and more interparticulate associations are broken, exhibited as a greater tendency to flow. Similarly, for macromolecules dispersed in a solvent, the applied shear stress tends to align the molecules in the direction of the stress. The molecules straighten out, becoming less entangled as shear increases, lessening the resistance to flow. The classification of fluids have two categories. These include: Newtonian and Non-Newtonian.

Newtonian Fluids

This type of flow behavior Newton assumed for all fluids is called, not surprisingly, “Newtonian.” It is, however, only one of several types of flow behavior you may encounter. A Newtonian fluid is represented graphically in figure 3 Graph A shows that the relationship between shear stress (F') and shear rate (S) is a straight line. Graph B shows that the fluid’s viscosity remains constant as the shear rate is varied. Typical Newtonian fluids include water and glycerin.

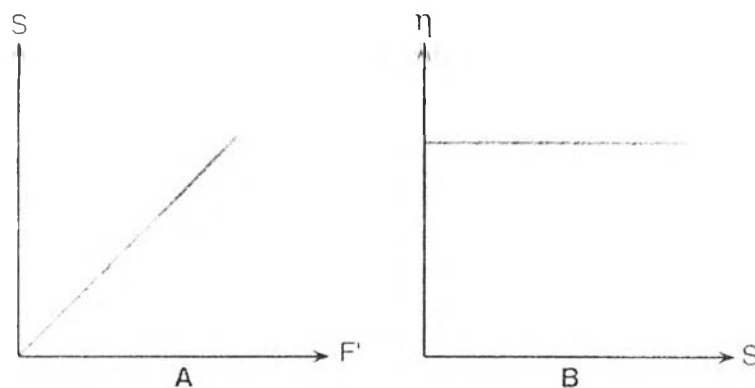


Figure 3 Newtonian behavior

Non-Newtonian Fluids

A non-Newtonian fluid is broadly defined as one for which the relationship F'/S is not a constant. In other words, when the shear rate is varied, the shear stress doesn't vary in the same proportion (or even necessarily in the same direction). The viscosity of such fluids will therefore change as the shear rate is varied. Thus, the experimental parameters of Viscometer model, spindle and speed all have an effect on the measured viscosity of a non-Newtonian fluid. This measured viscosity is called the “apparent viscosity” of the fluid and is accurate only when explicit experimental parameters are furnished and adhered to.

Non-Newtonian flow can be envisioned by thinking of any fluid as a mixture of molecules with different shapes and sizes. As they pass by each other, as happens during flow, their size, shape, and cohesiveness will determine how much force is required to move them. At each specific rate of shear, the alignment may be different and more or less force may be required to maintain motion.

There are several types of non-Newtonian flow behavior, characterized by the way a fluid's viscosity changes in response to variations in shear rate. The most common types of non-Newtonian fluids you may encounter include:

Plastic: This type of fluid will behave as a solid under static conditions. A certain amount of force must be applied to the fluid before any flow is induced; this force is called the "yield value." Tomato catsup is a good example of this type fluid; its yield value will often make it refuse to pour from the bottle until the bottle is shaken or struck, allowing the catsup to gush freely. Once the yield value is exceeded and flow begins, plastic fluids may display Newtonian, pseudoplastic, or dilatant flow characteristics. See Figure 4.

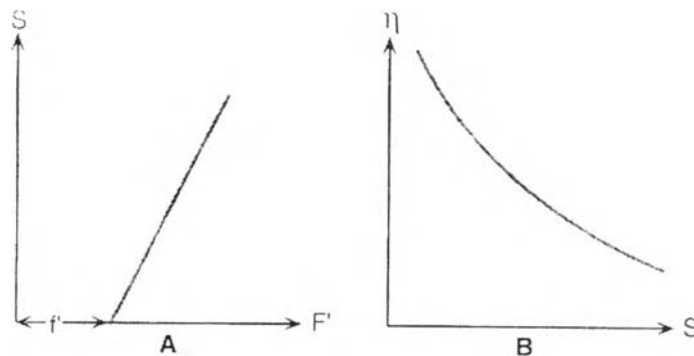


Figure 4 Plastic behavior

Pseudoplastic: This type of fluid will display a decreasing viscosity with an increasing shear rate, as shown in figure 5. Probably the most common of the non-Newtonian fluids, pseudoplastics include paints, emulsions, and dispersions of many types. This type of flow behavior is sometimes called "shear-thinning."

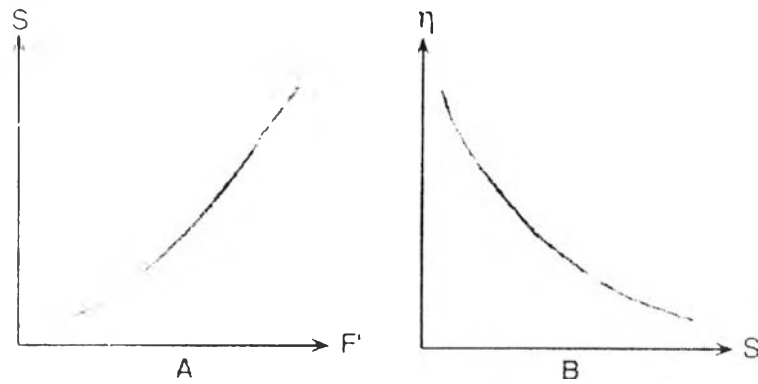


Figure 5 Pseudoplastic behavior

Dilatant: Increasing viscosity with an increase in shear rate characterizes the dilatant fluid; see figure 6. Although rarer than pseudoplasticity, dilatancy is frequently observed in fluids containing high levels of deflocculated solids, such as clay slurries, candy compounds, corn starch in water, and sand/water mixtures. Dilatancy is also referred to as “shear-thickening” flow behavior.

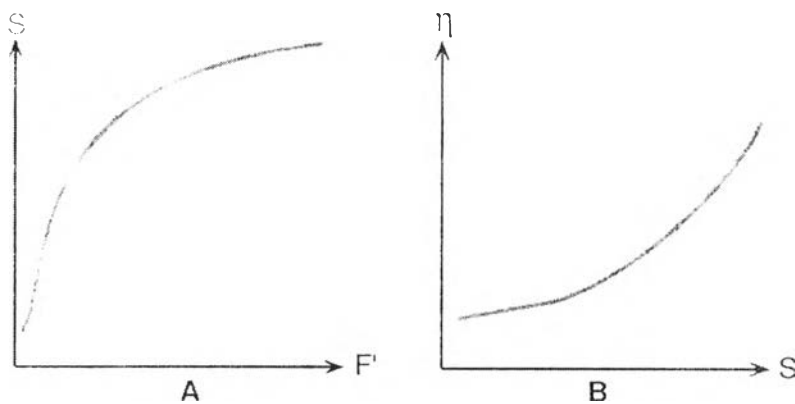


Figure 6 Dilatant behavior

Thixotropy: As shown in figure 7, a thixotropic fluid undergoes a decrease in viscosity with time, while it is subjected to constant shearing. Thixotropy is frequently observed in materials such as greases, heavy printing inks, and paints.

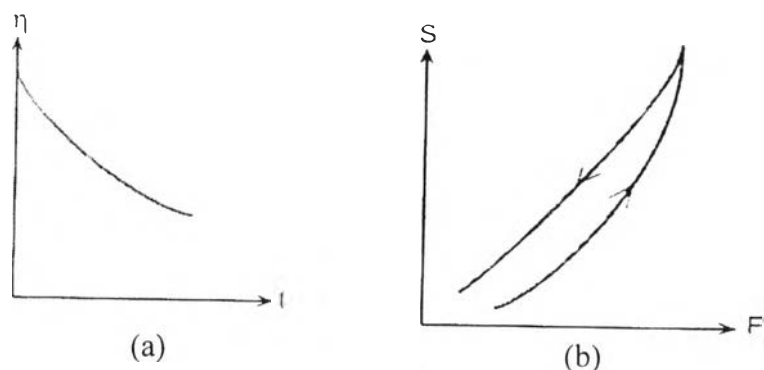


Figure 7 Thixotropy behavior

When subjected to varying rates of shear, a thixotropic fluid will react as illustrated in figure 7. A plot of shear stress versus shear rate was made as the shear rate was increased to a certain value, then immediately decreased to the starting point. Note that the “up” and “down” curves do not coincide. This “hysteresis loop” is caused by the decrease in the fluid’s viscosity with increasing time of shearing. Such effects may or may not be reversible; some thixotropic fluids, if allowed to stand undisturbed for a while, will regain their initial viscosity, while others never will.

The classification of a gel is determined by considering some characteristic of either of the two phases. Gels are divided into inorganic and organic gels on the basis of the nature of the colloidal phase. These are further subdivided according to the chemical nature of the dispersed organic molecules. Most natural gums such as acacia, carrageenan, and xanthan gum, are anionic polysaccharide. A number of cellulose derivatives have been synthesized and are effective gellants; among them are sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and methylhydroxypropyl cellulose. Polypeptides (gelatin) and synthetic block copolymers, like poloxamers are two additional chemical classes.

The use of gels and gelling agents are quite widespread, even in limiting our consideration to the pharmaceutical and cosmetic fields only. Gels find use as delivery systems for oral administration, as gels proper, or as capsule shells made from gelatin; for topical drugs applied directly to the skin, mucous membranes, or eye; and for long-acting forms of drugs injected intramuscularly. Gelling agents are useful as binders in tablet granulations, protective colloids in suspensions, thickeners in oral liquids, and suppository bases. Cosmetically, gels have been employed in a

wide variety of products, including shampoos, fragrance products, dentifrices, and skin and hair care preparations.

Polymer gels are produced through the cross-linking of polymer chains, by the formation of either covalent bonds (chemical cross-linking) or non-covalent bonds (physical cross-linking) (Figure 8). Non-covalent bonds can for example, be hydrogen bonds and ion-bridges the latter being common in the gelation of polyelectrolytes.

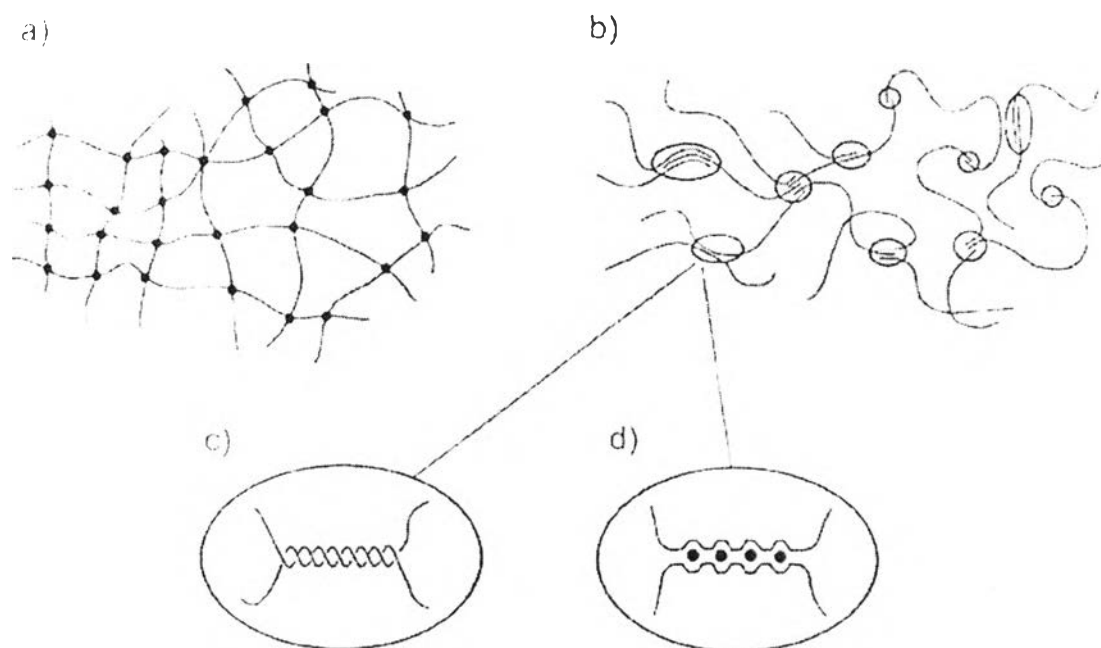


Figure 8 Schematic illustration of (a) chemical (covalent) cross-linking and (b) physical (non-covalent) cross-linking in polymer gels. Examples of physical cross-linking are (c) helix formation by hydrogen bonding, as for, e.g., carrageenans and agars, and (d) chelation of cations (\bullet), as for, e.g., alginates.

The in situ gelling properties of gellan gum are attributed to its responsiveness to cations present in physiological conditions. Several models have been put forward to explain the gelation, and the model proposed by Robinson *et al.* (Figure 9) will be discussed in more detail here. In an ion-free aqueous medium at room temperature, the polymer chains form double helices, resulting in a fluid that has a viscosity close to that of water. Upon contact with gel-promoting cations (Na^+ , K^+ , Ca^{2+}) present in tear fluid and nasal secretion a portion of the helices associate and cation-mediated aggregates are formed, acting as cross-links in the gel network. However, the gelation

of gellan gum is also affected by temperature. On heating a gellan sample in an ion-free medium, the polymer chains adopt a disordered coil conformation. Two transitions are seen on heating a sample with cations present: firstly, the non-aggregated helices melt out and, secondly, the aggregated helices melt out at a higher temperature.

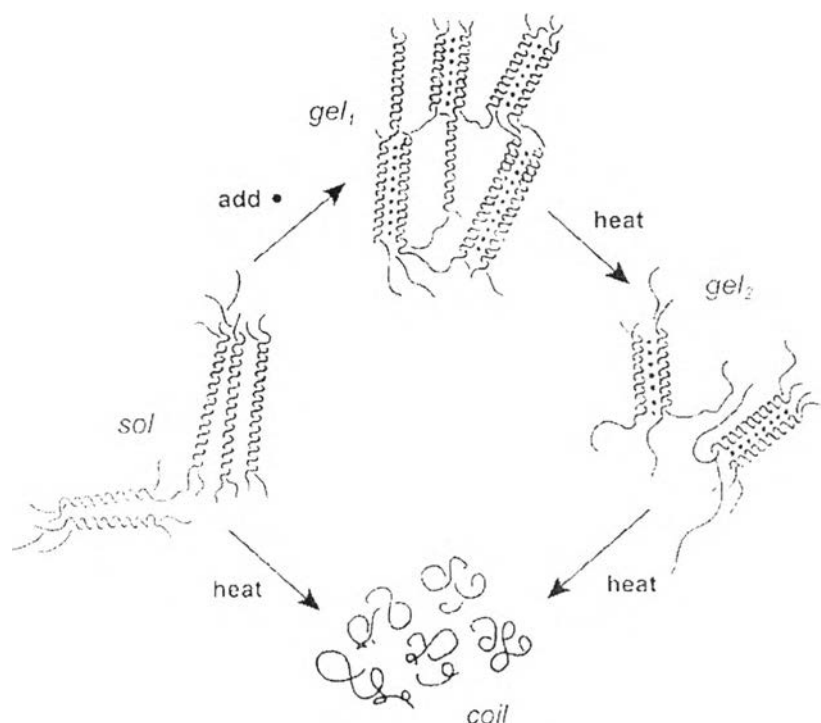


Figure 9 The model for the gelation of gellan gum on addition of cations (•).
(Robinson *et al.*, 1991)

The use of polysaccharide in cosmetics has been as ubiquitous as the use of cosmetics themselves. Historically, because of their ready availability from common natural sources and their varied and unique multifunctionality, polysaccharides have been included in cosmetics for centuries, for example, the use of β -glucan, derived from yeast extracts, as a natural healing agent. Today, polysaccharide play an even larger role in cosmetic formulation technology. The interplay of polysaccharides with other ingredients in a formulation (e.g., actives, surfactants, salts, other polymers, etc.) and their facile chemical modification has allowed their preeminent use in cosmetics. In addition, polysaccharides of natural origin and polymeric are renewable and have a safety profile not accorded synthetic-based polymers.

Polysaccharides in solution can exist as loose random coils or rigid helices. They can be anionic, cationic, nonionic, or even amphoteric depending on the chemical identity expressed on or pendant to their native backbones. They can be

single coils, double coils, and even aggregates of coils the nature of which can be influenced by, among other things, temperature, concentrations, and other species such as salts.

Polysaccharides perform a myriad of cosmetic functions. For example, they act as rheology modifiers, suspending, emulsifying agent, wound-healing, moisturizing, hydrating agents.

Natural and Semi-Natural Polymer

Natural gums have long been used commercially since the beginning of recorded history. Typically, they are branched-chain polysaccharides. Most are anionic (negatively charged in aqueous solution or dispersion), although a few, such as guar gum are neutral molecules. Differences in proportion of the sugar building blocks that make up these molecules and their arrangement and molecular weight result in significant variations in gum properties.

Because of their chemical makeup, natural gums are subject to microbial degradation and support microbial growth. Aqueous systems containing gums should contain a suitable preservative. As mentioned earlier, cationic antimicrobials are not generally compatible with the anionic gums and should usually be avoided.

Although many of the most familiar gums are plant exudates or extracts, other sources are also used. Xanthan gum is produced microbiologically. Many derivatives of natural materials, such as cellulose, starch, and alginate have been prepared. Several are very important commercially and are considered below.

The gums are used widely in food and in various industrial products as well as pharmaceuticals. Not all of these applications depend on gelation. Acacia (gum arabic) is an effective emulsifier; gum karaya has remarkable adhesive properties; xanthan gum is an excellent retardant of sedimentation in suspensions and emulsions in which water is the external phase.

Gums employed as gel formers may produce the desired effect as a result of simple dispersion in water (e.g. tragacanth) or through chemical interaction (e.g., sodium alginate and calcium). In any case, the gel exists because of cross links that the sections of polysaccharide molecules together while the remainder is solvated.

The behavior of polysaccharides is also critically influenced by the nature of the substituent groups bound to the individual monosaccharides. These substituents

can be of natural origin or they may be synthesized and thus of seminatural quality. Whether they are natural or seminatural, the classification of polysaccharides falls into one of five categories, based primarily on the polysaccharide charge. These include: anionic, cationic, nonionic, amphoteric, and hydrophobic.

Some influences, like anionic charge can occur naturally in the polysaccharide. Others, like cationicity or hydrophobicity, are primarily the result of human invention. Various cosmetically popular polysaccharides, both natural and seminatural, are explored in this section and influences of the polysaccharide's structure and functionality on solution behavior are addressed. The effects of additional components (e.g., surfactants, salts, other polysaccharides, or polymers) will be explored in each category with the aim of understanding how these factors modify the principal solution behavior of polysaccharides.

Anionic Polysaccharides

The cosmetically interesting anionic polysaccharides are predominantly comprised of a group of naturally occurring materials. Water soluble polymers are widely found in nature; they are derived from plant exudates, seaweed extracts, seed extracts, and fermentation processes of certain microorganisms. Indeed, of the available polysaccharides made anionic by human intervention, there are only two commercially interesting derivatives, cellulose gum (carboxymethylcellulose). These derivatives are anionic as a result of the carboxymethylation of naturally occurring cellulose and chitin, respectively. The list of naturally occurring anionic polysaccharides is more extensive and includes alginic acid, pectin, carrageenans, xanthan gum and the gum exudates including, arabic, karaya, and tragacanth.

Alginic acid (Alginates, Algin)

The alginates are an anionic seaweed polysaccharide made up of linear groupings of mannuronic and guluronic acids (Figure 10). In figure 10 is comprised of two different monosaccharides, β -D-(1,4)-mannuronic acid, **4**, and α -L-(1,4)-guluronic acid, **5**. They function in the algae and bacteria to provide cellular support to the cells, which keeps the cells from collapsing. These two monosaccharides can link glycosidically as polymannuronic acid, as polyguluronic acid, or as combinations. The β -(1,4)-linkage of the D-mannuronic acid, characteristic of many structural

polysaccharides, gives the alginates an extended helical structure. The α -(1,4)-linkage of the L-guluronic acid, on the other hand, is more characteristic of the polysaccharides used by plants for energy storage and gives the polysaccharide a tighter helical coil. Alginates comprised primarily of D-mannuronic acid residues tend to be extended coils in solution whereas the presence of L-guluronic acid compresses the coil.

Monovalent salts and some salts of divalent ions (notably magnesium) are water soluble. A firm gel is produced if a hydrated alginate is brought into contact with calcium or certain other polyvalent ions. The rate of gel formation may be controlled, or its onset delayed, by the use of slightly soluble calcium salts or sequestrants. Sodium alginate gels below a pH of 3-4 due to protonation of carboxyl groups.

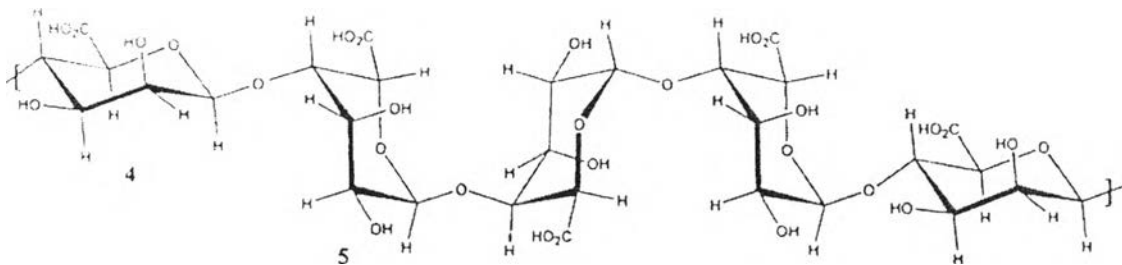


Figure 10 Partial structure of alginic acid showing β -D-(1,4)-mannuronic acid, 4, and α -L-(1,4)-guluronic acid, 5, residues.

Because the polyglycan in alginates is made up of both D-mannuronic acid and L-guluronic acid residues, both of which have carboxylic acid groups located at carbon 6, they are highly anionic. These acid groups are frequently esterified in bacterially derived alginates. Every monosaccharide, however, has a carboxylic acid group appended to it, which strongly influences solution behavior. For example, polyvalent cations can cause strong intra- and intermolecular bonding with polysaccharides containing L-guluronic acid residues, leading to cross-linked systems.

The cross-linking sites that occur when a polyvalent cation causes interpolysaccharide binding (i.e., between polysaccharide chains) are called "junction zones". Furthermore, the "egg box model" has been used to describe the relationship between the polyglycan (the box) and the cation (the egg).

Calcium ion, Ca^{2+} , in particular, is well known for its ability to form junction zones in alginate solutions. The formation of these zones requires at least two L-guluronic acid residues to be sequential in the chain as shown in Figure 11; this number must be much higher to form strong junction zones.

The aqueous solution viscosity increases with concentration of the polyvalent cation until the polysaccharide eventually gels. Further addition of calcium then causes the alginic acid to precipitate from solution.

The viscosities of aqueous alginate solutions are influenced by pH due to the dependent carboxylic acid groups. Indeed, most of the anionic polysaccharides are affected to some degree by fluctuations in pH, particularly at the higher and lower extremes. The effect of pH on alginates is most pronounced near the isoelectric point of the carboxylic acid, near pH 4.0. The solution viscosity below this pH rises rapidly as the carboxylic acid salts are protonated. Like most polysaccharides, alginates are not stable at $\text{pH} < 3.0$ owing to hydrolysis of the glycosidic bonds holding the polysaccharides together. They are also unstable at high pH (above 10) and their use is not recommended at either pH extreme.

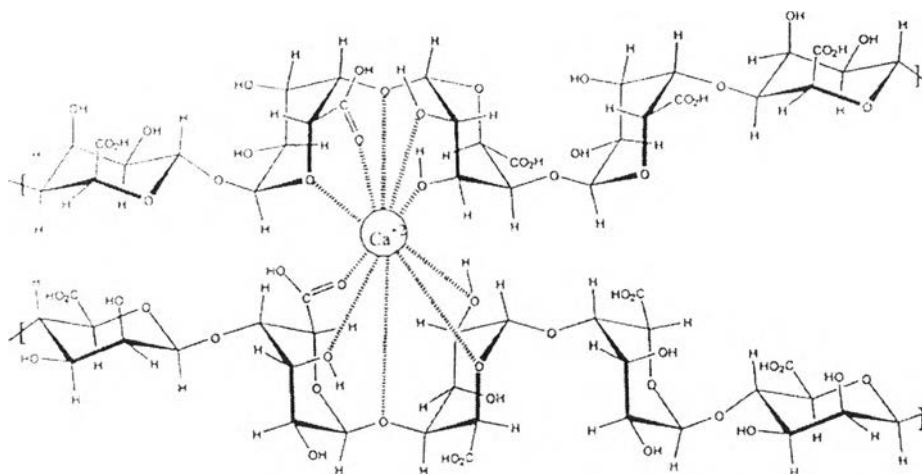


Figure 11 Junction zones formed between alginic acid and Ca^{2+} ions.
(Gruber, 1999)

Pectin

Pectin, the polysaccharide extracted from the inner rind of citrus fruits or apple pomace may be used in pharmaceutical jellies as well as in foods. Its structure is similar to that of alginic acid, except pectin in figure 12 is comprised of repeating α -D-(1,4)-galacturonic acid units (6), which are interrupted occasionally by an α -L-(1,2)-rhamanose (7) as shown in Figure 12. Rhamanose is a form of mannose that has been fully reduced to a methyl group at carbon 6. The α -D-(1,4) linkage of the pectin galacturonic acids affords a shortened chain structure for pectin, and each C6 carbon atom is fully oxidized to a carboxylic acid group. A portion of the carboxylic acid groups of pectin are naturally esterified with *o*-methyl groups, much like the bacterial-derived alginates. This renders these acidic species partially nonionic and results in gels that behave differently than those formed by nonesterified alginates.

The gel is formed at an acid pH in aqueous solutions containing calcium and possibly another agent that acts to dehydrate the gum. In foods, this agent commonly is sugar, which is often included in the pectin of commerce. Needless to say, the pectin used in drug or cosmetic products should be free of such additives. Gel formation is more extensive in pectins with a low methoxyl content. Such properties as gel strength depend on a host of factors, which include concentration of additives and pH, in addition to the characteristics of the raw material.

The level of methyl ester is monitored by gas chromatography, and pectin is sold in grades designated by this level. Lower levels of ester groups make the pectin more anionic. Pectin behaves much like alginic acid when its methyl ester levels are below 50%; it forms turbid gels in the presence of divalent metal ions, calcium in particular. At high levels, it can form gels without divalent ion, but the concentration of polysaccharide required is typically much higher.

It is not surprising to find that pectin is well suited for low-pH applications considering its source. Pectin functions ideally at pHs near 3.5. Below this pH, it suffers from hydrolysis of both the glycosidic linkage and the ester, and in highly alkaline solutions, hydrolysis of the ester is rapid. Changes in the number of ester groups over time cause unstable viscosities in cosmetic formulations.

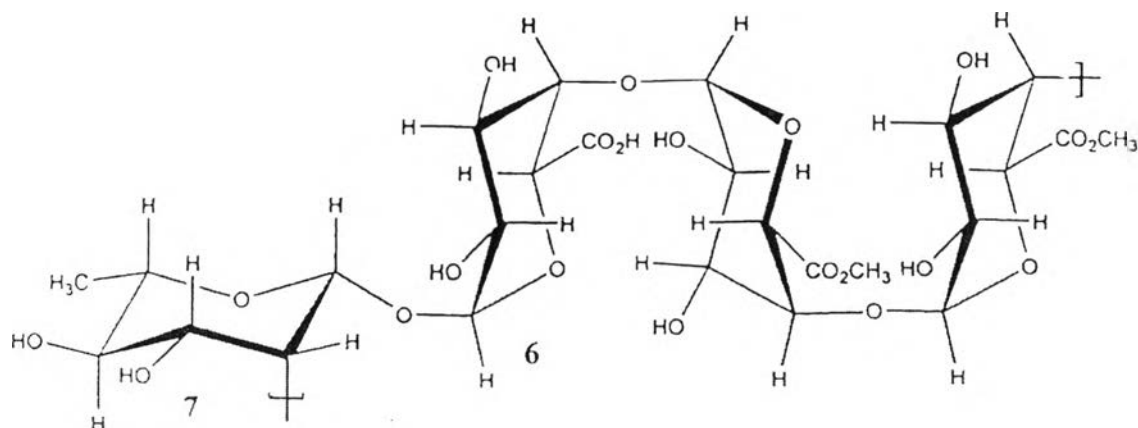


Figure 12 Partial structure of pectin showing α -D-(1,4)-galacturonic acid, 6, and α -L-Rhamanose, 7. Note methylated esters of two galacturoic acid residues.

Gum Arabic

Gum Arabic (Acacia Gum) is the dried exudate of trees of the genus *Acacia*. Gum arabic results from an infection of the tree and is produced only by unhealthy trees. The tree bark is cut to accelerate exudation and formation of the gum exudate.

Arabic gum is comprised of a neutral backbone of β -D-(1,3)-galactose residues that have multiple branching glycans, some of which impart anionic charge to the gum. Arabic gum, because of its relatively low molecular weight, is used in applications where high levels of polysaccharide solids are desired without significant viscosity buildup.

Gum arabic is soluble in hot or cold water with almost no solubility in organic solvents. Addition of ethanol to aqueous solutions of gum arabic rapidly decrease viscosity, and finally causes precipitation at a 60% ethanol concentration. Unlike most natural gums, acacia exhibits very low solution viscosities; concentrations of 40-50% polymer in water are possible. At concentrations under 40%, solutions exhibit Newtonian flow; higher concentrations behave in a pseudoplastic manner. The solution viscosity of non-sterile gum arabic declines with time because it is very susceptible to bacterial contamination and growth, but this effect can be slowed with proper use of preservatives.

Gum arabic solutions are influenced by pH and by the presence of salts. The gum has its maximum viscosifying effect near pH 6.0; the viscosity drops quickly

when the solution pH becomes higher or lower. Multivalent cations reduce the viscosity of solutions of arabic gum, but the gum will not precipitate in the same way many anionic polysaccharides are salted out.

Gum arabic is most often used in emulsification and colloid stabilization. The gum is surface active, and this helps to form and stabilize emulsions. The low viscosity characteristic is also useful in obtaining minimum particle size in emulsification. It has been especially useful in the emulsification of flavor oils for beverages or baking.

Carrageenans

The carrageenans are anionic, cellular structural polysaccharide derived from some of the red seaweeds. They are highly functional owing to the nature of the anionic substituents, and quite diverse structurally. The carrageenans of greatest commercial interest are primarily comprised of two repeating monosaccharides shown in figure 13, including β -D-(1,3)-galactose (8) and α -D-(1,4)-galactose (9). Different types of carrageenan can be identified by the structure of the basic repeating units. The possible structures are identified by the greek letters include kappa (κ)-, iota (ι)-, and lambda (λ)-carrageenan.

Kappa- and iota-carrageenans are structurally similar in that the (1,4)-linked D-galactose (9) is made more rigid by formation of a five-membered cyclic anhydride ether group between the C6 (R_5) and C3 (R_3) carbon atoms. The presence of the 3,6-anhydride ether causes the chains of these carrageenans to more fully extend in solution by making the monosaccharides more rigid. Lambda-carrageenan, lacking this structural rigidity, assumes a more crimped α -(1,4)-linkage like that already seen in the L-guluronic acid portion of the alginates. The anhydride also creates a more hydrophobic (water-avoiding) environment in this portion of the monosaccharide. To minimize interaction of the anhydride ether with water, these two polysaccharides form tightly wound double helices when dissolved, the interiors of which house the anhydride ether functionality. The lambda-carrageenan does not form double-helical coils and as discussed below can not form aqueous solution gels.

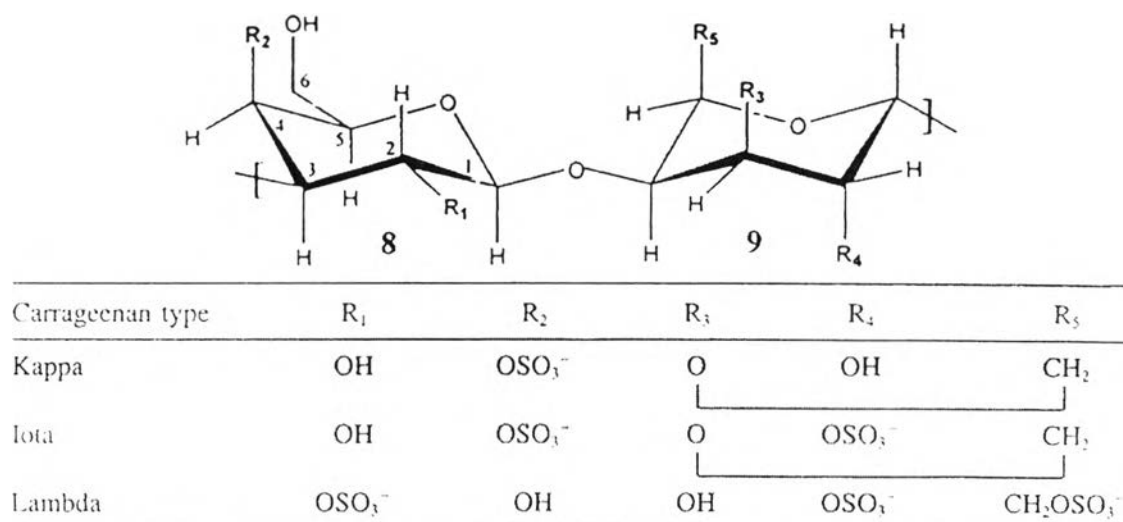


Figure 13 Structure of Kappa-, Iota-, and Lambda-Carrageenan (β -D-(1,3)galactose, **8**, and (α -D-(1,4)-galactose, **9**, monosaccharides)

The carrageenans are anionic because some of the pyranose hydroxyl groups are substituted with sulfate half-esters. The sulfate groups are highly acidic (similar to the acidity of sulfuric acid) and hydrophilic (water-loving). As a result, the double helices of kappa- and iota-carrageenan are peppered on their exteriors with anionic sulfate groups making their exterior very hydrophilic.

All of the carrageenans are anionic. Gels of kappa-carrageenan, which tend to be brittle, are strongest in the presence of potassium ion, while iota-carrageenan gels are elastic, and remain clear in the presence of calcium. Various commercial grades are available for particular applications, most of which are in the food industry.

Properties such as water solubility and gelation are greatly affected by the composition of carrageenan. For example, while all the forms of carrageenan are soluble in hot water, only the lambda salt forms are soluble in cold water. The lambda form is also the only nongelling form. Upon heating and cooling in the presence of certain ions, such as calcium and potassium gels form that can exhibit great strength and have definite melting temperatures depending on composition. Carrageenan is not soluble in organic solvents, but may tolerate the presence of some water miscible organic solvents in solutions or gels.

Solutions of carrageenan have a yield point when used in sufficient concentration. They are also thixotropic. Carrageenan solutions generally have a pH of 6-10, but exhibit increasing hydrolysis rates at a pH of less than 6. They are least

stable under strongly alkaline conditions, and strong oxidizing agents can cause depolymerization.

Formation of the carrageenan double helix is temperature sensitive; no polysaccharides spontaneously form double helices without a thermal stimulus. Because of this, following initial dissolution of the polysaccharide in hot water, the polymer chains exist as random coils (Fig 14). Cooling causes the hydrophobic domains of the kappa- and iota-carrageenans to unfavorably interact with the aqueous environment, causing these region of the polysaccharide chains to group and form, initially, a single helix and, eventually, the resultant double helix (Gel I). Lambda-carrageenan, by contrast, does not form single helices. Even so, it builds significant aqueous viscosities through random chain entanglement. In addition to being temperature dependent, the rheological effect of kappa-carrageenan is molecular weight dependent. As its molecular weight increases, so does its solution viscosity.

Formation of the double helix creates a unique environment that can, in the presence of various cations, especially K^+ and Ca^{2+} , result in further aggregation or junction-zone formation through the influence of the anionic sulfate groups. Kappa- and iota- carrageenans require the presence of cationic salts to form the strong gels they are capable of making. Formation of the junction zones creates interhelical cross-links that cause untill higher solution viscosities and, eventually, gelation (Gel II).

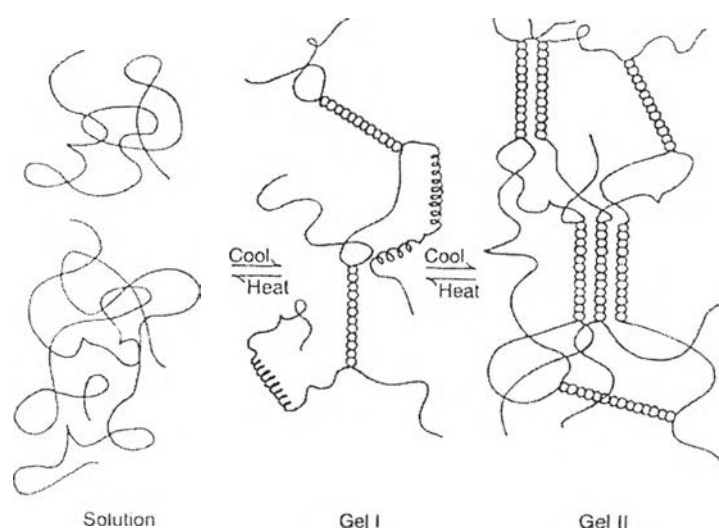


Figure 14 Coil to helix to aggregate transitions for gelling carrageenans.

(Guiseley, KB. *et al.* 1980)

Guar Gum

Guar gum N.F. is a nonionic seed polysaccharide made up of a straight chain mannose backbone with regular branching of a galactose unit on every second mannose. Guar gum is soluble in water. Solutions may exhibit turbidity due to the presence of insoluble endosperm components. It takes at least 3 hours at room temperature for guar to reach its maximum viscosity in water but hydration time can be shortened at elevated temperatures. Since guar gum retains some of its particulate characteristics in solution the use of a fine particle size product to ensure a smooth homogeneous solution is important. Guar gum is not soluble in organic solvents, and viscosity will rapidly decrease with the addition of miscible solvents to aqueous polymer solutions.

The rheology of an aqueous guar gum solution is pseudoplastic and exhibits no yield point. Guar gum may exhibit shear depolymerization when subjected to high shear rates for even a brief period of time. Maximum viscosity is obtained at a pH around 6 with a loss of viscosity above pH 10. Guar solutions thin reversibly with increasing temperature and may degrade irreversibly with time at elevated temperature.

Gum Karaya

Gum Karaya (Karaya gum) is an anionic exudate polysaccharide complex of galactose, rhamnose, and glucuronic acid, partially acetylated. It is composed primarily of a highly branched D-galacturonic acid backbone. Gum karaya is the least soluble of the exudate polymers. It does not form a true solution but its particles swell in water to form a colloidal dispersion. Many of the acidic monosaccharides are acetylated, which causes the water insolubility. Instead of dissolving, gum karaya swells in water and develops significant viscosity even at low concentration.

The viscosity of gum karaya in water increases rapidly with concentration so that a 2-3% concentration acts as a gel. Higher concentrations can be made as in bulk laxative applications. by cooking karaya in steam. This reduced dispersion viscosity, so that 20-25% dispersions can be made. Gum karaya has many acetylated acid groups, which allow its stability and viscosity to be strongly influenced by pH. Gum karaya dispersions in water produce a pH between 4 and 5. Viscosity increases with pH, but solutions become stringy above pH of 8. Karaya performs best at pH values between 7 and 9 where it is also least susceptible to hydrolysis. Interestingly, the

viscosity of gum karaya solutions depends on the order of hydration and pH adjustment. Gum karaya is not soluble in organic solvents and does not tolerate water-miscible organic solvents. The major pharmaceutical applications for gum karaya are bulk laxatives. Stickiness accompanies the swelling, which explains its popularity in denture adhesives.

Locust Bean Gum

Locust bean gum, a nonionic seed polysaccharide with a straight chain mannose backbone, has limited solubility in cold water. Complete hydration requires heating to 180°F. The method of solution preparation dramatically affects the final solution viscosity. Locust bean gum is not soluble in organic solvents. It is one of the more efficient thickening natural polymers along with guar, tragacanth, and karaya gums. Solutions of locust bean gum are pseudoplastic and have no yield point. Solutions of locust bean gum tend to react with inorganic salts, especially divalent ions which may cause insolubilization, precipitation, or gelation. Combinations with other gums such as xanthan form gels.

Tragacanth Gum (Tragacanth)

Tragacanth Gum N.F. is an anionic exudate polysaccharide made up of a soluble portion, tragacanthin, and an insoluble portion, bassorin. Tragacanth is, perhaps, the best characterized of these commercial gums. It is not a single gum, but is comprised of two, complex, highly branched polysaccharides: arabinogalactin, a water-soluble, neutral polysaccharide having a D-(1,6)-galactose backbone, and tragacanthic acid, an anionic polysaccharide polyglycan based on (α -D-(1,6)-galacturonic acid.

Tragacanth swells in cold water to produce a highly viscous colloidal dispersion. It is insoluble in alcohol or organic solvents. Tragacanth is one of the most efficient natural polymer thickeners. The highest viscosities are obtained when solutions are made in cold water. The use of heat in solution preparation causes a certain amount of degradation and a loss of at least 1/3 the original viscosity due to chain scission. Tragacanth is graded by its viscosity in water. Solutions of gum tragacanth exhibit pseudoplastic flow.

Gum tragacanth shares many of the functional properties found in xanthan gum. At low concentration it produces high solution viscosities. Its solutions also have a yield stress and make it suitable for suspending water-insoluble components. Tragacanth has high pH stability, but its viscosity, unlike that of xanthan, thins as the temperature increases.

Tragacanth solutions are stable over a wide pH range. In fact, these solutions exhibit good stability at low pH. For this reason, it is often chosen as the thickener for low pH food products such as salad dressings and sauces. Tragacanth strongly binds multivalent cations. Many, including calcium, precipitate the polysaccharide from solution. Divalent and trivalent cations as well as storage at elevated temperatures may cause a reduction in viscosity.

Xanthan gum

Xanthan gum is a high molecular weight exocellular polysaccharide derived from the bacterium *Xanthomonas campestris* using a natural, aerobic fermentation process. The process is conducted in sterile environment where the pH, oxygen content and temperature are rigorously controlled. After fermentation is complete, the broth is sterilized and the gum is recovered by precipitation with isopropyl alcohol, then dried, milled and packaged under sterile conditions.

Xanthan gum N.F. is a natural anionic biopolysaccharide made commercially by bacterial fermentation and made up of different monosaccharides, mannose, glucose, and glucuronic acids. Structurally, xanthan is a complex polysaccharide showed in figure 15, comprised of a primary chain of β -D-(1,4)-glucose (10), which has, on alternating glucose moieties, a branching trisaccharide side chain comprised of β -D-(1,2)-mannose (11), attached to β -D-(1,4)-glucuronic acid (12), which terminates in a final β -D-mannose (13).

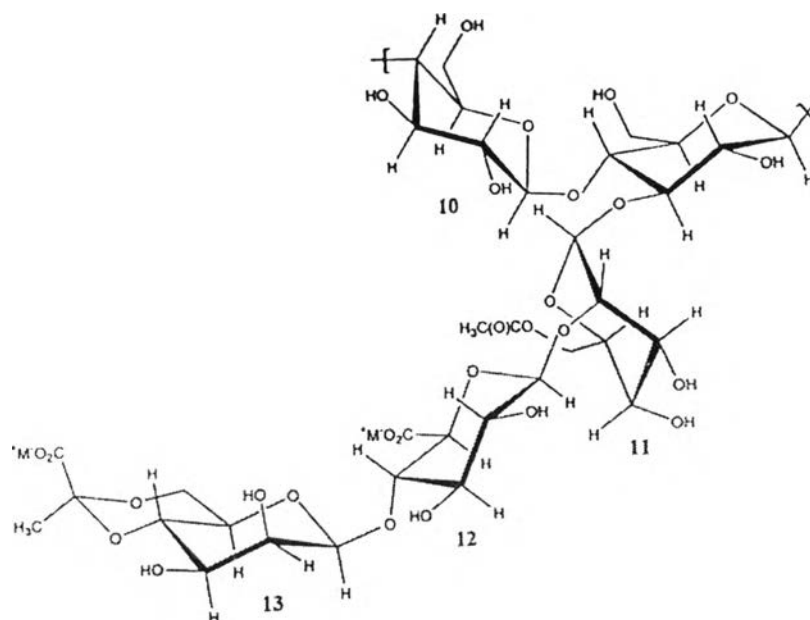


Figure 15 Partial structure of xanthan gum showing β -(1, 4)-glucose, **10**, acetylated β -D-(1,2)-mannose, **11**, β -D-(1,4)-glucuronic acid, **12**, and pyruvic acid terminated β -D-mannose, **13**.

It is generally accepted that xanthan forms helical coils. In the presence of cationic salts, but the need for salts to build solution viscosity, as seen, for example, with kappa- carrageenan, is minimized by the rigid xanthan backbone. Whether or not xanthan forms double helices in solution is still being debated. In any case, the mechanism of thickening and gelation still requires the formation of junction zones, which are thought to occur through the interaction of hydrophobic sites on the xanthan helix. Cations tend to "salt out" these sites, improve the strength of the junctions, and produce a slight increase in solution viscosity. These solutions also show remarkable viscosity stability at increasing temperatures because the viscosity is generated by hydrophobic interactions in the polysaccharide. This can be useful when developing thermally stable formulations. Xanthan forms lyotropic and isotropic liquid crystals in water at appropriate concentrations. Formation of the liquid crystal phase is influenced by salt concentration: the higher the salt concentration, the lower the xanthan concentration required to form the liquid crystal phase.

Seminatural anionic polysaccharide

Cellulose Gum (Sodium Carboxymethylcellulose, CMC)

The functional characteristics of many natural polysaccharides can be dramatically improved by chemical modification of the native polysaccharide. Cellulose gum, more precisely termed sodium carboxymethylcellulose (CMC), is a chemically altered derivative of cellulose. Cellulose is one of the most common starting materials for the manufacture of modified natural polymers. It is common to use highly purified cotton or wood cellulose in the manufacture of food or pharmaceutical grade cellulose ethers.

Cellulose is composed of one repeating monosaccharide, β -D-(1,4)-glucose. The β -(1,4)-linkage gives cellulose an extended helical structure and, because of the strength of the intermolecular hydrogen bonding, renders the polysaccharide highly crystalline and, consequently, water-insoluble. To make cellulose water-soluble, it is necessary to disrupt the highly ordered cellulose chains.

Sodium chloroacetate reacts with the hydroxyl groups on cellulose, of which theoretically there are three per glucose monosaccharide. The reaction is usually run in aqueous organic diluent in which both the cellulose and the carboxymethylcellulose are swellable, but insoluble. The term "degree of substitution (DS)" describes the average number of carboxymethyl groups attached to each glucose monosaccharide.

The presence of the substituted carboxymethyl groups makes the cellulose highly anionic; because their acidity is similar to that of acetic acid. Thus, at a pH above 4.5, the majority of acid groups are deprotonated and are in the salt form. The acid groups protonate below pH 4.5, making CMC water-insoluble. The insolubility appears first as an increase in viscosity as chain entanglement increases and phase separation occurs. Eventually, as the CMC continues to phase separate, the solution becomes hazy and precipitation occurs. It has been shown that solutions of CMC as high as 5 wt% are shear-thinning. Even at high gum concentrations, aqueous solutions of CMC do not possess a yield point.

Sodium carboxymethylcellulose (CMC), an anionic polymer is available in three grades: food, pharmaceutical, and technical. It is also available with a variety of molecular weights and degrees of substitution. Carboxymethylcellulose is soluble in

hot or cold water but not in organic solvents. Carboxymethylcellulose is offered in several degrees of substitution: 0.4, 0.7, 0.9, and 1.2. Higher substitution leads to greater water solubility and better tolerance to other solution components such as salts. The sodium content of the polymer increases with increasing substitution.

Carboxymethylcellulose is more resistant to microbial attack than most natural gums but still must be preserved in aqueous systems. Heat sterilization and chemical preservation of solutions is recommended. As with most hydrocolloids derivatives, long-term exposure to extremes in temperature, pH or oxidizers will result in chain scission and consequent viscosity loss. The viscosity of carboxymethylcellulose solution decreases reversibly with increasing temperature. Permanent viscosity loss is seen only after extended times at elevated temperature or in combination with low pH. Salts containing the polyvalent cations (e.g. Al^{3+}) cause precipitation or gelation of cellulose gum. The rheology of aqueous carboxymethylcellulose solution depends on the degree of substitution. Low-substituted carboxymethyl cellulose products exhibit thixotropy; higher substitution leads to pseudoplastic behavior.

Carboxymethylcellulose, like the majority of anionic polysaccharides, strongly binds certain multivalent cations; even small amounts of Ca^{2+} or other multivalent metal ion cause it to gel. Simple monovalent salts, too, can lower aqueous solution viscosities. Carboxymethylcellulose increases solution viscosity through entanglement of its high molecular weight chains. It does not rely on the presence of divalent-metal-ion-induced cross-linked junction zones to impart viscosity. Recent investigations suggest that incompletely derivatized CMC forms more viscous aqueous solutions than fully substituted CMC. This suggests that, although the partially substituted CMC is still water-soluble, underivatized crystalline regions form interpolysaccharide junction zones through hydrogen bonding of the pyranose rings.

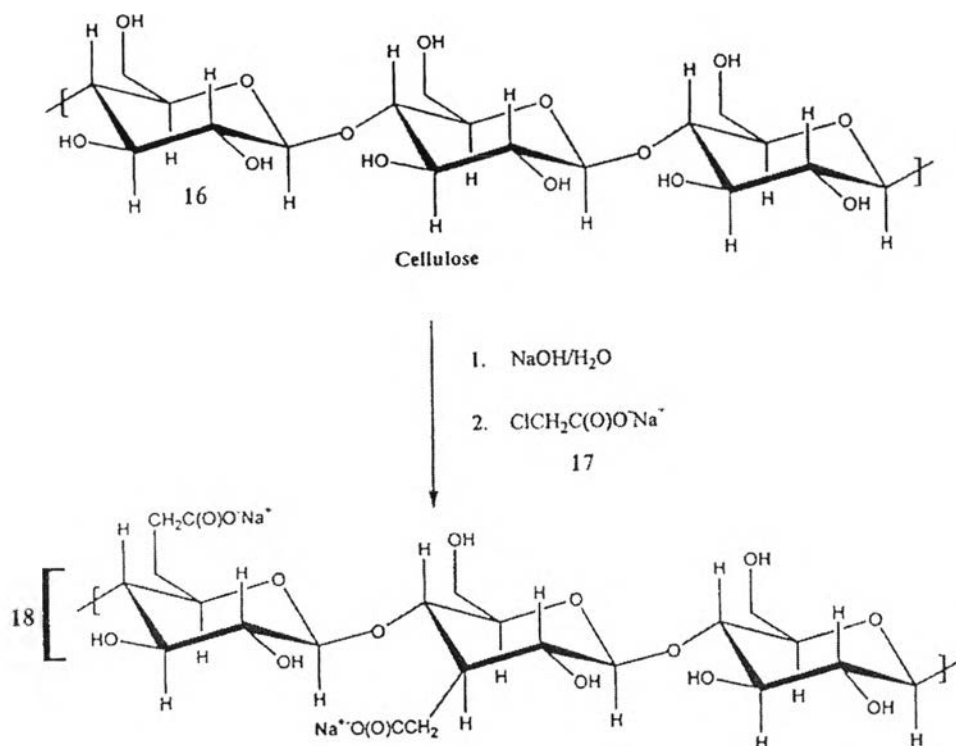


Figure 16 Partial structure and synthesis of cellulose gum, **18**, showing repeating β -D-(1,4)-glucose, **16**, in cellulose backbone.

Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a nonionic cellulose ether available in a variety of types and viscosities. There are four distinct USP grades of hydroxypropyl methylcellulose with varying levels of methyl and hydroxypropyl substitution.

The methyl substitution imparts to HPMC one of its unique features thermal gelation. Solutions of hydroxypropyl methylcellulose may be sterilized by autoclaving without a loss of viscosity. Hydroxypropyl methylcellulose is surface active and reduces surface tension and interfacial tension. Solutions of HPMC exhibit pseudoplastic rheology and there is no yield point

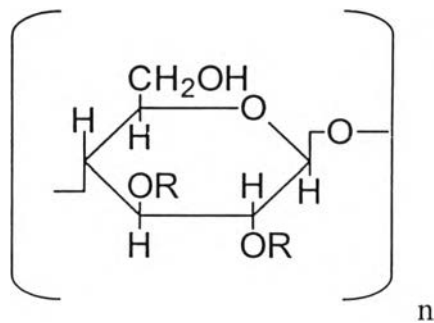


Figure 17 Molecular structure of hydroxypropylmethylcellulose (HPMC).
 $R = -H, -CH_3$ or $-CH_2-CH(OH)-CH_3$.

Chitosan (Dee, *et al.*, 2001)

Chitosan is a derivative of chitin, the important organic component in the skeletal material of invertebrates. The major available commercial source of chitin is the exoskeletons of crustaceans. Chitin is produced by first removing the protein and calcium carbonate found in crustacean shell. Deacetylation to form chitosan is carried out in strong alkaline solutions at elevated temperature. The molecular structure is shown in Figure 18. Chitosan is soluble in water only under acidic conditions. The pH of a chitosan solution must be kept below 6.0 to prevent precipitation or gelation. Chitosan may best be formulated to the pH 2-3 region. The acid solutions of chitosan are compatible with nonionic polymers but are incompatible with sulphates and most anionic water soluble polymers.

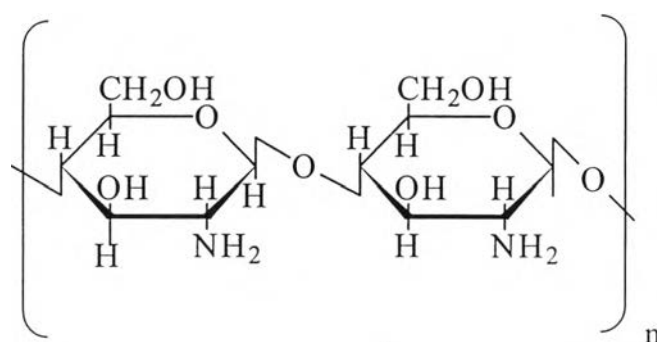


Figure 18 Structure formula of Chitosan

Synthetic Polymers

Carbomer (Polyacrylic Acid)

Carbomer xxxP is the official name given to one member of a group of acrylic polymers crosslinked with a polyalkenyl ether. Manufactured under the trade name of Carbopol 934P and 940P, it is used as a thickening agent in a variety of pharmaceutical and cosmetic products. The suffix "P" identifies a highly purified polymer, suitable for use in orally administered dosage forms, although carbomer 934P, 940P is also used widely in topical preparations.

The acid form of this polymer (Carbopol, Goodrich) can be dispersed in water to give a pH of 2.8-3.2, but it does not dissolve. Neutralization of the acid functionality with a base such as sodium, potassium, or ammonium hydroxide produces negatively charged carboxylate groups.

This causes the polymer to uncoil and allow it to thicken aqueous systems. Carbomer also has solubility in a wide variety of polar organic solvents. Carbomer is an extremely efficient thickener in the neutralized state. The viscosity of a carbomer solution drops rapidly in the presence of a mono-valent salt and even more rapidly with salts containing di- and trivalent cations. Below a pH of 10, carbomer solutions are subject to viscosity loss under prolonged ultraviolet light exposure.

Solutions of carbomer are very pseudoplastic. They exhibit a yield value. Due to the extreme shear-thinning, thick gels may be pumped easily. This shear-thinning has made it an excellent choice as a thickener in creams and lotions.

Carbomer forms gels at concentrations as low as 0.5%. In aqueous media, the polymer, which is marketed in the free acid form, is first uniformly dispersed. After entrapped air has been allowed to escape, the gel is produced by neutralization with a suitable base. The introduction of negative charges along the polymer chain causes it to uncoil and expand.

In aqueous systems, a simple inorganic base such as sodium, ammonium or potassium hydroxide, or a basic salt such as sodium carbonate may be employed. The pH should be adjusted to a neutral value; gel character will be adversely affected by either insufficient neutralization or excessive pH. Certain amines, such as triethanolamine, are sometimes used in cosmetic products.

By employing organic amines as neutralizing agents, it is possible to gel many semipolar liquids or mixtures of these liquids with water. Compatibility of the polymer with nonaqueous liquids depends on the formation of ion pairs with the amine. Polyols are capable of hydrogen bonding with the polymer, forming reversible links that augment viscosity.

The viscosity of carbomer dispersions is lowered in the presence of ions; the addition of 1% sodium chloride causes more than a 50% drop in Brookfield viscosity (20 RPM) of neutralized carbomer 941, 1%, at neutral pH.

Commercial available polymers and their properties are summarized in Table1.

Table 1 Summary of Polymer properties (Zatz. *et al.*,1988)

Water soluble polymer	Derivation	Structure	Ionic charge	pH factors	Temperature factors	Rheology	Yield point	Relative viscosity	Important features or differences
Alginates, NF	Kelp extract	Polysaccharide	Anionic	Stable at pH3-10	Poor temperature stability	Pseudoplastic	No	Medium to high	Polyvalent ions will crosslink polymer to form gel.
Gum Arabic, NF	plant exudate	Polysaccharide	Anionic	Viscosity is affected by pH	Reversible viscosity loss at elevated temperature	Newtonian <40% conc.; ----- Pseudoplastic at >40% conc.	No	Very low	Low viscosity; ability to be made at high concentration: excellent sugar compatibility
Carrageenan	Seaweed extract	Polysaccharide	Anionic	Stable at pH3-10	Reversible viscosity loss at elevated temperature	Thixotropic	No	Moderate	Will complex with casein in milk; strong gel formation possible

Table 1 Summary of Polymer properties (cont.)

Water soluble polymer	Derivation	Structure	Ionic charge	pH factors	Temperature factors	Rheology	Yield point	Relative viscosity	Important features or differences
Guar gum, NF	Seed extract	Polysaccharide	Anionic	Stable at pH4-10	Viscosity degradation at elevated temperature and time	Pseudoplastic	No	High	High viscosity for natural gums
Gum Karaya	Plant exudate	Polysaccharide	Anionic	Becomes reppy above pH 7.0	Very poor, viscosity drops, irreversibly at elevated temperatures	Thixotropic	No	High	Insoluble but swells in water; degrades at low pH; limited dry shelf-life; used as a bulk laxative
Locust bean gum	Seed extract	Polysaccharide	Nonionic	-	Viscosity will degrade at elevated temperatures with time	Pseudoplastic	No	High	Subject to shear depolymerization; viscosity affected by temp. history

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Table1 Summary of Polymer properties (cont.)

Water soluble polymer	Derivation	Structure	Ionic charge	pH factors	Temperature factors	Rheology	Yield point	Relative viscosity	Important features or differences
Gum tragacanth, NF	plant exudate	Polysaccharide	Anionic	Stable at pH 1.9-8.5 excellent low pH stability	Good temperature stability; reversible viscosity loss at elevated temperatures	Pseudoplastic	No	High	Surface active; good low pH stability; composed of soluble and insoluble portions
Xanthan gum, NF	Biosynthesis polymer	Polysaccharide	Anionic	Good stability at pH 1-12	Good temperature stability; viscosity not affected by temperature changes	Pseudoplastic	Yes	High	Good enzyme resistance; yield point , viscosity unaffected , by pH; high viscosity (efficient) at low conc.

Table 1 Summary of Polymer properties (cont.)

Water soluble polymer	Derivation	Structure	Ionic charge	pH factors	Temperature factors	Rheology	Yield point	Relative viscosity	Important features or differences
Carboxy-methyl-cellulose USP	Cellulose	Cellulose ether	Anionic	Stable at pH 4-10	Good temperature stability; reversible loss of viscosity at elevated temperatures	Thixotropic at D.S. ^a = 0.4 ----- Pseudoplastic at D.S. ^a = 0.7, 0.9, 1.2	Yes No	Low to high	Not stable with some salts
Hydroxy-propyl-methyl-cellulose USP	Cellulose	Cellulose ether	Nonionic	Stable at pH 4-11	Good temperature stability; viscosity reduces reversibly with increasing temperature until a reversible thermal gel is formed.	Pseudoplastic	No	Low to very high	Reversible thermal gelation; wide range of viscosities available; good microbial resistance; food additive status

Table 1 Summary of Polymer properties (cont.)

Water soluble polymer	Derivation	Structure	Ionic charge	pH factors	Temperature factors	Rheology	Yield point	Relative viscosity	Important features or differences
Chitosan	Shells of crustaceans	Acetylated chitin	Anionic	Soluble only at pH < 6.0	Good	Not reported	Not reported	Moderate to low	Cationic; poor tolerance to anions; low pH stability
Carbomer, USP	Acrylic acid	Crosslinked polyacrylate	Anionic	Soluble at pH >4.0	Good temperature stability	Pseudoplastic	Yes	Very high	Very efficient thickener; poor salt tolerance reduces viscosity rapidly; good suspending agent; organic solubility; excellent rheology for topical medications

Emulsifiers/emulsion Stabilizers (Malmsten, 2002)

Emulsifiers

Natural polymers or macromolecules (e.g., hydrophilic gums, proteins) have effectively stabilized emulsions via interfacial adsorption and the subsequent formation of condensed films of high tensile strength, which resist droplet coalescence. A dramatic example of this has been published for emulsions stabilized with acacia. Many other hydrocolloids, such as the cellulose ethers (e.g., sodium carboxymethyl cellulose, methylcellulose) and the carbomer resins have long been employed as emulsion stabilizers though they primarily serve to increase the viscosity of the dispersion medium.

The reduction of interfacial tension by emulsifiers is a direct result of their adsorption at the interface. It has long been held that the affinity of such surface-active agents (surfactants) for the interfacial region facilitates the formation of a relatively rigid film of the emulsifier at the interface which acts as a mechanical barrier to droplet adhesion and coalescence. There is mounting evidence for emulsion stabilization by liquid crystal formation in the interphase, i.e., the interfacial region, and in the vicinity of adjacent droplets of the disperse phase. The nature and intensity of the interactive electrical forces between emulsion droplets may also be influenced by surfactants (especially ionic ones) with a concomitant effect on emulsion stability. The classification of surfactant types provided in Table 2 is based on the ionic charge of the surfactant.

Table 2 Miscellaneous Emulsion Stabilizers

Lyophilic colloids:	Polysaccharides	Amphoterics	Synthetic or semi-synthetic Polymers
	Acacia Agar Alginic acid Carrageenan Guar gum Karaya gum Tragacanth	Gelatin	Carbomer resins Cellulose ethers Carboxymethyl chitin PEG-n (ethylene oxide Polymer =H(OCH ₂ CH ₂) _n OH)
Finely divided solids:		Clays- Antacids-	attapulgate, bentonite, hectorite , kaolin, magnesium aluminum silicate , montmorillonite aluminum hydroxide, magnesium hydroxide Silica (pyrogenic or fumed)
Cybotactic promoters, gellants:			Amino acids, peptides, proteins Lecithin and other phospholipids Poloxamers

Film-Forming Properties

Various polysaccharide for forming film have been studied, Hyppolä, *et al.*, 1995 and Hutchings, *et al.*, 1993 prepared ethyl cellulose films. Gontard, *et al.*, 1992 produced edible film from wheat gluten by casting method. Nuntanid, *et al.*, 2001 prepared chitosan films by a casting technique using acetic acid as a dissolving vehicles and studied tensile strength, moisture sorption study and swelling property of chitosan films. Entwistle and Rowe, 1979 prepared ethyl cellulose and Hydroxypropyl methylcellulose films.

Film formation and the properties of several polysaccharide materials such as starch and starch derivatives, cellulose derivatives, alginates, carrageenan, chitosan, pectin, and various plant and microbial gums have been reviewed by Nisperos-Carriedo, 1994.

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.

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 macromolecules 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 views 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-polymer 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-dimensional 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 volume 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:

$$V_f = V_t - V^0$$

Where V_f is the free volume. V_t is the specific volume at temperature t , and V^0 the specific volume at some reference point.

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).

The basic requirements of any plasticizers in a polymer system are compatibility and permanence. The most effective plasticizers will generally resemble most closely in structure the polymer they plasticized. Thus, water soluble cellulose esters 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). Plasticizers are often added to these polymers in order to change their physical properties and enhance their film forming characteristics. To be effective a plasticizer must interpose itself between the polymer chains and interact with the forces holding the chains together thereby extending and softening the polymer matrix (Entwistle and Rowe, 1979).

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

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 preferred (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 glycerin, and the higher of the intrinsic viscosity.

The effect of plasticizer type and amount

Many polymers used for the film coating of pharmaceutical dosage forms display brittle properties at ambient temperature and humidity conditions, and the addition of a plasticizer is essential to achieve effective coatings without cracks or splitting defects. Plasticizers are added to polymeric solutions or dispersions to increase the workability, flexibility, or distensibility of the polymer. The plasticizer may also

lower the melt viscosity, glass transition temperature (T_g), or elastic modulus of the polymeric material. These effects are the result of the plasticizer's ability to weaken polymeric intermolecular attractions and to increase the free volume of the polymer. This allows the polymeric molecules to move more easily, thereby increasing flexibility. Plasticizers reduce the brittleness, improve flow, and improve flexibility of polymeric chains. In addition, they will also increase toughness, strength, and tear resistance.

For plasticizers that are soluble in the solvent phase these can be added directly to the mixture or may be dissolved first in the solvent prior to addition of the polymer. The degree of plasticization of the polymer is dependent to a large extent on the amount of plasticizer in the film and the interaction between the plasticizer and the polymer. For a plasticizer to be effective it must be able to diffuse into and interact with the polymer and have minimal or no tendency for migration or exudation from the polymer. The interaction of the plasticizer with the polymer generally decreases the elastic modulus, lowers the softening temperature and decreases the T_g . The decrease in the T_g of a polymeric film as the plasticizer concentration increases is a common measure of plasticizer effectiveness. If a plasticizer does not remain in the film, then changes in the chemical and/or physical-mechanical properties of the polymeric material could result. In vitro dissolution studies with cast films of Eudragit RS/RL have demonstrated that water-soluble plasticizers were leached more readily from the film when the level of hydrophilic polymer in the film was increased. Therefore the selection of a plasticizer by the pharmaceutical scientist for a film-coating formulation is a very important decision in order to develop and optimize the stability and drug release properties of a pharmaceutical dosage form.

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. Since most amorphous polymers behave as viscoelastic materials, their mechanical properties will depend on the temperature and the application rates of stress and strain. 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.

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. The effect of 10 different plasticizers representing three chemical classes (citrate esters, diacid 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 arose from further gradual coalescence of ethylcellulose pseudolatex particles (Hutchings, Clarson and Sakr, 1994)

Plasticized hydroxypropyl methylcellulose free films were 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).

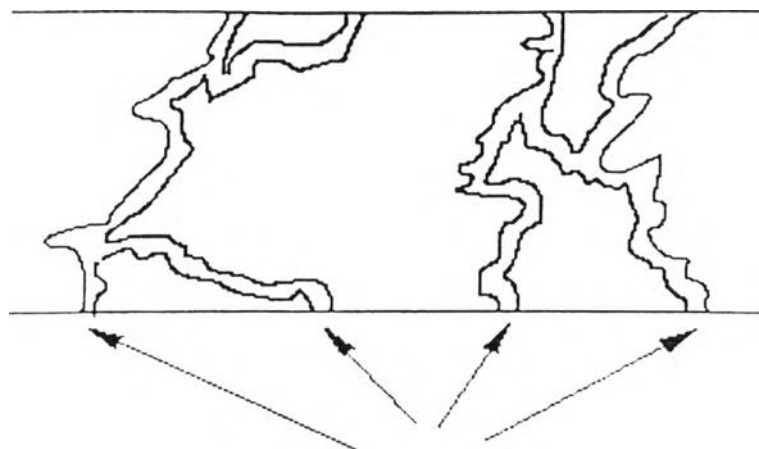
The effect of molecular weight and size of the plasticizer

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).

Antiplasticization

A plasticizer can be deferred in terms of the desired properties of a given polymer-plasticizer system. In pharmaceutical controlled release film coatings, plasticizers or low-molecular-weight diluents, are added to polymers to modify their physical properties and to improve their film forming characteristics. Plasticization, in general, refers to a change in the thermal and mechanical properties of a given polymer which involves: (a) lowering of rigidity at low temperature; (b) lowering of transition temperature, at which substantial deformations can be effected with not too large forces; (c) increase of the elongation of polymers. These changes in the mechanical properties also affect the permeabilities of polymer films. The effects of the plasticizers on the water permeation and mechanical properties of cellulose acetate were investigated by Guo. He found the water permeability of cellulose acetate decreased with increasing plasticizer to a minimum and then increased with higher concentration of plasticizer. Low plasticizer concentration cause a decrease of water permeability by antiplasticization. (Guo, 1994)

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. 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).



Plasticizer Channels

Figure 19 The schematic illustration of the plasticizer channels (Guo, 1994)

Traditionally, stress-strain testing in the tensile mode has been a popular and widely used mechanical test for the polymeric films. The tensile test is practical, and analysis of its data is relatively straightforward. The tensile test gives an indication not only of the elasticity and strength, but also of the toughness of the film. However, polymers are viscoelastic, and their mechanical behavior is dependent on many factors.

Environmental factors such as temperature, light, and humidity can have a significant influence on the stability and physical-mechanical properties of many materials. These changes in the polymer properties can be detrimental and lead to unpredictable drug release rates from a film coated dosage form. The diagram in figure 20 illustrates the interrelationship between these factors and potential problems that one may experience with a film-coated dosage form.

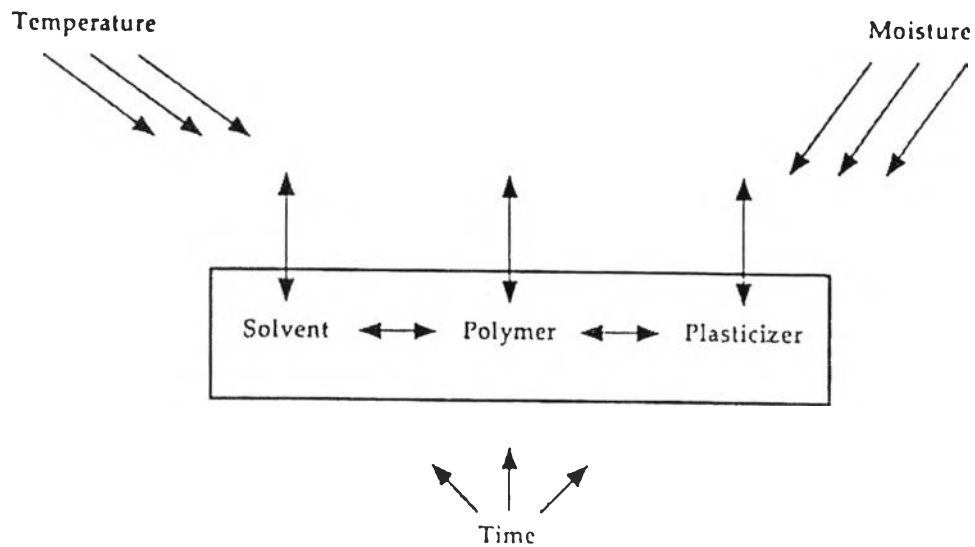


Figure 20 Factor affecting the chemical and physical-mechanical properties of polymeric films.

Mechanical Properties of film (Aulton, 1982).

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. Tensile strength can be computed from the applied load at rupture and the cross-sectional area of fractured film.

$$\text{Tensile strength} = \frac{\text{load at failure}}{\text{film thickness} \times \text{film width}}$$

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 abrasion resistance.

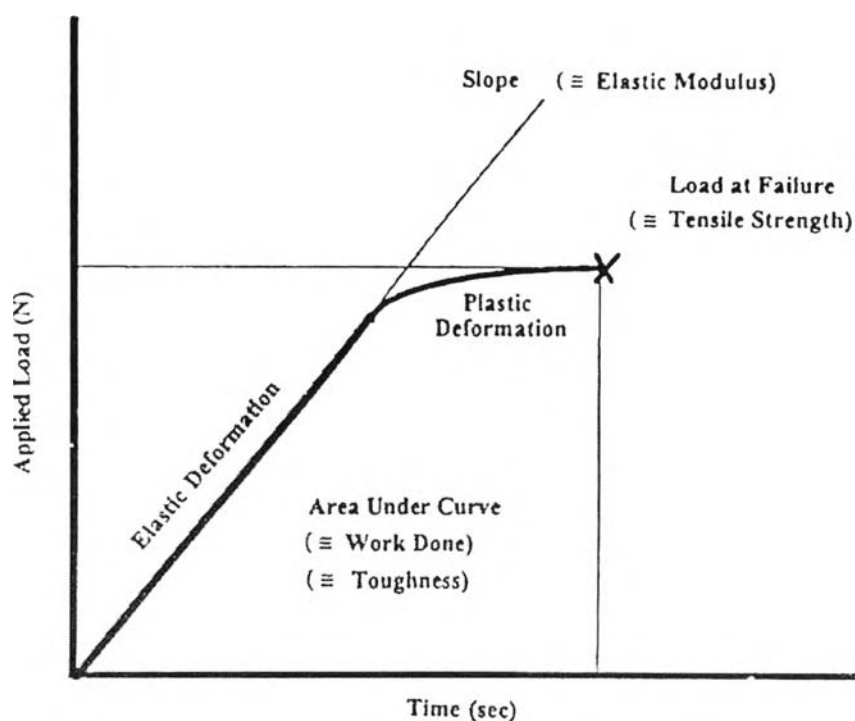


Figure 21 A typical load-time profile observed in the tensile testing of free films.

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 calculated from the area under curve of the load-time profile, cross-head speed, and the film dimensions.

$$\text{Work of failure} = \frac{\text{area under curve} \times \text{cross-head speed}}{\text{film thickness} \times \text{film width}}$$

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.

$$\text{Elastic modulus} = \frac{\text{Slope}}{\text{film thickness} \times \text{film width} \times \text{cross-head speed}}$$

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.

The profile in Figure 21 shows the typical response from a plasticized polymer when evaluated with a tensile tester such as an Instron. The ultimate tensile strength I_i 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 toughness. The energy to break per unit area is calculated by dividing the area under curve by the volume of the specimen between the clamps.

The method of preparing tested film is cast film method. Cast films method gives a more perfect specimen, uniform thickness and free from bubbles and defects. Cast films are reproducible because environmental factors affect the preparation less than with other method. Casting is therefore a better means of obtaining accurate data on the fundamental properties of the polymer and polymer formulation (Aulton, 1982)

An ideal film with respect to retaining its physical continuity should be soft and weak without being tough. Polymers are divided into five categories according to a qualitative description of their mechanical behavior and corresponding stress-strain characteristics as showed in the Table 3 and Figure 22.

Hard or stiff polymer are characterized by high moduli as opposed to soft ones. Strong (as opposed to weak) polymers have high tensile strengths. Tough (as opposed to brittle) polymers have large areas under their stress-strain curves and require large amounts of energy to break under stress, combining high or at least moderate tensile strength with high elongation. The desirable hard, tough film must have a high yield stress large extension before breaking and a high elastic modulus (Aulton, 1982)

Table 3 Qualitative description of polymer and its stress-strain characteristics.
(Aulton and Abdul, 1981)

Polymer Description	Characteristics of stress-strain curve			
	Young's Modulus	Yield Stress	Tensile Strength	Elongation to break
Soft, weak	Low	Low	Low	Low to moderate
Soft, tough	Low	Low	Moderate	Very High (20-1000%)
Hard, brittle	High	None (break around yield point)	Moderate to high	Very low (<2%)
Hard, strong	High	High	High	Moderate (~5%)
Hard, tough	High	High	High	High

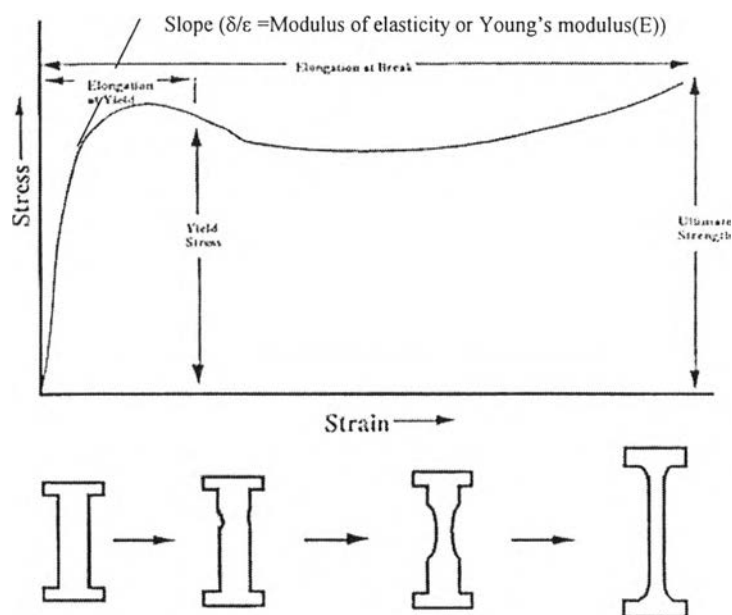


Figure 22 Typical stress-strain curve.

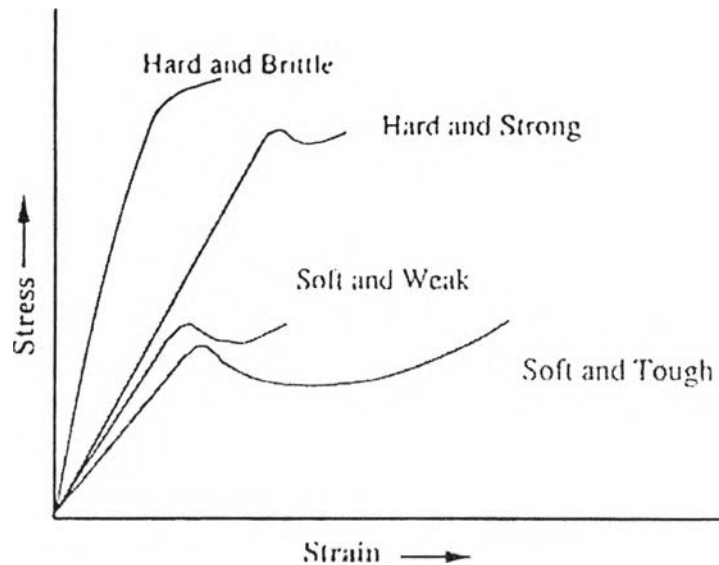


Figure 23 Characteristic of polymer properties in stress-strain curves.

A typical stress-strain data curve is shown in Figure 22. Along the linear portion has relation between stress and strain. The elongation is directly proportional to the applied stress, following Hooke's law is given in this equation.

$$\delta = E \times \epsilon$$

Where δ , ϵ and E represent tensile stress, strain and Young's modulus, respectively.

Tensile strength, ultimate strength or breaking stress is the maximum stress applied to a point at which the film specimen breaks. Tensile strength can be computed from the applied load at rupture divided by the cross sectional area of fractured film. 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 abrasion resistance.

Strain or elongation (ϵ) is a measure of the ductility of the film. Strain is deformation of materials after applied stress. Strain in tension is called elongation. It is the increase in length relative to the original length. Elongation is dimension less because it is expressed as a fraction of the original length. It can also be expressed as a percentage.

Young's modulus or Modulus of elasticity (E) is the most basic and structurally important of all mechanical properties and is a measure of stiffness and rigidity of the film. It is calculated as applied stress divided by the corresponding strain in the region of linear elastic deformation (slope). The greater slope of the curve, the higher the elastic modulus. The high value of the elastic modulus indicates the stiffness and

the strength of film and more stress will be required to produce a given amount of deformation (O'Donnell and MacGinity, 1997).

Elastic limit is the maximum stress, which may be developed during a simple tension test that does not cause the permanent or residual deformation when the load is entirely removed. The region of stress-strain curve extending from the origin to the elastic limit is called the elastic range, and the region extending from the elastic limit to the point of rupture is called the plastic range.

Yield point is the point that there is an increase in strain with no increase in stress. Stress at this point called yield stress. When the applied stresses exceed yield stress the specimen exhibits plasticity, becoming ductile and flowing or creeping under nearly constant stress, resembling a highly viscous liquid and the sample undergoes permanent elongation.

Area under the stress-strain curve is a function of work done in breaking the film specimen and is representative of the film toughness. The sample that has more area under the stress-strain curve also has more hardness and toughness.