CHAPTER II

LITERATURE REVIEW

1. General background on hydrophilic matrix systems

The hydrophilic matrices are defined as a well-mixed composite of ingredients fixed into a shape by tabletting or use of a hard shell-capsule. When a water-soluble polymer is used as a binder for the ingredients and the tablet is placed in a dissolution medium, a gelatinous-layer is formed at the tablet surface. The gel layer that forms is an aggregate mass of water-soluble polymer, drug and excipients experiencing various degrees of hydration (Alderman, 1984).

Hydrophilic matrices have become popular as modified release dosage form for oral administration. They are capable of slow release of an embedded drug, with release controlled by the rate of swelling and relaxation of the polymer. The major application of hydrophilic matrices is in the delivery of drugs over an extended period.

The swellable property of hydrophilic matrices is activated by water, and drug release control depends on the interactions between water, polymer, and drug. Water penetration into the matrices is the first step leading to polymer swelling and polymer and drug dissolution. The presence of water decreases the glassy-rubbery temperature (e.g., for hydroxypropyl methylcellulose from 184 $^{\circ}$C to lower than 37 $^{\circ}$C), giving rise to the transformation of glassy polymer into a rubbery phase (gel layer). The enhanced mobility of the polymeric chains favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The latter may add a convective contribution to the drug transport mechanism in drug delivery.

Depending on the polymer characteristics, the polymer amount in the rubbery phase at the surface of the matrices can reach the disentanglement concentration; therefore, the gel layer varies in thickness and the matrix dissolves or erodes.

The gel layer thickness depends on the relative contributions of water penetration, chain disentanglement, and mass (polymer and drug) transfer in the water. At the beginning, the water penetration is more rapid than chain disentanglement and a quick buildup of gel layer thickness takes place. But when the water penetrates slowly, due to the increase of the diffusional distance, little chance in gel thickness is obtained because water penetration and polymer disentanglement rates are similar. Thus, the gel layer thickness dynamics in swellable matrix tablet shows three distinct regimes: it increases when the penetration of water is the fastest phenomenon, stays constant when the disentanglement rate is similar to the penetration and decreases when all of the polymer is in the rubbery phase.

The release mechanisms have the gel layer formed around the matrix in response to water penetration as a central element of their analysis. The gel must be capable of preventing matrix disintegration and controlling additional water penetration. Phenomena governing gel layer formation and, consequently, drug release rate are water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion. The drug release control is obtained by diffusion of molecules through the gel layer that can dissolve or erode.

The boundaries of gel layer correspond to the fronts separating different matrix phases. Their movements determine the dynamics of gel layer formation. It is common knowledge that gel layer thickness is defined by the front separating the matrix from the dissolution medium, i.e., the erosion front, and by the front separating the glassy from the rubbery polymer (i.e., the swelling front). Therefore, erosion and swelling front movements are the controllers of gel layer behavior.

The presence of a third front inside the gel layer was described by Lee and Kim (1991) in swellable matrices containing diclofenac, as the consequence of precipitation in gel layer of this poorly soluble drug already molecularly dispersed in

the glassy matrix. This front, named diffusion front, corresponds to the boundary between undissolved and dissolved drug. Therefore, in swellable matrix tablets, conditions exist under which the following three fronts can be present at the same time (see Figure 1).

a. The swelling front, the boundary between the still glassy polymer and its ruberry phase
b. The diffusion front, the boundary between the solid as yet undissolved drug and the dissolved drug in gel layer, and
c. The erosion front, the boundary between the matrix and the dissolution medium.

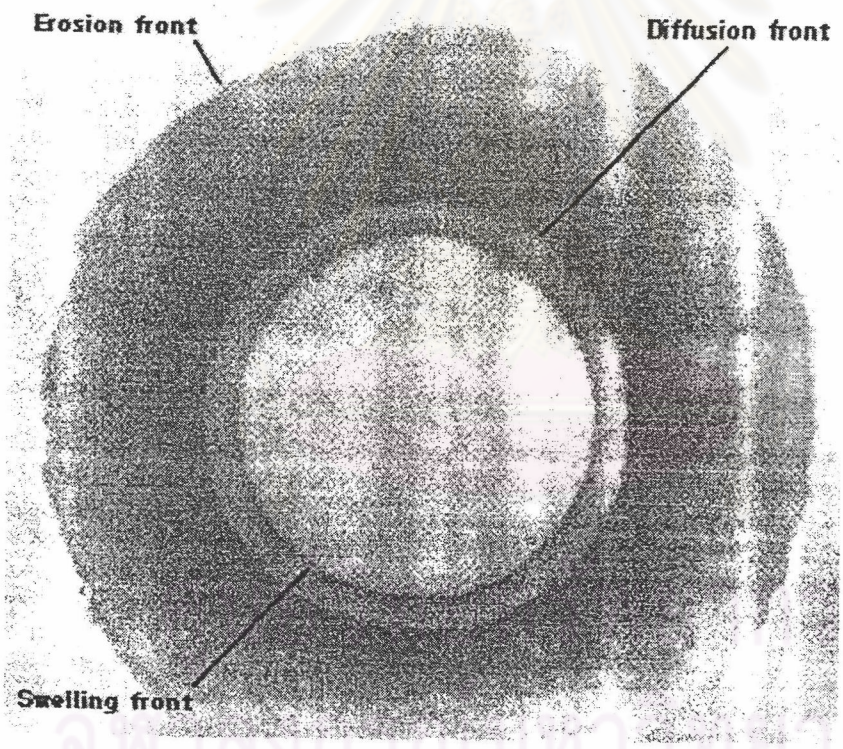

Figure 1 Picture of the top of a swellable matrix tablet during drug release showing the three fronts (Colombo et al., 2000)

The swelling front movement is associated with the rate of water uptake, the diffusion with the drug dissolution rate, and the erosion front with the matrix erosion rate.

Rate and kinetics of drug release from hydrophilic matrix tablet are controlled by the dynamics of gel layer thickness as determined by the front movement. In some cases, by using sufficiently soluble polymers, the gel layer thickness remains constant, since the fronts in the matrix move in a synchronized way. Keeping constant the releasing area, this situation leads to zero-order release. However, as the matrix is a three-dimensional system, the importance of the increase of releasing area due to the swelling phenomenon must also be considered.

2. Polymer used in hydrophilic matrix system

The polymer used in the preparation of hydrophilic matrices is divided into three broad groups (Salsa et al., 1997)

2.1 Cellulose ethers

The group of cellulose ethers contains methylcellulose (MC) and methylcellulose derivatives: hydroxypropyl methylcellulose (HPMC), hydroxyethyl methylcellulose (HEMC) and hydroxybuthyl methylcellulose (HBMC). These cellulose derivatives are the ones of which we have founded the most application in hydrophilic matrices. Among these polymers, HPMC is the most widely used in the matrix tablets and other types of controlled-release pharmaceutical dosage forms.

2.2 Noncellulose natural or semisynthetic polymers

The hydrophilic polymer in this group includes those such as alginates, xanthan gum, molasses, carrageenans, chitosan, polysaccharides of mannose and galactose and modified starches.

2.3 Polymers of acrylic acid

The most common use of this polymer group is commercialized under name of Carbopol®. Since Carbopol® is an ionic polymer, the gelling formation is dependent on the pH of medium.

3. Factors affecting drug release from hydrophilic matrices

There have been several studies which evaluated the influence of various factors on sustained drug release from hydrophilic matrices. These factors can be classified into two broad groups: formulation factors and technological factors.

3.1 Formulation factors

The formulation factors affecting drug release from hydrophilic matrices include polymer concentration, drug and polymer particle size, viscosity of polymer, drug solubility, type of diluent and type of polymer.

3.1.1 Polymer concentration

The effect of polymer concentration on drug release rate was reported by several researchers (Velasco et al., 1999; Dhopeshwaskar and Zatz, 1993; Sujja–areevath et al., 1996; Talukdar and Plaizier–Vercammen, 1993; Xu and Sunada, 1995). These studies revealed that the rate of drug release from matrices was mainly controlled by polymer concentration. An increase in polymer concentration leads to a decrease in drug release rate. This can explained in terms of an increase in viscosity of the gel layer around the matrices containing higher polymer content. This can also result in a decrease in effective diffusion coefficient of the drug and, therefore, the drug release rate decreases. Moreover, as the concentration of polymer increases in the matrices, the resulting gelatinous diffusion layer become stronger and more resistant to erosion (Alderman, 1984).

3.1.2 Drug particle size

The drug particle size also affect drug release from hydrophilic matrices. The drug particle size is important in the case of insoluble drugs. For soluble drugs, differences are only noticeable at low levels of polymer and when the drug particle size is large (Ford et al., 1985). Valasco el al. (1999) reported that the release exponent (n) of matrix containing the lower size of diclofenac sodium particles was small. This result may be explained in terms of the effective surface areas of drug particles. The small drug particles can dissolve more easily when dissolution medium penetrates through the matrix, resulting in a greater role of diffusion. The larger drug particles slowly dissolve and the formulations therefore are more prone to erosion at the matrix surface.

3.1.3 Polymer particle size

The influence of polymer particle size on drug release rate was also studied. Alderman (1984) stated that the coarse particle size of HPMC hydrated too slowly to give adequate sustained release. Therefore, the polymer selected for controlling drug release from hydrophilic matrices should hydrate quickly enough to form a gel layer before the contents of the tablet can dissolve prematurely. Moreover, Mitchell et al. (1993) indicated that, when the HPMC content was higher, the effect of the particle size was less important on the release of propanolol hydrochloride, while the effect of this variable was more important when the HPMC content was low. In addition, Dhopeshwarker and Zatz (1993) found that a fine particle size of xanthan gum produced the slow and reproducible release profiles.

3.1.4 Polymer viscosity

An increase in HPMC viscosity results in a decrease in drug release rate (Kurahashi et al., 1996, Liu et al.,1995, Sung et al., 1996, and Vázquez et al., 1996). However, In case of high viscosity grade of HPMC (more than 4000 cps), the HPMC viscosity is a less important in controlling drug release from the matrices (Kurahashi

et al., 1996.) The diffusion coefficient is unchanged with increasing viscosity, implying that gel tortuosity do not increase when the viscosity was increased.

3.1.5 Drug solubility

The solubility of drug is one of the important factors that is related to mechanism of drug release. Alderman (1984) studied the mechanism of drug release from HPMC matrices and concluded that water-soluble drugs were released by diffusion out of dissolved drug molecules across the gel layer and by erosion of gel layer, whereas water-insoluble drugs were released mainly by erosion. Talukdar et al. (1996) studied the influence of drug solubility on drug release. They found that the release of soluble drugs (caffeine and sodium indomethacin) was faster than the release of insoluble drug (indomethacin) from HPMC and xanthan gum matrices. Moreover, the difference in drug release mechanisms was also observed. Being soluble drugs, caffeine and sodium indomethacin are released by the mechanism of diffusion, while indomethacin, being an insoluble drug, is released by predominantly via erosion.

In addition, Cox et al. (1999) studied the effect of pH of the dissolution medium on drug release from mini-matrices. They found that the release of *S* (+)–ibuprofen from mini-matrices containing xanthan gum or HPMC and lactose depended greatly on the pH of the medium. This result is consistent with the pH solubility profile of *S* (+)–ibuprofen. At low pH values, the solubility of the drug was very poor (0.1 mg/ml at pH 2.0). With increasing pH, the solubility of the drug improved dramatically. The dissolution studies using the pH change method demonstrated a similar trend. Consequently they concluded that the pH of the dissolution medium was a critical factor is in determining the dissolution rate of *S* (+) – ibuprofen.

3.1.6 Type of diluent

Replacement of HPMC by either a soluble or insoluble diluent increases dissolution rate (Lapidus and Lordi, 1966). Additionally, only at high diluent level, difference in drug release between soluble and insoluble diluents exists. This is consistent with other studies. Ford et al. (1987) found that the replacement of portions of HPMC within the matrices by diluents increased the drug release rate, irrespective of whether the diluents were water soluble or water insoluble. Moreover, Cox et al. (1999) summarized that the drug release rates of xanthan gum mini–matrices containing either lactose or Emcompress ® were very similar and slower than those containing Avicel ®. Although Avicel ® and Emcompress ® are water–insoluble excipients, their drug release rates in the above study were different. This may be due to the disintegration property of Avicel ®.

3.1.7 Type of polymer

The polymer used in the formulation of hydrophilic matrices is divided into three broad groups as previously mentioned. The difference in physicochemical properties of polymer can result in the difference in drug release characteristics. There have been several comparative studies of these polymers in controlling drug release from hydrophilic matrices (Cox et al., 1999; Dhopeshwarker and Zatz, 1993; Sujja-areevath et al., 1996; Talukdar et al., 1996).

The comparative study of xanthan gum and hydroxypropyl methylcellulose for controlled–release drug delivery was reported by many researchers (Cox et al., 1999; Talukdar et al., 1996 and Dhopeshwarker and Zatz, 1993). Cox et al. (1999) found that the encapsulated *S*(+)–ibuprofen mini–matrices containing hydroxypropyl methylcellulose showed superior release profile than those containing xanthan gum. The performance of xanthan gum and hydroxypropyl methylcellulose as hydrophilic matrix-forming agents in respect of compaction characteristics and *in vitro* drug release behaviour was assessed by Talukdar et al. (1996). They found that the overall compaction characteristics of these two polymers similar. However, the flow characteristics were different, i.e., xanthan gum was more readily flowable than

hydroxypropyl methylcellulose. In addition, they concluded that, in respect of controlled drug release behaviour, xanthan gum matrices had some important pharmaceutical as well as economical advantages (e.g. absence of initial burst release, higher drug–retarding ability, more reproducibility in drug release rate, and the possibility of zero–order release kinetics) over hydroxypropyl methylcellulose matrices.

The higher drug retarding ability of xanthan gum can be explained in terms of the higher strength of the hydrated gel layer around xanthan gum matrices. Talukdar et al. (1996) studied the rheological characteristic of xanthan gum and hydroxypropyl methylcellulose solution. They proved that xanthan gum showed gel–like properties and hydroxypropyl methylcellulose showed simple polymer solution behaviour. This result indicates that hydroxypropyl methylcellulose matrices are more susceptible to erosion than xanthan gum matrices.

Moreover, Dhopeshwarker and Zatz (1993) concluded that matrices containing 5% xanthan gum exhibited release profiles similar to tablets containing 15% hydroxypropyl methylcellulose (Methocel ® K4MCRP) Therefore, xanthan gum can be used in very small quantity (approximately 1/3 that of hydroxypropyl methylcellulose) to achieve a comparable sustained release profile. This is a distinct advantage in formulating high dose drugs without excessive increase in tablet weight. Consequently, xanthan gum is suitable for matrix tablets containing both low and high dose drugs.

A number of sustained release matrix formulations involving the use of natural gums as regarding polymer have been studied. The natural gums have been used such as xanthan gum, karaya gum, locust bean gum and carrageenan. The difference in type of gums shows variable degrees of sustained release. (Sujja-areevath et al., 1996). Cox et al. (1999) found that xanthan gum produced a greater sustaining effect on the release of *S* (+) – ibuprofen than karaya gum. Moreover, Sujja–areevath (1996) found that sustained release of diclofenac was achieved from mini–matrices containing locust bean gum, xanthan gum and karaya gum, while carrageenan did not produce sufficient sustained release

3.2 Technological variables

3.2.1 Tablet shape and size

The influences of tablet shape and size on the rate of drug release from HPMC matrices were examined by Ford et al. (1987). They summarized that the rate of drug release was proportional to the surface of tablet since release rate decreased as the tablet surface area decreased.

3.2.2 Compression force

Although compression pressure affects the porosity of the matrices, it has little effect on the dissolution rate (Talukdar and Plaizier-Vercammen,1993; Vázquez et al.,1996 and Veslasco et al., 1999).

4. Mechanism and kinetics of drug release

4.1 The mechanisms of drug release

When the matrix is immersed in dissolution medium, the dissolution medium dissolves the drug at the surface, resulting in immediately release and partial hydration/swelling of the polymer take places, causing the formation of gel layer. As dissolution medium penetrates into the matrix, the gel layer expands, getting the thickness of gel layer around the matrix. Here the polymer chains are entangled and the strongly gel layer is formed. Consequently, the gel layer acts as a hydrophilic barrier that controls dissolution, penetration and drug diffusion. Nevertheless, moving away from this hydration position, when sufficient dissolution medium has accumulated, the gel layer becomes progressively hydrated and chains disentangle followed by polymer dissolution/erosion. Finally, the process of dissolution medium penetration can continue until the matrix is completely dissolved.

According to the proposed drug release mechanism as mentioned above, the drug liberation from hydrophilic matrix is produced by two simultaneously mechanisms as follows: the dissolution of drug in dissolution medium and diffusion through the gel barrier and the erosion or dissolution of the outer gel layer.

Moreover, Alderman (1984) concluded that the mechanisms of drug release of water-soluble and water-insoluble drug content matrices are different. Water soluble drugs are released by diffusion out of the gelatinous layer. Drug may also be released by erosion of the gel regardless of the drug's solubility in the dissolution medium. However, water-insoluble drug is exposed strictly through erosion.

4.2 The kinetics of drug release

The amount of drug release from polymeric matrix is often analyzed in terms of square root of time (Higuchi model), in accordance with following equation (Higuchi, 1963):

$$Q = \frac{[D\epsilon(2A-\epsilon C_s)\, C_s t]^{1/2}}{\tau}$$

where Q = the amount of drug released per unit surface area

D = the diffusion coefficient of the drug in the release medium

ϵ = the porosity of the matrix

τ = the tortuosity of the matrix

A = the total amount of drug present in the matrix per unit volume

C_s = the solubility of drug in the release medium

t = time.

In general Higuchi's equation is usually desired and used as in equation

$$Q = kt^{1/2}$$

where k = Higuchi constant.

Nevertheless, the use of Higuchi model is not justified because the conditions applied by Higuchi model are not valid for the hydrophilic matrix having swelling process. In addition, the Higuchi's equation does not take into consideration that the matrix system can be erodible and that relaxation of polymeric chain can contribute to drug transport. Therefore, an empirical was proposed by Ritger and Peppas (1987) that is well-known for analysis of dissolution data from polymeric system. This equation is based on a power law dependence of the fractional release on time. The expression is given below.

$$\frac{M_t}{M_\infty} = kt^n$$

Where, M_t/M_∞ = the fractional release of drug up to time t

t = the release time

k = a constant incorporating structure and geometric characteristics of the controlled release device

n = the release exponent, indicative of mechanism of drug release.

The determination of the exponent n is valid for the first 60% of the total released drug which also applied only to the early times of release. The n values can assume and their meanings are presented in Table 1 (Peppas, N., and Peppas B., 1994).

Table 1 Diffusion exponent and solute release mechanism

Diffusion exponent (n)			Mechanism of drug release
Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1	0.45<n<0.89	0.43<n<0.85	Anomalous transport
1	0.89	0.85	Case II transport
n>1	n>0.89	n>0.85	Super case II transport

5. Acyclovir

5.1 Description (Laskin, 1983 and Wagstaff et al., 1994)

The chemical structure of acyclovir is presented in Figure 2.

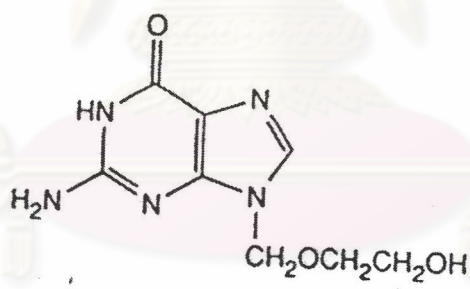

Figure 2 The chemical structure of acyclovir

Empirical Formula $C_8H_{11}N_5O_3$

Molecular Weight 225.2

Chemical Name 9-(2-Hydroxyethoxymethyl) guanine; 2-Amino-1, 9-dihydro-9-(2-hydroxyethoxymethyl)-6H-purin-6-one

Characteristics A white or almost white crystalline powder

5.2 Physical properties (Wagstaff et al., 1994)

Melting point	Acyclovir is stated to melt at temperatures higher than 250°C, with decomposition.
Dissociation constant	pK_a 2.27, 9.25
Partition coefficient	0.022-0.024 (between water and n-octanol)
Solubility	Acyclovir is slightly soluble in water; insoluble in ethanol; practically insoluble in most organic solvents; soluble in dilute aqueous solutions of alkali hydroxides and mineral acids. The maximum solubility of acyclovir in water at 37 °C is 2.5 mg/ml.

5.3 Stability

Acyclovir appears to be very stable and exhibits greater stability in an alkaline solution than in acidic solution (Dubhashi and Vavia, 1999).

5.4 Pharmacology (Laskin, 1983; O' Brien and Campoli-Richards, 1989; Wagstaff et al., 1994)

Acyclovir is a synthetic acyclic purine nucleoside analog of natural nucleoside 2'-deoxyguanosine. It has *in vitro* inhibitory activity against herpes simplex viruses types I and II (HSVI and HSVII), varicella zoster virus, Epstain-Barr virus and cytomegalovirus.

5.5 Pharmacokinetics (Laskin, 1983; O' Brien and Campoli-Richards, 1989; Wagstaff et al., 1994)

Oral acyclovir is slowly and incompletely absorbed form the GI tract. Peak concentrations are reached in 1.5 to 2 hours and its absorption is unaffected by food. Bioavailability is between 15% and 30%. Acyclovir is widely distributed in tissues

and body fluids. The volume of distribution (v_d) is about 70% of total body weight. The elimination half-life ($t_{1/2}$) of acyclovir after IV administration is 2 to 3 hours.

5.6 Indications (Laskin, 1983; O' Brien and Campoli-Richard, 1989; Wagstaff et al., 1994)

The oral forms of acyclovir can be used for treatment of initial and recurrent episodes of genital herpes in certain patients and acute treatment of herpes zoster (shingles) and chickenpox (varicella). For the parenteral form of acyclovir, it is used for treatment of initial and recurrent mucosal and continuous HSV-I and HSV-II and varicella-zoster (shingles) infections in immunocompromised patients.

5.7 Adverse reactions (Wagstaff et al., 1994)

Acyclovir appears to have a very large therapeutic index. The toxicity with oral acyclovir has been minor. The most frequently reported adverse reactions are nausea and vomiting. The most frequent adverse reaction with parenteral acyclovir is the inflammation at injection site.

6. Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder. It is soluble in cold water, forming a viscous colloidal solution. It is not soluble in hot water (Kibbe, 2000). HPMC undergoes a reversible sol to gel transformation upon heating and cooling, respectively. The gel point is 50-90 °C, depending on the ratio of methyl and hydroxypropyl substitution. HPMC is neutral, non-ionic polymer that are not susceptible to chemical gelation or precipitation with di-or trivalent metals, with borates, or by interaction with other polymers to form complexes or coacervates. However, HPMC can be gelled or salted out of solution when the concentration of added solutes or electrolytes exceeds certain limits (Greminger and Krumel, 1980). HPMC solution is generally stable in the pH range of 3 to11. Below pH 3, acid-catalyzed hydrolysis of the glucose linkage becomes significant, and above pH 11,

oxidative degradation takes place (Greminger and Krumel, 1980). The chemical structure of HPMC is shown in Figure 3.

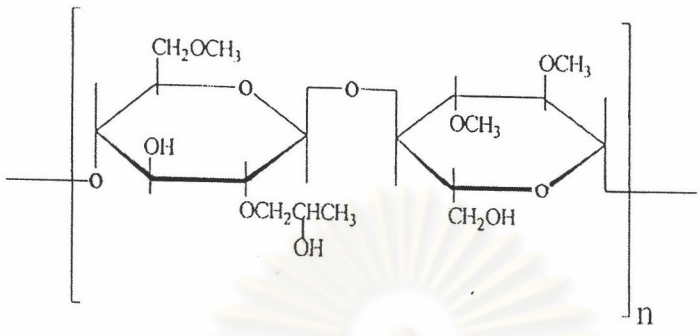

Figure 3 The chemical structure of hydroxypropyl methylcellulose

7. Xanthan gum

Xanthan gum is a high-molecular-weight natural carbohydrate. It is a polysaccharide produced in a pure culture fermentation by microorganism *Xanthomonas campestris*, an organism originally isolated from the rutabaga plant. Following fermentation, xanthan gum is recovered by precipitation in isopropyl alcohol, then dried and milled. It occurs as a cream or white-colored, odorless, free-flowing and fine powder (Kibbe, 2000).

Xanthan gum contains three differrent monosacharides: mannose, glucose, and glucuronic acid (as a mixed potassium, sodium, and calcium salts). Each repeating block of the polymer chain has five sugar units (two glucoses, two mannose, one glucuronic acid). The polymer's main chain is made up of β-D-glucose units linked through the 1- and 4 positions; thus, the chemical structure of the main chain is identical to that of cellulose.

Two mannose units and the glucuronic acid unit make up the side chain. The terminal β-D-mannose unit is glycosidically linked to the 4-position of β-D-glucuronic acid, which in turn is glycosidically linked to the 2-position of α-D-

mannose. This side chain is linked to the 3-position of every other glucose residue on average in the polymer main chain. Roughly half of the terminal D-mannose residues carry a pyruvic acid residue linked ketalically to the 4- and 6-positions. The nonterminal D-mannose unit on the side chain has an acetyl group at the 6-position. Therefore, xanthan gum is anoionic by virtue of carboxylic acid residues on the β-D-glucuronic acid and the pyruvic acid moiety on the terminal D-mannose (Cottrell et al., 1980).

The shielding of the backbone of xanthan gum by its side chains can explain its extraordinary resistance to enzymes. Also unique among the natural gums are the unvarying chemical structure and the uniformity of chemical and physical properties of xanthan gum. The structural rigidity of xanthan gum produces several unusual properties. Contrary to the behavior expected from a typical anionic polysaccharide, the addition of salts to a salt-free xanthan gum solution causes the viscosity to increase when the gum concentration is greater than 0.15%. Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12) and temperatures between 10-60°C (Kibbe, 2000). The chemical structure of xanthan gum is shown in Figure 4.

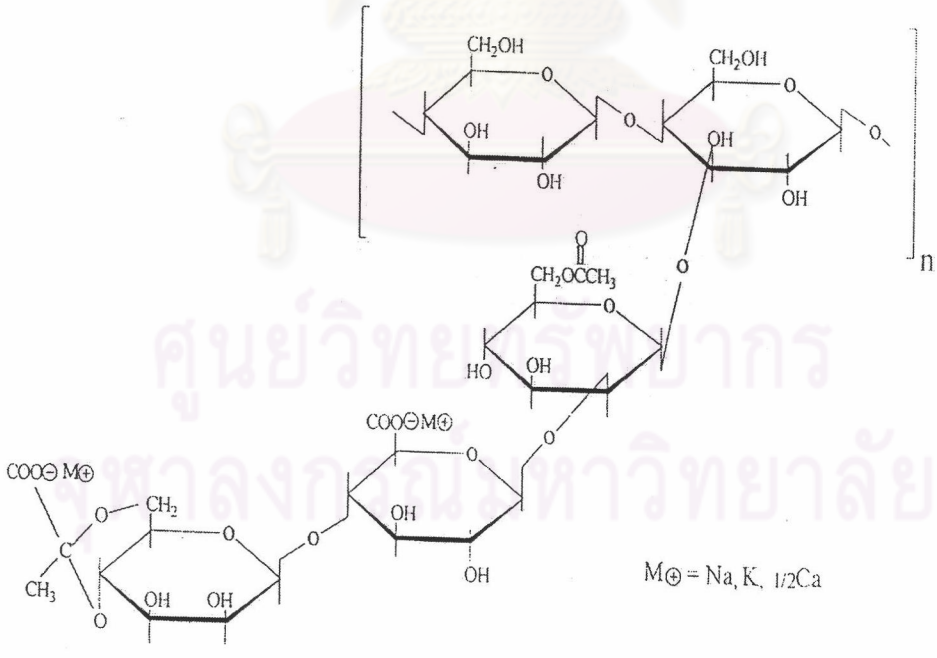

Figure 4 The chemical structure of xanthan gu

8. Alginates (Cottrell and Kovacs, 1980)

Algin is polysaccharide found in all brown seaweeds. Only a few species of brown seaweeds are used for commercial production of algin. The principal source of the world's supply of algin is the giant kelp, *Macrocysis pyrifera.* Other seaweeds used for algin manufacture are *Ascophyllum nodosum* and species of *Laminaria* and *Ecklonia.* Algin exists in the kelp cell wall as the insoluble mixed salt (calcium, magnesium, sodium, potassium) of alginic acid. Alginic acid is a high-molecular-weight linear glycuronan comprising solely D-mannuronic acid L-guluronic acid. Figure 5 illustrates the structures of alginate monomer (a), chain conformation (b) block distribution (c).

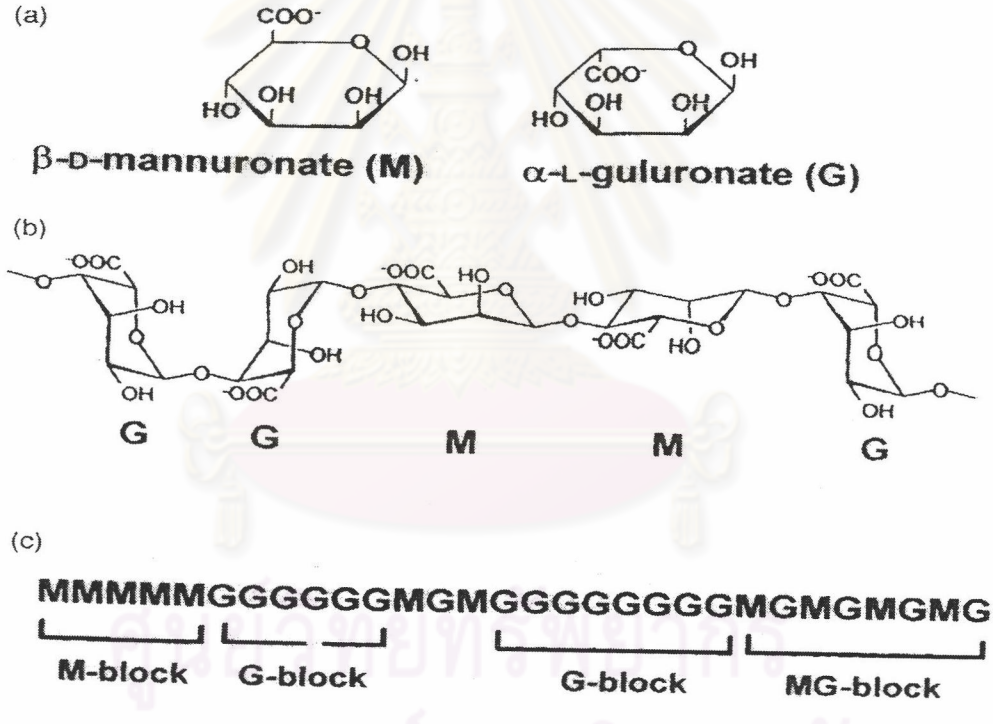

Figure 5 Structural characteristics of (a) alginate monomers, (b) chain conformation, (c) block distribution

In the seaweeds, the algin is apparently present as a mixed salt of sodium and/or potassium, calcium, magnesium and is a high-molecular-weight polymer. The exact composition varies considerably with the type of seaweed but does not affect processing.

Commercially available, water-soluble alginates include the sodium, potassism, ammonium, calcium, and mixed ammonium-calcium salts of alginic acid, propylene glycol alginate, and alginic acid itself.

Pure alginates dissolved in distilled water form smooth solutions with long-flow characteristics. The physical variables that affect the flow properties of alginate solutions are temperature, shear rate, polymer size, concentration, and the presence of solvents miscible with the distilled water. The chemical variables that affect algin solutions are pH and the presence of sequestrants, monovalent salts, polyvalent cations, and quaternary ammonium compounds.

9. Carbomer (Kibbe, 2000)

Carbomer are synthetic high molecular weight polymers of acrylic acid that are crosslinked with either allylsucrose or allyl ethers of pentaerythritol. The polymerization solvent is normally benzene; however, some of the newer commercially available grades of carbomer are manufactured using either ethyl acetate or a cyclolhexane/ethyl acetate cosolvent mixture. They contain between 56-68% of carboxylic acid (-COOH) groups as calculated on the dry basis.

Carbomer is commercialized under name of Carbopol®. It is white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor. Carbomer grades with a low residual benzene content, such as carbomer 934P or 974P, and low residual ethyl acetate levels, such as carbomer 971P, may additionally be used in oral preparation, in suspensions, tablets, or sustained-release tablet formulations. In tablet formulations, carbomers are used as dry or wet binders and as a rate-controlling excipient.

Carbomer dispersed in water forms acidic colloidal solutions of low viscosity that when neutralized produce highly viscous gels. Agents that may be used to neutralize carbomer polymers include amino acids, borax, potassium hydroxide, sodium bicarbonate, sodium hydroxide, and polar organic amines such as triethanolamine. Neutralized aqueous gels are more viscous at pH 6-11. The viscosity is considerably reduced at pH values less than 3 or greater than 12 or in the presence of strong electrolytes. The chemical structure of carbomer is represented in Figure 6

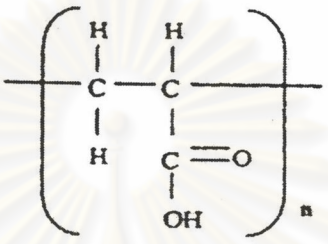

Figure 6 Chemical structure of carbomer