CHAPTER II

REVIEW OF LITERATURE

1. Polymers for hydrophilic matrices

The polymers used in the preparation of hydrophilic matrices can be divided into three main groups depending on chemical nature; cellulose derivatives, non-cellulose natural and polymers of acrylic acid (Salsa, Veiga, and Pina, 1997).

1.1 Cellulose ethers

The hydrophilic polymers in this group are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose (MC) and sodium carboxymethylcellulose (CMC). These cellulose derivatives have been popular in the formulation of controlled-release solid dosage forms. Hydroxypropyl methylcellulose (HPMC) is most widely used in matrix tablets and other types of controlled-release dosage forms because of its characteristics, non-toxic nature of polymer, its capacity to incorporate active ingredients and manufacture of matrix tablets by direct compression without previous granulation. Its variety is dependent on viscosity and proportions between its substitutions. In this study, a high viscosity grade of HPMC is used as retarding agent in the formulation of gliclazide matrix tablet.

HPMC is a water-soluble cellulose ether. It is an odorless and tasteless, white or creamy-white colored fibrous or granular powder. Melting point of HPMC is between 190-200 $^{\circ}$C (browns) and 225-230 $^{\circ}$C (chars). It is soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ether and ethanol (95%),

but soluble in aqueous acetone solutions, mixtures of methanol and dichloromethane, mixtures of ethanol and dichloromethane and mixtures of alcohol and water.

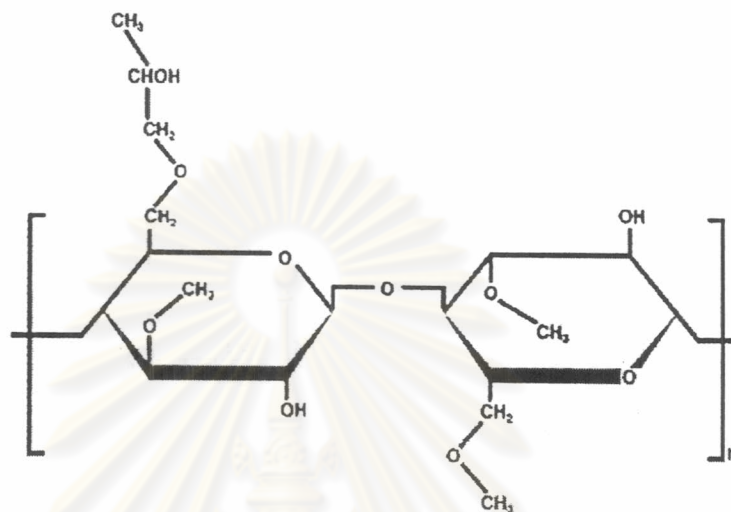### 1.1.1 Physicochemical properties

Figure 1 The chemical structure of hydroxypropyl methylcellulose.

The powder of HPMC is a stable material. Solutions are stable at pH 3-11. HPMC is incompatibility with some oxidizing agents. It is nonionic. Report on the safety assessment of HPMC is regarded as a nontoxic and nonirritant material. It is also used in food and cosmetics products (Coll, 1986)

1.1.2 Applications in matrix system

Researchers have performed extensive studies on HPMC as a polymer for controlled drug delivery. Changing variables such as the amounts of HPMC, viscosity grade and the particle size of HPMC can modify the drug release from HPMC-tablets. Sheskey and Williams (1990) investigated the effects of granulation technique (high-shear versus low-shear) and level of water addition on the physical properties of, and

drug release from, tablets made from HPMC matrix formulation. The results indicated that the method of wet granulation and level of water addition had little effect on tablet physical properties and drug release. Sheskey and Hendren (1999) studied the effects of amounts of HPMC polymer on the physical properties (bulk and tap densities) and drug release. Increased HPMC polymer levels resulted in increased time to release.

Krogel and Bodmeier (1999) investigated the release behavior of the different HPMC viscosity grade and HPMC content on drug release. The drug release increased with a reduced HPMC viscosity grade and decreased HPMC content. Increasing the molecular weight or viscosity of the polymer in a matrix formulation increased the gel layer viscosity and thus slowed drug dissolution. The greater the viscosity of the gel, the more resistant the gel was to dilution and erosion, thus controlling the drug dissolution. High viscosity grades are widely used to retard the release of drugs from a matrix approximately levels 10-80% w/w in tablets and capsules. HPMC with low content in methoxy groups hydrates quickly which justifies its application in controlled-release matrices. The swelling of HPMC can be one of the parameters that influence and control the drug release, because it exhibits an inverse relationship between the HPMC constant rate swelling and constant rate dissolution by Higuchi's equation.

The characteristics of used drugs can also affect the drug release. The soluble drug release in water is mainly controlled by drug diffusion through the gel; the insoluble drugs are release in water by gel erosion. One of the mechanisms for drug release from matrices of HPMC implies water penetration in the matrix, hydration and swelling of HPMC, diffusion of the dissolved drug, and the erosion of gelatinous polymer layer. When the water reaches the center of the tablets, and the concentration of drug begins to reduce, the time lag in the changing of release mechanism is recorded.

1.2 <u>Non-cellulose natural or semisynthetic polymers</u>

The group of non-cellulose natural or semisynthetic polymers includes alginates, agar-agar, carob gum, molasses, polysaccharides of mannose and galactose, chitosan, modified starchs and xanthan gum. For this study, only the information of xanthan gum is mentioned.

Xanthan gum is a linear polysaccharide produced by viscous fermentation of the bacterium *Xanthomonas campestris*. Xanthan gum has been also used as an effective excipient for controlled-release formulations: It is considered to be useful since these have high biocompatibility and biological safety.
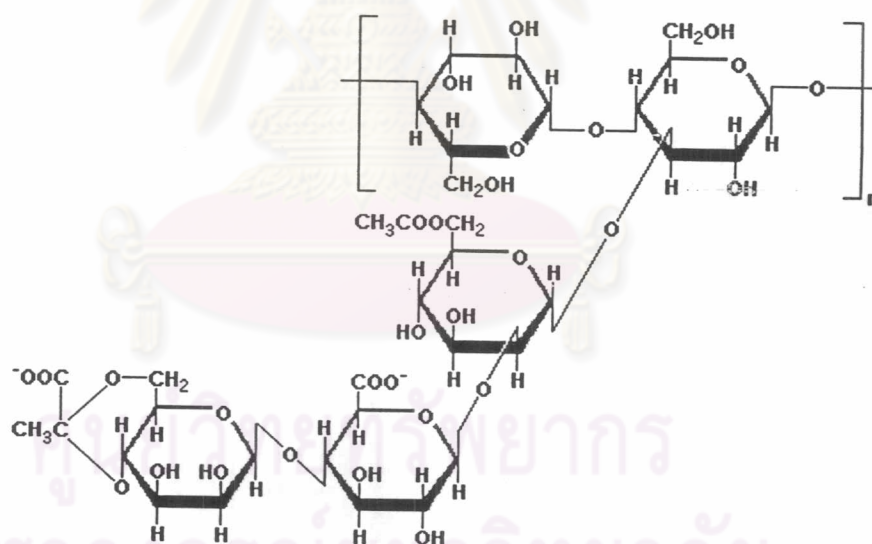
1.2.1 <u>Physicochemical properties</u>

Figure 2 The chemical structure of xanthan gum.

Xanthan gum is a high molecular weight polysaccharide produced by viscous fermentation. The polymer backbone is made up of ß-1, 4-linked D-glucose residues

and, therefore, is identical to the cellulose molecule. A trisaccharide branch containing one glucuronic acid unit between two mannose units is linked to every other glucose unit at the number 3 position. It occurs as a white-colored or cream, odorless, free-flowing and fine powder. Melting point of xanthan gum is at 270 °C (chars). It is soluble in cold or warm water, practically insoluble in ethanol and ether.

Xanthan gum is a stable material. Aqueous solutions are stable at pH 3-12. It is incompatibility with most synthetic, natural viscosity-increasing agents and oxidizing agents. Xanthan gum is generally regarded as a nontoxic and nonirritant material at the levels employed as a pharmaceutical excipient. It is widely used in oral, food products and cosmetics.

1.2.2 Applications in matrix system

Dhopeshwarkar and Zatz (1993) evaluated xanthan gum as a matrix former for the preparation of sustained release tablets. They concluded that release of a soluble drug and an insoluble drug from tablets containing low concentrations of xanthan gum was mainly via diffusion and erosion, respectively. Drug release from tablets containing xanthan gum was slightly faster in acidic media due to more rapid initial surface erosion than at higher pH. After hydration of the gum, drug release was essentially pH-independent. It seems likely that the viscosity of the xanthan gum gel, which forms on the tablet surface, is also relatively independent of environmental pH. The amount released was directly proportional to the loading dose of drug and inversely proportional to gum concentration in tablets. Xanthan gum can be used in very small quantity to achieve a comparable controlled-release profile. This is a distinct advantage in formulating high dose drugs without excessive increase in tablet weight. Disadvantage of xanthan gum is rotation speed and ionic strength of dissolution medium has influence on drug release.

The study of drug release from hydrogel prepared with xanthan gum and locust bean gums was reported by Wattanabe et al (1992). The release rate of prednisolone from the hydrogel decreased with increasing gum concentration. Drug release was significantly lowered by the addition of additives such as glycerin and sucrose.

In the study of El-Gazayerly (2003), xanthan gum was used as hydrophilic matrix polymer for controlling the release of the water-soluble pentoxifylline. The effects of polymer concentration, rotation speed, ionic strength, and pH of the dissolution medium were studied. The release rate decreased with increasing polymer concentration in the tablet. A higher rotation speed, increased ionic strength and pH of the dissolution medium resulted in a higher rate of drug release.

To compare the effect of the polymeric type between HPMC and xanthan gum were investigated by Talukdar and Kinget (1997). This investigation was comparative study on HPMC and xanthan gum in terms of physical properties (compaction and flowability), in vitro drug release characteristic. Results indicated that compaction property between the two polymers was quite similar, but the flowability of xanthan gum was better than HPMC. The xanthan gum had some advantages over the HPMC in relation to in vitro drug release behavior. Xanthan gum matrices exhibited absence of initial burst release, higher drug-retarding ability due to less drug diffusion, drug release was essentially pH-independent and the possibility of zero-order release kinetics. However, xanthan gum had some disadvantages in that the drug release was influenced by ionic strength of the dissolution media, whereas the drug release from HPMC was independent to ionic strength.

2. Model drug:

Gliclazide

Gliclazide is an oral hypoglycaemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It has an N-containing heterocyclic ring with an endocyclic bond.
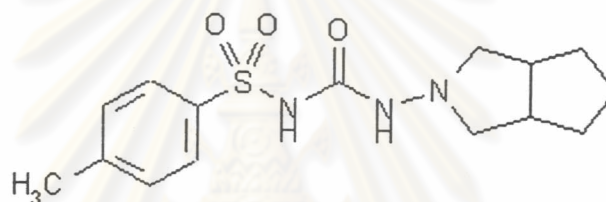
Physicochemical properties

Figure 3 The chemical structure of gliclazide.

Chemical Name   : 1-(3-azabicyclo [3.3.0] oct-3-yl)-3-p-tolylsulfonylurea

Empirical formula   : $C_{15}H_{21}N_3O_3S$

Molecular weight   : 323.4

Characteristics   : A white or almost white powder

Solubility   : Insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in alcohol.

Melting point   : 168 $^{\circ}$C

pKa   : 5.8

Therapeutic and toxic effects

Gliclazide reduces the glucose level by stimulating insulin secretion from pancreatic beta cells of pancreatic islet. The high affinity, strong selectivity, and free reversibility of gliclazide binding to pancreatic sulfonylurea receptors are thought to contribute to the optimized cardiovascular acceptability, reduced risk of hypoglycemia and weight-neutrality of this agent. Its plasma half-life is 6-14 hours (Moffat, 1986).

A new formulation of modified release gliclazide administered once has been developed. It consists of hydrophilic-based polymer that expands to form a gel when exposed to gastrointestinal fluid, progressively releasing gliclazide. The formulation is given once daily. This formulation optimizes patient's compliance and improves efficacy (Crepaldi and Fioretto, 2000).

The mean absolute bioavailability of gliclazide was 97% after administration of a single oral dose of gliclazide MR 30 mg. In patients with type 2 diabetes mellitus the apparent clearance of gliclazide MR was 0.9 L/h, with an apparent volume of distribution of 19 L. Gliclazide is highly bound to albumin (95%). No active metabolites have been detected in plasma. Plasma concentration declined exponentially, with elimination half–life of approximately 16 hours. It is mainly metabolized in the liver, the products of which are extensively excreted in the urine. Less than 1% of unchanged drug was recovered in the urine (Campbell et al, 1991).

Dosage and administration

The initial recommended dosage of gliclazide MR in patients with type 2 diabetics mellitus uncontrolled by diet, exercise and weight loss is 30 mg once daily with breakfast. Gliclazide MR should be taken with food because there is increased

risk of hypoglycemia if a meal is taken late. The dosage may be titrated by 30-mg increments at intervals of 2 to 4 weeks, to a maximum of 120 mg/day. No dosage adjustments are needed for elderly patients or those with mild to moderate renal insufficiency. Gliclazide MR tablets is a modified release tablet and therefore should be neither broken nor chewed.