CHAPTER II

REVIEW OF LITERATURE

1. Polymer in hydrophilic matrices

Polymer in hydrophilic matrices can be devided into three groups (Salsa et al, 1997).

1.1 Cellulose ethers

Cellulose ethers comprised methylcellulose and methylcellulose derivatives such as hydroxypropylmethylcellulose (HPMC) and hydroxyethylmethylcellulose (HEMC). HPMC is the most widely used as matrix in tablets and other types of modified-release pharmaceutical dosage forms.

Powder of HPMC is odorless and tasteless, white to off white in color, fibrous or granular characteristic. It can be solubilized in cold water but insolubilized in hot water. HPMC solution is generally stable at the pH range of 3 to 11 (Wade and Weller, 1994). The chemical structure of HPMC was shown in Figure 1.

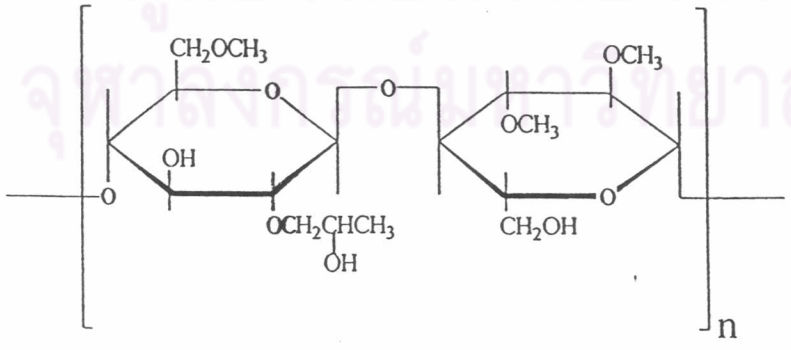

Figure 1. Chemical structure of hydroxypropylmethylcellulose

1.2 Noncellulose natural or semisynthetic polymers

Hydrophilic polymers in this group include carageenans, XG and molasses.

XG is a high molecular weight polysaccharide gum produced in a pure culture fermentation by the microorganism *Xanthomonas compertris*, an organism originally isolated from rutabaga plant. XG contains three different monosaccharides: mannose, glucose and glucuronic acid (as a mixed potassium, sodium and calcium salts) as shown in Figure 2. XG occurs as a cream or white-colored, odorless, free-flowing and fine powder. The effect of salts on viscosity of XG depends on the concentration of gum in the solution. XG solutions are stable over a wide pH range of 3 to 12 and temperature between 10-60^{o}C (Wade and Weller,1994).

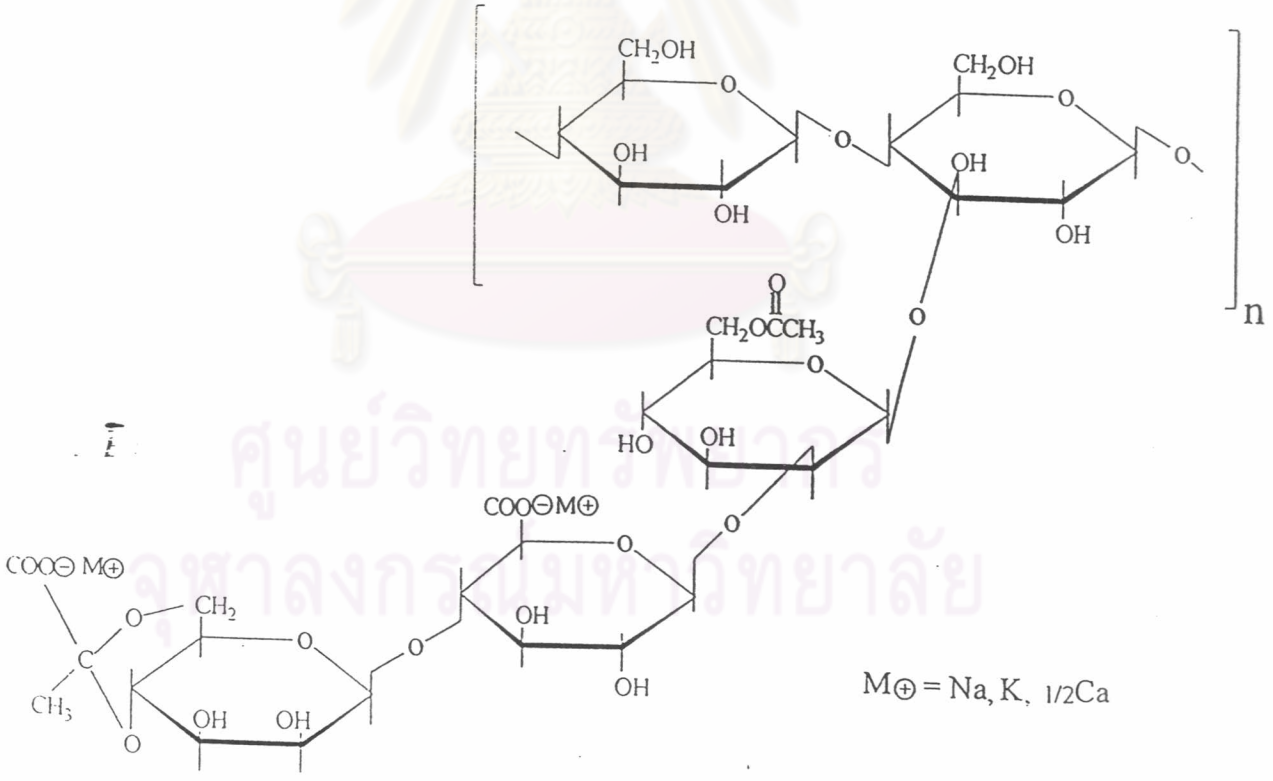

Figure 2. Chemical structure of xanthan gum

1.3 Polymers of acrylic acid

The most widely used of this group is commercialized under the name of Carbopol®. Due to the ionic characteristic of these polymers, gelling formation is dependent on the pH of dissolution medium.

Effect of HPMC on drug release was studied by several researchers (Ford et al, 1985; Kurahashi et al, 1996). As increasing of polymer concentration led to decrease in the rate of drug release. Because of increasing polymer chain entanglement in gels containing higher HPMC content, the concentrated gel and gel tortuosity augmented and the diffusion path became more convoluted and the diffusion rate decreased. Moreover, HPMC grade affected the gel viscosity. The various HPMC viscosity grades as follows; HPMC K100LV, K4M, K15M and K100M (the viscosities were 100, 4000, 1500 and 100000 cps, respectively). The fastest drug release rate was observed for the matrix containing HPMC K100LV. The matrixs containing high viscosity (more than 4000 cps) had the release profiles slightly different.

In the part of XG, the drug release profile of the matrix consisted of XG and that of HPMC was compared. It was found that XG matrix exhibited absence of initial burst effect release, higher drug retarding ability due to less drug diffusion, and the possibility of zero-order release kinetic (Talukdar et al, 1996).

Moreover, some researchers used the combination of polymers for studying the release kinetics. The matrix containing binary polymers of pectin and HPMC exhibited the zero order release kinetics. It involved the predictable swelling/erosion and final polymer chain desegregation and dissolution that were regulated by the gelling characteristics of polymers in the formulations (Kim and Fassihi, 1996).

2. Dissolution characteristics evaluation

Several methods have been proposed for the comparison of dissolution profiles, such as a multivariate analysis of variance method to test for the difference between two dissolution profiles (Shah et al., 1997). The difference factor and similarity factor were applied as screening and optimization tool during development of controlled release preparations (Pillay and Fassihi., 1998; Shah et al., 1998 and Peh and Wong, 2000). Furthermore, the recommended method for dissolution profile comparison in FDA Guidance for industry is the difference factor (f_1) and similarity factor (f_2). Difference factor is a function of the average absolute difference between two dissolution curves that lower than 15. Similarity factor is a measure of the similarity in the percent dissolution between two curve. The FDA accepts the sameness of the dissolution profiles between two drug products as when f_1 is between 0 and 15, and f_2 is between 50 and 100. The f_1 and f_2 values were obtained from equation as follows:

$$f_1 = \left\{ \sum_{t=1}^{n} \left| R_t - T_t \right| \Big/ \sum_{t=1}^{n} R_t \right\} \times 100$$

$$f_2 = 50 \times \log \left\{ \left(1 + 1/n \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

where R_t and T_t = the average percentage of drug dissolved measured at the i th time point of the reference and test preparations, respectively.

n = the number of time points tested.

In this study, the difference factor and similarity factor were used to selected the formulations.

3. Diltiazem hydrochloride

Physicochemical properties

Chemical name	: (2S-cis)-3-(acetyloxy-5-[2-dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothia-zepin-4(5H)-one monohydrochloride
Molecular formula	: $C_{22}H_{26}N_2O_4S$. HCl
Molecular weight	: 450.98
Appearance	: white to off-white crystalline powder with bitter taste
Stability	: Diltiazem hydrochloride is highly stable in solid state
Solubility	: Diltiazem hydrochloride is freely soluble in water, methanol, chloroform and insoluble in ether

Pharmacological and Pharmacokinetic Properties (Kirsten, 1998)

Diltiazem hydrochloride is a calcium channel blocker. It is used for treatment of angina pectoris and hypertension. It's chemical structure is shown in Figure 3.

Diltiazem hydrochloride is absorbed after oral dosing in human. It has been reported to be 80% protein bound. It is lipophilic and has a large volume of distribution (3-8 L/Kg). Many researchers studied pharmacokinetic parameters of diltiazem hydrochloride in animal and human (Homsy et al, 1995, Tsui et al, 1997, and Yeung et al, 1998). It was found that diltiazem hydrochloride rapidly underwent first pass metabolism mainly via cytochrome P-450 and less than 4% of an oral dose was excreted unchanged in urine. This results in low bioavailability (35-40%). Patients had to take the drug 3-4 times/day.

Thus, hydrophilic matrix is one of the modified release formulations that can reduce frequency of administration of diltiazem hydrochloride.

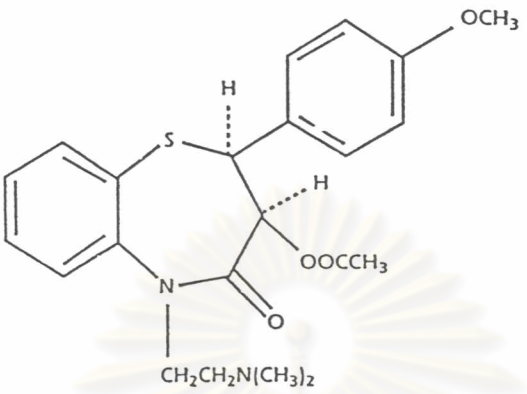

Figure 3. Chemical structure of diltiazem hydrochloride

4. Study of controlled release products

Bioequivalence is a relative term which indicates that the drug substance from two or more pharmaceutically equivalents or pharmaceutical alternatives reach the systemic circulation at the same relative rates and to the same relative extents (Abdou, 1989).

Two pharmacokinetic parameters are used to assess bioequivalence, the area under the plasma concentration-time curve (AUC_0^{∞}) and the peak plasma concentration (C_{max}). They were applied to determine the extent and rate of absorption, respectively.

Several studies were reported about the bioavailability testing of diltiazem hydrochloride sustained release in various types of subjects such as human, rabbit or dog (Murata and Noda, 1992; Bialer et al.,1995; Homsy et al,1995; and Scheiwe et al, 1996). It was concluded that the rabbit is one of the suitable animal model for investigating the kinetics and metabolism of diltiazem hydrochloride (Yeung et al, 1991).