CHAPTER I

INTRODUCTION

Presently, various types of peroral modified release formulations have been developed and can be devided into delayed release and extended release depending on the properties of drugs. These were designed to deliver the drugs at a controlled rate to improve patient compliance, reduce frequency of taking medicines as well as side effects.

Many researchers reported about modified release dosage forms of diltiazem hydrochloride. Delayed release product such as diltiazem-(o-carboxymethyl-o-ethyl-β-cyclodextrin) (diltiazem-CME-β-CyD) complex was developed. Release rate of the drug was suppressed at low pH, while increased with increase in pH. It was due to the higher solubility of CME-β-CyD at higher pH regions (Uekama et al, 1992). Another report was the system consisted of a core containing a drug and an outer shell of hydroxyethylcellulose (HEC) which was formed as gel matrix. In this system, water penetrated through matrix to dissolve the drug and rapidly released through the outer gel layer. Consequently, the delayed release product using HEC was considered to be applicable to the time related systems which need time controlled delivery in the gastrointestinal tract (Matsua et al, 1996).

In the case of extended release dosage form, for example, controlled release diltiazem HCl microparticle using cross-linked poly(vinyl alcohol) (PVA) was reported. Cross-linking of PVA was found to give a denser network where the drug was tightly held in the hydrogel network. If the density of cross-linking network increase, a decrease in the free hydrogel group of polymer will occur. So, it was able to retard drug release (Shah et al, 1997). Other systems, for instance, there were systems which consisted of two or three-layer tablets. The outer layers were drug-free modulating barrier while the active ingredient was contained in the core. All layers contained a hydrophilic polymer. In this system, the researchers used polyethylene oxides (PEOs) and hydroxypropyl-

methyl cellulose (HPMC) for evaluating the influence of polymer type and viscosity grade. HPMC appeared to be more efficient than PEOs in reducing the delivery rate of soluble drug such as diltiazem hydrochloride. The active core and barrier layer gave apparently stronger control of drug release kinetics (Maggi et al, 2000). Additionally, a study revealed that using mixed polymer (HPMC and xanthan gum (XG)) could reduce burst effect of theophylline, a slightly soluble drug (Parinda, 2000). Nevertheless, such techniques have not applied to water soluble drug . Therefore, polymeric matrices containing diltiazem hydrochloride (a soluble drug) prepared using HPMC and XG in association with either soluble filler (lactose) or insoluble filler (dibasic calcium phosphate) were formulated in this study. The resultant products were evaluated for their controlled release properties both *in vitro* and *in vivo*.

Objectives of the Study

The objectives of this study were to :

1. Study the effect of HPMC and XG for controlling the delivery of diltiazem hydrochloride in rabbits.
2. Evaluate *in vitro* diltiazem hydrochloride release using HPMC and XG as rate-controlling polymers.
3. Evaluate *in vitro* diltiazem hydrochloride release using lactose and/or dibasic calcium phosphate as fillers.