FACTORS AFFECTING THE RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM HYDROXYPROPYL METHYLCELLULOSE MATRIX SYSTEM FILLED IN CAPSULE AS SINGLE-UNIT AND MULTIPLE-UNIT

By

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ปัจจัยที่มีผลต่อการปลดปล่อยโปรโปรปราโนลอลไฮโดรคลอไรด์จากระบบเมทริกซ์ที่ใช้เฟอร์โรคิฟิล
เมทิลเซลลูโลสน์สารกอเมทริกซ์บรรจุในแคปซูลในลักษณะที่เป็นยาหน่วยเดียวและชนิดหลากหลาย

โดย
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สาขาวิชาเทคโนโลยีเภสัชกรรม ค้ากําเนิด: เกษษฐ/ โปรดปรานโโลกไคลโอได/ ไตรศังค์โพลิศิคมแอลกอฮอล/ แมทริกซ์

วรรณไววิ ครูสิริพงษ์: ปัจจัยที่มีผลต่อการปลดปล่อยยาโปรดปานโโลกไ clitโอไคลโอไดไตรศังค์โพลิศิคมแอลกอฮอลเป็นสารก่อมเวริคซ์บรรจุในแก๊ปชูในลักษณะที่เป็นยาหน่วยเดียวและเคยดัดแปลง

วรรณวิไล ดรุณไกรศร: ปัจจัยที่มีผลต่อการปลดปล่อยยาโปรปราโนลอลไฮโดรคลอไรด์จากระบบแมทริกซ์ที่ใช้ไตรศังค์โพลิศิคมแอลกอฮอลเป็นสารก่อมเวริคซ์บรรจุในแก๊ปชูในลักษณะที่เป็นยาหน่วยเดียวและเคยดัดแปลง

อาจารย์ผู้ควบคุมวิทยานิพนธ์: ฯ ค. อรทัยชัย แพชมัด 145 หน้า.

การใช้ไตรศังค์โพลิศิคมแอลกอฮอลเป็นสารก่อมเวริคซ์ในการเตรียมยาโปรปราโนลอลไฮโดรคลอไรด์ ได้รับการยอมรับจากกู้ษาในข้อเป็นการศึกษาในลักษณะที่เป็นยาหน่วยเดียวและเคยดัดแปลง

การปลดปล่อยยาurent ที่ใช้ไตรศังค์โพลิศิคมแอลกอฮอลเป็นสารก่อมเวริคซ์สามารถทําให้ยาปลดปล่อยได้ช้าจากแคปซูลที่มีความหนืดต่างกันของไฮดรอกซีโพปิลเมทิลเซลลูโลส และการเปลี่ยนจากแลคโตสเป็นไดเบสิคแคลเซียมฟอสเฟตไม่ได้ impact อย่างมาก

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The utilization of hydroxypropyl methylcellulose (HPMC) as matrix former in propranolol HCl matrix system filled in hard capsules was able to extend the release time of propranolol HCl from the capsules. The viscosity grades of HPMC and the change from lactose to dibasic calcium phosphate had no significant effect on the drug release from matrices in capsules. The propranolol HCl release from HPMC matrices depended on the types and amounts of polymer blends. The incorporation of sodium bicarbonate in the concentration of 40% into HPMC matrix could prolong drug release. The propranolol HCl matrix was also prepared as granule by wet granulation technique and filled in capsule as multiparticulate dosage form. The type of granulating liquid and components in formulation influenced on the granule properties. The utilization of isopropyl alcohol as granulating liquid and subsequently adding with water was a suitable system for agglomeration of powders. The amount of water was determined as an important factor in preparing the granule due to the hydrophilicity of HPMC. Most of dissolution profiles of propranolol HCl were fast release from matrix granules filled into capsule. Preparation of matrix granule by mixing propranolol HCl dispersed in melted phytowax with HPMC and xanthan gum and subsequently wetting with the granulating liquid could provide slower drug release. The mechanism of the drug release was found to be matrix diffusion control. The release of propranolol HCl from HPMC matrix in capsule was faster in water comparing to those in the other dissolution medium. The pH of dissolution medium did not affect the release of propranolol HCl from matrix granules filled into capsule. The paddle rotation speed influenced the release of propranolol HCl from both the matrix powder and the matrix granules filled into capsule.
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<tr>
<td>ºC</td>
<td>degree Celsius</td>
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<tr>
<td>cd</td>
<td>coefficient of determination</td>
</tr>
<tr>
<td>et al.</td>
<td>and others</td>
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<tr>
<td>e.g.</td>
<td>exempli gratia</td>
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<tr>
<td>g</td>
<td>gram</td>
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<tr>
<td>HPMC</td>
<td>hydroxypropyl methylcellulose</td>
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<tr>
<td>HCl</td>
<td>hydrochloride</td>
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<tr>
<td>i.e.</td>
<td>idest</td>
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<tr>
<td>IPA</td>
<td>isopropyl alcohol</td>
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<tr>
<td>mg</td>
<td>milligram</td>
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<td>ml</td>
<td>milliliter</td>
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<tr>
<td>msc</td>
<td>model selection criterion</td>
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<tr>
<td>No.</td>
<td>number</td>
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<tr>
<td>rpm</td>
<td>round per minute</td>
</tr>
<tr>
<td>S.D.</td>
<td>standard deviation</td>
</tr>
<tr>
<td>PVP</td>
<td>polyvinyl pyrrolidone</td>
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<tr>
<td>%CV</td>
<td>percent coefficient of variation</td>
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<tr>
<td>%v/v</td>
<td>percent volume by volume</td>
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<tr>
<td>%w/v</td>
<td>percent weight by volume</td>
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<tr>
<td>µg</td>
<td>microgram</td>
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<td>µm</td>
<td>micrometer</td>
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CHAPTER I
INTRODUCTION

The oral controlled release dosage forms are able to improve the patient compliance due to a reduced dosing frequency. Furthermore, these systems might provide a decreased incidence or intensity of the side effect, prolonged therapeutic effect, as well as an increase of cost effectiveness. Controlled-release solid dosage form systems are available either as single-unit (nondivided formulation) or as multiple-unit (divided formulation) forms. The single-unit dosage forms usually refer to diffusion-controlled systems where the drug is dissolved or dispersed throughout a solid matrix and the release of drug is controlled or sustained either by incorporating suitable filler within the matrix or by coating the matrix with swellable or nonswellable polymer film (Efentakis et al., 2000). Capsules can also be used as single-unit controlled-release delivery systems in case of the suitable excipients are used (Ojantakanen, 1992; Efentakis and Vlachou, 2000). Multiple-unit dosage forms usually are based on subunits such as granules, pellets and minitablets or microparticles (microcapsules or microsphere). Multiparticulates can be filled into capsule, after the capsules dissolved, multiparticulate will be widely dispersed throughout the gastrointestinal tract. The advantages of multiple-unit dosage forms offer over the single-unit systems are less absorption variability and a lesser risk of dose dumping. The dispersion of multiparticulates also reduces the risk of local irritation of gastric mucosa (Kramer and Blume, 1994). On the other hand, multiple-unit preparations exhibit several disadvantages. Their manufacturing is more complicated and more expensive, the filling into gelatin capsules is difficult to accomplish especially in the case of the different subunits are involved in the filling
process. The pellets are one kind of matrix type dosage forms used to achieve sustained release.

The pellets are wildly used as sustained release dosage form but the pellets production has many drawbacks, which gives undesirable pellet for sustained release dosage form such as broad size distribution, the irregularity of shape and/or surface structure (Rey et al., 2000). Additionally, the solvent in this process affects the porous structure of the products. The pellets with undesirable characteristics are not suitable for producing the effective sustained release dosage form. These disadvantage properties could be overcomed by the microtablets (Pich et al., 1989; Ney et al., 1991). However, the preparation process of microtablets or minitablets necessitates the extra care and the fine adjustments of the tabletting machines (Celik, 1994; Foolnier and Doelker, 1992). The most awareness factor for producing the microtablets is the flowability of powder because this affects the properties of the obtained microtablets (Lennartz et al., 1998; Rey et al., 2000).

Propranolol hydrochloride (PPHCl) is a \( \beta \)-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at \( \beta \)-adrenergic receptor sites. It is widely used in therapeutics for the antihypertensive, antiangorous and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3 hours, which makes it as a suitable candidate to be delivered at a controlled rate (Kwong et al., 1988).

Hydroxypropyl methylcellulose has been employed extensively as hydrophilic matrix former in the oral controlled-release dosage forms for different drugs including propranolol HCl. Its popularity can be attributed to the non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate the high levels of drug loading (Ganga et al., 1992, Taylan et al., 1996 and Chattaraj and Das, 1996).
Although the single-unit matrices of propranolol HCl sustained release tablets are widely developed in order to reduce the frequency of dosing and to produce steady pharmacological effects. There were not the developments of this drug into single matrix or granule containing HPMC and filled into capsules. The purpose of this study was to develop a new dosage form that overcomes the biological and technological problems. Propranolol HCl sustained release capsules (single-unit) using HPMC as matrix former was prepared. In addition, the development of multiple-unit sustained release dosage form as matrix granules filled into capsule using wet granulation technique was also performed since there are rarely reports on the preparation of propranolol HCl matrix granules. Therefore, the aim of this study was to study factors affecting the release of propranolol HCl from HPMC matrix system filled in capsule as single-unit and multiple-unit

The objective of this study was to:

1. Investigate the effects of type and amount of soluble and insoluble fillers, sodium bicarbonate and polymers on the release of propranolol HCl from HPMC matrix filled in capsule
2. Develop the multiple-unit sustained release dosage form by formulating propranolol HCl matrix granules containing HPMC by wet granulation method
3. Investigate the effects of pH of dissolution medium and rotation speed on the drug release from HPMC matrix system filled in capsule both as single-unit and multiple-unit dosage form
4. Investigate the mechanism of drug release from the prepared capsules.
CHAPTER II
REVIEW OF RELATED LITERATURE

1. Capsule

The word “capsule” in the English language is derived from the Latin word “capsula” which means a small box or container. In pharmacy, capsule has been used to describe a glass ampoule (e.g. amyl nitrite capsules) and also as a name for a protective cap over the stopper of a bottle containing the medicine. In more recent times, capsule has been used primarily to describe a solid oral dosage form, which consists of a container, usually made of gelatin, filled with a medicinal substance (Jones, 2004).

Capsules have been made from gelatin since they were first patented by Mr. Mothes in Paris in 1834 as an edible container to mask the taste and odor of medicines (Jones, 2004). In more recent times the stimulus to find gelatin alternatives has come from looking for materials from non-animal sources to overcome religious and dietary restriction and to overcome the problems of gelatin associated with its high moisture content (13–16%) (Ogura et al., 1998).

HPMC is a widely acceptable cellulose derived material, has proven to be a polymer whose solution properties can be relatively simply modified so that it can be used to produce hard two-piece capsules on standard manufacturing machines. HPMC capsules have low moisture content (4–6%); they do not become brittle when exposed to low humidities; they are chemically stable and do not cross-link. Nevertheless, for HPMC capsules to be used as a replacement for gelatin ones they need to have similar solubility properties both in vitro and in vivo. Previous studies to measure the in vivo disintegration properties of HPMC capsules was used to Gamma scintigraphy (Cole et al., 2004, Honkanen et al., 2004 and Tuleu et al., 2002). There was a significant
difference in the *in vitro* and *in vivo* disintegration times of HPMC capsules made from gellan gum compared to gelatin capsules: HPMC capsules released the drug slower than gelatin capsules (Cole et al., 2004). There was the dissolution from *in vivo* study of HPMC capsules made from carrageenan containing different viscosity grades of HPMC powder in order to measure their *in vivo* performance. This prolonged release diluent governed the long disintegration time (Honkanen et al., 2004).

2. **Type of capsule controlled release systems**

2.1 **Matrix system**

Both hydrophilic and hydrophobic polymeric matrix systems are widely used to modulate controlled delivery of drug substances because of their versatility, effectiveness, and low production cost. In a matrix system, a drug can be incorporated into the polymer matrix in form of particle or molecular dispersion. The former is simply a suspension of drug particles homogeneously distributed in the polymer matrix, whereas the later is a matrix with drug molecules dissolved in the polymer. Drug release occurs by diffusion and/or erosion of the matrix system. The type of matrix system can be divided into hydrophilic and hydrophobic matrix systems.

2.1.1 **Hydrophilic matrix system**

When hydrophilic polymer contacts with a liquid, a gel layer is formed, which essential for sustaining and controlling drug release. The thickness of this hydrate layer determines the diffusion of the drug molecules through the polymer mass into the liquid medium. Commonly available hydrophilic polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide) and crosslinked homopolymers and copolymers of acrylic acid.
Hydroxypropyl methylcellulose is a nonionic water-soluble cellulose ether made by Dow Chemical under the brand name Methocel. Methocel is available in four different chemistries (E, F, J and K series) based on varying degrees of hydroxypropyl and methyl substitution. The specially produced Methocels with ultrafine particle size for controlled release formulations include K100LV, K4M, K15M, K100M, E4M and E10M. When these products dissolved at a concentration of 2% in water, the viscosity ranges from 100 to 100,000 cps.

Both HPC and HEC are also nonionic water-soluble cellulose ethers made by the Aqualon division of Hercules Inc. under the brand names Klucel and Natrosol, respectively. For controlled release application, they are available in high- and low-viscosity grades, such as Klucel HXF, EXF and Natrosol 250HX.

Xanthan gum is a water-soluble polysaccharide gum produced by the Kelco division of Monsanto Co. under the brand name of Keltrol. It is composed of D-glucosyl, D-mannosyl and D-glucosyluronic acid residues and differing proportions of O-acetyl and pyruvic acid acetal. The primary structure consists of a cellulose backbone with trisaccharide side chains.

Sodium alginate is a water-soluble gelling polysaccharide also made by Kelco under the brand name Keltone. Keltone HVCR and LVCR are forms that are used in controlled release products.

Poly (ethylene oxide) polymer is a nonionic water-soluble resins made by Union Carbide under the brand name of Polyox. Its common structure is \(-\text{OCH}_2\text{CH}_2\)_n-\text{OH}\). For controlled release application it is available in a variety of viscosity grades.

Crosslinked homopolymers and copolymers of acrylic acid are water-swellable, but insoluble, resins made by the B.F. Goodrich Company under the brand name Carbopol. Carbopol 971P NF, 974P and 934P NF are specifically designed for preparing hydrogel controlled release systems.
Highly substituted galactomannan and xanthan were used as the hydrophilic matrix systems to control the release of diclofenac sodium from tablets and capsules. The drug release from these developed systems were compared to commercial product (tablet containing hydroxypropyl methylcellulose (HPMC)). All formulations containing galactomannan and xanthan exhibited more prolongation of a drug release than that of a commercial product. But the release profiles of the capsule were closer to that of the commercial product than that of the tablets. Accordingly, the capsules showed a higher swelling with a strong degree of water uptake in comparison to the tablets. However, the capsule showed a faster rate of drug release compared to the tablets. The increasing amount of a drug led to a decrease in the drug release in both capsules and tablets. This indicated that the matrix containing a lower proportion of gum decreased the ability of the matrix to absorb the water (Ughini and Andreazza, 2004).

2.1.2 Hydrophobic matrix system

Hydrophobic monolithic matrix systems usually used waxes and water-insoluble polymers in their formulation. Many waxes are long carbon chain wax esters, glycerides and fatty acids. Natural and synthetic waxes with having different melting points have been used as controlled release matrix materials. Insoluble polymers used in preparing controlled release matrices include fine particles of ammoniomethacrylate copolymers (Eudragit RL100, PO, RS 100, PO) produced from Rohm America, Inc., ethylcellulose (Ethocel FP7, FP10, FP100) produced from Dow Chemical Co., cellulose acetate (CA-398-10), cellulose acetate butyrate (CAB-381-20), cellulose acetate propionate (CAP-482-20) produced from Eastman Chemical Co., and latex dispersion of methacrylic ester copolymers (Eudragit NE30D).

The lipid system in the molten state can be directly filled into hard gelatin capsules for controlling the drug release. Gelucire® is a saturated
polyglycolysed glycerides. The various grades are characterized by their hydrophile-lipophile-balance (HLB) value and melting point which lead to a specific behaviour when placed in the gastrointestinal fluids in respect of hydrodispersibility, melting and floatability. A diffusion-controlled system was obtained with the Gelucire® grade 46/07, 48/09 or 62/05 containing 660 mg lithium sulfate, which all three Gelucire® grades remained inert in the aqueous environment at 37°C. On the contrary, erosion was proved to control the release of indomethacin when the dispersible Gelucire® 33/01 was added to the inert Gelucire® 46/07 (Buri et al., 1995). Djimbo et al. (1984) showed some retardation in the urinary excretion of total salicylate when administering capsules of aspirin mixed with Gelucire® 50/13.

### 2.2 Cross-linked capsule

Under specific conditions of storage (high humidity and/or elevated temperature) or exposure to formaldehyde, gelatin molecules can become cross-linking (or stressed). As a result, the formation of a rubbery translucent film around the hard gelatin capsule shell could be observed during *in vitro* dissolution test, because gelatin became partially insoluble in water. This water-insoluble gelatin thin film acted as a barrier restricting a drug release. Brown et al. (1998) investigated the *in vitro* dissolution of acetaminophen from hard gelatin capsules stressed by contact with lactose containing 20 ppm formaldehyde. These moderately stressed capsules failed the USP dissolution specification of drug dissolution when tested in water and simulated gastric fluid without enzyme but passed with an addition of pepsin. Guyot et al. (1989) studied the *in vitro* release of theophylline from the cross-linked hard gelatin capsules. They found that the amount of drug release was lowered as the cross-linking reaction time was increased. The percentage of carbamazepine dissolved was successfully reduced by increasing the degree of gelatin cross-linking. (Maechais and Cayzeele, 2003)
2.3 Asymmetric membrane capsule system

An asymmetric membrane capsule system was developed to improve an osmotic effect to control the drug liberation. The release mechanisms were investigated for drugs with both moderate to high water solubility and poor water solubility. The capsule wall membrane was produced by a phase-inversion process (Figure 1). An asymmetric membrane was formed on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymeric material which was a water insoluble polymer such as cellulose acetate, and then followed by dipping into a quenching solution.

![Figure 1](image.png)

**Figure 1** Dip-coating process manufacturing of asymmetric membrane capsules (Ende et al., 1989).

There are several important advantages of an asymmetric membrane capsule. The crucial advantage is the higher rate of water influx allowing the release of drug with lower osmotic pressure or lower solubility. A controlled drug delivery device of asymmetric membrane capsule consists of asymmetric structure (relatively thin, dense region supported in a thicker porous region). The drug release rate from asymmetric membrane capsule system was manipulated by varying the composition of
asymmetric coating. Three different amounts (5%, 10% and 20% w/v) of glycerol were incorporated in the capsule wall. The higher concentration of glycerol (more than 25% w/v) led to damage of a capsule shell and caused a burst release of drug. Furthermore, asymmetric membrane coating had a significant advantage over the membrane coating used in conventional osmotic system. Semipermeable and dense membrane coatings was necessary to control a delivery of relatively more soluble drugs, but a delivery port is needed to deliver the drug at a required rate. An aperture was drilled through the semipermeable coating for controlled delivery of drug. Rifampicin was slightly soluble from asymmetric capsule system and was released with the higher release rate. This drug was released from asymmetric capsule system that had high glycerol content with a higher amount of drug release and initial burst release because of the dissolution through many pores in the coating membrane. On the other hand, in case of dense semipermeable membrane system, the drug release rates was slower and no initial burst release was found. This might be due to the absorption of dissolution medium by a semipermeable membrane and a capsule core. Whereas, the release of isoniazid from the asymmetric membrane system was very high because of its higher solubility. Therefore, asymmetric membrane systems are suitable for rifampicin release but not for isoniazid. The dense semipermeable membrane systems could control the release of both drugs but lacked a desirable initial burst release of isoniazid. Nevertheless, asymmetric membrane systems are simpler to prepare and more cost effective since they are without aperture for drug release (Prabakaran et al., 2004). In addition, the case of poorly water-soluble drug, such as nifedipine, was unable to create enough osmotic effect to activate the drug release. Hence, a modified asymmetric system was developed by addition of solubility enhancer such as sodium lauryl sulfate or by fabricating into a solid dispersion with hydrophilic polymer such as HPMC. These techniques could increase the solubility of
nifedipine sufficient to activate drug release, which led to increasing the drug release rate (Lin and Ho, 2003).

### 2.4 Site-specific delivery capsules system

Site-specific targeting of drug to the colon has been conducted by several different approaches i.e. pH-control, time-control, pressure-control, prodrug and colon-specific polymer. There was an attempt to utilize chitosan powder for colon-specific drug delivery system by dispersing chitosan powder in aminooalkyl methacrylate copolymer RS (Eudragit® RS) (Norithito et al., 2002). These chitosan dispersed systems could control the drug release as time-dependent and site-specific. The capsules containing an active ingredient were coated with the chitosan dispersed system (Figure 2). The release rate could be controlled by changing the thickness of coated layer. Furthermore, for colon-specific drug delivery an additional outer enteric coating was necessary to prevent the drug release in the stomach since chitosan dispersed in the layer could dissolve easily under acidic condition. Resultant enteric-coated chitosan dispersed system capsules reached the large intestine within 1-3 hours after oral administration and they were degraded in the colon (Shimono et al, 2002).

**Figure 2**  Fundamental structure of chitosan dispersed system capsules (Shimono et al., 2002).
2.5 Hydrophilic plug in capsule

Pulsatile drug delivery system was developed using hard gelatin capsules, which had a water insoluble capsule body containing a water soluble drug, diltiazem HCl, and hydrophilic plug (HPMC or guar gum). The body portion of the hard gelatin capsules was cross-linked by the combined effect of formaldehyde and heat treatment. Hence, the drug could be released from a limited surface area of open end of the hard gelatin capsule body. This formulation was similar to the Pulsincap™ system (Figure 3) that consisted of the insoluble capsule body (Gothoskar et al., 2001). After oral administration, the water soluble capsule cap dissolved in the gastric juices and the hydrogel plug swelled. At a controlled time after the ingestion, the swollen plug was subsequently ejected from the dosage form. The formulation factors affecting the drug release were the type of plug (powder or tablet), the plug thickness and the fill material. Immediate drug release, after a lag time of 4 hours obtained if the plug was pushed off by the CO₂ gas generated by interaction of NaHCO₃ and citric acid. On the other hand, the slow drug release was observed from the swollen unejected plug. Moreover, type of swellable hyprophilic agent (HPMC or guar gum) and molecular weight of HPMC affected to the drug release (Mukesh and Sumitra, 2001).
2.6 Multiparticulate filled into capsule

Multiparticulate dosage form such as matrix or coated pellets and granules, microtablets or microparticles (microcapsules or microsphere) have gained interests in oral sustained release formulations. Multiparticulates can be filled into capsule, thereafter the capsules dissolved, multiparticulate will be widely dispersed throughout the gastrointestinal tract (Kramer and Blume, 1994). The main advantage of a multiparticulate dosage form relating to its \textit{in vivo} behaviour because the subunits spread into the gastrointestinal tract as soon as the hard gelatin capsule or the tablet disintegrates. Hence, drug release occurs over a large area avoiding high local drug concentrations. In addition, less inter- and intra-subject variability can be expected as well as a decreased risk of dose dumping (Remon et al., 2003).

Saettone et al. (1995) prepared sustained release timolol maleate microtablets by direct compression and coated with Eudragit RS and Eudragit RL. They observed that an adequate control of drug release from this microtablet could be obtained by adjusting the amount of acrylic polymer coating.
Kedziewicz et al. (1998) prepared gellan gum bead of propranolol HCl by solubilising the drug in a dispersion of gellan gum and dropping the dispersion into calcium chloride solution.

Cox et al. (1999) prepared mini-matrix tablets containing S(+) ibuprofen by the wet granulation method. The hydrophilic matrix was formed with either xanthan gum, karaya gum or HPMC together with a choice of additives from lactose, Emcompress®, Avicel® PH101, talcum and Lubritab®.

Brabander et al. (2003) developed ibuprofen sustained release mini-matrices (multiple-unit dosage form) by means of hot-melt extrusion using ethyl cellulose as sustained release agent. Drug release from the mini-matrices was mainly diffusion controlled and swelling played an important role to obtain the complete drug release within 24 hours.

Merwe et al. (2003) developed the minitablets and granule formulations for the delivery of peptide drugs with the absorption enhancer N-trimethyl chitosan chloride (TMC). The optimized minitablet formulation consisted of two types of granules, namely desmopressin (1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (DDAVP) and TMC granules. DDAVP granules containing tetraglycerol pentastearate were specifically aimed at delaying the release of the peptide from dosage form. Burst release of TMC was attempted with TMC granules. Release profiles for both the optimized minitablet formulation as well as the granule formulation showed that the release of DDAVP was effectively delayed from the formulation compared to the formulation where no attempt at delaying the release was made. TMC was released and at a faster rate from the granule formulation than the optimized minitablet formulation. Both the optimized minitablet formulation and the granule formulation show suitable release profiles for the delivery of peptide drugs with TMC as absorption enhancer in solid oral dosage forms.
The application of saturated polyglycolysed glyceride (Gelucire® 50/02) and glycerol palmitostearate (Precirol® ATO5) as drug release regulators for propranolol HCl pellets was investigated by Sinchaipanid et al. (2004).

The swelling polymer incorporation layer systems, referred to as SPILA system, consist of core granules coated with a mixture of carboxyvinyl polymer (CP), water-insoluble polymer and water-soluble polymer (WP). This system was studied by Nakamura et al. (2006). Release profiles of metoprolol tartrate from SPILA system were pH dependent, drug release was slower in the medium of pH 1.2 than in the medium of pH 6.8 due to a coating layer with pH-dependent swelling polymer.

3. **Hydroxypropyl methylecellulose (HPMC)**

Hydroxypropyl methylecellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. HPMC offers the advantages of being non-toxic and relatively inexpensive; it can be compressed directly into matrices and is available in different chemical substitution and hydration rates and viscosity grades (Rekhi et al., 1999; Mitchell et al., 1993; Taylan et al., 1996 and Chattaraj and Das, 1996). One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion. Then, the incorporated drug diffuses out of the system (Brannon-Peppas, 1990).
3.1 Physicochemical characterization of HPMC

HPMC is a propylene glycol ether of methylcellulose; its chemical structure is illustrated in Figure 4. The substituent R represents either a $\text{CH}_3$, or a $\text{CH}_2\text{CH}($$\text{CH}_3$$)$OH group, or a hydrogen atom. The physicochemical properties of this polymer are strongly affected by: (i) the methoxy group content; (ii) the hydroxypropoxy group content; and (iii) the molecular weight. The USP distinguishes four different types of HPMC, classified according to their relative $-\text{OCH}_3$ and $-\text{OCH}_2\text{CH}($$\text{CH}_3$$)$OH content: HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy-groups, the last two numbers the percentage of hydroxypropoxy-groups, determined after drying at 105°C for 2 hours. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 1 (Siepmann and Peppas, 2001).
Table 1  USP specifications for different types of HPMC, classified according to their degree of methoxy- and hydroxypropoxy-substitution (Siepmann and Peppas, 2001).

<table>
<thead>
<tr>
<th>Substitution type</th>
<th>Methoxy (%)</th>
<th>Hydroxypropoxy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min.</td>
<td>Max.</td>
</tr>
<tr>
<td>1828</td>
<td>16.5</td>
<td>20.0</td>
</tr>
<tr>
<td>2208</td>
<td>19.0</td>
<td>24.0</td>
</tr>
<tr>
<td>2906</td>
<td>27.0</td>
<td>30.0</td>
</tr>
<tr>
<td>2910</td>
<td>28.0</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Interestingly, Dahl et al. (1990) reported broad variations concerning important characteristics of seven batches HPMC 2208 with a labeled viscosity of 15,000 mPa s, provided by two different manufacturers. All samples had similar viscosities, except one batch which was outside the USP specifications. The methoxy-group content was uniformly high and three batches fell outside the USP limits of 19.0 to 24.0%. The hydroxypropoxy-group content (although within the USP specifications of 4.0 to 12.0%) varied relatively more than the methoxy group content. These variations led to significant differences concerning the resulting release rate of naproxen from compressed matrix tablets in vitro (Dahl et al., 1990).

3.2  Physicochemical properties of HPMC

3.2.1  Melting point: browns at 190-200°C; chars at 225-230°C. Glass transition temperature is 170-180°C.

3.2.2  Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of water and alcohol. Certain
grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

3.2.3 Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although HPMC may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous HPMC solutions. Solutions prepared using organic solvents tend to be more viscous.

Herder et al. (2006) investigated the water granulation mechanism of the hydrophilic matrix polymer HPMC in a high shear mixer and to relate the properties of the granules and tablets to the molecular weight and the degree of substitution for eight HPMC grades. Although the hydrophilic matrix system is a well known drug delivery one, there is a difficulty in that the desirable water granulation technique often causes problems in the presence of relatively large amounts of HPMC due to its hydrophilicity. Wet granulation techniques that require the organic solvent or a mixture of organic solvent and water are undesirable for environmental and health care reasons, whereas the use of pure water as the granulation liquid for hydrophilic matrix compositions may give lump formation (Shah et al., 1996). On the other hand, Timmins et al. (1992) have pointed out that water can be used as the granulation liquid for hydrophilic based matrix tablets.

3.3 Factors influencing the release drug from HPMC matrix system

3.3.1 Type and amount of HPMC

Increasing the HPMC concentration from 10 to 40% (w/w) could decrease the ibuprofen release, probably because of the formation of a denser gel and slower erosion at the higher HPMC-content (Krogel and Bodmeier, 1999). Nerurkar et al. (2005) found that the increasing the concentration of the gelling
polymer such as Gelcarin or HPMC in the matrix led to slower drug release.

Different viscosity grades of HPMC (K100, K4M and K15M) powders were utilized as diluents for ibuprofen sustained-release from HPMC capsules and gelatin capsules. The dissolution rate of drug from HPMC capsules was little lesser than gelatin capsules. The molecular weight of HPMC powder had a crucial influence on the drug release. However, an increasing the molecular weight of HPMC powder from K4M grade to K15M grade had no effect on the dissolution rate of drug from both gelatine and HPMC capsules (Honkanen et al., 2002).

### 3.3.2 Type and amount of various fillers

It has been reported that the use of insoluble excipients such as dicalcium phosphate dihydrate in matrix tablets containing insoluble drug, alprazolam, and 40% HPMC K4M decreased the rate and extent of drug release compared with the same matrix containing soluble excipients like lactose (Williams et al., 2002). Tiwari et al. (2003) incorporated ethylcellulose in HPMC matrix and that matrix could release the drug up to 14 hours. It is also reported that non-ionic polymer did not alter drug release signigicantly. However, ionic polymers were capable of retarding the release of oppositely charged molecules, but the effect was found to be small (Feely and Davis, 1988).

The different concentrations of surfactants were incorporated into HPMC-Eudragit matrices. The release rate of propranolol HCl decreased as the concentration of sodium lauryl sulphate (SLS) increased since SLS is able to form complex with propranolol HCl. In contrast Tween 65 caused an increase in the release rate of the drug. The enhancement of the ratio of cetyl trimethyl ammonium bromide (CTAB): SLS increased the release rate of propranolol HCl from matrices. This indicated that CTAB was able to interact with SLS molecules (Nokhodchi et al., 2002).
The retarding effect of ionic surfactants was owing to a drug-surfactant ionic interaction (Feely and Davis, 1988).

Pillay and Fassihi (1999) demonstrated the effectiveness of modulating matrix swelling (HPMC or poly(ethylene oxide)) through inclusion of appropriate electrolyte for achieving steady-state drug release kinetics. One of the most desirable features of this approach is the ability to demonstrate zero-order release for a 100% water-soluble drug over as extended period of time in a pH-independent manner. Through matrix textural profiling the process of matrix stiffening via electrolyte interaction was accomplished with pronounced stiffening and densification in the case of sodium carbonate-pentasodium tripolyphosphate combination.

### 3.3.3 Type of drug

The solubility of the drug influenced the release from HPMC matrix tablets. With the higher viscosity grades, Methocel® E4M and K15M, the water-soluble drug, chlorpheniramine maleate (CPM), was released faster than the less soluble ibuprofen. The freely soluble CPM was able to diffuse through the gelled layer of the tablets, while the slightly soluble ibuprofen was only partly dissolved in the penetrating buffer and was primarily released by the gradual erosion of the HPMC matrix (Krogel and Bodmeier, 1999). The release of soluble drugs from HPMC tablets is controlled by the rate of diffusion through such a gel but in case of poorly water-soluble drugs by a combination of diffusion and gel erosion (Mitchell et al., 1993; Katzhenler et al., 1997 and Gao et al., 1995).

### 3.3.4 Effect of pH of dissolution medium

The dissolution rates of levodopa were tested at 60 rpm in phosphate buffers at pH values of 1.5, 3.0 and 6.5. These pH values were selected to simulate gastric pH in fasted and fed conditions and duodenal pH, respectively. At
each of three pH values, a sustained release of levodopa occurred immediately after immersion, with no burst effect. Even through the release of the drug was faster at pH 1.5, all dissolution profiles were statistically similar. It seems that the dissolution rate depends more on the prolonged-release ability of Methocel® K15M than on the pH-dependent solubility of the drug (Goole et al., 2007). Takka et al. (2001) observed that propranolol hydrochloride gave pH dependent release from HPMC-based matrix formulations due to its pH-dependent solubility.

3.3.5 The agitation rate of the release medium

The rotation speed (50-150 rpm) only slightly affected the drug release from HPMC E4M-based matrix tablets (Krogel and Bodmeier, 1999). Normally, agitation speed effects are seen with gellable/erodible systems, with the release increasing with increasing rotation speed (Abrahamsson et al., 1998). Goole et al. (2007) reported that the release rate of the drug increased as the stirring rate increased but there was no burst effect and no disintegration of the minitablets composed of HPMC K15M.

4. Propranolol hydrochloride (PPHCl)

![Chemical structure of propranolol hydrochloride (C₁₆H₂₁NO₂, HCl)](image)

Propranolol hydrochloride (PPHCl) is a β-adrenergic blocking agent, a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. Propranolol HCl appears as white or almost white powder, odourless and a bitter taste.
Melting point is 163°C to 166°C. The pH of 1% solution of propranolol HCl in water lies between 5.0 and 6.0. The pKa is 9.5. Propranolol HCl is soluble 1 in 20 of water and 1 in 20 of ethanol; slightly soluble in chloroform and practically insoluble in ether. It shows a pH-dependent solubility in the pH range of the gastrointestinal tract. The solubility is found to be 225 mg/ml at pH 1.2, 130 mg/ml at pH 6.8, and 360 mg/ml in water (Takka et al., 2001).

It is widely used in therapeutics for its antihypertensive, antiangorous and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3 hours, which makes it a suitable candidate to be delivered at a controlled rate (Kwong et al., 1988).

5. **The release pattern of matrix system**

The pattern of delivery achieved by a sustained release system can vary over a wide range but release profiles can be mainly categorized into three type:

1. Zero-order release model
2. Square-root-time release model
3. First order release model

5.1 **Zero-order release model**

An ideal controlled release device is one which can delivery the drug at constant rate until the device is exhausted of active agent. Mathematically, the release rate from this device is given as:

\[
\frac{dM}{dt} = k
\]

Where \( k \) is a constant, \( t \) is a time and \( M_t \) is the mass of active agent released. This model of release is called zero-order release model.
5.2 Square-root time release model (Higuchi’s model)

The second common release model is frequently referred to as square-root-of-time or \( t^{1/2} \) release, providing compound release that is linear with the reciprocal of the square root of time. The release rate is then given as:

\[
\frac{dM}{dt} = \frac{k}{\sqrt{t}} \tag{2}
\]

In contrast to first-order release, the release rate here remained finite as the device approached exhaustion.

The release model of this type can be described by Higuchi’s equation (Higuchi, 1963)

\[
Q = [D\varepsilon\tau(2A-\varepsilon C_s) C_st]^{1/2} \tag{3}
\]

Where \( Q \) is weight in grams of drug release per unit surface area, \( D \) is diffusion coefficient of drug in the release medium, \( \varepsilon \) is porosity of the matrix, \( \tau \) is tortuosity of matrix, \( C_s \) is solubility of drug in the release medium and \( A \) is concentration of drug in the tablet, expressed as g/ml.

The assumptions made deriving equation are as follows:

1. A pseudo-steady state is maintained during release
2. \( A \gg C_s \), i.e. excess solute is present
3. The system is in perfectly sink condition in which \( C_s \) is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix
5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs
In general Higuchi’s equation is usually desired and used as:

\[ Q = k_h t^{1/2} \]  \[4\]

Where \( k_h \) = higuchi’s constant

Therefore the plot of amount of drug released from matrix versus square root of time should be increased linearity if drug release from the matrix is diffusion controlled. Although the above equation is based on release from a single face, it may use to describe diffusion-controlled release from all surface matrices.

In order to further verify that the release follows Higuchi’s model, Higuchi’s equation is converted into logarithmic form as:

\[ \log Q = \log k_h + 0.5\log t \] \[5\]

The plot of \( \log Q \) versus \( \log t \) must not only yield a straight line, but must have a slope of 0.5.

5.3 First-order release model

The first-order release model is the third common type of the release model. The release rate in this case is proportional to the mass of active agent contained within the device. The rate is then given as:

\[ \frac{dM_i}{dt} = k(M_0 - M_i) \] \[6\]

Where \( M_0 \) is the mass of agent on the device at \( t = 0 \). On rearrangement, this given

\[ \frac{dM_i}{dt} = kM_i e^{-kt} \] \[7\]

In first-order model, therefore, the rate declines exponentially with time, approaching a release rate of zero as the device approaches exhaustion.

On the assumption that the exposed surface area of matrix decreases exponential of time, Wagner (1969) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics, thus:
\[ A_t = A_0 e^{-k_1 t} \] \[ 8 \]

Where \( k_1 \) is first order release constant, \( A_0 \) is initial amount of drug and \( A_t \) is amount of drug remaining in the matrix at time \( t \)

Simplifying and taking the logarithm of equation 8 yields

\[ \log A_t = \log A_0 - k_1 t \] \[ 9 \]

2.303

First order model can be predicted by plotting the logarithm of the percentage of drug remaining against time. If the drug release pattern follows first order model, linear relationship is obtained. Since both the square root of time release and first-order release plots are linear, as indicated by correlation coefficient, it is necessary to distinguish between the models. The treatment has been based upon using the differential forms of the first order and square root of time equations (Schwartz et al., 1968)

For Higuchi’s model, the rate will be inversely proportional to the total amount of drug release in accordance with equation (Sa et al., 1990)

\[ \frac{dQ}{dt} = \frac{k_0^2 S^2}{2Q'} \] \[ 10 \]

Where \( Q' = QS \) (S is the surface area of matrix). The rate predicted by first-order model was given by:

\[ \frac{dQ}{dt} = kA_0 - kQ \] \[ 11 \]

Where \( A = A_0 - Q' \). This indicated rate will be proportional to \( Q' \). The rates of release are determined by measuring the slopes at different points on the percentage of drug release versus times curves.
The plots of rates of release versus $1/Q'$ are linear, indicating that the release is fitted with Higuchi model. If the plots of rates of release versus $Q'$ are linear, indicating that first order model is operative.

The release model for each classes of device is illustrated in Figure 6. The release models of zero-order, square-root time and first-order are depicted, respectively (equation 1, 2 and 6).

![Figure 6](image)

**Figure 6** Zero-order, first-order and square-root time release patterns from devices containing the same initial active agent content (Koontz, 2006).

Baveja et al. (1987) used blends of HPMC and sodium carboxymethylcellulose (NaCMC) to achieve a zero-order release of propranolol. Dabbagh et al. (1999) reported that the use of HPMC or NaCMC alone could not provide a zero-order release of propranolol HCl and this was achieved only from matrices containing the combination of NaCMC-HPMC. Samani et al. (2003) showed that only HPMC (500
mPa.s) in high polymer/drug ratio could extend the release time up to 10 hours but the correlation coefficient does not fit to zero order kinetic. The mini-matrices containing xanthan gum and HPMC were particularly suitable with release exponents approaching zero order release over 12 hours periods in vitro, especially when using the pH change method (Cox et al., 1999).

6. Release mechanism of controlled release system

In order to analyze the mechanism of the drug from the matrices, the dissolution data may be analyzed using the semiempirical equation of Peppas (1985) given below.

\[ M_t = k t^n \]  \[12\]

Where, \( M_t \) = the fractional of release of drug up to time \( t \),

\( M_\alpha \) = the release time

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

\( n \) = the release exponent, indicative of the mechanism of drug release

Clearly, at desirable mechanism for many applications that which leads to be equals 1, this characterizes zero-order release behavior. Table 2 summarizes the general dependence of \( n \) on the diffusional mechanism (Peppas, 1985).
Table 2: Interpretation of diffusional release mechanisms from drug release data from thin polymer film.

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug transport mechanism</th>
<th>Rate as a function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>( t^{0.5} )</td>
</tr>
<tr>
<td>0.5&lt;n&lt;1.0</td>
<td>Anomalous (non-Fickian) transport</td>
<td>( t^{n-1} )</td>
</tr>
<tr>
<td>1.0</td>
<td>Case-II transport</td>
<td>Zero-order (time-independent)</td>
</tr>
<tr>
<td>n&gt;1.0</td>
<td>Super case-II transport</td>
<td>( t^{n-1} )</td>
</tr>
</tbody>
</table>

The empirical equation 12 could be modified for application to non-planar geometric. The relationship between the diffusional exponent \( n \) and the corresponding release mechanism is clearly dependent on the geometry employed as shown in Table 2, 3, and 4 (Rittger and Peppas, 1987).

In non-swellable matrices, the values of \( n \) are 0.45 and 1.0 for Fickian and case-II transport, respectively. Case-II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion. When the value of \( n \) is \( > 0.45 \) and \( < 1.0 \), the release was said to be non-Fickian (Rittger and Peppas, 1987). A value of \( n = 1 \), however, means that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry.
Table 3  Diffusional exponent and mechanisms of diffusional release from various non-swellable controlled release systems.

<table>
<thead>
<tr>
<th>Diffusional exponent, n</th>
<th>Drug release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin film</td>
<td>Cylindrical sample</td>
</tr>
<tr>
<td>0.5</td>
<td>0.45</td>
</tr>
<tr>
<td>0.5&lt;n&lt;1.0</td>
<td>0.45&lt;n&lt;1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

In swellable controlled release systems, case-II (Fickian diffusion) and case-II solute release behavior are unique in that each can be described in terms of a single parameter. Case-I transport described by diffusion coefficient, while case-II transport described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, requires two or more parameters to describe the coupling of diffusion and relaxation phenomena.

In case of swellable matrices, when the system does not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and case-II transport, respectively. When the value of n is > 0.45 and < 0.89, the release was said to be non-Fickian (Rittger and Peppas, 1987). When the value of n was greater than that of the case-II transport, the release is said to be super case-II transport. Table 4 summarizes the range of values of diffusional exponent, n, and the released transport mechanism for each a geometry (Rittger and Peppas, 1987). A value of n = 1, mean that the drug release can exist for any geometry; only slabs do this release coincide with case-II transport.
Table 4  Diffusional exponent and mechanisms of drug from various swellable controlled release systems.

<table>
<thead>
<tr>
<th>Diffusional exponent, n</th>
<th>Thin film</th>
<th>Cylindrical sample</th>
<th>Spherical sample</th>
<th>Drug release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.45</td>
<td>0.43</td>
<td></td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5&lt;n&lt;1.0</td>
<td>0.45&lt;n&lt;0.89</td>
<td>0.43&lt;n&lt;0.89</td>
<td></td>
<td>Anomalous (non-Fickian) transport</td>
</tr>
<tr>
<td>1.0</td>
<td>0.89</td>
<td>0.89</td>
<td></td>
<td>Zero-order (time-independent)</td>
</tr>
</tbody>
</table>

7. **MicroMath® Scientist™ for Windows™**

It is specifically designed to fit model equations to experimental data. Other programs focus on technical graphics, symbolic manipulation, matrix operations or worksheets for engineering calculations. Scientist™ incorporates all these elements, but its primary function is fitting equations to experimental data. Scientist™ can fit almost any mathematical model from the simplest linear functions to complex systems of differential equations, non-linear algebraic equations or models expressed as Laplace transforms. The Scientist Chemical Kinetic Library is a set of chemical kinetics models that can be used to simulate or analyze experimental data. The Chemical Kinetic Library includes models for zero, first and second order irreversible reactions, first order reversible reactions, and parallel first order irreversible reactions with up to three products.

Least square fitting the experimental dissolution data (cumulative drug release >10% and up to 80%) to the mathematical equations (power law, first order, Higuchi’s and zero order) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA).
The coefficient of determination (cd) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (msc) (MicroMath Scientist Handbook, 1995), given below.

\[
msc = \ln \left\{ \frac{\sum_{i=1}^{n} w_i \left( Y_{obs_i} - \bar{Y}_{obs} \right)^2}{\sum_{i=1}^{n} w_i \left( Y_{obs_i} - Y_{cal_i} \right)^2} \right\} - \frac{2p}{n}
\]

Where \( Y_{obs_i} \) and \( Y_{cal_i} \) are observed and calculated values of the i-th point, respectively, and \( w_i \) is the weight that applies to the i-th point, \( n \) is number of points and \( p \) is number of parameters.
CHAPTER III
METHOD OF STUDY

1. Materials

1.1 Model drug

Propranolol hydrochloride (lot no. 941002, China National Chemical Imp.Exp., China)

1.2 Additives

Chitosan (Aqua premier, Chonburi, Thailand)

Dibasic calcium phosphate (lot no. 5F/269, Sudeep Pharma Ltd., India)

Eudragit L 100 (lot no. 1200403005, Rohm GmbH Chemische Fabrick, Germany)

Hydroxypropyl methylcellulose K 4M (Methocel® K 4M) (lot no. QC 14012N01, Colorcon Asia Pracific Pte., Ltd.)

Hydroxypropyl methylcellulose K 15M (Methocel® K 15M) (lot no. NH 16012N11, Colorcon Asia Pracific Pte., Ltd.)

Hydroxypropyl methylcellulose K 100M (Methocel® K 100M) (lot no. QF 05012N12, Colorcon Asia Pracific Pte., Ltd.)

Hydroxypropyl methylcellulose E 15LV (Methocel® E 15LV) (lot no. MM94012721E, Rama Production Co., Ltd., England)

Lactose (lot no. 080200 A9249, Auckland, New Zealand)

Phytowax L48 (Sophim, Parc dela Cassine, France)

Polyvinylplasdone XL (lot no. 90870, U.S.A)

Sodium bicarbonate (lot no. 2020506, P.C. Drug Center Co., Ltd., Thailand)
Xanthan gum (Xantural 75°®, CP Kelco U.S., Inc. USA.)

1.3 Chemicals

Dichloromethane (lot no. 02110176, Reagent chemical industry Ltd., Thailand)

Dibasic sodium phosphate (lot no. 190502, P.C. Drug Center Co., Ltd., Thailand)

Ethanol (lot no. 0501252, VWR International Ltd., England)

HCl solution (lot no. A01025, BAKER ANALYZED° A.C.S. Reagent, USA)

Isopropyl alcohol (lot no. K33157272, VWR International Ltd., England)

Monobasic potassium phosphate (lot no. 45-2, P.C. Drug Center Co., Ltd., Thailand)

Methanol (S.R. Lab. Co., Ltd., Thailand)

Sodium hydroxide pellet (lot no. 03/07/157A, P.C. Drug Center Co., Ltd., Thailand)

Sodium chloride (lot no. 1149, P.C. Drug Center Co., Ltd., Thailand)

1.4 Capsules

HPMC capsule No.1 (Capsugel, Thailand)

NP™ caps No.1 (Capsugel, Thailand)

1.5 Equipments

Analytical balance (Sartorius model BP2100S and Sartorius model CP224S, Germany)
Brookfield viscometer (Brookfield Engineering Laboratories, Inc.,
USA.)

Capsule filling machine No.1 (S.T.P No.1 B.M., Thailand)

Differential scanning calorimetry (Pyris Sapphire DSC, Standard 115V,
Perkin Elmer instruments, Japan)

Dissolution apparatus (Prolabo, France)

Mortar and pestle

Magnetic stirrer and magnetic bar (Thermolyne, USA)

Friabilitator (220, YEO HENG Factory, Thailand)

Scanning electron microscope (Maxim 200 Camscan, Cambridge,
England)

Sieve

Sonicator bath (transonic cleaning bath, Elma, Germany)

UV spectrophotometer (Perkin-Elmer, Germany)

X-ray diffractometer (Philips PW 1830 diffractometer, Netherlands)

2. Methods

2.1 Determination of approximate volume of capsule body

Hard hydroxypropyl methylcellulose capsule size No.1 was used in this study. The approximate volume (ml) of capsule body was determined by gradually dropping mineral oil from measuring pipet into the individual capsule body. The replication was performed for 6 times. The mean and standard deviation were obtained from six capsule bodies determination. The coefficient of variation of approximate volume of capsule body was evaluated.
2.2 Formulation and preparation of single-unit controlled release capsules

2.2.1 Capsule preparation

Propranolol hydrochloride was used as a model drug used for sustained-release capsule preparation. The amount of propranolol hydrochloride per capsule was 40 mg. Hydroxypropyl methylcellulose was used as matrix former in formulations. The effect of composition filled in capsule on physical properties and drug release were determined by varying of material individually. Tapped density of each excipients was used to determine the amount of them to fill in capsules. The powders were mixed manually with mortar and pestle and filled in capsules using manual filling capsule machine No.1.

2.2.2 Investigation the effect of viscosity grade of HPMC on the drug release from matrix capsules

The different viscosity grades of HPMC i.e. Methocel® K4M, Methocel® K15M, Methocel® K100M and Methocel® E15LV were utilized as matrix former to investigate the effect of viscosity grade of HPMC on the drug release (F1-F4).
Table 5  Composition of capsules containing different viscosity grades of HPMC

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PPHCl (mg)</th>
<th>Excipients (%w/v)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPMC K4M</td>
</tr>
<tr>
<td>F1</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>F2</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>F4</td>
<td>40</td>
<td>-</td>
</tr>
</tbody>
</table>

*The amount of drug was included.

2.2.3 Investigation the effect of diluents on the drug release from HPMC matrices

Table 6 exhibits the formula (F5-F27) for investigation the effect of types and amounts of diluents (lactose, dibasic calcium phosphate (DCP) and sodium bicarbonate (NaHCO₃)) and polymers (chitosan, xanthan gum and Eudragit® L100) on the drug release from HPMC matrices.

Table 6 Composition formula of propranolol HCl matrices capsule containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PPHCl (mg)</th>
<th>Excipients (%w/v)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPMC K15M</td>
</tr>
<tr>
<td>F5</td>
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</tr>
<tr>
<td>F6</td>
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<td>25</td>
</tr>
<tr>
<td>F7</td>
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<tr>
<td>F8</td>
<td>40</td>
<td>75</td>
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</table>
Table 6 (Cont.) Composition formula of propranolol HCl matrices capsule containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PPHCl (mg)</th>
<th>HPMC K15M</th>
<th>Lactose</th>
<th>DCP</th>
<th>Xanthan</th>
<th>Eudragit L100</th>
<th>Chitosan</th>
<th>NaHCO₃</th>
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<tbody>
<tr>
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<td>-</td>
<td>-</td>
<td>100</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F11</td>
<td>40</td>
<td>50</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
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<td>25</td>
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<td>-</td>
<td>-</td>
</tr>
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<td>F13</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>F14</td>
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<td>25</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F15</td>
<td>40</td>
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<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F16</td>
<td>40</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>-</td>
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<td>75</td>
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<tr>
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<td>-</td>
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<td>25</td>
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<tr>
<td>F21</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>F22</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>75</td>
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</tr>
<tr>
<td>F23</td>
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<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>F24</td>
<td>40</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
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</tr>
<tr>
<td>F25</td>
<td>40</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>F26</td>
<td>40</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>F27</td>
<td>40</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
</tr>
</tbody>
</table>

*The amount of drug was included.
2.3 Formulation and preparation of multiple-unit controlled release capsules

2.3.1 Determination the solubility property of HPMC

Solubility of HPMC in various solvents was determined. The solubility data was utilized to select the granulating liquids for producing multiple-unit dosage form. The solvents used in this determination considered from solubility of HPMC and their physicochemical property. These selected liquids employed in wet granulation were water, 95% ethanol, dichloromethane, isopropyl alcohol (IPA), mixtures of ethanol and dichloromethane, and mixtures of isopropyl alcohol and water. HPMC powder (3 g) was dispersed in 150 ml of various liquid and stirred with magnetic stirrer for 24 hour. The appearance of mixture was observed and then the viscosity was measured using Brookfield viscometer (n=3).

2.3.2 Preparation of matrix granules

The compositions of matrix granule formulations are presented in Table 7.

Preparation of hydrophilic matrix granule

Matrix granules were prepared by wet granulation method. All materials were mixed in a porcelain mortar by geometric dilution and then wetted with granulating liquid in quantity sufficient to achieve the funicular state of agglomeration. The wet mass was passed through a sieve No. 20 mesh and dried in a hot air oven at 50°C for 5 hours, then left to cool down to room temperature. The dried granules were rescreened through the sieve No. 20 mesh.

Preparation of hydrophobic matrix granules

Hydrophobic wax granules (formulation F30 and F32) were prepared by melting phytowax. HPMC and propranolol HCl were gradually dispersed in melted phytowax. The mass was passed through a sieve No. 20 mesh and then dried.
at room temperature. The dried granules were rescreened through the sieve No. 20 mesh.

**Preparation of hydrophilic polymer combined with hydrophobic matrix granules**

Hydrophobic wax granules (formulation F31, F32 and F38) were prepared by melting phytowax, and then propranolol HCl was dispersed in melted phytowax. The mass was passed through a sieve No. 20 mesh to obtain the hydrophobic wax granules. These granules were mixed with HPMC and other diluents in a porcelain mortar by geometric dilution and then wetted with granulating liquid in quantity sufficient to achieve the funicular state of agglomeration. The wet mass was passed through a sieve No. 20 or 16 mesh and dried in a hot air oven at 40°C for 4 hours, then left to cool down to room temperature. The dried granules were rescreened through the sieve No. 20 or 16 mesh.

**Table 7** Composition of propranolol HCl matrices granules containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PPHCL (mg)</th>
<th>Excipients (%w/v)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPMC K15M</td>
<td>Phytowax</td>
</tr>
<tr>
<td>F28</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F29</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>F30</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>F31</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>F32</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F33</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F34</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>
Table 7 (cont.) Composition of propranolol HCl matrices granules containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PPHCL (mg)</th>
<th>Excipients (%w/v)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPMC K15M</td>
<td>Phytowax</td>
</tr>
<tr>
<td>F35</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F36</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F37</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>F38</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

*The amount of drug was included.

2.3.3 Evaluation of matrix granules

2.3.3.1 Bulk density, tapped density, and compressibility index

The bulk density of granules was determined by pouring 10 g of the granules into a 50 ml cylinder and measuring the volume of granules. Tapped density was determined after tapping the cylinder until no further decrease in the granules volume. The carr’s (compressibility) index was calculated from the following equation:

\[
\text{Carr’s index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100
\]

This index is interpreted in the following way: the higher the compressibility index, the poorer the flowability.
2.3.3.2 Particle size distribution

Particle size distribution was determined by sieve analysis. The set of standard sieve consisted of ranging from sieve No. 20, 40, 60, 80, 100, 200 mesh and collection pan, respectively. Approximately 20 g of granules were put on top sieve series. The sieve series were placed on the sieve shaker and shaked for 5 minutes. The granules retained on each sieve size were weighed and calculated in percentage of total weight. These values were plotted against particle size.

2.3.3.3 Flowability

The angle of repose was used to determine the flowability of powder and granules. The angles of repose measured from pouring the granules into a teflon pipe (3 inch height and 4.3 cm diameter) that placed on graph paper (Figure 7). After that, the teflon pipe was raised up until became to desired condition (Figure 8). The angle of repose was calculated as:

\[ \tan \theta = \frac{h}{r} \]

h = height of cone
r = radial of cone

Figure 7  Equipments for flowability testing
Figure 8  Model of powders or granules formation for measured the angle of repose

Table 8  Criteria of the angle of repose

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Pass</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Not flow</td>
</tr>
</tbody>
</table>

2.3.3.4 Friability

The friability of granules was determined by a friabilator. One gram of granules with average particle size of 850 µm was accurately weighed by an analytical balance “W₀”. The granules were filled into a spherical container and rotated at 25 rpm for 4 minutes with friabilator (Figure 9). These granules were rescreened through the sieve No. 40 mesh and reweighed “W”. The percent of friability was calculated based on the following equation. The resulted obtained from the average of three determinations.

\[
\% \text{ Friability} = \left( \frac{W₀ - W}{W₀} \right) \times 100
\]
2.3.3.5 Determination of shape and surface topography of granules

The shape and surface topography of prepared granules were analyzed with scanning electron microscopy (SEM). The samples were prepared by gold sputtering technique before SEM examination.

2.3.3.6 The differential scanning calorimetry (DSC)

The DSC thermograms of drug, HPMC, lactose and prepared granules were obtained using a differential scanning calorimeter (DSC). The sample was milled and weighed into the aluminum pan. The sample was taken into the condition that had been purged with liquid nitrogen gas with the heating rate of 10°C/min and temperature between 25°C and 250°C.

2.3.3.7 The powder X-ray diffraction

The powder X-ray diffractometer was used to determine the crystalline transformation and interaction between each component after mixing and wet granulation process of granules preparation. The X-ray diffraction patterns were recorded from $5^\circ 2\theta$ - $50^\circ 2\theta$. 

Figure 9  Spherical container and friabilator
2.4 Evaluation of capsules

2.4.1 Weight variation

Weight variation of capsule was determined by an analytical balance. Twenty capsules were individually weighed. The contents of each capsule were removed by a suitable means. The emptied shells were individually accurately weighed and calculated for each capsule the net weight of its contents by subtracting the weight of shell from the respective gross weight.

2.4.2 Drug content and uniformity of drug

The drug content and uniformity of propranolol HCl was determined using UV-spectrophotometer. Methanol was used to dissolve propranolol HCl for content uniformity assay. The contents of 1 capsule transfer to a 100 ml volumetric flask. About 70 ml of methanol was added and sonicated for about 15 minute. This solution adjusted with methanol to volume in 100 ml volumetric flask. The solution was used as stock solution and filtered using filter paper (Whatman® No. 1). The 0.5 ml stock solution was pipetted and adjusted to volume in 10 ml volumetric flask. The amount of drug was determined using UV-spectrophotometer at 290 nm.

*Calibration curve of propranolol hydrochloride in methanol*

Propranolol hydrochloride of 1000 mg was accurately weighed, dissolved in methanol, then adjusted to volume. This solution was used as a standard stock solution. The 0.25 and 0.5 ml stock solution was pipetted and adjusted to volume in 100 and 50 ml volumetric flask. The 0.2, 0.3 and 0.4 ml stock solution was pipetted and adjusted to volume in 10 ml volumetric flask to make approximately 5-40 µg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 290 nm.
2.4.3 Study of drug release

The dissolution of propranolol hydrochloride was studied using the basket and paddle methods. The dissolution fluid used was 900 ml HCl buffer pH 1.2. The speed of basket and paddle rotation was 50 rpm maintained at 37°C. The amount of propranolol hydrochloride was 40 mg/capsule for all formulations. The samples were withdrawn at predetermined time intervals (5, 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 hours). The amount of drug released was measured using UV spectrophotometer at 320 nm. The cumulative percentage of propranolol hydrochloride released was calculated and plotted against time.

In order to investigate the effect of pH of dissolution medium on the release of propranolol HCl from capsules, the three dissolution systems, phosphate buffer pH 6.8, water and pH change system were used in this study. The pH change dissolution method was performed to simulate the environment of the gastrointestinal tract by changing the pH of the dissolution medium during the dissolution testing. The dissolution media used were HCl buffer pH 1.2 for the first 1.5 h, then the pH was increased to 6.8 (by adding 3.6 g of sodium hydroxide, 3.06 g of monobasic potassium phosphate and 4.005 g of dibasic sodium phosphate dissolved in HCl buffer pH 1.2) until 8 hours.

Moreover, in the dissolution testing, the speed of basket rotation at 50, 100 and 150 rpm were used in this study to investigate the effect of hydrodynamic force on the release of propranolol HCl from prepared capsules.

Calibration curve of propranolol hydrochloride in HCl buffer pH 1.2

Propranolol hydrochloride of 1000 mg was accurately weighed, dissolved in 50 ml of methanol and adjusted to volume with HCl buffer pH 1.2. This solution was used as a standard stock solution. The 0.1, 0.25, 0.5, 0.75 and 1 ml of stock solutions were pipetted and adjusted with HCl buffer pH 1.2 to volume in 10 ml
volumetric flask to yield 10-100 µg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 320 nm.

**Calibration curve of propranolol hydrochloride in water**

Propranolol hydrochloride of 1000 mg was accurately weighed, dissolved in 50 ml of methanol and adjusted to volume with water. This solution was used as a standard stock solution. The 0.1, 0.25, 0.5, 0.75 and 1 ml of stock solutions were pipetted and adjusted with water to volume in 10 ml volumetric flask to yield 10-100 µg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 320 nm.

**Calibration curve of propranolol hydrochloride in phosphate buffer pH 6.8**

Propranolol hydrochloride of 1000 mg was accurately weighed, dissolved in 50 ml of methanol and adjusted to volume with phosphate buffer pH 6.8. This solution was used as a standard stock solution. The 0.1, 0.25, 0.5, 0.75 and 1 ml of stock solution was pipetted and adjusted with phosphate buffer pH 6.8 to volume in 10 ml volumetric flask to yield 10-100 µg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 320 nm.

### 2.5 Data evaluation

To investigate the mechanism of drug release, the cumulative percentage of drug released versus time profiles were used. Least square fitting the experimental dissolution data (cumulative drug release>10% and up to 80%) to the mathematical equations (power law, first order, Higuchi’s and zero order) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (cd) was used to indicate the degree of curve fitting. Goodness-of-fit
was also evaluated using the Model Selection Criterion (msc) (MicroMath Scientist Handbook, 1995). Model files are shown in Table 9.

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Model files used with Scientist™</th>
</tr>
</thead>
<tbody>
<tr>
<td>// MicroMath Scientist Model File: <strong>Power law</strong></td>
<td></td>
</tr>
<tr>
<td>IndVars: T</td>
<td></td>
</tr>
<tr>
<td>DepVars: F</td>
<td></td>
</tr>
<tr>
<td>Params: K, Tl, N</td>
<td></td>
</tr>
<tr>
<td>F = K * ((T - Tl) ^ N)</td>
<td></td>
</tr>
<tr>
<td>***</td>
<td></td>
</tr>
<tr>
<td>// MicroMath Scientist Model File: <strong>Zero order</strong></td>
<td></td>
</tr>
<tr>
<td>IndVars: T</td>
<td></td>
</tr>
<tr>
<td>DepVars: F</td>
<td></td>
</tr>
<tr>
<td>Params: K, Tl</td>
<td></td>
</tr>
<tr>
<td>F = K * (T - Tl)</td>
<td></td>
</tr>
<tr>
<td>***</td>
<td></td>
</tr>
<tr>
<td>// MicroMath Scientist Model File: <strong>First order</strong></td>
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<tr>
<td>IndVars: T</td>
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</tr>
<tr>
<td>DepVars: F</td>
<td></td>
</tr>
<tr>
<td>Params: K, Tl</td>
<td></td>
</tr>
<tr>
<td>F = 1 - EXP(-K * (T - Tl))</td>
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<td>***</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>DepVars: F</td>
<td></td>
</tr>
<tr>
<td>Params: K, Tl</td>
<td></td>
</tr>
<tr>
<td>F = K * ((T - Tl) ^ (1/2))</td>
<td></td>
</tr>
<tr>
<td>***</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER IV
ANALYSIS OF THE DATA

1. Physical properties of capsule and materials

1.1 The approximate volume of capsule body

The average volume (ml) of hydroxypropyl methylcellulose capsule body size No.1 was 0.49 ml. This volume of a capsule body was used to calculate the content of additives for filling into capsules. The standard deviation and the coefficient of variation of approximate volume of capsule body are showed in Table 10.

Table 10 The approximate volume of hydroxypropyl methylcellulose capsule body

<table>
<thead>
<tr>
<th>Name</th>
<th>approximate volume (ml) (n = 6)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC capsule size No. 1</td>
<td>0.49</td>
<td>0.01</td>
<td>2.04</td>
</tr>
</tbody>
</table>

1.2 Tapped density of materials

The tapped densities of propranolol hydrochloride and diluents are presented in Table 11. The tapped densities of these materials depended on specific characteristic of individually materials. Phytowax exhibited the highest tapped densities. The lowest tapped densities were found in case of chitosan and ethyl cellulose. The tapped densities of different grade of HPMC were in range of 0.46 - 0.51 g/ml.
Table 11  Tapped density of drug and materials

<table>
<thead>
<tr>
<th>Materials</th>
<th>Tapped density (g/ml) (n=3)</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol HCl</td>
<td>0.42</td>
<td>0.00</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Chitosan (180 mesh passed)</td>
<td>0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>Corn starch 1500</td>
<td>0.70</td>
<td>0.01</td>
</tr>
<tr>
<td>Dibasic calcium phosphate</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>0.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Eudragit L100</td>
<td>0.56</td>
<td>0.00</td>
</tr>
<tr>
<td>HPMC K15 M</td>
<td>0.46</td>
<td>0.01</td>
</tr>
<tr>
<td>HPMC K4M</td>
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<td>0.00</td>
</tr>
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<td>HPMC K100M</td>
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<td>0.01</td>
</tr>
<tr>
<td>HPMC E15LV</td>
<td>0.51</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.67</td>
<td>0.00</td>
</tr>
<tr>
<td>Phytowax</td>
<td>0.91</td>
<td>0.00</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>0.67</td>
<td>0.00</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.69</td>
<td>0.02</td>
</tr>
</tbody>
</table>

2. Factors affecting the drug release of single-unit controlled release capsules

2.1 The influence of viscosity grade of matrix former on the drug release

The dissolution profiles of propranolol hydrochloride released from matrix system in HPMC capsules containing different viscosity grade of HPMC,
Methocel® K4M, K15M, K100M and low viscosity grade, E 15LV are shown in Figure 10. The drug release from capsules containing HPMC E 15LV was faster than those from capsules containing K4M, K15M and K100M, which showed similar release profiles. The drug release profile from HPMC K100M matrix was slightly lower than that containing HPMC type K4M and K15M. The result showed that HPMC could extend the release time of propranolol HCl longer than 8 hours. The dissolutions data of capsule containing HPMC K4M, K15M and K100M were fitted well to first order model. Whereas the dissolution data of capsule containing HPMC E 15LV was fitted well with zero order model as presented in Table 12.

![Dissolution profiles of propranolol HCl released from the matrix containing the different viscosity grade HPMC in HCl buffer pH 1.2](image)

**Figure 10** Dissolution profiles of propranolol HCl released from the matrix containing the different viscosity grade HPMC in HCl buffer pH 1.2

2.2 The influence of types and amounts of diluents on the drug release

2.2.1 Effect of water soluble and insoluble fillers

Lactose (L) and dibasic calcium phosphate (D) were chosen for investigation of the influence of these fillers on the propranolol hydrochloride released
from HPMC matrix in HPMC capsule. Increasing concentration of lactose from 25% to 75% in HPMC matrix resulted in an enhancement of the release rate of propranolol hydrochloride (Figure 11). The concentration of dibasic calcium phosphate increased in HPMC matrices led to the increase in drug release rate (Figure 12). By comparison, lactose and dibasic calcium phosphate exhibited similar effect on the release of propranolol hydrochloride from matrices (Figure 13-15). Except that the matrix containing 100% dibasic calcium phosphate showed the drug release greater than that containing 100% lactose as filler (Figure 16). The dissolution data from matrices containing only lactose and dibasic calcium phosphate were not used for curve fitting because of the fast release of drug form the capsule. However, the incorporation of lactose or dibasic calcium phosphate in HPMC matrix could obtain the drug release closer to zero-order model as presented in Table 12. From the release exponent (n), the release mechanism of formulations containing 25%, 50% and 75% lactose or dibasic calcium phosphate indicating non-Fickian transport (Table 13).

![Graph of dissolution profiles](image)

**Figure 11** Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of lactose in HCl buffer pH 1.2
Figure 12  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of dibasic calcium phosphate in HCl buffer pH 1.2

Figure 13  Comparison the dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing dibasic calcium phosphate and lactose of 25% in HCl buffer pH 1.2
Figure 14  Comparison the dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing dibasic calcium phosphate and lactose of 50% in HCl buffer pH 1.2

Figure 15  Comparison the dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing dibasic calcium phosphate and lactose of 75% in HCl buffer pH 1.2
2.2.2 Effect of polymer

The dissolution of propranolol hydrochloride from capsule filled with different matrices containing various polymers i.e. HPMC K15M, xanthan gum (X), chitosan (C) and Eudragit L100 (E) are shown in Figure 17. All polymers could sustain drug release in HCl buffer pH 1.2 longer than 8 hours. Whereas only chitosan was able to control the drug release for 4 hours following the immediate drug release. In addition, the release of propranolol hydrochloride from matrix system containing HPMC K15M was slower than that containing other polymers. The percentage of propranolol hydrochloride released from the matrices system containing HPMC K15M, Eudragit L100, xanthan gum and chitosan were 68.42%, 75.82%, 77.45% and 116.94%, respectively, at 8 hours in HCl buffer pH 1.2.

The propranolol hydrochloride released from HPMC-xanthan gum matrices was rather complex. The release profile of the formulation containing 50%
xanthan gum in HPMC matrix exhibited slightly slower than the formulation containing only HPMC. Whereas the release profile of the formulation containing 25% xanthan gum in HPMC matrix showed similar drug release profile to the formulation containing only HPMC (Figure 18). However, the drug release of all formula was not significantly different.

**Figure 17** Dissolution profiles of propranolol HCl released from capsule filled with the various polymers matrix in HCl buffer pH 1.2
Figure 18  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of xanthan gum in HCl buffer pH 1.2

The release of propranolol hydrochloride from capsule containing HPMC and Eudragit L100 matrices is presented in Figure 19. These matrix systems exhibited almost similar drug released in HCl buffer pH 1.2 except the formulation containing only Eudragit L100. Moreover, the propranolol hydrochloride release profile from formulation containing 25% and 50% of Eudragit L100 in HPMC matrices were slower than formulation that containing only HPMC. The percentage of propranolol hydrochloride released at 8 hours in HCl buffer pH 1.2 from capsule with varying amount of Eudragit L100 at 100%, 75%, 50% and 25% in HPMC matrices were 75.82%, 73.39%, 61.31% and 63.68%, respectively.

The propranolol HCl release was faster in HCl buffer pH 1.2 from matrix system containing chitosan are shown in Figure 20. Especially, the formulation that contained only chitosan exhibited immediate release after 4 hours. Capsule
containing 75% chitosan in HPMC matrices also exhibited fast release after 4 hours. This formulation released propranolol hydrochloride nearly to 100% at 6 hour. The HPMC matrices containing 25% chitosan showed faster drug released than formulation containing 50% chitosan at the first 4 hours. And after 4 hours, the formulation containing 50% chitosan showed drug release slightly faster than formulation containing 25% chitosan in HPMC matrices. However, all formulation that incorporated chitosan in HPMC matrices exhibited faster drug release in HCl buffer pH 1.2 than formulation containing only HPMC.

The dissolution data of the formulation containing HPMC-xanthan gum matrices and HPMC-Eudragit L 100 matrices were best fitted to first order model (Table 12). The release mechanism of them was non-Fickian transport with n values ranged of 0.57-0.65 (Table 13).

The dissolution data of the formulation containing HPMC-chitosan matrices was fitted well to zero order model as presented in Table 12. The release mechanism of the formulation containing 50% and 75% chitosan in HPMC matrices were non-Fickian transport with n values of 0.64 and 0.84, respectively (Table 13).
**Figure 19** Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of Eudragit L100 in HCl buffer pH 1.2

**Figure 20** Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of chitosan in HCl buffer pH 1.2
2.2.3 Effect of sodium bicarbonate

The incorporation of sodium bicarbonate (S) in the concentration of 40% into HPMC matrix could slight prolong drug release in HCl buffer pH 1.2 (Figure 21). Increasing proportion of sodium bicarbonate up to 60% in HPMC-bicarbonate matrices provided slow drug release during the first 2 hours and following faster release. Whereas, the capsule containing sodium bicarbonate of 20% in HPMC matrix showed similar drug release to the formulation containing only HPMC during first 4 hours. Subsequently, this formulation exhibited the drug release faster than that of formulation containing only HPMC. The dissolutions data of the formulations containing 40% and 60% sodium bicarbonate were fitted well to zero order model while the formulation containing 20% sodium bicarbonate in HPMC matrix approached to first order model as presented in Table 12. The release mechanism of all formulation containing sodium bicarbonate in HPMC matrices were non-Fickian transport with n values of 0.66, 0.86 and 0.68, respectively (Table 13).

![Figure 21](image)

**Figure 21** Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing different amount of sodium bicarbonate in HCl buffer pH 1.2
Table 12  
Comparison of degree of goodness-of-fit from curve fitting of drug dissolution in HCl buffer pH 1.2 to different release models.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Power law</th>
<th>First order</th>
<th>Higuchi's</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cd</td>
<td>msc</td>
<td>cd</td>
<td>msc</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>0.9997</td>
<td>7.59</td>
<td>0.9962</td>
<td>5.20</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>0.9983</td>
<td>5.84</td>
<td>0.9947</td>
<td>4.89</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>0.9992</td>
<td>6.60</td>
<td>0.9955</td>
<td>5.04</td>
</tr>
<tr>
<td>HPMC E15LV</td>
<td>0.9989</td>
<td>6.28</td>
<td>0.9845</td>
<td>3.81</td>
</tr>
<tr>
<td>Lactose 25%</td>
<td>0.9880</td>
<td>3.82</td>
<td>0.9489</td>
<td>2.57</td>
</tr>
<tr>
<td>Lactose 50%</td>
<td>0.9990</td>
<td>6.33</td>
<td>0.9676</td>
<td>3.03</td>
</tr>
<tr>
<td>Lactose 75%</td>
<td>0.9979</td>
<td>5.39</td>
<td>0.9306</td>
<td>2.17</td>
</tr>
<tr>
<td>Dibasic calcium phosphate 25%</td>
<td>0.9939</td>
<td>4.55</td>
<td>0.9381</td>
<td>2.42</td>
</tr>
<tr>
<td>Dibasic calcium phosphate 50%</td>
<td>0.9972</td>
<td>5.27</td>
<td>0.9726</td>
<td>3.20</td>
</tr>
<tr>
<td>Dibasic calcium phosphate 75%</td>
<td>0.9999</td>
<td>9.11</td>
<td>0.9187</td>
<td>2.01</td>
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<tr>
<td>Eudragit L100; 25%</td>
<td>0.9995</td>
<td>7.02</td>
<td>0.9978</td>
<td>5.74</td>
</tr>
<tr>
<td>Eudragit L100; 50%</td>
<td>0.9992</td>
<td>6.54</td>
<td>0.9962</td>
<td>5.22</td>
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<tr>
<td>Eudragit L100; 75%</td>
<td>0.9982</td>
<td>5.79</td>
<td>0.9923</td>
<td>4.50</td>
</tr>
<tr>
<td>Xanthan 25%</td>
<td>0.9992</td>
<td>6.53</td>
<td>0.9884</td>
<td>4.06</td>
</tr>
<tr>
<td>Xanthan 50%</td>
<td>0.9998</td>
<td>8.01</td>
<td>0.9906</td>
<td>4.27</td>
</tr>
<tr>
<td>Xanthan 75%</td>
<td>0.9995</td>
<td>7.05</td>
<td>0.9972</td>
<td>5.50</td>
</tr>
<tr>
<td>Chitosan 25%</td>
<td>0.9998</td>
<td>8.19</td>
<td>0.9816</td>
<td>3.66</td>
</tr>
</tbody>
</table>
Table 12 (cont.) Comparison of degree of goodness-of-fit from curve fitting of drug dissolution in HCl buffer pH 1.2 to different release models.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Power law</th>
<th>First order</th>
<th>Higuchi's</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cd</td>
<td>msc</td>
<td>cd</td>
<td>msc</td>
</tr>
<tr>
<td>Chitosan 50%</td>
<td>0.9989</td>
<td>6.25</td>
<td>0.9132</td>
<td>2.08</td>
</tr>
<tr>
<td>Chitosan 75%</td>
<td>0.9990</td>
<td>6.26</td>
<td>0.9257</td>
<td>2.15</td>
</tr>
<tr>
<td>Sodium bicarbonate 20%</td>
<td>0.9995</td>
<td>7.24</td>
<td>0.9871</td>
<td>3.98</td>
</tr>
<tr>
<td>Sodium bicarbonate 40%</td>
<td>0.9982</td>
<td>5.70</td>
<td>0.8680</td>
<td>1.58</td>
</tr>
<tr>
<td>Sodium bicarbonate 60%</td>
<td>0.9979</td>
<td>5.18</td>
<td>0.6876</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Table 13 Estimate parameters from curve fitting of drug dissolution in HCl buffer pH 1.2 to power law expression.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>k ± sd^10^-1</th>
<th>tl ± sd (hr)</th>
<th>n ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K4M</td>
<td>0.1835 ± 0.0039</td>
<td>0.59 ± 0.04</td>
<td>0.66 ± 0.01</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>0.2081 ± 0.0081</td>
<td>0.73 ± 0.06</td>
<td>0.60 ± 0.02</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>0.1855 ± 0.0062</td>
<td>0.51 ± 0.06</td>
<td>0.60 ± 0.02</td>
</tr>
<tr>
<td>HPMC E15LV</td>
<td>0.2179 ± 0.0095</td>
<td>0.53 ± 0.07</td>
<td>0.66 ± 0.02</td>
</tr>
<tr>
<td>Lactose 25%</td>
<td>1.8687 ± 0.0493</td>
<td>0.49 ± 0.49</td>
<td>0.73 ± 0.11</td>
</tr>
<tr>
<td>Lactose 50%</td>
<td>2.8426 ± 0.0081</td>
<td>0.57 ± 0.03</td>
<td>0.64 ± 0.02</td>
</tr>
<tr>
<td>Lactose 75%</td>
<td>3.4537 ± 0.0178</td>
<td>0.72 ± 0.06</td>
<td>0.62 ± 0.03</td>
</tr>
<tr>
<td>Dibasic calcium phosphate 25%</td>
<td>1.7769 ± 0.0267</td>
<td>0.40 ± 0.23</td>
<td>0.79 ± 0.07</td>
</tr>
<tr>
<td>Dibasic calcium phosphate 50%</td>
<td>2.8539 ± 0.0151</td>
<td>0.52 ± 0.06</td>
<td>0.64 ± 0.03</td>
</tr>
</tbody>
</table>
Table 13 (cont.)  Estimate parameters from curve fitting of drug dissolution in HCl buffer pH 1.2 to power law expression.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>k ± sd 10^-1</th>
<th>t₀ ± sd (hr)</th>
<th>n ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibasic calcium phosphate 75%</td>
<td>2.9159 ± 0.0032</td>
<td>0.64 ± 0.01</td>
<td>0.72 ± 0.01</td>
</tr>
<tr>
<td>Eudragit L100 25%</td>
<td>1.8583 ± 0.0044</td>
<td>0.67 ± 0.03</td>
<td>0.62 ± 0.01</td>
</tr>
<tr>
<td>Eudragit L100 50%</td>
<td>1.8159 ± 0.0057</td>
<td>0.61 ± 0.05</td>
<td>0.60 ± 0.02</td>
</tr>
<tr>
<td>Eudragit L100 75%</td>
<td>2.1078 ± 0.0093</td>
<td>0.66 ± 0.07</td>
<td>0.61 ± 0.02</td>
</tr>
<tr>
<td>Xanthan 25%</td>
<td>2.3112 ± 0.0048</td>
<td>0.69 ± 0.03</td>
<td>0.57 ± 0.11</td>
</tr>
<tr>
<td>Xanthan 50%</td>
<td>1.8118 ± 0.0042</td>
<td>0.78 ± 0.04</td>
<td>0.65 ± 0.11</td>
</tr>
<tr>
<td>Xanthan 75%</td>
<td>2.1705 ± 0.0074</td>
<td>1.03 ± 0.06</td>
<td>0.58 ± 0.02</td>
</tr>
<tr>
<td>Chitosan 25%</td>
<td>1.5776 ± 0.0152</td>
<td>0.07 ± 0.10</td>
<td>1.01 ± 0.05</td>
</tr>
<tr>
<td>Chitosan 50%</td>
<td>1.7580 ± 0.0132</td>
<td>0.28 ± 0.11</td>
<td>0.84 ± 0.03</td>
</tr>
<tr>
<td>Chitosan 75%</td>
<td>2.3897 ± 0.0031</td>
<td>0.48 ± 0.01</td>
<td>0.64 ± 0.01</td>
</tr>
<tr>
<td>Sodium bicarbonate 20%</td>
<td>2.0049 ± 0.0049</td>
<td>0.63 ± 0.03</td>
<td>0.66 ± 0.01</td>
</tr>
<tr>
<td>Sodium bicarbonate 40%</td>
<td>1.3499 ± 0.0149</td>
<td>1.34 ± 0.15</td>
<td>0.86 ± 0.05</td>
</tr>
<tr>
<td>Sodium bicarbonate 60%</td>
<td>3.7267 ± 0.0219</td>
<td>1.78 ± 0.06</td>
<td>0.68 ± 0.05</td>
</tr>
</tbody>
</table>

2.3 The influence of pH of dissolution medium on the drug release

The formulation containing 75% lactose and 25% HPMC was chosen for investigation of the influence of pH of dissolution medium on the propranolol HCl release (Figure 22). The dissolution of propranolol HCl was studied using paddle method. The dissolution fluids were HCl buffer pH 1.2, phosphate buffer pH 6.8, pH change and water. The speed of rotation was 50 rpm. The dissolution profile of propranolol HCl release was faster in water as compared to that in HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH
change. Whereas, the release profiles of propranolol HCl in HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change were similar.

![Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing 75% lactose in the different pH of dissolution medium](image)

**Figure 22** Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing 75% lactose in the different pH of dissolution medium

### 2.4 The influence of hydrodynamic force on the drug release

The formulation containing both 75% lactose and 25% HPMC was chosen for investigation of the influence of hydrodynamic force on the release of propranolol HCl (Figure 23). The dissolution of propranolol HCl was studied using paddle method by varying the speed of rotation of paddle. The rate of propranolol HCl release using rotational speed at 150 rpm was faster than those using rotational speed at 100 rpm, 50 rpm and 25 rpm.
3. Selection of appropriate granulating liquid for granule preparation

3.1 Solubility of HPMC

The physical appearances of systems containing HPMC in various solvents are shown in Figure 24. HPMC could form a viscous colloidal solution in water and mixtures of ethanol and dichloromethane (E:D) in ratio of 50:50, 40:60 and 30:70 (Figure 24A, 24B). There was a precipitation of HPMC powder in ethanol and isopropyl alcohol (Figure 24A, 24C). The viscosity values of systems containing HPMC are shown in Table 14. The viscosity of HPMC solution in different type of liquid were ranked as water > E:D;40:60 > E:D;30:70 > E:D;50:50 > E:D;60:40 > IPA-water (10%) mixture > E:D;70:30 > IPA > dichloromethane > ethanol, respectively. HPMC could be soluble in water and mixtures of ethanol and dichloromethane in ratio of 50:50, 40:60 and 30:70 (Figure 24A). Moreover, by visually inspection it was partially soluble in Figure 23  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrices containing 75% lactose by varying rotation speed of paddle in HCl buffer pH 1.2.
dichloromethane, mixtures of ethanol and dichloromethane in ratio of 70:30, 40:60 and mixtures of isopropyl alcohol and water (10%) but insoluble in ethanol and isopropyl alcohol.

**Table 14** Viscosity of the systems containing HPMC in various solvents (n=3)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>viscosity (mPa·s) (n=3)</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol 95% (E)</td>
<td>6.53</td>
<td>0.31</td>
</tr>
<tr>
<td>Dichloromethane (D)</td>
<td>7.47</td>
<td>0.12</td>
</tr>
<tr>
<td>E:D, 50:50</td>
<td>263.73</td>
<td>16.48</td>
</tr>
<tr>
<td>E:D, 70:30</td>
<td>12.60</td>
<td>0.35</td>
</tr>
<tr>
<td>E:D, 60:40</td>
<td>32.20</td>
<td>1.20</td>
</tr>
<tr>
<td>E:D, 30:70</td>
<td>1092.00</td>
<td>26.00</td>
</tr>
<tr>
<td>E:D, 40:60</td>
<td>1210.67</td>
<td>18.90</td>
</tr>
<tr>
<td>Water</td>
<td>2686.67</td>
<td>18.90</td>
</tr>
<tr>
<td>Isopropyl alcohol (IPA)</td>
<td>10.13</td>
<td>0.46</td>
</tr>
<tr>
<td>IPA + water</td>
<td>13.60</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Figure 24  Appearance of systems containing 2% (w/v) Methocel K 15M in various liquids; (A) ethanol, dichloromethane, mixtures of ethanol and dichloromethane in ratio of 50:50, 70:30, 60:40, 30:70 and 40:60, respectively (left to right); (B) water; (C) isopropyl alcohol and (D) mixtures of isopropyl alcohol and water (10%)

3.2 Characterization of granules

Initially, the preparation of granules containing propranolol HCl, lactose (75%) and HPMC (25%) or the formulation F6 was attempted using water as granulating liquid. The large amount of lump was appeared during the preparation the wet mass and it was difficult to pass through sieve to form the granules (Figure 25B). Hence, an organic solvent was employed to use as solvent for granulating fluid containing HPMC. The first
organic solvent used was 95% ethanol but the large volume of ethanol had to be utilized. The solid mixture was rather difficult to be wet and the large amount of fine powder was obviously occurred. The addition of the water into the system that using 95% ethanol as granulating fluid resulted to the lump formation similar to the system using water (Figure 25D). Therefore, the addition the water in wet granulation process containing HPMC generated the above mentioned problem. The systems containing HPMC in the mixtures of ethanol and dichloromethane in ratio of 50:50, 40:60 and 30:70 exhibited viscous solution similar to the system containing HPMC dispersed in water. Hence, these solvent systems were following to be utilized as granulating fluid. They could promote the good granules formation without losing of wet mass owing to the lump formation. Therefore, the mixtures of ethanol and dichloromethane could be applied as granulating fluid. Especially, the E:D mixtures in ratio of 50:50 and 40:60 provided the granules with good appearance but the mixture of E:D in ratio 30:70 obviously provided a lot of fine particles in the granulation process (Figure 26A, 26B, 26C).

The utilization of isopropyl alcohol as granulating liquid for production tablets comprising HPMC K 4M by wet granulation method has been previously reported (Kiortsis et al., 2004). In addition, isopropyl alcohol was demonstrated to use as granulating fluid in this experiment. Obviously, an amount of isopropyl alcohol used for agglomeration of powder mixture to obtain the wet mass was less than that of ethanol. Moreover, it exhibited a good wetting or slower evaporation than ethanol, thereby HPMC powder could not swell. After screening, the system contained large amount of quite fine particles (Figure 26D). Therefore, water in amount of 10% (v/v) was added to the solid mixture. By visually inspection, there was the less swelling of solid mixture but the agglomeration of solid mixture could be formed. The lump formation was disappeared from the obtained wet mass.
Figure 25 Appearance of granules prepared using different granulating liquid; water (A) granules, (B) wet mass; mixtures of ethanol and water (C) granules and (D) wet mass.
3.3 Bulk density, Tapped density and Compressibility index

Emcompress granules were used as a reference for testing the physical properties of granules in this experiment. The bulk and tapped densities of the granules made from different granulating liquids are presented in Table 15. The bulk and tapped densities of granules which were screened through sieve no.40 mesh were higher than the granules that were screened through sieve no.20 mesh. The Carr’s indexes of powders were higher than all prepared granules and emcompress granules. This result indicated that the prepared granules had better flow properties than the powders. The Carr’s index of the granules produced from the granulating fluid containing mixtures of ethanol and dichloromethane in ratio 50:50 and 40:60 and isopropyl alcohol and subsequently adding with water in amount of 10% v/v.
with water in amount of 10% v/v after rescreening pass through sieve no.20 mesh were 6.47, 8.33 and 3.92%, respectively. Therefore, these granules exhibited the fairly good flow properties. The Carr’s index of emcompress granules (reference) was higher than those granules because of the smaller granules size of emcompress granules. There was a high value of Carr’s index of the granules that made from mixtures of ethanol and dichloromethane in ratio 30:70 and the granules pass through sieve no.40 mesh before test. This might be due to the formation of the large amount of fine particles during granulation.

3.4 The angle of repose

The angle of repose of powders and the granules made from different granulating liquids are reported in Table 15. The angle of repose of the granules (29°-34°) exhibited lower value than the powder (37°-40°), indicating better flow properties for all prepared granules.

3.5 The particle size distribution

The particle size distribution of the granules made from different granulating liquids (mixtures of E:D in ratio of 50:50, 40:60, 30:70 and isopropyl alcohol and subsequently adding with water in amount of 10% v/v) is showed in Figure 27. Almost, the particle size distributions of the granules that rescreened through sieve no. 20 mesh were 850-425 µm. The utilization of the mixture of E:D in ratio of 50:50 as granulating liquid and isopropyl alcohol and subsequently adding with water in amount of 10% v/v obviously provided more granules with particle size of 850 µm than that with the particle size of 425 µm.
Table 15  The flow properties of PPHCl granules prepared from different granulating liquids

<table>
<thead>
<tr>
<th>Granulating liquid</th>
<th>Bulk density (g/ml) (n=3)</th>
<th>Tapped density (g/ml) (n=3)</th>
<th>Carr's index (%) (n=3)</th>
<th>Angle of repose (θ) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPHCl powder</td>
<td>0.30 ± 0.01</td>
<td>0.42 ± 0.00</td>
<td>28.90 ± 0.89</td>
<td>37.31 ± 2.34</td>
</tr>
<tr>
<td>HPMC powder</td>
<td>0.30 ± 0.01</td>
<td>0.46 ± 0.01</td>
<td>34.48 ± 1.98</td>
<td>38.22 ± 3.15</td>
</tr>
<tr>
<td>Lactose powder</td>
<td>0.45 ± 0.01</td>
<td>0.67 ± 0.00</td>
<td>32.81 ± 1.71</td>
<td>40.36 ± 0.00</td>
</tr>
<tr>
<td>Emcompress granules</td>
<td>0.91 ± 0.00</td>
<td>1.00 ± 0.00</td>
<td>9.06 ± 0.05</td>
<td>26.26 ± 0.53</td>
</tr>
<tr>
<td>E:D, 50:50, 20# passed</td>
<td>0.35 ± 0.01</td>
<td>0.38 ± 0.01</td>
<td>6.47 ± 0.97</td>
<td>31.90 ± 2.37</td>
</tr>
<tr>
<td>E:D, 50:50, 40# passed</td>
<td>0.41 ± 0.01</td>
<td>0.48 ± 0.01</td>
<td>15.50 ± 2.78</td>
<td>27.77 ± 0.52</td>
</tr>
<tr>
<td>E:D, 40:60, 20# passed</td>
<td>0.36 ± 0.00</td>
<td>0.39 ± 0.00</td>
<td>8.33 ± 1.03</td>
<td>31.23 ± 1.27</td>
</tr>
<tr>
<td>E:D, 30:70, 20# passed</td>
<td>0.38 ± 0.02</td>
<td>0.43 ± 0.01</td>
<td>10.88 ± 0.79</td>
<td>29.25 ± 0.00</td>
</tr>
<tr>
<td>IPA, 20# passed</td>
<td>0.40 ± 0.01</td>
<td>0.50 ± 0.01</td>
<td>18.79 ± 1.07</td>
<td>33.02 ± 0.70</td>
</tr>
<tr>
<td>IPA + water (10%), 20# passed</td>
<td>0.39 ± 0.01</td>
<td>0.41 ± 0.01</td>
<td>3.92 ± 1.89</td>
<td>29.80 ± 1.94</td>
</tr>
<tr>
<td>IPA + water (10%), 40# passed</td>
<td>0.43 ± 0.01</td>
<td>0.50 ± 0.00</td>
<td>14.25 ± 2.09</td>
<td>30.11 ± 0.00</td>
</tr>
</tbody>
</table>
Figure 27  Particle size distribution of granules made from different granulating liquids

3.6 Friability

The %friability of the granules made from different granulating liquids were ranked as E:D; 30:70 mixture > E:D; 60:40 mixture > E:D; 50:50 mixture > IPA-water (10%), respectively (Table 16). This result signified that the granules produced using isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v were stronger than those produced using other solvents.
Table 16  The friability of PPHCl granules produced using different granulating liquids

<table>
<thead>
<tr>
<th>Granulating liquid</th>
<th>% Friability</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>E:D, 50:50</td>
<td>10.14</td>
<td>1.01</td>
</tr>
<tr>
<td>E:D, 40:60</td>
<td>10.48</td>
<td>0.58</td>
</tr>
<tr>
<td>E:D, 30:70</td>
<td>16.49</td>
<td>2.09</td>
</tr>
<tr>
<td>IPA + water (10%)</td>
<td>7.14</td>
<td>1.01</td>
</tr>
</tbody>
</table>

3.7  Morphology of granules

The observation of surface and shape of the obtained granules was conducted using scanning electron microscopy (SEM). The scanning electron micrographs of the granules produced with the mixtures of ethanol and dichloromethane in ratio of 50:50 and 40:60 are presented in Figure 28A-28D. All granules obtained from the agglomeration of particles contained a more porous surface. After rescreening, the granules were smaller and more spherical characteristics. The surface of the granules produced with using isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v showed the dense agglomerated particles and exhibited the less porous surface than the granules that produced with mixtures of ethanol and dichloromethane in ratio of 50:50 and 40:60 (Figure 28G-28H, 29A-29C). Whereas, scanning electron micrographs of the granules made from isopropyl alcohol exhibited fine particles and wide size distribution (Figure 28E-28F).
Figure 28  Scanning electron micrographs of granules produced from various granulating liquid (10X): mixtures of ethanol and dichloromethane in ratio 50:50 (A) after drying (B) rescreened through sieve no.20 mesh; mixtures of ethanol and dichloromethane in ratio 40:60 (C) after drying (D) rescreened through sieve no.20 mesh; isopropyl alcohol (E) after drying (F) rescreened through sieve no.20 mesh; isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v (G) After drying and (H) rescreened through sieve no.20 mesh
Figure 29 Scanning electron micrographs of granules produced using isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v and rescreened through sieve no. 40 mesh: (A) 10X ; (B) 100X and (C) 400X

3.8 Differential scanning calorimetry

The DSC thermograms of propranolol HCl, HPMC, lactose, physical mixture and propranolol HCl granule produced from various granulating liquids are shown in Figure 30-33. Propranolol HCl and HPMC exhibited the endothermic peak at 163.6 °C and 49.8 °C, respectively. The DSC thermogram of lactose showed two dominant endothermic peaks at 149.5 °C and 217.9 °C. From the thermograms of physical mixture between drug and excipient, all major peaks of each component could be still detected. All propranolol HCl granules showed the characteristic peaks in DSC thermograms of each component in formulation. Moreover, the thermograms of the propranolol HCl granule that produced using the mixtures of E:D ; 50:50 as granulating liquid and using
isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v exhibited decreasing intensity of propranolol HCl melting peak.

**Figure 30** DSC thermograms of lactose (A); HPMC K15M (B); propranolol HCl (C); physical mixture (D) and granule produced using mixtures of E:D, 50:50 as granulating liquid (E)
Figure 31  DSC thermograms of lactose (A); HPMC K15M (B); propranolol HCl (C); physical mixture (D) and granule produced using IPA as granulating liquid (E).
Figure 32  DSC thermograms of lactose (A); HPMC K15M (B); propranolol HCl (C); physical mixture (D) and granule produced using mixtures of IPA and water (10%) as granulating liquid (E)
Figure 33 DSC thermograms of lactose (A); HPMC K15M (B); propranolol HCl (C); physical mixture (D) and granule produced using water as granulating liquid (E).

3.9 Powder X-ray diffraction

The powder X-ray diffraction pattern of propranolol HCl, HPMC K15M, lactose and physical mixture are presented in Figure 34. The X-ray diffraction pattern of propranolol HCl matrix granules prepared with different granulating liquids are shown in Figure 35. The X-ray diffraction pattern of propranolol HCl displayed peak at diffraction angle between 10°2θ and 30°2θ. The X-ray diffraction pattern of lactose showed shape peak at diffraction angle between 18°2θ and 22°2θ. However, the characteristic peaks of physical mixture did not present a different peak from pure propranolol HCl, lactose and HPMC peak.
The X-ray diffraction pattern of propranolol HCl matrix granule was not different from physical mixture. But the intensity of diffraction peaks of propranolol HCl matrix granule at diffraction angle about $38^\circ 2\theta$ was decreased. This might be due to partially solubilization of lactose in these granulating liquids.

**Figure 34** X-ray diffraction spectra of lactose (A); HPMC K15M (B); propranolol HCl (C) and physical mixture (D)
Figure 35  X-ray diffraction spectra of propranolol HCl matrix granule made with different granulating liquids; (A) physical mixture; (B) water; (C) IPA; (D) IPA-water and (E) E:D, 50:50

4. Development of matrix granules for multiple-unit controlled release

The composition of propranolol HCl matrix granules prepared with various types and amounts of diluent to obtain the controlled release systems are presented in Table 7.

4.1 Evaluation of propranolol HCl matrix granule

4.1.1 Particle size distribution

4.1.1.1 The influence of types and amounts of diluents on the particle size distribution

The particle size distributions of propranolol HCl granules are shown in Figure 36. The particle size distributions depended on by the composition of
formulation such as types and amounts of diluents. The amount of large fine particles were found in the formulation combined lactose with HPMC and the formulation containing phytowax. The formulations containing 75% lactose and 25% HPMC showed the wide size distributions. The increasing amount of phytowax led to the high amount of large fine particles.

4.1.1.2 The influence of size of granule on the particle size distribution

The particle size of the almost granules rescreened through sieve no. 20 mesh were 850-425 µm. Obviously, the granules rescreened through sieve no. 16 mesh contained more the granules with particle size of 850 µm than that with the particle size of 425 µm.

Figure 36  Particle size distribution of granules produced from different diluents
4.1.2 Bulk density, Tapped density and Compressibility index

4.1.2.1 The influence of types and amounts of diluents on bulk density, tapped density and compressibility index

The bulk density and tapped density of propranolol HCl granules containing various types and amounts of diluents are presented in Table 17. The enhancement of bulk density and tapped density was found in cases of the formulation combined lactose with HPMC and the formulation containing phytowax. There was also a tendency of increase in the bulk density and the tapped density as the amount of phytowax was increased.

The compressibility indexes of powders were higher than the granules. As a result, the granules showed a better flow than the powders. Because of the wide particle size distribution characteristic, the compressibility index of formulations containing phytowax was higher than that of the other formula.

4.1.2.2 The influence of size of granule on bulk density, tapped density and compressibility index

The bulk density and tapped density of granules containing 75% xanthan and 25% HPMC rescreened through sieve no. 16 mesh were higher than the granules rescreened through sieve no. 20 mesh. The bulk density and tapped density of all granule formulations rescreened through sieve no. 16 mesh were similar, since the compressibility index was near to zero (Table 18).

4.1.3 Angle of repose

4.1.3.1 The influence of types and amounts of diluents on angle of repose

The angle of repose of powders was higher than that of the granules. This result indicated that the granules could flow better than the powders (Table
17). The granules containing 75% lactose and 25% HPMC that produced from 3% (w/v) and 5% (w/v) of PVP K90 in ethanol as binder solution in formulation and formulation F30 exhibited the angle of repose were in range of 22°-24° indicating the very good flowability. Whereas, the angle of repose of the others granule formulations was within ranged of 24°-30°. These revealed that they had a good flowability.

4.1.3.2 The influence of size of granule on angle of repose

The granules containing 75% xanthan and 25% HPMC rescreened through sieve no. 16 mesh and sieve no. 20 mesh exhibited not different values of angle of repose. This signified that the granule characteristic showed funicular state more than capillary state (Table 18).

4.1.4 Friability

4.1.4.1 The influence of types and amounts of diluents on granule friability

The friability of the granules depended on types and amounts of diluents and content of granulating liquid. The percentage of friability of the granules containing 75% lactose and 25% HPMC was higher than the granules containing 75% lactose and 25% HPMC that produced from 3% (w/v) and 5% (w/v) of PVP K90 in ethanol as binder solution in formulation (Table 19). In addition, the enhancement amount of phytowax resulted in the increase in the percentage of friability.

4.1.4.2 The influence of size of granule on friability

The friability of granules containing 75% xanthan and 25% HPMC rescreened through sieve no. 16 mesh was less than that of the granule passed through sieve no. 20 mesh, because the amount of water used in wet granulation of
granule size 16 mesh was greater than that of the granule size 20 mesh (Table 20). Therefore, percentage of friability of granule depended on the composition of formulation and % water used in wet granulation.

**Table 17** The flow properties of PPHCl granules containing different diluents rescreened through sieve no. 20 mesh

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (g/ml) (n=3)</th>
<th>Tapped density (g/ml) (n=3)</th>
<th>Carr's index (%) (n=3)</th>
<th>Angle of repose (θ) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose 75%</td>
<td>0.39 ± 0.01</td>
<td>0.41 ± 0.01</td>
<td>3.92 ± 1.89</td>
<td>29.80 ± 1.94</td>
</tr>
<tr>
<td>Phytowax 75%; melt method</td>
<td>0.45 ± 0.01</td>
<td>0.52 ± 0.01</td>
<td>14.13 ± 3.04</td>
<td>25.89 ± 1.52</td>
</tr>
<tr>
<td>Phytowax 100%</td>
<td>0.45 ± 0.01</td>
<td>0.52 ± 0.01</td>
<td>14.13 ± 3.04</td>
<td>26.10 ± 0.00</td>
</tr>
<tr>
<td>HPMC 100%</td>
<td>0.25 ± 0.00</td>
<td>0.27 ± 0.00</td>
<td>7.38 ± 0.11</td>
<td>24.70 ± 0.00</td>
</tr>
<tr>
<td>Avicel 75%</td>
<td>0.28 ± 0.01</td>
<td>0.29 ± 0.00</td>
<td>3.76 ± 1.56</td>
<td>28.40 ± 0.57</td>
</tr>
<tr>
<td>Xanthan 75%</td>
<td>0.42 ± 0.00</td>
<td>0.44 ± 0.01</td>
<td>5.56 ± 2.41</td>
<td>28.72 ± 2.85</td>
</tr>
<tr>
<td>Phytowax 75%*</td>
<td>0.39 ± 0.01</td>
<td>0.43 ± 0.00</td>
<td>9.18 ± 2.04</td>
<td>24.53 ± 2.25</td>
</tr>
<tr>
<td>Phytowax 50%*</td>
<td>0.37 ± 0.00</td>
<td>0.41 ± 0.01</td>
<td>9.88 ± 2.14</td>
<td>22.78 ± 0.98</td>
</tr>
<tr>
<td>Lactose 75%-PVP 3%</td>
<td>0.38 ± 0.01</td>
<td>0.41 ± 0.01</td>
<td>7.50 ± 0.16</td>
<td>22.93 ± 1.55</td>
</tr>
<tr>
<td>Lactose 75%-PVP 5%</td>
<td>0.45 ± 0.01</td>
<td>0.45 ± 0.01</td>
<td>0.00 ± 0.00</td>
<td>23.43 ± 0.56</td>
</tr>
</tbody>
</table>

* Propranolol HCl entrapped in phytowax.
Table 18  The flow properties of PPHCl granules containing different diluents rescreened through sieve no. 16 mesh

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (g/ml) (n=3)</th>
<th>Tapped density (g/ml) (n=3)</th>
<th>Carr's index (%) (n=3)</th>
<th>Angle of repose (θ) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel 50%+Ethocel 25%; 16# mesh passed</td>
<td>0.36 ± 0.00</td>
<td>0.36 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>26.25 ± 1.22</td>
</tr>
<tr>
<td>Xanthan 75%; 16# mesh passed</td>
<td>0.53 ± 0.00</td>
<td>0.53 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>28.95 ± 1.10</td>
</tr>
<tr>
<td>Xanthan 50%+ Eudragit L100 25%; 16# mesh passed</td>
<td>0.43 ± 0.00</td>
<td>0.43 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>26.54 ± 1.43</td>
</tr>
<tr>
<td>Xanthan 50%+Phytowax 25%*; 16# mesh passed</td>
<td>0.38 ± 0.01</td>
<td>0.38 ± 0.01</td>
<td>0.00 ± 0.00</td>
<td>24.07 ± 0.55</td>
</tr>
<tr>
<td>Corn strach 75%; 16# mesh passed</td>
<td>0.45 ± 0.01</td>
<td>0.45 ± 0.00</td>
<td>1.45 ± 2.51</td>
<td>24.84 ± 1.80</td>
</tr>
</tbody>
</table>

*Propranolol HCl entrapped in phytowax.

Table 19  The friability of PPHCl granules containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Friability (n=3)</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>xanthan 75%</td>
<td>3.14</td>
<td>1.71</td>
</tr>
<tr>
<td>avicel 75%</td>
<td>2.81</td>
<td>0.58</td>
</tr>
<tr>
<td>phytowax 75%</td>
<td>4.18</td>
<td>1.03</td>
</tr>
<tr>
<td>lactose 75%</td>
<td>7.14</td>
<td>1.01</td>
</tr>
<tr>
<td>lactose 75%-PVP 3%</td>
<td>6.49</td>
<td>0.58</td>
</tr>
</tbody>
</table>
The friability of PPHCl granules containing different diluents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Friability (n=3)</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactose 75%-PVP 5%</td>
<td>1.47</td>
<td>0.61</td>
</tr>
<tr>
<td>HPMC 100%</td>
<td>3.50</td>
<td>0.58</td>
</tr>
<tr>
<td>Phytowax 100%**</td>
<td>4.49</td>
<td>0.58</td>
</tr>
<tr>
<td>Phytowax 75%**</td>
<td>3.21</td>
<td>0.03</td>
</tr>
<tr>
<td>Phytowax 50%*</td>
<td>2.72</td>
<td>0.83</td>
</tr>
<tr>
<td>Xanthan 50%+Phytowax 25%*; 16# mesh passed</td>
<td>2.16</td>
<td>1.72</td>
</tr>
<tr>
<td>Xanthan 75% ; 16# mesh passed</td>
<td>1.23</td>
<td>0.07</td>
</tr>
<tr>
<td>Corn strach 75% ; 16# mesh passed</td>
<td>3.52</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Propranolol HCl entrapped in phytowax.
** The system was prepared with melt granulation method.

The volume of granulating liquid used for matrix granules prepared with wet granulation method

<table>
<thead>
<tr>
<th>Type of diluent</th>
<th>granulating liquid volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPA (ml)</td>
</tr>
<tr>
<td>xanthan 75%</td>
<td>70</td>
</tr>
<tr>
<td>avicel 75%</td>
<td>50</td>
</tr>
<tr>
<td>phytowax 75%</td>
<td>40</td>
</tr>
<tr>
<td>lactose 75%</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 20 (cont.) The volume of granulating liquid used for matrix granules prepared with wet granulation method

<table>
<thead>
<tr>
<th>Type of diluent</th>
<th>granulating liquid volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPA (ml)</td>
</tr>
<tr>
<td>lactose 75%-PVP 3%*</td>
<td>-</td>
</tr>
<tr>
<td>lactose 75%-PVP 5%*</td>
<td>-</td>
</tr>
<tr>
<td>HPMC 100%</td>
<td>100</td>
</tr>
<tr>
<td>Phytowax 100%**</td>
<td>-</td>
</tr>
<tr>
<td>Xanthan 50%+Phytowax 25%***; 16# mesh passed</td>
<td>50</td>
</tr>
<tr>
<td>Xanthan 75%; 16# mesh passed</td>
<td>60</td>
</tr>
<tr>
<td>Corn strach 75%; 16# mesh passed</td>
<td>50</td>
</tr>
</tbody>
</table>

* PVP solution (%w/v in 95% ethyl alcohol)
** The system was prepared with melt granulation method.
*** Propranolol HCl entrapped in phytowax.

4.2 Screening of formulation of matrix granule formulations using the dissolution test

The dissolution of propranolol HCl from granules filled into capsule was studied using basket method. The dissolution medium was HCl buffer pH 1.2. The speed of basket rotation was 50 rpm. The drug dissolution was tested for matrix granules formulation F28 that containing lactose 75% and HPMC 25% prepared with isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v (Figure 37). These propranolol HCl granules were filled into HPMC capsules and NP caps™ capsules.
4.2.1 The influence of type of capsule on the drug release

The release of propranolol HCl from granules filled into NP caps™ was faster than that of the granules filled into HPMC capsule. The granules filled into HPMC capsule exhibited a tendency to adhere to one another, because HPMC capsule could be hydrated slower than NP caps™. On the other hand, the NP caps™ could disintegrate quickly when it was contacted to the dissolution medium. Therefore, the NP caps™ capsule was chosen for development of the multiple-unit preparations. The polyplasdone XL which is a superdisintegrant was used to add into multiple-unit formulation to decrease the adhesion of the granules.

![Dissolution profiles of propranolol HCl released from HPMC matrix granules containing 75% lactose in HCl buffer pH 1.2 using basket method](image)

**Figure 37** Dissolution profiles of propranolol HCl released from HPMC matrix granules containing 75% lactose in HCl buffer pH 1.2 using basket method
4.2.2 The influence of types and amounts of diluents on the drug release from matrix granules

All granule matrix formulations were filled into NP caps™ capsule in this experiment. Additionally, the granules and polyplasdone XL of 20% were mixed together in plastic bag for 5 minutes before filled into capsules. The release of drug from these developed matrix granule capsules was as following:

**Hydrophilic matrix granules formulation**

The matrix granules containing 100% HPMC (formulation F29) showed slower drug release than the system containing 25% HPMC and 75% lactose (Figure 38). The percentage of drug release from these formula was more than 50% within 1 hours. The granules containing 75% lactose and 25% HPMC that produced from 3% (w/v) and 5% (w/v) of PVP K90 in ethanol as binder solution in formulation could decrease the amount of drug release at the first 2 hours (Figure 39).

---

**Figure 38** Dissolution profiles of propranolol HCl released from capsule filled with various hydrophilic components in HCl buffer pH 1.2 using basket method.
Figure 39  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing 75% lactose and PVP K90 in HCl buffer pH 1.2 using paddle method

Hydrophobic matrix granules and HPMC combined with hydrophobic matrix granules formulation

Hydrophobic wax granule was prepared in this study with melt granulation method. The hydrophobic wax granules (formulation F30) showed faster drug release than formulation F32 which containing 25% HPMC in formulation (Figure 40). The release profile of formulation F34 exhibited fast release in first 1 hours similar to the formulation F30.

The release profile of the formulation containing 75% avicel (formulation F35) was not different from that of formulation containing 75% lactose (Figure 41). The percentage of drug release from these formulations was more than 60% within 1 hours. Whereas, the formulation containing 75% xanthan (formulation F33) exhibited the drug release profile similar to the formulation containing 75% phytowax
(formulation F32) that was prepared by melt components in formulation (HPMC and propranolol HCl dispersed in melted phytowax).

Figure 40  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing various hydrophobic components in HCl buffer pH 1.2 using basket method.
**Figure 41** Dissolution profiles of propranolol HCl granules released from formulation containing 75% of various components in HCl buffer pH 1.2 using basket method.

*Comparison the release of drug which was tested with basket method and paddle method*

The above mentioned dissolution of propranolol HCl granules filled into capsule was studied using basket method. The dissolution release tested with basket method was compared to that with paddle method at 50 rpm as shown in Figure 42. The faster drug released was found in case of granules tested using paddle method. The release profile of formulation F32 was different from formulation F33 when both were tested with paddle method. The percentage of drug release within 2 hours of formulation F32 and formulation F33 was 90.37% and 75.79%, respectively.
The preparation of granules by entrapment of propranolol HCl into phytowax decreased the amount of drug release. The percentage of drug release from formulation that propranolol HCl entrapped into 75% phytowax was 71.05% at first 2 hours. Whereas, the percentage of drug release from formulation F32 prepared with melting the components of formulation was 90.37%.
Figure 43  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granules containing phytowax and xanthan at various ratios in HCl buffer pH 1.2 using paddle method.

4.2.3 The influence of granule size on the drug release from matrix granules

The matrix granules of formulation F33 was prepared into two sizes by passing the wet mass through sieve no. 16 mesh and sieve no. 20 mesh. The dissolution profile of the formulation F33 in different size of granule showed similar release profile.
Figure 44  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing 75% xanthan at granule size 16 mesh and 20 mesh in HCl buffer pH 1.2 using paddle method.

Figure 45 showed the drug release profiles of the matrix granules containing various compositions which were passed through sieve no. 16 mesh. The formulation F38 could prolong drug release longer than other formulations. This formulation was prepared by entrapment propranolol HCl into melted phytowax and passing through sieve no. 20 mesh. Subsequently, it was mixed with HPMC and xanthan by wet granulation before passing through a sieve no. 16 mesh.

The percentage of drug release from formulation F38 was less than 50% at the first 1 hours and could reach to 80% after 3.5 hours. The maximum percentage of drug release from this formulation was 95.50% at 8 hours. Whereas, the percentage of drug release from other formulations showed a fast drug release at the first 1 hours. The dissolution data of this formulation was fitted to higuchi’s model (Table 21). The release
exponent (n) of this formulation was 0.31 which was less than 0.45, indicating the release mechanisms was close to Fickian transport (Table 22).

![Dissolution profiles of propranolol HCl granules released from capsule filled with HPMC matrix granule containing various amounts and types of diluents in HCl buffer pH 1.2 using paddle method](image)

**Figure 45** Dissolution profiles of propranolol HCl granules released from capsule filled with HPMC matrix granule containing various amounts and types of diluents in HCl buffer pH 1.2 using paddle method

**Table 21** Comparison of degree of goodness-of-fit from curve fitting of drug dissolution in HCl buffer pH 1.2 to different release models.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Power law</th>
<th>First order</th>
<th>Higuchi's</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cd</td>
<td>msc</td>
<td>cd</td>
<td>msc</td>
</tr>
<tr>
<td>Formulation F38</td>
<td>0.9982</td>
<td>5.48</td>
<td>0.8729</td>
<td>1.49</td>
</tr>
</tbody>
</table>
Table 22  Estimate parameters from curve fitting of drug dissolution in HCl buffer pH 1.2 to power law expression.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>cd</th>
<th>k ± sd(^{10^{-1}})</th>
<th>tl ± sd (hr)</th>
<th>n ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation F38</td>
<td>0.9982</td>
<td>0.5713 ± 0.0172</td>
<td>0.38 ± 0.08</td>
<td>0.31 ± 0.02</td>
</tr>
</tbody>
</table>

4.2.4 The influence of pH of dissolution medium on the drug release from matrix granules

The matrix granule containing 75% lactose and 25% HPMC was chosen for investigation of the influence of pH of dissolution medium on the propranolol HCl release (Figure 46). The dissolution of propranolol HCl was studied using paddle method. The dissolution fluids were HCl buffer pH 1.2, phosphate buffer pH 6.8, pH change and distilled water. The speed of rotation was 50 rpm. The dissolution profile of propranolol HCl release in water was similar to that in buffer pH 6.8. Whereas, the dissolution profile of propranolol HCl release in HCl buffer pH 1.2 was similar to the release profile in pH change.
4.2.5 The influence of hydrodynamic force on the drug release from matrix granules

The matrix granule containing 75% lactose and 25% HPMC was chosen to investigate the influence of hydrodynamic force on the propranolol HCl release (Figure 47). The dissolution of propranolol HCl was studied using paddle method by varying the rotation speed of paddle as 25, 50, 100 and 150 rpm. As the rotation speed of paddle was increased, the rate of propranolol HCl release was increased.
Figure 47  Dissolution profiles of propranolol HCl released from capsule filled with HPMC matrix granule containing 75% lactose with different rotational speed of paddle in HCl buffer pH 1.2 using paddle method.

5. Weight variation

The mean and standard deviation of weight variation of single-unit and multiple-unit controlled release capsules of all formulations (F1-F38) are displayed in Table 23-24. All formulations were filled into capsules using manual filling capsule machine No.1. The weight variation of all formulations conformed the specification of standard official USP XXVIII (percentage deviation < 6). This indicated that all formulations could be uniformly filled into capsules.
Table 23  Weight variation of propranolol HCl controlled release capsule preparations (n=20)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>Weight variation (mg) (n=20)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>HPMC K4M</td>
<td>0.3246</td>
<td>0.005</td>
<td>1.54</td>
</tr>
<tr>
<td>F2</td>
<td>HPMC K15M</td>
<td>0.3114</td>
<td>0.003</td>
<td>0.96</td>
</tr>
<tr>
<td>F3</td>
<td>HPMC K100M</td>
<td>0.3196</td>
<td>0.003</td>
<td>0.94</td>
</tr>
<tr>
<td>F4</td>
<td>HPMC E15LV</td>
<td>0.3218</td>
<td>0.005</td>
<td>1.55</td>
</tr>
<tr>
<td>F5</td>
<td>Lactose 100%</td>
<td>0.4141</td>
<td>0.010</td>
<td>2.41</td>
</tr>
<tr>
<td>F6</td>
<td>Lactose 75%</td>
<td>0.3504</td>
<td>0.013</td>
<td>3.71</td>
</tr>
<tr>
<td>F7</td>
<td>Lactose 50%</td>
<td>0.3639</td>
<td>0.005</td>
<td>1.37</td>
</tr>
<tr>
<td>F8</td>
<td>Lactose 25%</td>
<td>0.3309</td>
<td>0.008</td>
<td>2.42</td>
</tr>
<tr>
<td>F9</td>
<td>DCP 100%</td>
<td>0.4755</td>
<td>0.018</td>
<td>3.79</td>
</tr>
<tr>
<td>F10</td>
<td>DCP75%</td>
<td>0.4394</td>
<td>0.004</td>
<td>0.91</td>
</tr>
<tr>
<td>F11</td>
<td>DCP 50%</td>
<td>0.4007</td>
<td>0.010</td>
<td>2.50</td>
</tr>
<tr>
<td>F12</td>
<td>DCP 25%</td>
<td>0.3508</td>
<td>0.005</td>
<td>1.43</td>
</tr>
<tr>
<td>F13</td>
<td>Xanthan 100%</td>
<td>0.3978</td>
<td>0.015</td>
<td>3.77</td>
</tr>
<tr>
<td>F14</td>
<td>Xanthan 75%</td>
<td>0.3840</td>
<td>0.005</td>
<td>1.30</td>
</tr>
<tr>
<td>F15</td>
<td>Xanthan 50%</td>
<td>0.3608</td>
<td>0.006</td>
<td>1.66</td>
</tr>
<tr>
<td>F16</td>
<td>Xanthan 25%</td>
<td>0.3399</td>
<td>0.004</td>
<td>1.18</td>
</tr>
<tr>
<td>F17</td>
<td>Eudragit L100; 100%</td>
<td>0.3389</td>
<td>0.004</td>
<td>1.18</td>
</tr>
<tr>
<td>F18</td>
<td>Eudragit L100; 75%</td>
<td>0.3344</td>
<td>0.002</td>
<td>0.60</td>
</tr>
<tr>
<td>F19</td>
<td>Eudragit L100; 50%</td>
<td>0.3266</td>
<td>0.002</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Table 23 (cont.)  Weight variation of propranolol HCl controlled release capsule preparations (n=20)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>Weight variation (mg)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F20</td>
<td>Eudragit L100; 25%</td>
<td>0.3229</td>
<td>0.003</td>
<td>0.93</td>
</tr>
<tr>
<td>F21</td>
<td>Chitosan 100%</td>
<td>0.2432</td>
<td>0.003</td>
<td>1.23</td>
</tr>
<tr>
<td>F22</td>
<td>Chitosan 75%</td>
<td>0.2614</td>
<td>0.006</td>
<td>2.30</td>
</tr>
<tr>
<td>F23</td>
<td>Chitosan 50%</td>
<td>0.2745</td>
<td>0.006</td>
<td>2.19</td>
</tr>
<tr>
<td>F24</td>
<td>Chitosan 25%</td>
<td>0.2941</td>
<td>0.003</td>
<td>1.02</td>
</tr>
<tr>
<td>F25</td>
<td>NaHCO₃ 60%</td>
<td>0.3493</td>
<td>0.004</td>
<td>1.15</td>
</tr>
<tr>
<td>F26</td>
<td>NaHCO₃ 40%</td>
<td>0.3377</td>
<td>0.004</td>
<td>1.18</td>
</tr>
<tr>
<td>F27</td>
<td>NaHCO₃ 20%</td>
<td>0.3315</td>
<td>0.004</td>
<td>1.21</td>
</tr>
</tbody>
</table>

Table 24  Weight variation of propranolol HCl granules filled in capsules (n=20)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>weight variation (mg)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F28</td>
<td>Lactose 75%+ HPMC 25%</td>
<td>0.2998</td>
<td>0.008</td>
<td>2.67</td>
</tr>
<tr>
<td>F29</td>
<td>HPMC 100%</td>
<td>0.2311</td>
<td>0.005</td>
<td>2.16</td>
</tr>
<tr>
<td>F30</td>
<td>Phytowax 100%</td>
<td>0.3728</td>
<td>0.010</td>
<td>2.68</td>
</tr>
<tr>
<td>F31</td>
<td>Phytowax 50%+ HPMC 50%</td>
<td>0.3109</td>
<td>0.015</td>
<td>4.82</td>
</tr>
<tr>
<td>F32</td>
<td>Phytowax 75%+ HPMC 25%</td>
<td>0.3058</td>
<td>0.007</td>
<td>2.29</td>
</tr>
<tr>
<td>F33</td>
<td>Xanthan 75%+ HPMC 25%</td>
<td>0.3345</td>
<td>0.005</td>
<td>1.49</td>
</tr>
</tbody>
</table>
Table 24 (cont.) Weight variation of propranolol HCl granules filled in capsules (n=20)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>weight variation (mg) (n=20)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F34</td>
<td>Avicel 75%+ HPMC 25%</td>
<td>0.2413</td>
<td>0.005</td>
<td>2.07</td>
</tr>
<tr>
<td>F35</td>
<td>Cornstarch 75%+ HPMC 25%; 16m</td>
<td>0.3291</td>
<td>0.005</td>
<td>1.52</td>
</tr>
<tr>
<td>F36</td>
<td>Avicel 50%+ Ethocel 25%+HPMC 25%; 16# mesh passed</td>
<td>0.2784</td>
<td>0.006</td>
<td>2.16</td>
</tr>
<tr>
<td>F37</td>
<td>Eudragit 25% + Xanthan 50%+ HPMC 25%; 16# mesh passed</td>
<td>0.3175</td>
<td>0.005</td>
<td>1.57</td>
</tr>
<tr>
<td>F38</td>
<td>Phytowax 25%+ Xanthan 50%+ HPMC 25%; 16# mesh passed</td>
<td>0.2908</td>
<td>0.005</td>
<td>1.72</td>
</tr>
</tbody>
</table>

6. Content uniformity

The content of single-unit controlled release capsules containing various diluents are shown in Table 25. The percentage of drug contents of all formulations (F1-F27) passed the specification of standard official USP XXVIII that the percentage of drug content for extended-release propranolol HCl capsule was not less than 90.0 percent and not more than 110.0 percent. But the percentage of drug contents of the propranolol HCl matrix granule formulations filled into capsules did not pass the specification of standard official USP XXVIII since they were less than 90.0 percent (Table 26).

The formulations that passed the specification of drug content must be examined on the uniformity of content. The content uniformity was determined by percentage of coefficient variation (%CV) as shown in Table 25. The percentages of coefficient variation were less than 6%, which passed the specification of standard official USP.
XXVIII. All formulation had percentages of coefficient variation less than 6% that signified the uniformity of drug content.

Table 25  Percentage of label amount of propranolol HCl in capsules preparation (n=10)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>% Label amount (n=10)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>HPMC K4M</td>
<td>104.07</td>
<td>2.36</td>
<td>2.27</td>
</tr>
<tr>
<td>F2</td>
<td>HPMC K15M</td>
<td>104.63</td>
<td>3.92</td>
<td>3.75</td>
</tr>
<tr>
<td>F3</td>
<td>HPMC K100M</td>
<td>105.61</td>
<td>1.72</td>
<td>1.63</td>
</tr>
<tr>
<td>F4</td>
<td>HPMC E15LV</td>
<td>104.97</td>
<td>1.94</td>
<td>1.85</td>
</tr>
<tr>
<td>F5</td>
<td>Lactose 100%</td>
<td>109.16</td>
<td>3.93</td>
<td>3.60</td>
</tr>
<tr>
<td>F6</td>
<td>Lactose 75%</td>
<td>93.12</td>
<td>4.29</td>
<td>4.61</td>
</tr>
<tr>
<td>F7</td>
<td>Lactose 50%</td>
<td>105.37</td>
<td>2.90</td>
<td>2.75</td>
</tr>
<tr>
<td>F8</td>
<td>Lactose 25%</td>
<td>109.97</td>
<td>3.73</td>
<td>3.39</td>
</tr>
<tr>
<td>F9</td>
<td>DCP 100%</td>
<td>106.95</td>
<td>4.37</td>
<td>4.09</td>
</tr>
<tr>
<td>F10</td>
<td>DCP 75%</td>
<td>107.15</td>
<td>2.81</td>
<td>2.62</td>
</tr>
<tr>
<td>F11</td>
<td>DCP 50%</td>
<td>108.93</td>
<td>2.53</td>
<td>2.32</td>
</tr>
<tr>
<td>F12</td>
<td>DCP 25%</td>
<td>106.52</td>
<td>3.19</td>
<td>2.99</td>
</tr>
<tr>
<td>F13</td>
<td>Xanthan 100%</td>
<td>94.04</td>
<td>2.42</td>
<td>2.57</td>
</tr>
<tr>
<td>F14</td>
<td>Xanthan 75%</td>
<td>98.95</td>
<td>2.23</td>
<td>2.25</td>
</tr>
<tr>
<td>F15</td>
<td>Xanthan 50%</td>
<td>98.29</td>
<td>3.07</td>
<td>3.12</td>
</tr>
<tr>
<td>F16</td>
<td>Xanthan 25%</td>
<td>99.97</td>
<td>1.85</td>
<td>1.85</td>
</tr>
<tr>
<td>F17</td>
<td>Eudragit L100; 100%</td>
<td>96.81</td>
<td>4.35</td>
<td>4.49</td>
</tr>
</tbody>
</table>
Table 25 (cont.) Percentage of label amount of propranolol HCl in capsules preparation (n=10)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Name</th>
<th>% Label amount (n=10)</th>
<th>S.D.</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F18</td>
<td>Eudragit L100; 75%</td>
<td>97.25</td>
<td>3.79</td>
<td>3.90</td>
</tr>
<tr>
<td>F19</td>
<td>Eudragit L100; 50%</td>
<td>96.30</td>
<td>1.27</td>
<td>1.32</td>
</tr>
<tr>
<td>F20</td>
<td>Eudragit L100; 25%</td>
<td>99.07</td>
<td>1.95</td>
<td>1.97</td>
</tr>
<tr>
<td>F21</td>
<td>Chitosan 100%</td>
<td>100.15</td>
<td>3.24</td>
<td>3.24</td>
</tr>
<tr>
<td>F22</td>
<td>Chitosan 75%</td>
<td>100.60</td>
<td>3.58</td>
<td>3.56</td>
</tr>
<tr>
<td>F23</td>
<td>Chitosan 50%</td>
<td>99.28</td>
<td>2.75</td>
<td>2.77</td>
</tr>
<tr>
<td>F24</td>
<td>Chitosan 25%</td>
<td>100.00</td>
<td>2.20</td>
<td>2.20</td>
</tr>
<tr>
<td>F25</td>
<td>NaHCO₃ 60%</td>
<td>106.30</td>
<td>1.98</td>
<td>1.86</td>
</tr>
<tr>
<td>F26</td>
<td>NaHCO₃ 40%</td>
<td>103.00</td>
<td>3.89</td>
<td>3.78</td>
</tr>
<tr>
<td>F27</td>
<td>NaHCO₃ 20%</td>
<td>100.32</td>
<td>2.04</td>
<td>2.03</td>
</tr>
<tr>
<td>Formulation</td>
<td>Name</td>
<td>% Label amount (n=10)</td>
<td>S.D.</td>
<td>% CV</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>----------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>F28</td>
<td>Lactose 75%+HPMC 25%</td>
<td>62.01</td>
<td>3.93</td>
<td>6.34</td>
</tr>
<tr>
<td>F29</td>
<td>HPMC 100%</td>
<td>56.35</td>
<td>1.41</td>
<td>2.50</td>
</tr>
<tr>
<td>F30</td>
<td>Phytowax 100%</td>
<td>61.45</td>
<td>4.65</td>
<td>7.57</td>
</tr>
<tr>
<td>F31</td>
<td>Phytowax 50%+HPMC 50%</td>
<td>62.41</td>
<td>4.92</td>
<td>7.88</td>
</tr>
<tr>
<td>F32</td>
<td>Phytowax 75%+HPMC 25%</td>
<td>57.55</td>
<td>3.71</td>
<td>6.45</td>
</tr>
<tr>
<td>F33</td>
<td>Xanthan 75%+HPMC 25%</td>
<td>61.15</td>
<td>2.02</td>
<td>3.30</td>
</tr>
<tr>
<td>F34</td>
<td>Avicel 75%+HPMC 25%</td>
<td>67.27</td>
<td>3.08</td>
<td>4.58</td>
</tr>
<tr>
<td>F35</td>
<td>Cornstarch 75%+ HPMC 25%; 16# passed</td>
<td>76.76</td>
<td>4.73</td>
<td>6.16</td>
</tr>
<tr>
<td>F36</td>
<td>Avicel 50%+ Ethocel 25%+HPMC25%; 16# passed</td>
<td>85.28</td>
<td>4.54</td>
<td>5.32</td>
</tr>
<tr>
<td>F37</td>
<td>Eudragit 25% +Xanthan 50%+ HPMC 25%; 16# passed</td>
<td>68.52</td>
<td>2.26</td>
<td>3.30</td>
</tr>
<tr>
<td>F38</td>
<td>Phytowax 25%+Xanthan 50%+HPMC 25%; 16# passed</td>
<td>51.89</td>
<td>2.83</td>
<td>5.45</td>
</tr>
</tbody>
</table>
CHAPTER V
DISCUSSION

In this study, the propranolol HCl sustained release capsule prepared from HPMC-based matrices were prepared and evaluated. The utilization of HPMC as matrix former could extend the release time of propranolol HCl from capsule. Owing to the hydrophilic nature of HPMC, it swelled on contact with water or biological fluid and thereafter the medium diffuses into the device. Generally, the thickness of swollen layer formed around the matrix core was greater in matrices containing HPMC with higher viscosity grade (Wan et al., 1994). Increasing the molecular weight of HPMC powder from K4M grade to K15M grade had no effect on the drug release. A possible explanation was the existence of a limiting HPMC viscosity, which no further decrease in drug release was appeared probably due to the time necessary to form the release-limiting gel barrier (Sung et al., 1996; Krogel and Bodmeier, 1999). While the drug release profile from HPMC K100M matrix was slightly lower than previous two viscosity grades. In this case, the increasing viscosity grade of HPMC could cause the thickness of gel layer increased and subsequently the tortuosity of the diffusion path of drug increased. In addition, the HPMC particles of increasing viscosity grades swelled slower and produced swollen particles of smaller volumes. As the result, matrices made of particles of HPMC with higher viscosity grades showed slower drug release rates than those made of HPMC particles with lower viscosity grades (Panomsuk et al., 1995; Campos-Aldrete et al., 1996). On the other hand, the increasing burst effect produced by higher viscosity grades might be attributed to slower swelling rates with increasing viscosity grades, allowing greater time for the free dissolution of drug before the gel barrier established (Campos-Aldrete et al., 1996).

Besides the development of propranolol HCl sustained release matrix in capsule (single-unit dosage form), the other goal of this study was to prepare
propranolol HCl matrix granule containing HPMC-based by wet granulation method and then filled into capsule for development as the multiple-unit dosage form. Therefore, the viscosity grade of HPMC used in this study had to be considered in order to select for a matrix granule preparation. The viscosity of HPMC in this study should not be too high or low and it could control the drug release. From preliminary study, the drug release rate was no longer decreased when the viscosity grade was increased above HPMC K15M grade or viscosity value above 15000 cps (Table 27). Moreover, to compare with the two polymers that had a lower molecular weight, the rather higher molecular weight HPMC polymers, such as Methocel® K15M, swelled but did not erode to a significant extent because of their higher intrinsic water-holding capacity (Kavanah and Corrigan, 2004). These properties consequently allowed avoidance of the burst effect and improved prolonged release. Hence, HPMC K 15M was chosen as matrix former in the formulations for investigation the factors affecting the release of propranolol HCl from HPMC matrix system filled in capsule as single-unit and multiple-unit.

### Table 27

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C (Rowe et al., 2003).

<table>
<thead>
<tr>
<th>Methocel grade</th>
<th>Nominal</th>
<th>Viscosity (mPa.s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K 100LVP</td>
<td>100</td>
<td>80-120</td>
</tr>
<tr>
<td>K 4M</td>
<td>4000</td>
<td>3000-5600</td>
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<tr>
<td>E 4MP</td>
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</tr>
<tr>
<td>E 3 PREM.LV</td>
<td>-</td>
<td>2.4-3.6</td>
</tr>
</tbody>
</table>
Table 27 (cont.)  Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C (Rowe et al., 2003).

<table>
<thead>
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<th>Methocel grade</th>
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<td>12-18</td>
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<tr>
<td>K 3 PREM.LV</td>
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<td>2.4-3.6</td>
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</table>

Effect of the water soluble and insoluble fillers on the drug release from HPMC matrix in capsule (single-unit dosage form)

Incorporation of lactose or dibasic calcium phosphate in HPMC matrix system decreased the concentration of polymer in gel layer. Therefore, the diffusion of medium into the capsule was facilitated and then this enhanced the diffusivity of drug out of matrix. As a result, the release rate of drug from matrices was increased. Changing the polymer/filler ratio increased the release rate by altering the diffusivity of drug in gel layer (Lotfipour et al., 2004). Because pH of dibasic calcium phosphate is 7.3, it led to increase the drug release in HCl buffer pH 1.2. Lactose or dibasic calcium phosphate had similar effect on the release of propranolol HCl from HPMC matrices. This result indicated hydrophilicity and hydrophobicity of fillers had no significant effect on the release profile (Williams et al., 2002; Lotfipour et al., 2004).
Effect of polymer on the drug release from HPMC matrix in capsule (single-unit dosage form)

The propranolol HCl release from matrix system containing HPMC was slower than that containing other polymers because of high swelling capacity and gel formation of HPMC to retard the drug release. The propranolol HCl released from HPMC-xanthan gum matrices was rather complex. Because HPMC and xanthan gum are hydrophilic polymer and upon contact with aqueous fluid both are able to form quite viscous gel. Xanthan gum might also increase the viscous gel layer around the matrix core. In addition, the synergism attributed to the intermolecular hydrogen-bonding between them could be occurred. The addition of sodium carboxymethylcellulose (NaCMC) to HPMC increased the viscosity of system, since there was the strong hydrogen bonding between the carboxyl groups on NaCMC and the hydroxyl groups on HPMC, leading to strong cross-linking between the two polymers (Walker and Wells, 1982). Hence, the formulation containing 50% xanthan gum and 50% HPMC resulted in the increase in the viscosity of gel layer and subsequently the retardation of drug diffusion from the capsule.

The other reason for retardation of drug release with xanthan gum could be the contribution to the ionic interactions between drug and anionic polymers. There was a considerable propranolol HCl and anionic polymer interaction depending on the carboxyl functional groups of anionic polymers (Takka, 2003). The formulation containing various amount of Eudragit L 100 in HPMC matrices showed almost similar release profile in HCl buffer pH 1.2 except the formulation containing only Eudragit L 100. These results indicated that HPMC played a dominant role in the drug release from these mixtures. Eudragit L 100 is a pH-dependent polymer which, dissolves in medium with > pH 6 lead to less solubility in medium with pH 1.2. The incorporation of basic excipients into matrices would not only keep the solubility of the highly soluble basic drugs low in the low pH range but provide the prolongation of
drug release without burst effect (Varma et al., 2004). Furthermore, the retarding effect was probably caused by the interaction of cationic propranolol HCl with the anionic polymer in the dissolution medium as the above mentioned.

The hydrophilicity of chitosan, due to the presence of amine and hydroxy functional groups in its repeat unit, makes the polymer soluble in dilute acidic solutions (Schellekens & Bastiansen, 1991). It is insoluble in water but soluble at pH values under 6.5 in most acidic media (Oungbho and Muller, 1997). Therefore, the dissolution profile of propranolol HCl released from chitosan matrix exhibited fast release after 4 hours in HCl buffer pH 1.2. The incorporation of chitosan in HPMC matrices could decrease the amount of drug released. Because of gel forming ability of chitosan, the synergism attributed to the intermolecular hydrogen-bonding between hydroxy functional groups on chitosan and hydroxyl groups on HPMC could be occurred. The release of propranolol HCl was increased as the chitosan content was increased.

**Effect of sodium bicarbonate on the drug release from HPMC matrix in capsule (single-unit dosage form)**

The incorporation of sodium bicarbonate in concentration of 40% into HPMC matrix could slightly prolong drug release in HCl buffer pH 1.2. Increasing proportion of sodium bicarbonate up to 60% in HPMC-bicarbonate matrices provided a slow drug release during the first 2 hours and following faster release. Since, sodium bicarbonate posed as effervescence at the high concentration in acid condition, it could promote a sustain drug release when a suitable concentration was employed. Sodium bicarbonate provided gas generation in HCl buffer pH 1.2. Therefore, the air bubbles appeared in swollen matrix might be as a transport barrier. It has been reported that the incorporation of sodium bicarbonate into HPMC K4M matrix tablets reduced the release rate of diltiazem hydrochloride. *In situ* chemical interaction within the gelled
structure might induce the alteration of matrix-swelling dynamics and inhibition of drug dissolution (Pillay and Fassihi, 1999).

**Effect of granulating liquid on the granulation mechanism**

The formulation containing 25% HPMC and 75% lactose was used to prepare as the matrix granule. Utilization of water as granulating liquid in wet granulation method led to the large amount of lump formation in wet mass and the obtained wet mass was difficult to pass through sieve to form the granules due to hydrophilicity and gel formation of HPMC in the formulation. HPMC could be soluble in mixtures of ethanol and dichloromethane in ratio of 50:50, 40:60 and 30:70 similar to in the water but the viscosity of HPMC solution using these liquids were less than that in the water (Figure 24-26 and Table 14). This result indicated that HPMC could swell in mixtures of ethanol and dichloromethane less than in the water. Ethanol and dichloromethane were rapidly evaporated. Thus, the utilization of mixtures between ethanol and dichloromethane in ratio of 50:50, 40:60 and 30:70 as granulating liquid provided the granules with a good characteristic thereby the lump formation was not occurred.

In addition, isopropyl alcohol could be used for agglomeration of powder mixture since it exhibited a good wetting and slower evaporation than ethanol. The lump formation was disappeared but the large amount of fine particle was occurred when isopropyl alcohol was utilized as granulating liquid. In order to increase a binding property, the water was added about 10% (v/v). HPMC could act as its own binder by forming a gel layer in contact with water (Herder et al., 2006). Therefore, the water was an important factor in the HPMC matrix granule preparation.

**Effect of granulating liquid on the granule properties**

During wet mass granulation and the stages of drying, the drug and any soluble excipients will dissolve and then recrystalize, forming solid interparticulate bridges
after the binder vehicle is evaporated. The strength of the crystalline bridges depends on the amount deposited and rate of crystallization. Both these properties are dependent on the solubility of the drug and other excipients in the granulating solvent (Khankari and Hontz, 1997). The granules produced using the mixtures of ethanol and dichloromethane in ratio of 50:50 and 40:60 contained a more porous surface (Figure 28A-28D) because lactose in formulation was not soluble in mixtures of ethanol and dichloromethane in ratio of 50:50 but HPMC and propranolol HCl could soluble in this liquid (Figure 24, 48-49). Therefore, solid interparticulate bridges of the granules might be less compact and this resulted in the more porous on surface of granule. Moreover, the percentage of friability of these granules was higher than that of the granules matrix that was produced using isopropyl alcohol and subsequently adding with water in amount of 10% v/v. The surface of the granules produced using isopropyl alcohol and subsequently adding with water in amount of 10% v/v showed the dense agglomerated particles and exhibited the less porous surface than the granules that were produced with mixtures of ethanol and dichloromethane in ratio of 50:50 and 40:60 (Figure 28G-28H, 29A-29C). Because lactose and propranolol HCl could be soluble in the former solvent (Figure 48-49) and HPMC in formulation acted as binder after exposure to the water, resulted in the stronger adhesional and cohesional forces in bonding between particles. Furthermore, the percentage of friability of the granules was decreased. Wells and Walker (1983) reported the effect of wet-massing acetylsalicylic acid with aqueous and hydroalcoholic solutions of PVP. The greater drug solubility produced the granules of larger size, tighter particle size distribution and reduced a friability.

Therefore, using isopropyl alcohol as granulating liquid and subsequently adding with water in amount of 10% v/v was the appropriate system in wet granulation method in this experiment. This granulating liquid was used for development of the propranolol HCl matrix granules.
The DSC thermogram of physical mixture (propranolol HCl, HPMC and lactose) and the matrix granule exhibited all major peaks of each component indicating the mixtures to be compatible. The DSC thermogram of lactose exhibited two endothermic peaks. The first endothermic corresponded to the loss of water of crystallization and the second endothermic peak corresponded to the melting of lactose followed by its decomposition (Larhrib et al., 2003).

From X-ray powder diffractograms, propranolol HCl and lactose showed a crystalline characteristic. The intensity of diffraction peaks of propranolol HCl in matrix granule at diffraction angle about $38^\circ 2\theta$ was decreased. This might be due to partially solubilization of lactose in the granulating liquids.

**Figure 48** Appearance of systems containing lactose in water, mixtures of ethanol and dichloromethane in ratio of 50:50, mixtures of isopropyl alcohol and water (10% v/v) and IPA, respectively (left to right).
Figure 49  Appearance of systems containing lactose in IPA, mixtures of isopropyl alcohol and water (10% v/v), water and mixtures of ethanol and dichloromethane in ratio of 50:50, respectively (left to right).

**Effect of excipients on the granule properties**

The matrix granule formulation containing phytowax exhibited wide particle size distribution and higher compressibility index. In addition, the bulk density, tapped density and percentage of friability were increased when the amount of phytowax increased. These results caused by the phytowax in formulation which was prepared by melt granulation, since the melted mass of phytowax rapidly became to solid state after passing through sieve resulted in the wide particle size distribution.

**Effect of development of HPMC matrix granule on the drug release from HPMC matrix granule filled into capsule (multiple-unit dosage form)**

The propranolol HCl matrix granule containing HPMC-based was developed for multiple-unit dosage form. Different excipients were used to achieve the sustained drug release. The prepared granules filled into NP cap™ capsule since this capsule could disintegrate quickly after contact to the dissolution medium. The polyplasdone XL was used to add into multiple-unit formulation as superdisintegrant to decrease the
adhesion of the granules during dissolution test. The drug release from the granule containing 75% lactose and 25% HPMC was more than 50% within 1 hour using basket method, since the granule comprised the more porous surface and the presence of water-soluble filler. The PVP K90 solution was also used as binder in the formulation for enhancement the strength of agglomerate of powders. This was expected that the stronger or more compact matrix granule could better sustain drug release. The propranolol HCl matrix granule containing PVP K90 as the binder in formulation showed fast drug release at first 2 hour and completed the drug release within 3 hour both in case of the formulation containing 3% PVP and 5% PVP using paddle method of dissolution test. Moreover, these granules exhibited a tendency to adhere to one another when the granules were hydrated. HPMC and PVP were highly miscible through hydrogen bonding between the free hydroxyl groups of HPMC and the carbonyl group of PVP (Hiremath et al., 2002). Through intimate mixing during hydration of the dosage form and through the formation of strong hydrogen bonds between PVP and HPMC, the strength of HPMC gel was reduced at a critical PVP concentration (Hardy et al., 2007). Thus, increasing content of PVP K90 to 5% posed the faster drug release than the formulation containing 3% PVP K90 even if percentage of friability was lower. The release of propranolol HCl still was rapid in case of the formulation containing 100% HPMC. This formulation limited of amount of water that used in wet granulation due to hydrophilicity of HPMC. As a result the granule quite loose compact powders and contained more porous surface. It could confirm by the values of bulk density and tapped density which it had the lowest bulk density and tapped density.

Therefore, the less hydrophilic materials were used in this study. The formulation containing 75% avicel and 25% HPMC showed similar release profile to the formulation containing 75% lactose and 25% HPMC using basket method of dissolution test. This could result from the disintegration property of avicel (Cox et
al., 1999). When contact with the dissolution medium, HPMC swelled and became the hydrated gel. At the same time avicel which had disintegration properties, promoted the disintegration of the granule. The dispersion of propranolol HCl in 100% phytowax by melt granulation did not decrease the drug release because propranolol HCl did not dissolve in phytowax. In addition, it deposited on the surface of the granule, thus the drug dissolved and diffused from the surface of the granules. There was a decrease in drug release from the formulation containing 75% phytowax and 25% HPMC that was prepared by melt granulation. Because propranolol HCl and HPMC were dispersed in melted phytowax, they were not dissolved in phytowax. Thus, HPMC in the formulation still could swell form gel when the granules were hydrated. The drug released from surface of the granule and hydrated gel of HPMC.

Previously it was demonstrated that the increase of gel viscosity was synergistic when mixtures of xanthan gum and HPMC were used in capsule (single-unit). Thus, this mixture was also prepared in wet granulation technique. The granule formulation containing 75% xanthan gum and 25% HPMC exhibited similar release profile to the formulation that containing 75% phytowax and 25% HPMC that prepared by melt granulation. The dissolution of propranolol HCl from matrix granules examined using basket method might able to increase the tendency of hydrated granule to adhere to one another of granule due to the limited dispersion of granules in basket. Therefore, the dissolution of propranolol HCl from matrix granules examined using paddle method. The granules formulation containing 75% xanthan gum and 25% HPMC and the formulation containing 75% phytowax and 25% HPMC that were prepared by melt granulation exhibited faster drug release than that examined using basket method. Since, a dispersion area of the granules was increased and a surface area of the granules contacting with dissolution medium was increased, the drug release was increased.
The formulation containing phytowax and HPMC was modified by dispersing propranolol HCl in melted phytowax to produce propranolol HCl wax granules. Thereafter propranolol HCl wax granules were mixed with HPMC to produce HPMC matrix granule by wet granulation. The amount of drug release decreased but the rate of drug release was still fast release at the first 1 hour (> 50%).

The matrix granules were attempted to produce into the larger size to decrease the surface area of granule, by passing the wet mass through the sieve no.16 mesh of wet mass. The various excipients were used in this preparation. Most of dissolution profiles exhibited fast release even they contained a hydrophobic polymer or a pH-dependent polymer in the formulations. Because the drug deposited at surface area of granule was dissolved and diffused out from matrix, the percentage of drug release was more than 60% within 1 hour. However, dispersion of propranolol HCl in melted phytowax (25%) to produce propranolol HCl wax granule by passing the wet mass through the sieve no.20 mesh. Thereafter propranolol HCl wax granules (20 mesh) were mixed with 25% HPMC and 50% xanthan gum to produce matrix granule size 16 mesh by wet granulation. This granule formulation exhibited the percentage of drug release of 50% within 1 hour and following sustained drug release, since propranolol HCl entrapped in phytowax was gradually dissolved and diffused through strong gel matrix. The increasing of the viscous of gel layer around matrix core attributed to the intermolecular hydrogen-bonding between HPMC and xanthan gum. This synergistic of gel structure could decrease the amount of drug release.

**Effect of pH of dissolution medium on the drug release**

The effect of pH of dissolution medium on the release of propranolol HCl from capsules was investigated to simulate the environment of the gastrointestinal tract. The release of propranolol HCl from HPMC matrix in capsule (single-unit) was faster in water compared to that in HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH
change. Whereas, the release of propranolol HCl from HPMC matrix in capsule (single-unit) in HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change had similar release profiles. HPMC polymers are non-ionic and therefore the solubility and swelling behavior were not influenced by pH (Verma et al., 2004). The hydrogel formulation based on high-viscosity HPMC was known to deliver the drug at a constant rate independent of, in relation to the hydration, gel viscosity and relative permeability of dosage form. Since, the rate of drug release was related directly to the solubility of the drug (Takka et al., 2001). Propranolol HCl is a weakly basic drug. Therefore, it gave pH-dependent release from HPMC-based matrix formulations due to its pH-dependent solubility. The solubility was found to be 225 mg/ml at pH 1.2, 130 mg/ml at pH 6.8 and 360 mg/ml in water. The release of propranolol HCl was faster in water and 0.1 N HCl compared to that in a phosphate buffer (Takka et al., 2001). However, in this study propranolol HCl did not show the pH-dependent solubility from HPMC matrix granule filled into capsule.

**Effect of rotation speed of paddle on the drug release**

The effect of hydrodynamic force on the release of propranolol HCl from prepared capsules was investigated. The dissolution of propranolol HCl was studied in HCl buffer pH 1.2 by using paddle method. The release rate of propranolol HCl increased when the rotation speed of paddle was increased both in HPMC matrix in capsule (single-unit) and HPMC matrix granule filled into capsule (multiple-unit). There were more rapid erosion of matrix at higher stirring rates because the increased rate of detachment of polymer chains away from the matrix surface. This led to the thinner layer of gel forming at surface of the dosage form at higher agitation rates (Goole et al., 2007). This suggests that the drug release could change easily due to physical agitation and probably peristaltic movement in the gastrointestinal tract.
CHAPTER VI
CONCLUSION

In conclusion, the utilization of HPMC as matrix former could extend the release time of propranolol HCl from capsule longer than 8 hours. The factors affecting to the propranolol HCl release from HPMC matrix filled in capsule were investigated in this study. The HPMC viscosity grades used in this study hardly affected the drug release. The increase in concentration of fillers resulted in the increase in the release rate of propranolol HCl from HPMC matrices. The lactose and dibasic calcium phosphate had no significant effect on the drug release. The types and amounts of polymer apparently affected the propranolol HCl release from HPMC matrices. The release of propranolol HCl from xanthan gum-HPMC matrices and Eudragit L100-HPMC matrices were rather complex. HPMC played the dominant role in the drug release from Eudragit L100-HPMC matrices. The physiochemical of polymers and interaction between HPMC and polymers were the important factor for prolongation of the drug release. The incorporation of sodium bicarbonate in the concentration of 40% into HPMC matrix could prolong drug release in HCl buffer pH 1.2. Thereby, sodium bicarbonate might induce in situ chemical interaction within the HPMC gel structure. The release mechanism from HPMC-based matrices in capsule was non-Fickian transport.

In addition, the controlled release propranolol HCl matrix in multiparticulate dosage form was developed with wet granulation technique. The type of granulating liquid influenced on the granule properties. The system containing isopropyl alcohol and water was a suitable granulating liquid for agglomeration of powders. Water was the important factor in preparing the propranolol HCl matrix granule containing HPMC. In HCl buffer pH 1.2, most dissolution profiles of propranolol HCl from matrix granules filled into capsule were fast release. The granule formulation containing 25% phytowax,
50% xanthan gum and 25% HPMC (propranolol HCl dispersed in melted phytowax before mixed with HPMC and xanthan gum) exhibited different dissolution profile. The percentage of drug released of this formulation reached to 80% within 4 hours whereas the other granule formulations showed fast release. The drug release kinetics of this propranolol HCl matrix granule was fitted well with the Higuchi’s model.

The release of propranolol HCl from HPMC matrix in capsule (single-unit) was faster in water compared to that in HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change. The release of propranolol HCl from matrix granules filled into capsule (multiple-unit) displayed similar release behavior in water, HCl buffer pH 1.2, phosphate buffer pH 6.8 and pH change. The paddle rotation speed affected the release of propranolol HCl from single-unit and multiple-unit.


Kiortsis, S., Kachrimanis, K. and Broussali, T. “Drug release from tablets wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component”. European Journal of Pharmaceutics and Biopharmaceutics 59 (2005): 73-83.


APPENDIX I

Figure 50  Calibration curve of propranolol hydrochloride in water

![Graph](image1)
y = 0.0061x - 0.0065
R² = 0.9997

Figure 51  Calibration curve of propranolol hydrochloride in HCl buffer pH 1.2

![Graph](image2)
y = 0.0059x + 0.0034
R² = 0.9999
**Figure 52**  Calibration curve of propranolol hydrochloride in phosphate buffer pH 6.8

**Figure 53**  Calibration curve of propranolol hydrochloride in methanol
APPENDIX II

Table 28  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into HCl buffer pH 1.2 using basket method at 50 rpm

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<th>TIME (min.)</th>
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<th>PPHCL+HPMC K4M</th>
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Table 29

The percentage of cumulative release of propranolol HCl from HPMC matrix granule (20 mesh) filled into capsule in HCl buffer pH 1.2 using basket method at 50 rpm

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Table 29 (continued)

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Table 30  The percentage of cumulative release of propranolol HCl from HPMC matrix granule (20 mesh) filled into capsule in HCl buffer pH 1.2 using paddle method at 50 rpm

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Time for F33: Xanthan (75%) granule  Time for F 32: Phytowax (75%) granule, Melt method  Time for F 32: Phytowax (75%) granule, Entrap PPHCl  Time for F 31: Phytowax (50%) granule, Entrap PPHCl  Time for F 28: Lactose (75%) + PVP K90 3% granule  Time for F 28: Lactose (75%) + PVP K90 5% granule
Table 31  The percentage of cumulative release of propranolol HCl from HPMC matrix granule (16 mesh) filled into capsule in HCl buffer pH 1.2 using paddle method at 50 rpm

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F 36: Avicel(50%) +Ethocel(25%) granule  F 33: Xanthan(75%) granule  F 37: Xanthan(50%)+Eudragit L100(25%) granule

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Table 32  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into water using paddle method at 50 rpm

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Table 33  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into phosphate buffer pH 6.8 using paddle method at 50 rpm

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Table 34  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into pH change using paddle method at 50 rpm

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Table 35  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into buffer pH 1.2 using paddle method at 50 rpm

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Table 36
The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into buffer pH 1.2 using paddle method at 25 rpm

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Table 37
The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into buffer pH 1.2 using paddle method at 100 rpm

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Table 38  The percentage of cumulative release of propranolol HCl from HPMC matrix in capsule into buffer pH 1.2 using paddle method at 150 rpm

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Biography

| NAME | Wanwilai Darunkaisorn, Miss. |
| DATE OF BIRTH | May 28, 1981 |
| PLACE OF BIRTH | Nakornpathom |
| INSTITUTION ATTENDED |  
  Silpakorn University, 2000 – 2005 Bachelor of Pharmacy  
  Silpakorn University, 2005 – 2007 Master of Pharmacy (Pharmaceutical Technology) |
  Wanwilai Darunkaisorn, Kosin Euboonyanan, Khorjun Ngamsritapparit, Peera Srisantiwade, Lakhana Somprasong and Thawatchai Phaechamud. “Preparation of sustainable drug
release capsule with polyelectrolyte complex system”. The thirdth Industrial and Research Projects for Undergraduate Students Exhibition, Rama 2 Hall, Central department store Rama 2, May 1-3, 2005.