คุณสมบัติการปลดปล่อยฤทธิ์นานของยาธีโอฟิลินเมทริกซ์ ซึ่งประกอบด้วยสารผสมระหว่างแซนแทนกัม และไฮดรอกซีโพรพิลเมทิลเซลลูโลส

นางสาวปรินดา ศรีณรงค์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม
คณะเภสัชศาตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2543
ISBN 974-13-0825-6

SUSTAINED RELEASE PROPERTIES OF THEOPHYLLINE MATRICES CONTAINING MIXTURES OF XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE

Miss Parinda Srinarong

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Sciences in Pharmacy

Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University

Academic Year 2000
ISBN 974-13-0825-6

Thesis Title	Sustained Release Properties of Theophylline Matrices Containing Mixtures of Xanthan Gum and Hydroxypropyl Methylcellulose
By	Miss Parinda Srinarong
Field of Study	Industrial Pharmacy
Thesis Advisor	Associate Professor Poj Kulvanich, Ph.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements of the Master's Degree.

…… Dean of Faculty of Pharmaceutical Sciences

(Associate Professor Sunibhond Pummangura, Ph.D.)

THESIS COMMITTEE

……Chairman

(Associate Professor Garnpimol C. Ritthidej, Ph.D.)

……Thesis Advisor

(Associate Professor Poj Kulvanich, Ph.D.)

……Member

(Assistant Professor Panida Vayumhasuwan, Ph.D.)

……Member

(Assistant Professor Sirisak Dumrongpisudthigul, M.Sc.)

……Member

(Narueporn Sutanthavibul, Ph.D.)

ปรินดา ศรีณรงค์ : คุณสมบัติการปลดปล่อยฤทธิ์นานของยาธีโอฟิลินเมทริกซ์ ซึ่งประกอบด้วยสารผสมระหว่างแซนแทนกัม และไฮดรอกซีโพรพิล เมทิลเซลลูโลส (SUSTAINED RELEASE PROPERTIES OF THEOPHYLLINE MATRICES CONTAINING MIXTURES OF XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE) อ. ที่ปรึกษา : รศ.ดร. พจน์ กุลวานิช, 214 หน้า. ISBN 974-13-0825-6

งานวิจัยนี้ศึกษาคุณสมบัติการปลดปล่อยฤทธิ์นานของยาธีโอฟิลินเมทริกซ์ซึ่งประกอบด้วยสารผสมระหว่างแซนแทนกัมและไฮดรอกซีโพรพิล เมทิลเซลลูโลส รวมทั้งศึกษาปัจจัยที่มีอิทธิพลต่อการปลดปล่อยยาคือ ปริมาณของพอลิเมอร์ อัตราส่วนของแซนแทนกัมต่อไฮดรอกซีโพรพิล เมทิลเซลลูโลส สารละลายตัวกลางซึ่งมีความแรงอิออน หรือความเป็นกรด-ด่างที่แตกต่างกันและแรงที่ใช้ตอกอัดเมทริกซ์ เมทริกซ์ที่ประกอบด้วยปริมาณพอลิเมอร์ที่เพิ่มขึ้น (10 15 และ 20 เปอร์เซ็นต์)มีอัตราการปลดปล่อยยาที่ลดลง เมทริกซ์ที่เตรียมจากส่วนผสมของพอลิเมอร์สองชนิดนี้และสารเพิ่มปริมาณที่ละลายได้(สเปรย์ดรายแลคโตส)มีการปลดปล่อยยาที่มากกว่าเมทริกซ์ที่ประกอบด้วยสารเพิ่มปริมาณที่ไม่ละลาย(ไดเบซิคแคลเซียมฟอสเฟส) แรงตอกอัดที่แตกต่างกัน (1000 2000 และ 4000 ปอนด์)มีผลเล็กน้อยต่อการปลดปล่อยยา เมทริกซ์ซึ่งประกอบด้วยไฮดรอกซีโพรพิล เมทิลเซลลูโลสเพียงอย่างเดียวแสดงการปลดปล่อยยาที่รวดเร็วในช่วงต้น อย่างไรก็ตามการแทนไฮดรอกซีโพรพิล เมทิลเซลลูโลสด้วยแซนแทนกัมในอัตราส่วนของแซนแทนกัมต่อไฮดรอกซีโพรพิล เมทิลเซลลูโลสที่ระดับ 3:7 5:5 7:3 และ 10:0 สามารถลดการปลดปล่อยยาที่รวดเร็วในช่วงต้น ความแรงอิออนของสารละลายตัวกลางและความหนืดของชั้นเจลรอบเมทริกซ์มีอิทธิพลต่อการปลดปล่อยยาจากเมทริกซ์ซึ่งประกอบด้วยสารผสมระหว่างแซนแทนกัมและไฮดรอกซีโพรพิล เมทิลเซลลูโลส การปลดปล่อยยาที่แตกต่างกันจากเมทริกซ์สามารถอธิบายได้ว่ามีผลจากการพองตัวและการกร่อนของเมทริกซ์ที่แตกต่างกัน กลไกการปลดปล่อยยาของเมทริกซ์ขึ้นอยู่กับส่วนประกอบของเมทริกซ์ และสภาวะของสารละลายตัวกลาง การปลดปล่อยยาถูกควบคุมโดยกลไกการแพร่และการกร่อน

ภาควิชา เภสัชอุตสาหกรรม	ลายมือชื่อนิสิต.....
สาขาวิชา เภสัชอุตสาหกรรม	ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา 2543	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม –

4176568033 : MAJOR INDUSTRIAL PHARMACY
KEY WORD: SUSTAINED RELEASE PROPERTIES/ THEOPHYLLINE MATRICES/ MIXTURES OF XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE
PARINDA SRINARONG : SUSTAINED RELEASE PROPERTIES OF THEOPHYLLINE MATRICES CONTAINING MIXTURES OF XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE. THESIS ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 214 pp. ISBN 974-13-0825-6

Theophylline matrices containing mixtures of xanthan gum and hydroxypropyl methylcellulose were studied for their sustained release properties. The following factors that might influence the drug release were also investigated: amounts of polymers, mixing ratios of xanthan gum and hydroxypropyl methylcellulose, types of fillers, dissolution media having different ionic strengths or pH, and compression forces employed to prepare the matrices. The matrices prepared with the increasing amounts of polymers (10, 15 and 20%) exhibited the decreased drug release rate. The amount of drug releases from matrices which were incorporated with soluble-filler (spray dried lactose) were greater than that from the matrices contained insoluble-filler (dibasic calcium phosphate). The different compression forces (1000, 2000 and 4000 lbs) slightly affected the drug releases. The matrices containing hydroxypropyl methylcellulose alone showed the initial rapid drug releases. However, the replacements of hydroxypropyl methylcellulose with xanthan gum at the ratios of 3:7, 5:5, 7:3 and 10:0 could reduce the initial rapid drug releases. The drug releases from matrices containing mixtures of xanthan gum and hydroxypropyl methylcellulose were influenced by the ionic strengths of dissolution media and the viscosities of hydrated gel layer around the matrices. The difference in drug release characteristics could be explained on the basis of the different swellings and erosions of matrices. The drug release mechanisms of matrices depended on the compositions of the matrices and the conditions of dissolution media. The drug releases were controlled by the diffusion and erosion mechanisms.

Department Manufacturing Pharmacy Student's signature……..….

Field of study Industrial Pharmacy Advisor's signature…….

Academic year 2000 Co-advisor's signature –

ACKNOWLEDGEMENT

I would like to express my truthful gratitude to my thesis advisor, Associate Professor Poj Kulvanich, Ph.D. for his invaluable advice, guidance, encouragement and understanding throughout this study. His kindness and helpfulness are also deeply appreciated.

The particular thanks are extended to the Research and Development Institute, Government Pharmaceutical Organization and the Graduate School, Chulalongkorn University for granting partial financial support to fulfill this study. The other special appreciation is given to Rama Production Co., Ltd. for their supplying Methocel® and Rheogel® in this study.

I also wish to express my gratefulness to the members of my thesis committee for spending their valuable times, comments and good suggestions.

The special acknowledgement is send to my friends and colleagues and other persons whose names have not been mentioned for friendship, helping and encouragement during the time of my study.

Ultimately, I would like to express plentiful gratitude to my parents for their eternal love, care, understanding and encouragement throughout my life.

CONTENTS

LIST OF TABLES

Table **Page**

Table **Page**

Table **Page**

Table **Page**

LIST OF FIGURES

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

LIST OF ABBREVIATIONS

^{O}C	degree Celsius (centigrade)
cps	centipoise (s)
CV	coefficient of variation
DI	deionized
e.g.	exampli gratia (for example)
et al.	et alli and others
Fig.	Figure
HBMC	hydroxybuthyl methylcellulose
HEMC	hydroxyethyl methylcellulose
HPC	hydroxypropyl cellulose
HPMC	hydroxypropyl methylcellulose
hr	hour (s)
kp	kilopound (s)
lbs	pound (s)
M	molarity
MC	methylcellulose
mcg	microgram (s)
mg	milligram (s)
ml	milliliter (s)
mm	millimeter (s)
mPa s	milliPascal second
N	normality

NaCMC	sodium carboxymethylcellulose
No.	number
nm	nanometer (s)
PBS	phosphate buffer solution
pH	the negative logarithm of the hydrogen ion concentration
pKa	the negative logarithm of the dissociation constant
PVA	polyvinyl alcohol
®	Registered
r	correlation coefficient
r^2	coefficient of determination
rpm	revolutions per minute
SD	standard deviation
UV	ultraviolet
w/v	weight by volume
w/w	weight by weight
XG	xanthan gum
μ	ionic strength
%	percentage
λ_{max}	wavelength of maximum absorbance
>	more than
<	less than

CHAPTER I

INTRODUCTION

Nowadays, the growing interest in controlled drug release in human medicines refers to its promise to increase patient compliance due to a reduced frequency of administration, to improve safety and efficacy of drug substances and to reduce undesirable side effect. Hydrophilic matrices are among the most widely used in controlled-release dosage forms due to its convenience and ease of manufacturing. In general, matrix system composed of drugs, hydrophilic polymer and other excipients for controlling the drug release.

Number of polymers is used in preparation of matrix system to control rate of drug release. Hydroxypropyl methylcellulose (HPMC) is one of hydrophilic cellulose ethers, which widely employed owing to its non-toxic nature and ease of manufacturing. The proposed mechanism of drug release from HPMC matrix is suggested as follows; penetration of water or physiological liquid into the matrix, hydration, swelling and gel formation of HPMC, diffusion of dissolved drug and erosion of the polymer gel layer around the matrix (Alderman, 1984). The drug release from HPMC matrix depends on several factors such as drug type, tablet shape, added diluents, HPMC viscosity grade and content of HPMC in the matrix (Alderman, 1984; Ford et al., 1987; Kurahashi et al., 1996; Sung et al., 1996 and Vargas and Ghaly, 1999). In addition to hydrophilic cellulose derivatives, various natural gums are also employed in hydrophilic matrices. Several natural gums; carrageenan, locust bean gum, gum tragacanth and sodium alginate are used as excipients in formulations to sustain drug liberation (Nakano and Ogata, 1984). Furthermore, xanthan gum is also contained in hydrophilic matrix that has been investigated for the release performances (Dhopeshwarkar and Zatz, 1993; Talukdar et al., 1993).

Moreover, Talukdar et al.(1996) studied the drug release behaviors from xanthan gum matrix compare to HPMC matrix. The apparent difference in drug release profiles of xanthan gum matrix and HPMC matrix was reported. Particularly, the initial burst drug release occurred in the HPMC matrix rather than the xanthan gum matrix. Interestingly, in order to adjust the initial drug release from the HPMC matrix and there is no study for release characteristics of matrices containing mixed polymers of xanthan gum and HPMC. Therefore, the present study is the continued investigation of other workers (Dhopeshwarkar and Zatz, 1993;Talukdar et al.,1996) in the sense to explore the influence of different ratios of xanthan gum and HPMC in the matrices on their release profile characteristics. Theophylline was employed as a model drug. Some variables affecting the drug release from these matrices are also examined, e.g., types of filler employed to prepare the matrices, pH and ionic strength of the dissolution media and the compression forces to make the matrices in this investigation.

Objectives of the study

1. Investigate sustained release properties of theophylline matrices containing mixtures of xanthan gum (200 mesh) and hydroxypropyl methylcellulose (4000 cps)
2. Study the effect of different fillers; spray dried lactose and dibasic calcium phosphate, in formulations on sustained release properties of matrices
3. Examine the effect of compression forces, dissolution media in the means of different pH and ionic strength on dissolution characteristics of matrices
4. Estimate the swelling and erosion properties of xanthan gum and hydroxypropyl methylcellulose matrices in varying dissolution media
5. Assess the mechanisms and kinetics of drug releases from matrices in different formulations and conditions of dissolution media

Literature reviews

1. Polymer in hydrophilic matrices

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

1.1 Cellulose ethers

The group of cellulose ethers comprises methylcellulose (MC) and methylcellulose derivatives; hydroxypropyl methylcellulose (HPMC), hydroxyethyl methylcellulose (HEMC) and hydroxybuthyl methylcellulose (HBMC). These cellulose derivatives are the ones of which have founded the most application in hydrophilic matrices. HPMC is the most widely used in the matrix tablets and other types of controlled-release pharmaceutical dosage forms. On the basis of this study, the general information of HPMC is solely noted.

HPMC is an odorless and tasteless, white to off white colored, fibrous or granular powder. It can be solubilized in cold water and insolubilized in hot water. Therefore, when a solution is heated, a three-dimensional gel structure is formed (Greminger and Krumel,1980). HPMC undergoes a reversible sol to gel transformation upon heating and cooling, respectively. The gel point is 50-90 ^{O}C, depending on the ratios of methyl and hydroxypropyl substitutions. HPMC solutions is generally stable in the pH range of 3 to 11 (Wade and Weller,1994). The chemical structure of HPMC was also shown in Figure1.

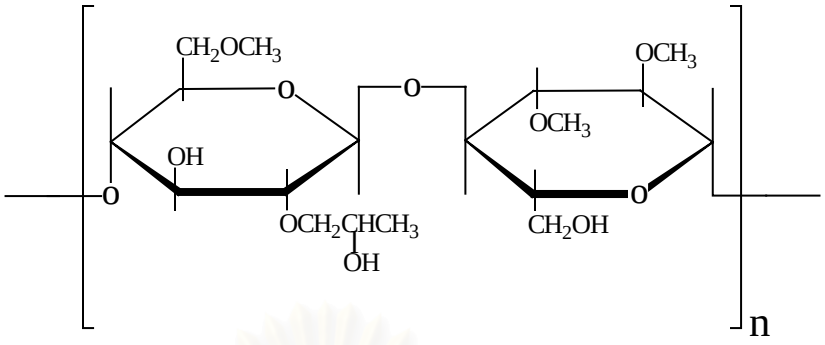


Figure 1 The chemical structure of hydroxypropyl methylcellulose

1.2 Noncellulose natural or semisynthetic polymers

The hydrophilic polymer in this group are used as such agar-agar, alginates, xanthan gum, carrageenans, molasses, polysaccharides of mannose and galactose, chitosan and modified starches. For the intention of this investigation, the general information of xanthan gum is only mentioned.

Xanthan gum is a high molecular weight polysaccharide gum produced in a pure culture fermentation by the microorganism *Xanthomonas compertris*, an organism originally isolated from the rutabaga plant, then purified by recovery with precipitation in isopropyl alcohol, dried and milled. Xanthan gum contained three different monosaccharides: mannose, glucose and glucuronic acid (as a mixed potassium, sodium and calcium salts). Each repeating block of polymer chain has two glucose, two mannose and one glucuronic acid. The polymer's main chain is made up of β-D-glucose units linked through the 1-and 4-positions; thus, the chemical structure of main chain is identical to that of cellulose. Two- mannose units and glucuronic acid unit make up the side chain. The terminal β-D-mannose unit is glycosidically linked to the 4-position of β-D-glucuronic acid, which in turn is glycosidically linked to the 2-position of α-D-mannose. Roughly half of the terminal D-mannose residues carry a pyruvic acid residue linked ketalically to the 4-and 6-positions. The nonterminal D-mannose unit on the side chain has an acetyl group at the 6-position. Therefore, xanthan gum is anionic by virtue

of carboxylic acid residues on the β-D-glucuronic acid and the pyruvic acid moiety on the terminal D-mannose (Cottrell et al.,1980). The chemical structure of xanthan gum was shown in Figure 2.

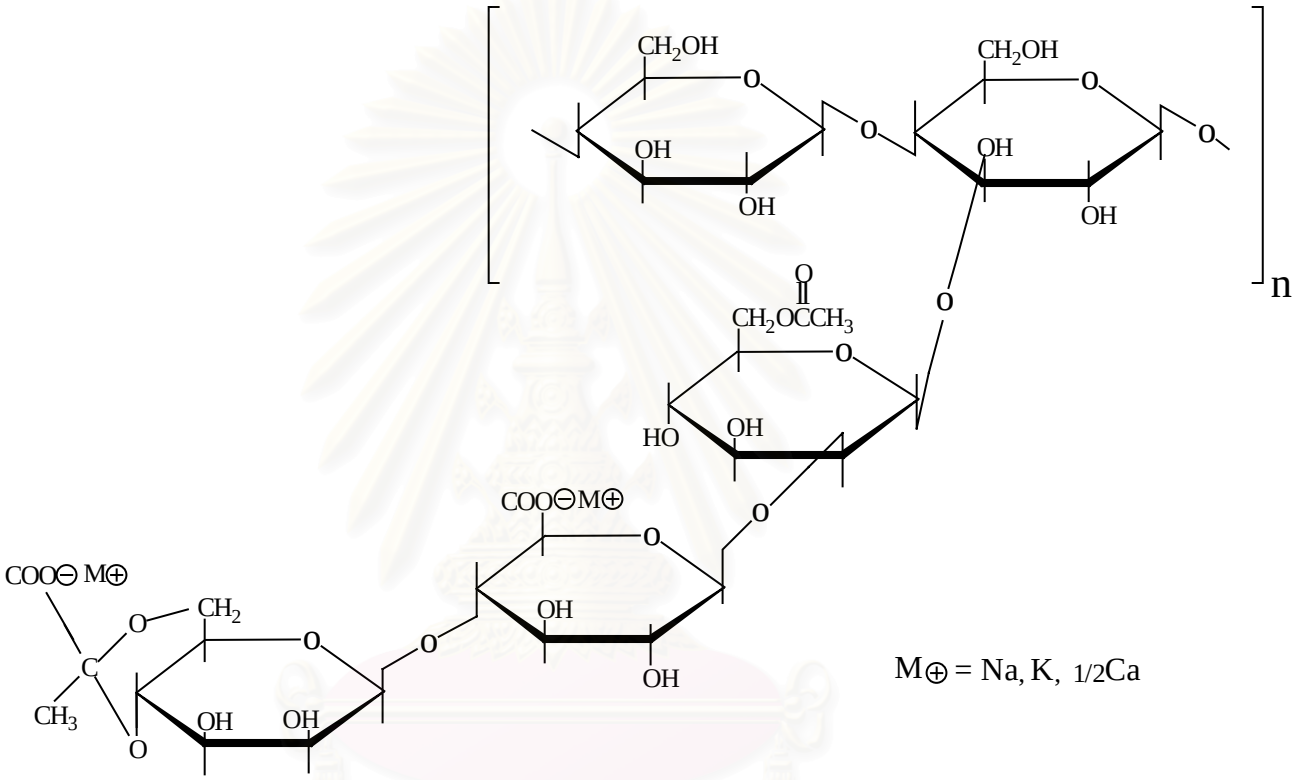


Figure 2 The chemical structure of xanthan gum

Xanthan gum occurs as a cream or white-colored, odorless, free-flowing and fine powder. The effect of salts on viscosity of xanthan gum depends on the concentration of the gum in the solution. Xanthan gum solutions are stable over a wide pH range of 3 to 12 and temperature between 10-60 ^{O}C (Wade and Weller,1994).

1.3 Polymers of acrylic acid

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

2. *Variables affecting drug release*

In considering to the variables affecting drug release from the hydrophilic matrix system, it could be classified into two groups; formulation variables and technological variables. In the case of the formulation variables, the composition of matrix system is the most important variables for drug release that included drugs, polymers and incorporating additives. In addition, the technological variables involve the preparation process of hydrophilic matrix system such as tablet shapes and compression forces.

2.1 Formulation variables

This variable influencing the drug release from compressed hydrophilic matrix such as viscosity of polymer, ratio of the polymer to drug, mixtures of polymer solubility of drug, particle sizes of drug or polymer and properties of added additives.

The effect of HPMC contents on the rate of drug releases was examined by several workers (Ford et al., 1985; Mitchell et al.,1993; Kurahashi et al., 1996; Dortung and Gunal, 1997; Tros de IIarduya et al., 1997; Velasco et al., 1999). Although these studies used different grades of HPMC and test drugs, their results were reported consistently. An increase in polymer concentration led to a decrease in the rate of drug release. This might be explained by an increasing polymer chain entanglement in gels containing higher HPMC content. This could also result in a more concentrated gel and

increased gel tortuosity. Therefore, the diffusion path became more convoluted and thus the diffusion rate decreased.

Sung et al. (1996) also investigated the influence of HPMC grade on drug release. They employed various HPMC viscosity grades as follows; HPMC K100LV, K4M, K15M and K100M. Their viscosities were approximately 100, 4000, 15000 and 100000 cps, respectively. At constant HPMC concentration, the fastest drug release rate was observed for the matrix containing HPMC K100LV. The matrix containing HPMC K4M exhibited a slightly greater drug release rate than the matrices containing HPMC K15M and K100M. This result was consistent with the study of Kurahashi et al. (1996) in that when HPMC viscosity was increased, the drug release rate had a tendency to decrease. The great difference in release rate between low viscosity grade (100 cps) and high viscosity grade (4000 cps) was observed. However, the little difference was founded in the matrices containing the higher viscosity grade (more than 4000 cps). Therefore, for high viscosity of HPMC (more than 4000 cps), the HPMC viscosity was a little importance in the control of drug release from matrices. The apparent diffusion coefficient did not change markedly with increasing the viscosity. It might be postulated that gel tortuosity did not increase with increasing the viscosity (Mitchell et al., 1993).

Basically, the solubility of drug is one of the important factors that is related to mechanism of drug release. Alderman (1984) studied the mechanism of drug release from HPMC matrix and concluded that water-soluble drugs were released by diffusion out of dissolved drug molecules across the gel layer and by erosion of gel layer, whereas poorly water-soluble drugs were released solely by erosion. Moreover, Kurahashi et al. (1996) also studied the influence of drug solubility on drug liberation. They summarized that with an increase in drug solubility, the rate of drug release also increased in matrix containing HPMC. This finding could be explained on the release mechanism in that water dissolved the drug at the matrix surface and then penetrated the matrix via pores, bringing about a gelling polymer. Dissolved drug was released by diffusion through the gel and finally the drug release rate began to fall when the water reached the center of the matrix and drug concentration decreased to less than its

solubility (Vazquez et al.,1992). Therefore, the rate of drug release at these steps depended on drug solubility. Colombo et al.(1996) examined the drug release from matrices containing 30% of polyvinyl alcohol (PVA) and 50% of drug which having different drug solubility. They founded that as drug solubility was increased, the matrices revealed thicker gel layer and shorter time to achieve complete drug release

The drug particle size also affected the drug release. Velasco et al. (1999) reported that the release exponent (n) of matrix containing the lowest size of diclofenac sodium particles was smallest. This result might be explained by the effective surface areas of drug particles. The smallest particle size of drug could dissolve more easily when dissolution media penetrated through the matrix, resulting in a greater role of diffusion. The larger particle sizes could dissolve less readily and therefore be more prone to erosion at the matrix surface. This finding is in accordance with the investigation of Tros de IIarduya et al. (1997) using oxazepam as a model drug. Besides using single polymer in hydrophilic matrices, Vazquez et al. (1996) studied the dissolution profiles from matrices containing mixtures of HPMC K100LV, K4M, K15M and K100M. The use of mixed polymers permitted efficient control of drug release. Attrition rates were high for all matrices but the drug releases were basically diffusion-limited.

In addition, the release of ionized drug from HPMC matrices could be delayed by incorporating an ion-exchange resin into the formulation. Due to the drug and the resin were oppositely charged, they could bind together in situ within the HPMC matrices. The drug was liberated when sufficient ions were available to displace the drug from its binding site (Feely and Davis, 1988b).

A number of extended release matrix formulations involving the uses of carbomer matrices have been studies. Khan and Zhu (1998) concluded that using Carbopol® 974P as the controlled-release agent could enhance the controlled-release properties of slightly water-soluble drug like ibuprofen. Carbopol® 974P could form strong matrices due to its inherently cross-linked structure. The drug release depended

on the concentration of Carbopol® 974P. Increasing the amount of Carbopol® 974P in the matrix resulted in a reduction of the drug release rate and linearization of the release profile, leading to a shift from the anomalous transport towards the case II transport.

In addition to the groups of cellulose ethers and carbomer, the group of natural hydrophilic gums was also employed in hydrophilic matrix formulations to produce sustained drug release. Sujja-areevath et al. (1996) evaluated the use of four natural hydrophilic gums (carrageenan, locust bean, karaya and xanthan gums) in mini-matrix formulations and enclosed in hard gelatin capsules. The release profiles from several encapsulated mini-matrices showed that sustained release of drug was achieved from mini-matrices containing locust bean, karaya and xanthan gums whereas carrageenan did not produce sufficient sustained release. The release behaviors of these encapsulated mini-matrices were anomalous. Moreover, the release characteristic from the individual mini-matrix containing xanthan gum was zero-order release kinetic. This was due to the larger surface area to volume ratio that provided an optimum balance between the diffusion and dissolution mechanisms.

The drug release behavior of xanthan gum matrices and their swelling in different experimental conditions were also studied using drugs having different properties; caffeine as a soluble neutral drug, indomethacin as an insoluble acidic drug and the salt of indomethacin as a soluble acidic drug (Talukdar and Kinget, 1995). The ionic strength of dissolution medium had a strong influence on both swelling and drug release behavior. Depending on the solubility of drug, the drug release from xanthan gum matrix was regulated by its swelling behavior. The release of an insoluble drug followed a direct relationship with swelling of the polymer matrix, whereas a reciprocal relationship was observed with soluble drugs. The swelling of xanthan gum matrix showed a square root of time dependence. However, the drug release was almost time independent (Fu Lu et al.,1991; Dhopeshwarkar and Zatz, 1993; Talukdar and Plaizier-Vercammen,1993).

Talukdar et al. (1996); Talukdar and Kinget (1997) investigated the further study of xanthan gum in hydrophilic matrices. This investigation was comparative study on xanthan gum and HPMC in terms of compaction, flowability, in vitro drug release characteristic and drug diffusion from matrices prepared with xanthan gum or HPMC. Compaction property between the two polymers was quite similar, but the flowability of xanthan gum was better than that of HPMC. In respect of controlled drug release behavior, the xanthan gum matrices had some advantages over the HPMC matrices. Xanthan gum matrices exhibited absence of initial burst release, higher drug-retarding ability due to less drug diffusion, and the possibility of zero-order release kinetics. Nevertheless, xanthan gum had a disadvantage in that the drug release was influenced by ionic strength of the dissolution media within the range of gastro-intestinal tract, while the drug release from HPMC matrices was independent to ionic strength.

In respect of controlled-release matrix formulations, several workers attempted to achieve zero-order release kinetics from matrices. The mixed polymers incorporating in matrix formulation was one of the practical methods that could modify the drug release pattern. In the case of carrageenan matrix, the relative insensitivity to the dissolution medium was proved after mixed with HPMC. The difference in erosion rate in various dissolution media was reduced and the overall release rate was also decreased (Bonferoni et al., 1993). Additionally, the drug release profiles from hydroxypropyl cellulose (HPC) or sodium carboxymethylcellulose (NaCMC) were first-order or sigmoidal in nature, respectively. However, by mixing the drug with an optimal amount of HPC and NaCMC, the zero-order release profiles with excellent reproducibility were obtained (Ranga Rao et al., 1988). A similar investigation of the release profiles from matrices containing mixtures of HPMC and NaCMC was also examined by Baveja et al. (1987). The release mechanisms from HPMC matrices were in the range of Fickian diffusion to anomalous transport. However, the release exponents (n) of matrices containing HPMC and NaCMC were closed to 1.0, indicating that the release mechanism approached zero-order release kinetics. This might be attributed to the high degree cross-linking between HPMC and NaCMC, leading to synergistic increase in gel viscosity at the matrix surface. As a consequence of this event, the rates of advancement

of swelling front into the glassy polymer (core) and the attrition of the rubbery state polymer (gel at matrix surface) were occurred equally. Therefore, the diffusional path length for the drug remained nearly constant, resulting in the linear drug release profiles. Vazquez et al. (1995) studied the rheological properties of different HPMC grades, NaCMC and various HPMC/NaCMC ratios possibly caused zero-order release kinetics typically observed in matrices prepared with HPMC and NaCMC.

Kim and Fassihi (1997a) examined the drug release rate from matrices containing binary polymers of pectin and HPMC. They revealed that by increasing pectin:HPMC ratios, release rates were increased but zero-order kinetics prevailed throughout the dissolution period. The achievement of zero-order kinetics involved the predictable swelling/erosion and final polymer chain desegregation and dissolution that were regulated by the gelling characteristics of polymers in the formulations.

Furthermore, the incorporating diluents or surfactants in the matrices also affected the rates of drug releases and release mechanisms. Xu and Sunada (1995) studied the effect of diluent types on mechanism of drug release from HPMC matrices. They reported that as a water-soluble diluent was added, the diffusion mechanism became more important due to the increasing of the porosity of matrices after the dissolution of diluent. On the other hand, a water-insoluble diluent did not diffuse outwards, but became entrapped in the matrices. Thus, the alteration of release mechanism from matrices containing the soluble diluent was not observed when the soluble diluent concentration was increased. The effect of diluents on matrix integrity was observed. At 10% HPMC in the matrices, Avicel® PH 101 matrices could not maintain integrity and thus gave the highest drug release. Emcompress® matrices allowed the lowest release while Lactose Fast Flo® matrices led to an intermediate release. The different drug release between Emcompress® and Lactose Fast Flo® matrices was due to the markedly different solubilites of these diluents (Vargas and Ghaly,1999). Therefore, it is important to note that the choice of appropriate diluent was crucial for successful formulation to achieve a sustained release effect (Zhang and Schwartz, 2000).

An another additive affecting the drug release was surfactant. Feely and David (1988a) investigated the influence of surfactants on drug release from HPMC matrices using chlorpheniramine maleate and sodium salicylate as test drugs. They found that the retarding effect of ionic surfactants in drug release was dependent on the drug and the surfactant having opposite charges. The principal mechanism of surfactants retarding drug release was a drug/surfactant ionic interaction.

To mimic the conditions of gastro-intestinal tract having different ionic strength and pH, the in vitro drug releases from controlled-release systems have been investigated for various dissolution media. In general, the different ionic strength and pH of dissolution media could affect the solubility of drug, the properties of polymers or added additives that involved the drug releases from systems. For instances, Dortung and Gunal (1997) reported that the release rate of acetazolamide was markedly influenced by the pH of dissolution medium. Acetazolamide is a weak acid with pK_a of 7.2 . The equilibrium solubility of pure acetazolamide in dissolution media pH 1.2, 5.4 and 7.4 were founded to be 1.25, 1.54 and 2.64 mg/ml, respectively. The solubility of acetazolamide increased with increasing pH. The dissolution rate of drug was in compliance with the solubility results. In addition, Sheu et al. (1992) pointed out that the addition of sodium or potassium chloride to dissolution media decreased the solubility of diclofenac sodium and slowed the dissolution rate. Again, it could be concluded that drug dissolution was a function of drug solubility at the various pH (Nokhodchi et al., 1997).

The polymers containing anionic or cationic group were also influenced by the dissolution media. Chlorpheniramine release from matrices containing cation-exchange resin into high ionic strength of dissolution medium was faster than its release into a dissolution medium with low ionic strength. This was expected since the presence of more sodium ions in high ionic strength of dissolution medium could encourage the displacement of drug from resin and promoted drug release (Feely and David, 1988b). Moreover, the dissolution of propranolol hydrochloride from matrices containing HPMC K4M and Carbopol® 974 was investigated using 0.1 N HCl, phosphate buffer

pH 4.5 and pH 7.5. In 0.1 N HCl solution, HPMC K4M predominantly controlled the drug release since Carbopol® 974 had a low solubility in this dissolution medium. At pH 4.5 and 7.5, propranolol formed a complex with Carbopol® 974 giving a reduction in the solubility of the drug. In addition, Carbopol® 974 formed the gel layer at the edge of the hydrating matrix at pH 7.5 that could retard the drug release (Perez-Marcos et al., 1996).

Hodsdon et al. (1995) studied the effect of pH in the release kinetics of sodium alginate matrices using chlorpheniramine maleate. The drug release was significantly faster in simulated gastric fluid (pH 1.2) than in simulated intestinal fluid (pH 7.5). The different drug release was due to the different hydration kinetics of polymer in these different fluids. At pH 1.2, sodium alginate was rapidly converted to alginic acid. Alginic acid had ability to swell on hydration but was virtually insoluble. The generation of swelling forces without surface stickiness was the basis for the use of alginic acid as a tablet disintegrant. Therefore, the hydrated layer at surface matrices was relatively porous at pH 1.2 and then did not contribute to the diffusional barrier. On the other hand, the continuous surface gel layer of hydrated matrices was observed in pH 7.5. In addition, their liquid uptake studied found that acidic medium was more absorbed significantly ($p < 0.01$) into sodium alginate matrices than its neutral counterpart.

2.2 Technological variables

The influences of tablet shape and size on the rate of drug release from HPMC matrices were examined by Ford et al.(1987). They summarized that the rate of drug release was proportional to the surface of tablet since release rate decreased as the tablet surface area decreased. Compression forces could also affect the drug release. Previous workers (Waaler et al., 1992; Sarisuta and Mahahpunt, 1994; Kim and Fassihi, 1997b; Velasco et al., 1999) concluded that the compression forces could produce the different porosity in the matrices involving in drug release via diffusion.

3. *Mechanisms and kinetics of drug release*

3.1 Drug release mechanism

For in vitro release, one of the proposed mechanisms of drug release from hydrophilic matrices implied that when the matrix comes in contact with dissolution medium, the dissolution medium dissolves the drug at the surface, causing it to immediately release and partial hydration/ swelling of the polymer take places, resulting in the formation of a gel layer. As dissolution medium penetrates into the matrix via pores at the rate that depends on the hydrophilicity of the polymer, consequently, the gel layer expands, getting the thickness of gel layer around the matrix. Here, the polymer chains are strongly entangle and the gel layer is resistant. Thus, the gel layer acts as a hydrophilic barrier that controls dissolution penetration and drug diffusion. However, moving away from this hydration position, when sufficient dissolution medium has accumulated, the gel layer becomes progressively hydrated and chains disentangle and following by polymer dissolution/ erosion. As the time pass, the process of dissolution penetration can continue until the matrix is completely dissolved.

According to the proposed mechanism of release as mentioned above, the drug liberation from hydrophilic matrix is produced by two simultaneously mechanisms as follows; the dissolution of drug in dissolution medium and diffusion through the gel barrier and the erosion or dissolution of the outer gel layer. The dynamical change of hydrophilic matrix in dissolution medium is schematically displayed in Figure 3 (Kim and Fassihi, 1997a).

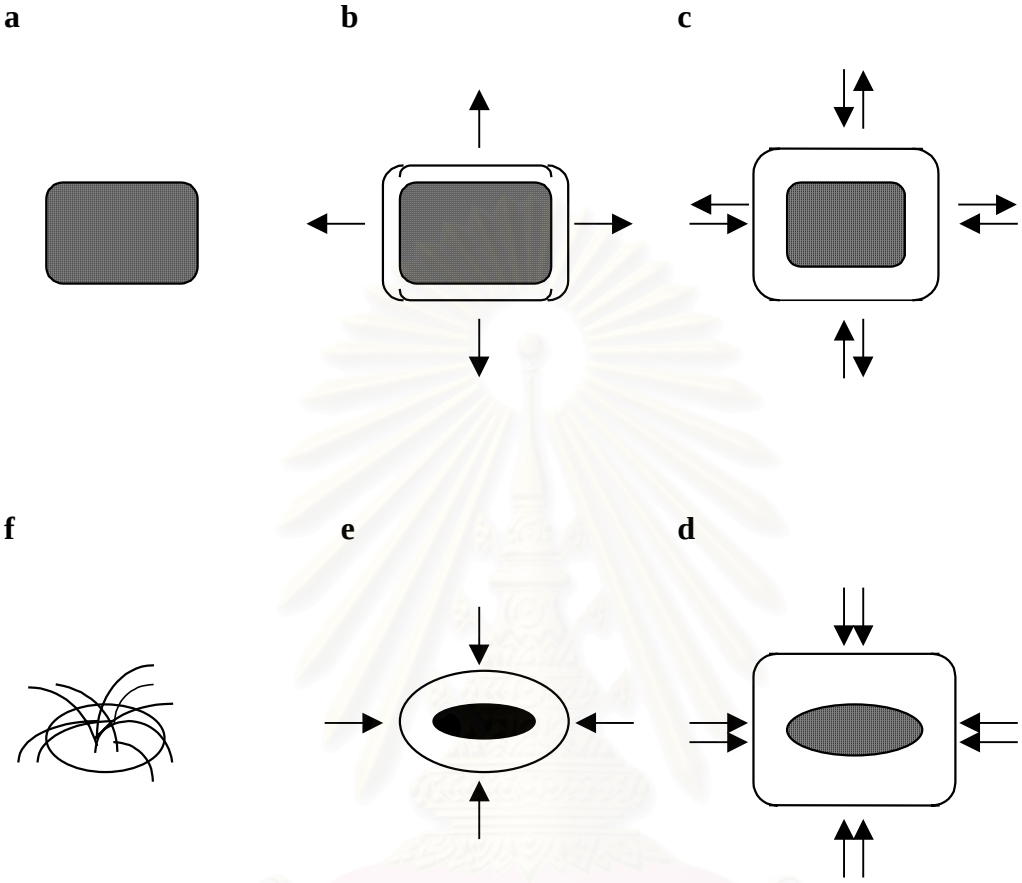


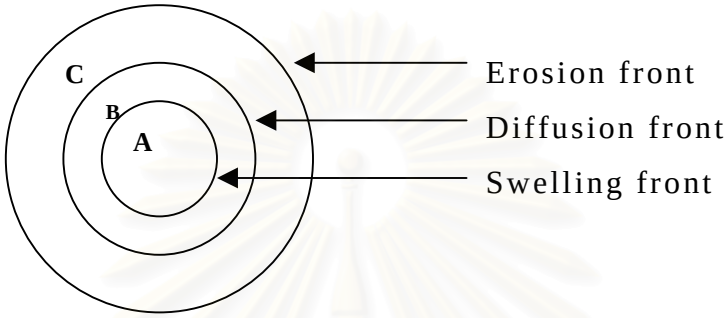
Figure 3 The dynamical change of hydrophilic matrix as dissolution progresses. The system starts hydration with formation of gel layer (a,b). The gel layer boundary is continued swelling and erosion (c,d and e). Finally, the system is completely dissolved (f).

In addition, Colombo et al. (1995) found distinct fronts during the swelling and release process from swellable matrices. From center to matrix periphery (see Fig.4), the following three fronts were described.

(i) A swelling front, identifying the boundary between the still glassy polymer (A) and its rubbery gel state (B)

(ii) A diffusion front, indicating the boundary between the still undissolved (solid) drug (B) and the dissolved drug in the gel layer

(iii) An erosion front, specifying the boundary between the matrix (C) and the dissolution medium



A Undissolved drug, glassy polymer layer
B Undissolved drug, gel layer
C Dissolved drug, gel layer

Figure4 Schematic representation of erosion, diffusion and swelling fronts during the swelling process

The erosion front moved outwards, owing to the swelling of the matrix, or inwards when matrix dissolved, whereas the swelling front moved inwards after dissolution medium penetration. The gel layer thickness was measured as the distance between erosion and swelling fronts (Colombo et al., 2000). In matrices that contained soluble drugs, the diffusion front moved inwards and was near to the swelling front. This was not always the case when using insoluble drugs, as the individual undissolved drug particles could be translocated by the polymer swelling and, therefore, the diffusion front could move outwards (Colombo et al., 1997: S532, cited in Colombo et al., 2000: 201).

3.2 The kinetics of drug release

In the literature, very often the amount of drug release from polymeric matrix can be analyzed in terms of square root of time (Higuchi's model), in accordance with the equation;

$$Q = (2ADC_s t)^{1/2}$$

where Q is the amount of drug release from the matrix system; A, the concentration of drug per unit volume; D, the diffusion coefficient (constant); C_s, the solubility of drug and t, representing time.

Nevertheless, the use of Higuchi's model is not justified because the conditions applied by Higuchi's model are not valid for the hydrophilic matrix having swelling process. In addition, the Higuchi 's equation does not take into consideration that the matrix system can be erodible and that relaxation of polymeric chain can contribute to drug transport. Therefore, an empirical equation was proposed by Ritger and Peppas (1987) that is well- known for analysis of dissolution data from polymeric system. This equation is based on a power law dependence of the fractional release on time. The exponent n has values that can range between 0.43 to 1, according to the geometry and the prevalence of the Fickian or the case II transport (relaxation). The expression is given below.

$$M_t/M_\infty = kt^n$$

or

$$\ln M_t/M_\infty = \ln k + n \ln t$$

where M_t/M_∞ is the fractional release of drug; t, the release time; k, a constant incorporating structural and geometric characteristics of the release system. The n values can assume and their meanings are presented in Table1 (Peppas, N. and Peppas B., 1994).

Table 1 Diffusion exponent and solute release mechanism

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

A more interesting equation for the analysis of dissolution data was proposed by Peppas and Salhin (1989), according to the following equation;

$$M_t/M_\infty = k_1 t^{1/2} + k_2 t$$

where the fractional drug release, M_t/M_∞ is the sum of a diffusional contribution (with $t^{1/2}$ dependence) and a relaxation contribution (with t dependence), and both k_1 and k_2 are constants describing the Fickian diffusion and case II transport, respectively.

Drug release from swelling matrices normally showed a square root of time dependency as observed in homogeneous matrices (Higuchi, 1963). By choice of the appropriated composition, linear drug release profiles could be achieved with swellable matrices as well, if the release surface stayed constant (Baveja et al.,1987; Colombo et al.,1987; Ranga Rao et al.,1990). Various phenomena connected with fluid intake and swelling were under discussion as the rate-limiting step for the zero-order release; (i) fluid-induced relaxation of the polymer matrix, (ii) erosion of the swollen gel layer, and (iii) diffusion through a swollen gel layer, the thickness of the layer being constant with respect to time (Mockel and Lippold, 1993).

CHAPTER II
EXPERIMENTAL

Materials

The following materials were obtained from commercial sources and deionized water was used throughout the experiment.

1. Model drug

Theophylline anhydrous (Lot. No. 951004, Asia drug and chemical Ltd., Part.)

2. Additives

- Hydroxypropyl methylcellulose (4000 cps)
  (Methocel® K4M Premium EP, Lot. No. ND24012 N01, Colorcon Limited., USA)
- Xanthan gum (200 mesh)
  (Rheogel® 200 mesh, Lot. No. 57161A, CNI Colloid natural internatural, France)
- Spray dried lactose
  (Supertab®, Lot. No. 2031104, The lactose company of New Zealand.,Ltd)
- Dibasic calcium phosphate dihydrate
  (Emcompress®, Lot. No. X05E, Penwest Pharmaceutical Co., Ltd., UK)
- Magnesium stearate USP
  (Lot. No. MAF07, Srichand United Dispensary Co., Ltd.)

3. Other chemicals

- Hydrochloric acid solution 37%, sp.gr. 1.18, AR grade
  (Analar, Lot. No. K22609252 923, England)

- Methanol, AR grade
  (Lot. No. M47A30, J.T. Baker, USA)
- Ortho phosphoric acid solution 85%, AR grade
  (Lot. No. 504431, Ajax chemicals, Austratia)
- Potassium dihydrogen orthophosphate, AR grade
  (Lot. No. 612612, Ajax chemicals, Austratia)
- Sodium chloride crystals, AR grade
  (Lot. No. 7581 MTVV, Mallinckrodt, USA)
- Sodium hydroxide pellets, AR grade
  (Lot. No. 7708 MVHT, Mallinckrodt, USA)

4. Eqiupments

- Analytical balance (Model A200S, Satorious GmbH, Germany and Model PB3002, Metler, Switzerland)
- Cubic mixer (Model AR 400, Erweka GmbH, Germany)
- Dissolution apparatus (Model DT-6R, Reweka GmbH, Germany)
- Hot air oven
- Hydraulic equipment (Model C, Carver Laboratory Press, USA)
- pH meter (Model 292, Pye Unicham, England)
- Paddle stirrer (Model RW 10R, Janke& Kunkel Labortechnik)
- Scanning-electron microscope (Model JSM 5410LV, Joel Ltd., Japan)
- Single punch tabletting machine (3/8 inch diameter round flat faced punch and die set, Viuhang Engineering., Ltd., Thailand)
- Tablet hardness tester (Model TBH 30, Erweka GmbH, Germany)
- Tablet thickness tester (Teclock Corp., Japan)
- Ultrasound transonic digital sonicator (Model T680/H, Elma, Germany)
- Ultraviolet-visible recording spectrophotometer (Model UV-160A, Shimadzu Corp., Japan)
- Viscometer (Model RI:2, Rheology International Shannon., Ltd., Ireland)
- Water bath (Model WB4P, Thermotek)

Methods

1. Preparation of theophylline matrices

1.1 Formulation of theophylline matrices

The amount of ingredients used in each formulation was shown in Table 2.

Table 2 Formulation of theophylline matrices

Ingredient	%w/w
Theophylline anhydrous	66.67
Polymers	*
Fillers	**
Magnesium stearate	1.0

* HPMC (4000 cps) or xanthan gum (200 mesh) or mixtures of HPMC and xanthan gum

** spray dried lactose or dibasic calcium phosphate

The composition of polymer, the amount and the type of filler used in each formulation were presented in Table 3.

Table 3 The composition of HPMC and xanthan gum (XG), the amount and the type of filler used in each formulation

Formulation	Ratio of HPMC: XG	% Polymer and filler			
		HPMC	XG	Spray dried lactose	Dibasic calcium phosphate
Blank 1	-	-	-	32.33	-
Blank 2	-	-	-	-	32.33

Table 3 (Continued) The composition of HPMC and xanthan gum (XG), the amount and the type of filler used in each formulation

Formulation	Ratio of HPMC: XG	% Polymer and filler			
		HPMC	XG	Spray dried lactose	Dibasic calcium phosphate
F1	10:0	10.0	-	22.33	-
F2	7:3	7.0	3.0	22.33	-
F3	5:5	5.0	5.0	22.33	-
F4	3:7	3.0	7.0	22.33	-
F5	0:10	-	10.0	22.33	-
F6	10:0	10.0	-	-	22.33
F7	7:3	7.0	3.0	-	22.33
F8	5:5	5.0	5.0	-	22.33
F9	3:7	3.0	7.0	-	22.33
F10	0:10	-	10.0	-	22.33
F11	10:0	15.0	-	17.33	-
F12	7:3	10.5	4.5	17.33	-
F13	5:5	7.5	7.5	17.33	-
F14	3:7	4.5	10.5	17.33	-
F15	0:10	-	15.0	17.33	-
F16	10:0	15.0	-	-	17.33
F17	7:3	10.5	4.5	-	17.33
F18	5:5	7.5	7.5	-	17.33
F19	3:7	4.5	10.5	-	17.33
F20	0:10	-	15.0	-	17.33
F21	10:0	20.0	-	12.33	-
F22	7:3	14.0	6.0	12.33	-
F23	5:5	10.0	10.0	12.33	-
F24	3:7	6.0	14.0	12.33	-
F25	0:10	-	20.0	12.33	-
F26	10:0	20.0	-	-	12.33
F27	7:3	14.0	6.0	-	12.33
F28	5:5	10.0	10.0	-	12.33
F29	3:7	6.0	14.0	-	12.33
F30	0:10	-	20.0	-	12.33

1.2 Preparation of theophylline matrices

Theophylline tablets were produced by direct compression method using a single punch tabletting machine with a 3/8-inch diameter round flat faced punch and die. The total weight of each tablet was about 300 mg and compressed to have hardnesses of 6-8 kp. The procedures of preparation were as follows.

1.2.1 Formulation F1-F30

All powders, HPMC or /and xanthan gum, spray dried lactose or dibasic calcium phosphate, in each formulation except magnesium stearate were weighed and mixed in a cubic mixer for 30 minutes. Then, magnesium stearate was added to the cubic mixer and the formulations were blended for an additional 5 minutes prior to compression.

1.2.2 Formulation blank 1 and blank 2

Theophylline, spray dried lactose or dibasic calcium phosphate and magnesium stearate were mixed and compressed with the same procedure as of the other formulations.

2. The property evaluations of theophylline matrices

2.1 Determination of weight variation

The weight of tablet after compression was measured by analytical balance. The mean and standard deviation were calculated from twenty tablets.

2.2 Determination of thickness and hardness

The thickness and hardness of tablets were evaluated by tablet thickness tester and hardness in terms of millimeters and kilopounds, respectively. The mean and standard deviation were calculated from twenty tablets.

2.3 Determination of theophylline content in matrices

2.3.1 Calibration curves of theophylline

Calibration curves of theophylline in different media were constructed; deionized water, 0.1 N HCl solution, phosphate buffer pH 3, pH 6.8 and pH 7.4 solutions, 0.01, 0.05, 0.1 and 0.2 M NaCl solutions.

Two hundred milligrams of theophylline was accurately weighed into a 100-ml volumetric flask. The drug was dissolved and adjusted to volume with various media as mentioned above. This standard stock solution was approximately diluted with the same medium to obtain the final standard solutions which had the concentrations of 1.6, 3.2, 6.4, 9.6, 12.8, 16.0 and 19.2 mcg/ml, respectively.

The absorbances of the standard solutions were determined by the UV/visible spectrophotometer at a wavelength of 272 nm, which was the λ_{max} of theophylline in each medium except in 0.1 N HCl solution. The λ_{max} of theophylline in 0.1 N HCl solution was at 270 nm. The calibration curve of each medium was carried out in duplicate. The relationship between absorbances and concentrations of theophylline was fitted using linear regression analysis.

2.3.2 Assay of theophylline content in matrices

Twenty tablets of each formulation were weighed and pulverized by mortar and pestle. Then, the powder was accurately weighed equivalent to one tablet into a 100-ml

volumetric flask, filled with 60 ml of methanol AR grade and sonicated for 15 minutes by using the sonicator. Afterwards, the volumetric flask was adjusted to volume by the same medium and mixed thoroughly. The solution was filtered through filter paper, Whatman No.1, and used as stock solution. This stock solution was appropriately diluted with 0.1 N HCl solution to obtain a suitable concentration prior to determination by UV/visible spectrophotometer at a wavelength of 270 nm.

The theophylline content was calculated from calibration curve of theophylline in 0.1 N HCl solution and performed in triplicate.

2.4 Determination of drug release from matrices

Dissolution tests were performed by means of USP XXIII standard apparatus II (paddle) at 37 ^{O}C $\pm$ 0.5 ^{O}C with a rotation speed of 50 rpm. In addition, nets of stainless steel were placed on the bottom of the vessels in order to keep the matrices from sticking to the walls. The distal paddles were calibrated at 2.5 cm above nets of stainless steel. The 900 ml of deionized water, 0.1 N HCl solution, phosphate buffer pH 3, pH 6.8 and pH 7.4 solutions (0.05 M KH_2PO_4, adjust the pH using either phosphoric acid or sodium hydroxide), 0.01, 0.05, 0.1 and 0.2 M NaCl solutions were employed as dissolution media to investigate the influences of pH and ionic strength of dissolution media on drug release from matrices. The release test of each formulation was done in triplicate.

The samples of 10 ml were withdrawn at the time intervals of 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours. The same volume of each dissolution medium was immediately added after each sampling to maintain the volume of dissolution medium constant until the end of the experiment.

Afterwards, the samples were clarified by filtration with filter paper. The filtrate was diluted, if necessary, to the range of 1.6-19.2 mcg/ml and measured by UV/visible spectrophotometer at the maximum wavelength of each dissolution medium. The

amounts of theophylline release at any times were computed from the calibration curve of each dissolution medium. A cumulative correction was achieved for the previously transferred sample to determine the total amount of drug release.

2.4.1 Dissolution tests of formulation F1-F10 and F21-F30

Dissolution tests of formulations F1-F10 and F21-F30 were performed by using deionized water as a dissolution medium. The absorbances of each sample were examined at maximum wavelength of 272 nm. The procedure was conducted according to specification above.

2.4.2 Dissolution tests of formulation F11-F20 and blank 1 and 2

Each formulation was tested for drug release in all dissolution media. The absorbances of each sample were measured at the maximum wavelength of each dissolution medium. The procedure was abided as previously described.

2.5 Effect of compression forces on drug release studies

Formulation F12, F14, F17 and F19 were designated to find the effect of compression forces on drug release. Each formulation was blended as described previously and compressed at the forces of 1000, 2000 and 4000 lbs using hydraulic equipment with a 3/8-inch diameter round flat faced punch and die set. The total weight of each tablet was about 300 mg. Next, the tablets were tested for hardness, the drug content and dissolution of drug. The dissolution tests were performed in accordance with the procedure as aforementioned and used deionized water as a dissolution medium.

2.6 Determination of drug solubility

The drug solubility was investigated in various media. Excess amounts of drug were mixed with 5 ml of deionized water, 0.1 N HCl solution, phosphate buffer pH 3, pH 6.8 and pH 7.4 solutions, 0.01. 0.05, 0.1 and 0.2 M NaCl solutions in screw-capped tubes to determine the solubility of theophylline. The samples were rotated for 48 hours at 37 ^{O}C $\pm$ 1^{O}C in the top to bottom rotor, filtered and assayed spectrophotometrically in triplicate. The solubility of theophylline was calculated from the calibration curve of each medium.

2.7 Determination of polymer gel viscosity

The polymer gels, 2% w/w of HPMC:XG ratios of 10:0, 7:3, 5:5, 3:7 and 0:10, were prepared with different media: deionized water, 0.1 N HCl solution, phosphate buffer pH 3, pH 6.8 and pH 7.4 solutions, 0.01, 0.05, 0.1 and 0.2 M NaCl solutions. The measurements of viscosity were performed employing the viscometer with a shear rate of 100 rpm at 37 ^{O}C $\pm$ 1^{O}C and each sample was determined in triplicate.

2.8 Determinations of matrix swelling and matrix erosion

The matrix swelling studied were carried out in different dissolution media as follows; deionized water, 0.1 N HCl solution, phosphate buffer pH 3, pH 6.8 solutions, 0.01 and 0.2 M NaCl solutions. Only formulations F11-F20 were investigated for matrix swelling and erosion. The dissolution apparatus was set as the method of release test. The matrix was placed on the net of stainless steel at the bottom of vessels. Individual tablet (n=3) on the net of stainless steel was removed at varying time intervals: 0.25, 0.5, 0.75, 1, 2, and 4 hours, and then put on a transparent glass disk containing the same dissolution medium. To determine the area of swollen tablet, this transparent glass disk was positioned on a projector that was at a constant distance from a screen. The dimensions of swollen tablets were determined at all time intervals by measuring the images on the screen and then calculated the areas of swollen tablets and

the percent swelling. Afterwards, these swollen tablets at time intervals as follows; 0.25, 0.5, 0.75, 1, 2, 4 and 6 hours, were dried in hot air oven at temperature 60 ^{O}C until constant weight which determined by analytical balance. The total weight losses of swollen tablets after drying were determined and estimated the percent erosion. The percent swelling and erosion of swollen tablets could be calculated according to the equation 1 and 2, respectively.

$$\% \text{ Swelling} = (A_t - A_0)/A_0 * 100 \qquad \text{(equation 1)}$$

where A_t is the area of swollen tablet at a time interval, A_0 is the area of tablet at initial time.

$$\% \text{ Erosion} = (W_0 - W_t)/W_0 * 100 \qquad \text{(equation 2)}$$

where W_t is the weight of dried tablet at a time interval, W_0 is the weight of tablet at initial time.

2.9 Morphology of theophylline matrices

Matrices of formulation F11, F13, F15, F16, F18 and F20 were chosen to investigate for their morphology after dissolution test by cryoelectron microscopy. In preparation of cryoelectron microscopy, tablet of each formulation was hydrated in deionized water, 0.1 N HCl solution, phosphate buffer pH 6.8 solution and 0.2 M NaCl solution using the same condition of dissolution test. After 2 hours, sample was carefully removed from the net of stainless steel and sectioned through an undisturbed portion of the gel from around the matrix in vertical direction. Rod of sample was then obtained, turned it in vertically again and positioned on the sample holder, afterwards, the sample was rapidly frozen with liquid nitrogen and put immediately to scanning electron microscope equipped with cryostation. The specimen was then observed after it had been cut with cold knife and coated with gold immediately.

CHAPTER III

RESULTS AND DISCUSSION

1. Weight variation , hardness and thickness of theophylline matrices

The experimental data of weight variation, hardness and thickness of theophylline matrices prepared were shown in Table 4.

The weight of theophylline matrices was in the range of 285.0-315.0 mg. The hardness was ranged from 6-9 kp. The lowest and the highest hardness values at 6.24 and 8.77 kp were obtained from formulation blank 1 and F15, respectively. In the case of different kinds of fillers, the thickness of dibasic calcium phosphate (Emcompress®) in formulation was lower than that of spray dried lactose (Supertab®). The thicknesses of the matrices were 2.77-3.25 mm.

2. Drug content

The percent drug contents of theophylline matrices from various formulations were presented in Table 5. The values of the percent drug content were in the range of 97.05-106.96 %.

Table 4 Physical properties of theophylline matrices containing various amounts of HPMC K4M or xanthan gum or mixtures of HPMC K4M and xanthan gum

Formulation	Physical properties of matrices		
	Weight variation [mg ± (SD)] (n = 20)	Hardness [kp ± (SD)] (n = 20)	Thickness [mm ± (SD)] (n = 20)
Blank 1	302.54 (0.60)	6.24 (0.40)	3.05 (0.01)
Blank 2	302.47 (1.19)	6.85 (0.39)	2.77 (0.02)
F 1	307.72 (2.43)	7.67 (0.50)	3.21 (0.05)
F 2	304.49 (1.82)	7.94 (0.55)	3.19 (0.04)
F 3	303.84 (2.53)	7.73 (0.58)	3.14 (0.02)
F 4	300.57 (1.44)	7.58 (0.51)	3.15 (0.02)
F 5	303.12 (1.54)	7.82 (0.46)	3.13 (0.02)
F 6	300.32 (2.57)	7.78 (0.39)	3.03 (0.03)
F 7	299.39 (2.86)	7.99 (0.47)	3.02 (0.03)
F 8	299.73 (2.55)	8.22 (0.43)	2.99 (0.03)
F 9	300.95 (2.86)	8.25 (0.50)	2.99 (0.04)
F 10	301.92 (3.82)	8.33 (0.50)	2.99 (0.04)
F 11	300.30 (4.97)	7.68 (0.80)	3.26 (0.03)
F 12	300.12 (3.59)	8.09 (0.51)	3.21 (0.02)
F 13	301.85 (3.15)	8.44 (0.48)	3.19 (0.02)
F 14	299.76 (3.07)	8.12 (0.44)	3.19 (0.04)
F 15	300.13 (3.55)	8.77 (0.36)	3.15 (0.02)
F 16	305.19 (4.42)	8.36 (0.70)	2.99 (0.03)
F 17	305.89 (5.59)	8.17 (0.59)	2.99 (0.05)
F 18	300.17 (3.24)	8.20 (0.68)	2.95 (0.03)
F 19	302.63 (3.78)	8.26 (0.57)	2.96 (0.02)
F 20	301.54 (4.43)	8.40 (0.66)	2.93 (0.03)

Table 4 (Continued) Physical properties of theophylline matrices containing various amounts of HPMC K4M or xanthan gum or mixtures of HPMC K4M and xanthan gum

Formulation	Physical properties of matrices		
	Weight variation [mg ± (SD)] (n = 20)	Hardness [kp ± (SD)] (n = 20)	Thickness [mm ± (SD)] (n = 20)
F 21	303.38 (5.38)	8.17 (0.76)	3.25 (0.03)
F 22	302.40 (4.34)	8.33 (0.53)	3.25 (0.02)
F 23	302.09 (4.48)	8.24 (0.47)	3.24 (0.02)
F 24	302.33 (4.95)	8.20 (0.56)	3.22 (0.02)
F 25	302.62 (4.22)	7.95 (0.40)	3.23 (0.01)
F 26	305.62 (5.47)	7.84 (0.32)	3.13 (0.02)
F 27	303.95 (4.47)	8.07 (0.42)	3.13 (0.01)
F 28	303.64 (4.59)	7.86 (0.55)	3.13 (0.02)
F 29	304.24 (4.39)	8.17 (0.53)	3.11 (0.02)
F 30	303.49 (5.35)	7.88 (0.38)	3.13 (0.01)

Table 5 The percent drug content of various formulations

Formulation	% Drug content ±(SD) (n = 3)	Formulation	% Drug content ±(SD) (n = 3)
Blank 1	101.42 (1.55)	F 15	97.05 (2.09)
Blank 2	100.98 (0.98)	F 16	101.48 (0.94)
F 1	106.88 (1.33)	F 17	100.32 (2.80)
F 2	103.78 (1.34)	F 18	99.68 (0.99)
F 3	104.39 (0.89)	F 19	104.91 (0.99)
F 4	104.26 (0.68)	F 20	100.12 (1.23)
F 5	105.80 (1.52)	F 21	106.96 (0.66)
F 6	100.75 (1.32)	F 22	106.04 (1.63)
F 7	101.09 (1.56)	F 23	105.36 (1.46)
F 8	101.91 (1.68)	F 24	106.36 (1.06)
F 9	102.77 (1.38)	F 25	105.65 (1.94)
F 10	103.75 (0.84)	F 26	102.15 (1.22)
F 11	98.40 (0.86)	F 27	104.69 (1.62)
F 12	105.69 (1.74)	F 28	104.70 (1.41)
F 13	104.54 (1.09)	F 29	105.81 (1.83)
F 14	99.53 (0.34)	F 30	106.57 (1.10)

3. The solubility of theophylline

Table 6 summarizes the solubility of theophylline in different media at temperature of 37 ^{O}C . The values of solubility were similar.

Table 6 The solubility of theophylline in various media at 37 ^{O}C

Medium	Solubility [(mg/ml)±(SD)] (n = 3)
Deionized water	11.87 (0.03)
0.1 N HCl solution	13.51 (0.03)
Phosphate buffer pH 3	10.87 (0.22)
Phosphate buffer pH 6.8	12.14 (0.06)
Phosphate buffer pH 7.4	12.74 (0.12)
0.01 M NaCl solution	12.23 (0.15)
0.05 M NaCl solution	11.66 (0.06)
0.1 M NaCl solution	12.16 (0.10)
0.2 M NaCl solution	11.62 (0.14)

4. The viscosity of polymer gels

The values of viscosity for polymer gels (2% w/v) with various ratios of HPMC:XG (10:0, 7:3, 5:5, 3:7 and 0:10) in different media at the shear rate of 100 rpm, 37 ^{O}C were illustrated in Figures 5-6.

4.1 The viscosity of polymer gels in various ionic strengths

The viscosity of different polymer ratios of HPMC to XG in these media (μ= 0, 0.01, 0.05, 0.1 and 0.2) were displayed in Figure 5. The ionic strength media were prepared using NaCl solutions in concentration of 0.01 M, 0.05 M, 0.1 M and 0.2 M giving ionic strengths of 0.01, 0.05, 0.1 and 0.2, respectively. Furthermore, DI water was used as zero ionic strength medium. For zero ionic strength, an increase in portion of xanthan gum in polymer ratio of HPMC:XG resulted in a decrease in viscosity.

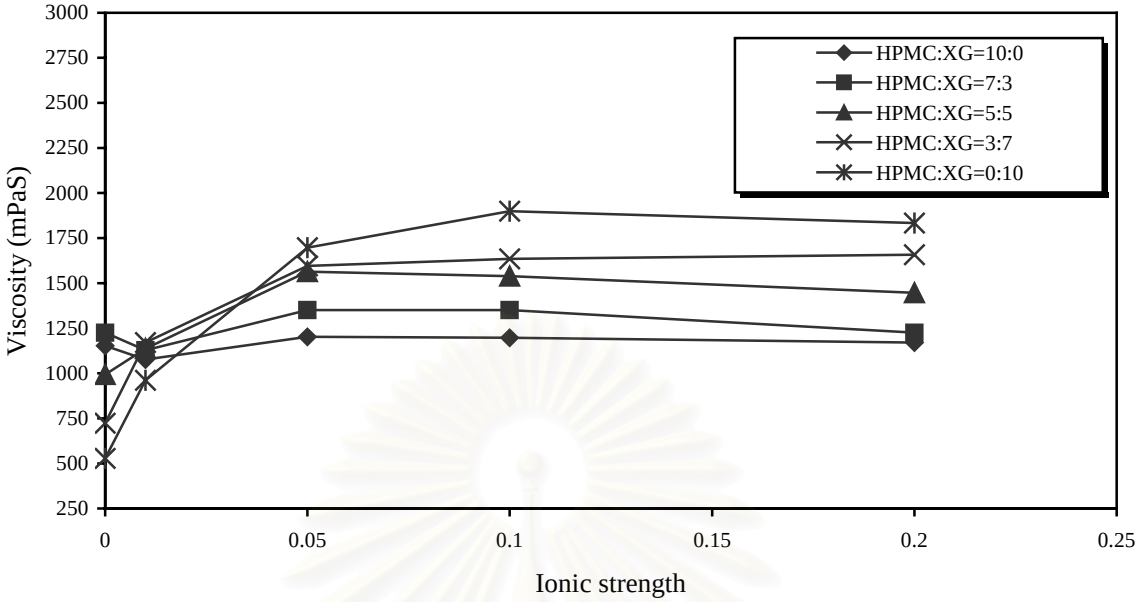


Figure 5 The viscosity of polymer gels in various ratios of HPMC:XG in various ionic strength media

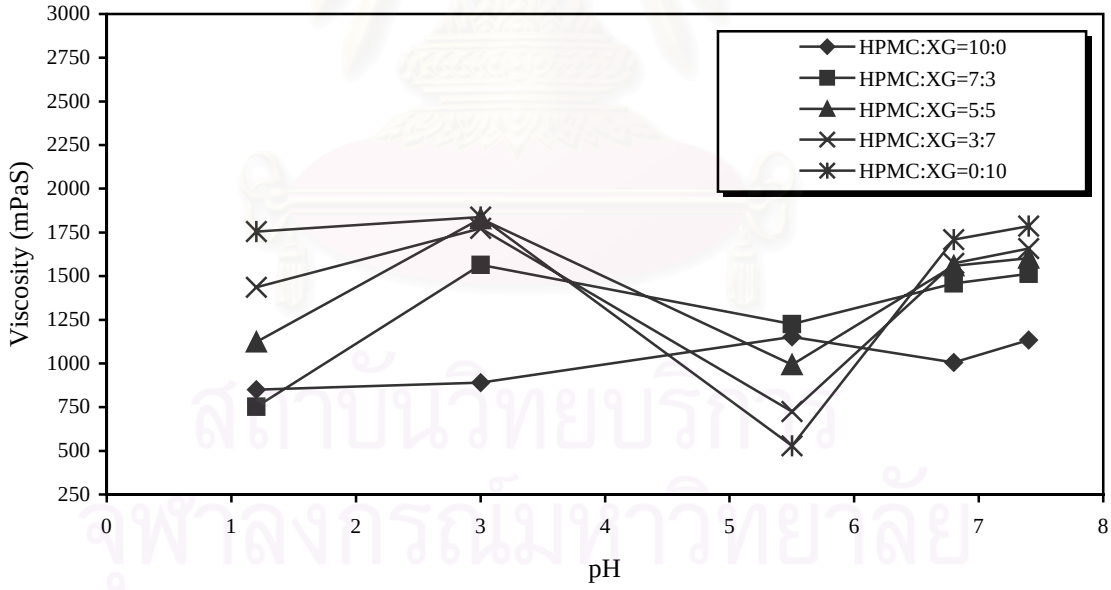


Figure 6 The viscosity of polymer gels in various of HPMC:XG in various pH media : 0.1 N HCl (pH1.2), phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4), and DI water (pH 5.5)

Additionally, at the ionic strength of 0.01, the viscosity of HPMC:XG in the ratios of 10:0, 7:3, 5:5 and 3:7 were comparable and were greater than that of when xanthan gum was used alone. In the cases of 0.05, 0.1 and 0.2 ionic strengths, higher part of xanthan gum in the polymer ratio of HPMC:XG led to greater viscosity.

At it was seen, the viscosities of HPMC:XG in the ratios of 10:0 and 7:3 in different ionic strength media were apparently unchanged. This might be due to no influence of the addition of salts on viscosity of HPMC solution (Talukdar et al., 1996). The viscosity of mixed polymer containing more HPMC concentration than xanthan gum concentration was, therefore, unaffected by ionic strength. On the other hand, for HPMC:XG ratios of 5:5, 3:7 and 0:10, an increase in viscosity of those occurred when increasing ionic strength of medium up to 0.05. Additionally, as the ionic strength of medium were increased above 0.05 to 0.2, the viscosity of HPMC:XG in the ratios of 5:5, 3:7 and 0:10 were apparently similar. Therefore, the obtained result is possible to denote that the viscosity of mixed polymer contained amount of xanthan gum equivalent to or more than that of HPMC were affected by ionic strength due to the property of xanthan gum. The result agrees with a previous study in that the viscosity was directly related to xanthan gum concentration. The effect of the addition of salts on viscosity depended on the xanthan gum concentration (Zatz and Knapp,1984). Moreover, in support of previous research (Talukdar et al., 1996) , the study found that the higher ionic strength in xanthan gum solution led to the stronger gel network, resulting in increasing viscosity. Interestingly, the previous study (Callet et al.,1987) found that, at an ionic strength of 0.1, xanthan gum is in stable form due to helix formation. Thus, further increase in ionic strength had no influence on the rheological properties, resulting in a somewhat constant viscosity. Nevertheless, the present study discovered that the effect of ionic strength on the viscosity of HPMC:XG ratio of 0:10 was limited up to 0.05. Above this ionic strength value, the viscosity of HPMC:XG ratio of 0:10 was not apparently different. The different limitation of ionic strength level on unchanged viscosity as increasing ionic strength between the present study and previous study is possibly due to the deviation in acetate and pyruvate content in

xanthan gum molecule which supplied by different manufacturer (Zatz and Knapp, 1984; Callet et al.,1987).

4.2 The viscosity of polymer gels in various pH

The viscosity of various polymer ratios of HPMC:XG in different pH media: pH 1.2 (0.1 N HCl solution), pH 5.5 (DI water), pH 3, pH 6.8 and pH 7.4 phosphate buffer solutions were shown in Figure 6.

For the pH 1.2, an increase in xanthan gum concentration in polymer ratio of HPMC:XG led to an augmentation in viscosity. Moreover, in the case of pH 3, the viscosity of HPMC:XG in the ratios of 7:3, 5:5,3:7 and 0:10 were comparable and were greater than that of HPMC:XG in the ratio of 10:0. For pH 6.8 and pH 7.4, an increase in amount of xanthan gum in mixed polymer resulted in an increase in viscosity. However, in the case of pH 5.5, an increase in xanthan gum concentration caused a decrease in the viscosity.

In addition, for HPMC:XG ratio of 10:0, the viscosity of that in pH 1.2 was less than that in pH levels of 3, 5.5, 6.8 and 7.4. This result is possibly attributed to the instability of HPMC solution in pH 1.2. Due to HPMC solution is stable in pH range of 3 to 11, the solution with pH 1.2, therefore, may disturb the HPMC molecule, causing an acid-catalyzed hydrolysis of glucose-glucose linkage structure of HPMC (Greminger and Krumel, 1980). Therefore, the occurrence of HPMC instability may result in the weak gel network and consequently small extent of viscosity.

In the case of HPMC:XG ratio of 7:3, 5:5, 3:7 and 0:10, the viscosities of all polymer ratios were not apparently related to the pH. Interestingly, in consideration of ionic strength of these media, the ionic strengths of pH 5.5 (DI water) and pH 1.2 (0.1 N HCl) and PBS pH 3, pH 6.8 and pH 7.4 were zero, 0.1 and more than 0.3, respectively. The obtained results were mostly related to the ionic strength of media. An increase in ionic strength of medium was prone to an increase in viscosity of polymer gel having

xanthan gum. Nonetheless, the extremely acidic medium (pH 1.2) affected the viscosity of mixed polymer. In particular, for the HPMC:XG ratio of 7:3, although the ionic strength of pH 1.2 medium (μ=0.1) was greater than that of DI water (μ=0) , its viscosity at 0.1 ionic strength was less than at zero ionic strength. This result might be attribute to the instability of the most HPMC content in the mixed polymer at pH 1.2.

Furthermore, the viscosity of HPMC:XG ratio of 5:5 at pH 1.2 (μ=0.1) was comparable to that at pH 5.5 (μ=0). This result is probably due to a decreased HPMC content and an increased xanthan gum content in the mixed polymer, resulting in a lessened unstable effect of HPMC and an increased strong gel layer of xanthan gum. In the cases of HPMC:XG ratios of 3:7 and 0:10, the viscosity of those at pH 1.2 (μ=0.1) were greater than that at pH 5.5 (μ=0). This outcome might be caused by an increase xanthan gum in mixed polymer that affected directly by ionic strength. In addition, the viscosity of HPMC:XG ratios of 3:7 and 0:10 at pH 1.2 (μ=0.1) were rather similar to that at pH 3, pH 6.8 and pH 7.4 (μ >0.3). This finding might be due to the stable form of xanthan gum at ionic strength above 0.1, exhibiting constant viscosity.

5. Dissolution study of theophylline matrices

The dissolution or release profiles were plotted between cumulative percentage of drug release against time.

5.1 Effect of dissolution media on drug release from blank matrices

In this study, the blank matrices composed of major ingredients; theophylline and filler. Two different fillers were spray-dried lactose (Supertab®) and dibasic calcium phosphate (Emcompress®) which were contained in matrix blank 1 and 2, respectively. The release profiles of those in various dissolution media were shown in Figures 7-10.

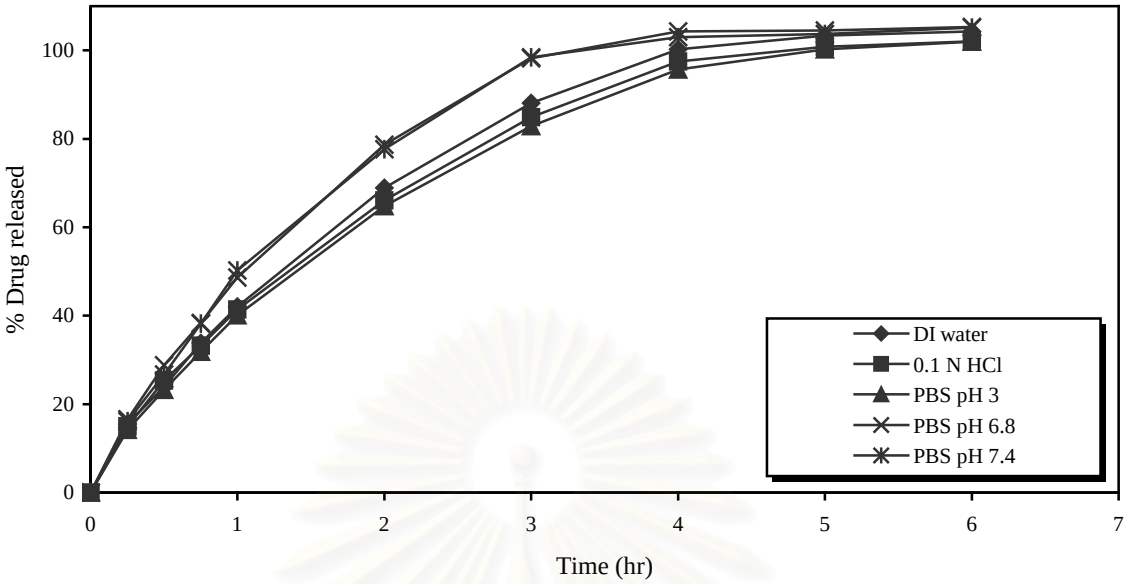


Figure 7 The release profiles of matrix blank 1 in various pH dissolution media

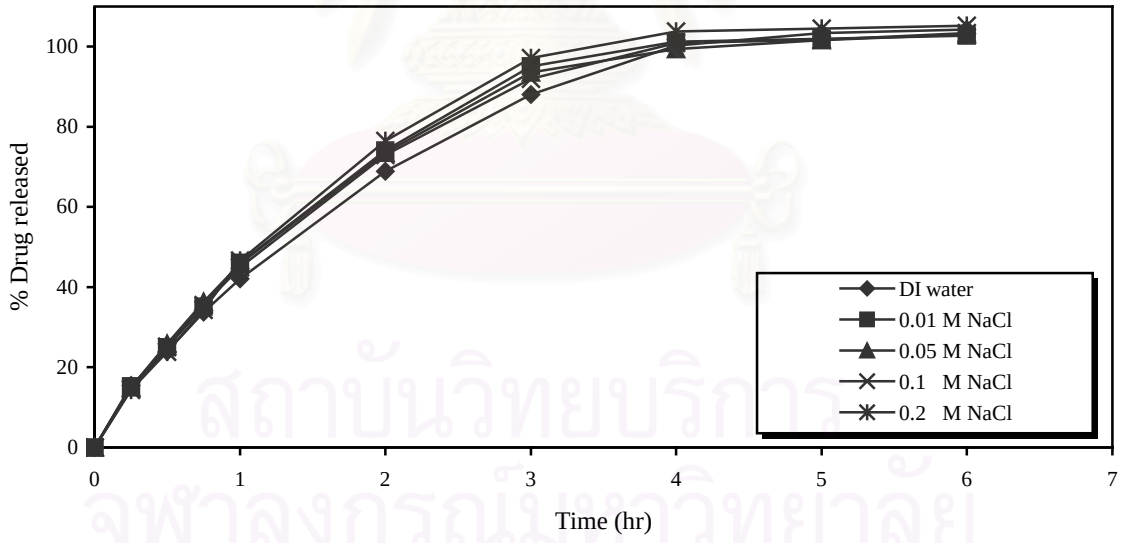


Figure 8 The release profiles of matrix blank 1 in various ionic strength dissolution media

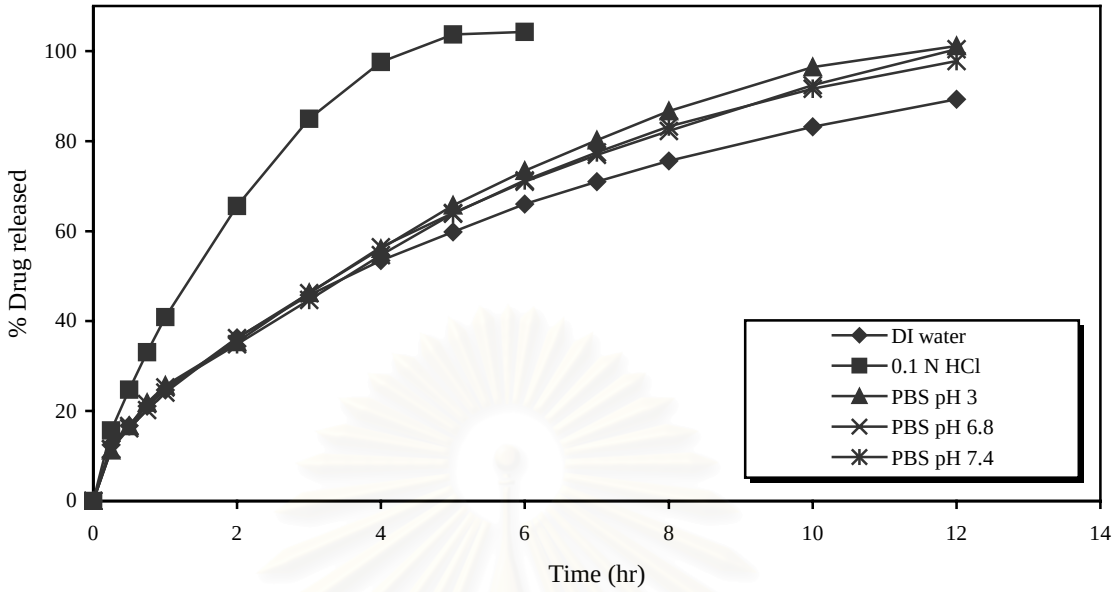


Figure 9 The release profiles of matrix blank 2 in various pH dissolution media

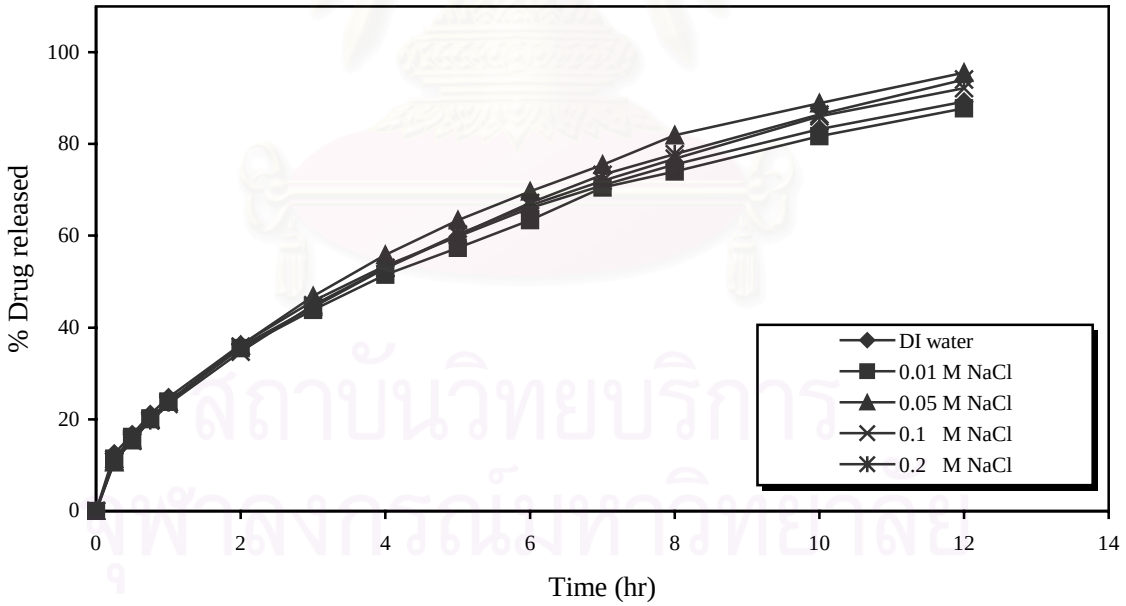


Figure 10 The release profiles of matrix blank 2 in various ionic strength dissolution media

As displayed in Figure 7, the release profiles from matrix blank1 in different pH in dissolution media was similar. During the first 4-5 hours of dissolution time, the matrices in these dissolution media were dissolved completely. In the case of different ionic strengths in dissolution media, the release profiles from matrix blank1 were not affected by ionic strength as shown in Figure 8. The percent drug release in these dissolution media reached approximately 100% at the 4^{th} hour.

The matrix blank 2 was investigated in the same way. The release profiles from matrix blank 2 in different pH in dissolution media were illustrated in Figure 9. The drug release in 0.1 N HCl solution was markedly faster than that in the other dissolution media. According to visual observation, no particles of the Emcompress® was observed in 0.1 N HCl solution while the particles of the Emcompress® were seen in DI water, PBS pH 3, pH 6.8 and pH 7.4 at the end of dissolution tests. Thus, the Emcompress® was slowly dissolved in 0.1 N HCl solution. This result indicated that the porosity of matrix in 0.1 N HCl solution was greater than that in DI water, PBS pH 3, pH 6.8 and pH 7.4. Consequently, the drug could readily diffuse out from the matrix when the matrix immersed in 0.1 N HCl solution. As a result, the drug release in 0.1 N HCl solution was completed within 5 hours while those in the other dissolution media were sustained through 12 hours.

In the case of various ionic strengths of dissolution media, the release profiles from matrix blank 2 were similar pattern as presented in Figure 10. The drug releases in these dissolution media were comparable and were prolonged for 12 hours. This finding is probably due to the important property of insoluble filler (Emcompress®) in reducing hydration of matrix.

5.2 Effect of various polymer concentrations and fillers on drug releases

The polymer concentrations in the matrices containing the Supertab®(spray dried lactose) or the Emcompress®(dibasic calcium phosphate) were 10%, 15% and 20%. All of polymer concentrations composed of HPMC and /or xanthan gum in the proportions of 10:0, 7:3, 5:5, 3:7 and 0:10. The drug releases from these matrices were tested in DI water as dissolution medium and the release profiles were illustrated in Figures 11-15.

In the case of matrices containing the Supertab® or the Emcompress® with the same polymer ratio of HPMC:XG but different polymer concentrations, an increase in the polymer concentration exhibited a decrease in the percent drug release which was found in the matrices prepared using HPMC:XG ratios of 10:0, 7:3 and 5:5 (see Fig.11-13). However, as unexpected for the matrices prepared using HPMC:XG ratio of 3:7 (see Fig.14), the percent drug release from matrix containing 10% polymer was comparable to that from matrix containing 15% polymer. Additionally, in the case of the matrices prepared using HPMC:XG ratio of 0:10 (see Fig.15), during intermediate release profiles, the amount of drug release from matrix containing 10% polymer were less than that from matrices containing 15% and 20% polymers. Therefore, in particular during intermediate release profiles, the dissolution profiles from matrix containing 10% polymer having the HPMC:XG ratios of 3:7 and 0:10 were different. This deviated result may be caused by the floatation of the matrices, which were observed visually during the 4^{th}-8^{th} hour of dissolution period. The matrix containing 10% polymer having the HPMC:XG ratios of 3:7 and 0:10 were swollen and eroded simultaneously until the matrices were floatable to the surface of dissolution medium. Considering the agitation forces during the paddle rotation, the forces at the upper part of dissolution medium may be less than that at the lower level of dissolution medium. Consequently, the agitation forces at the surface of dissolution medium could not eliminate the stagnant layer around the floatable matrices, resulting in slow rate of drug release. As the dissolution progressed, the floatable matrices were slowly dissolved.

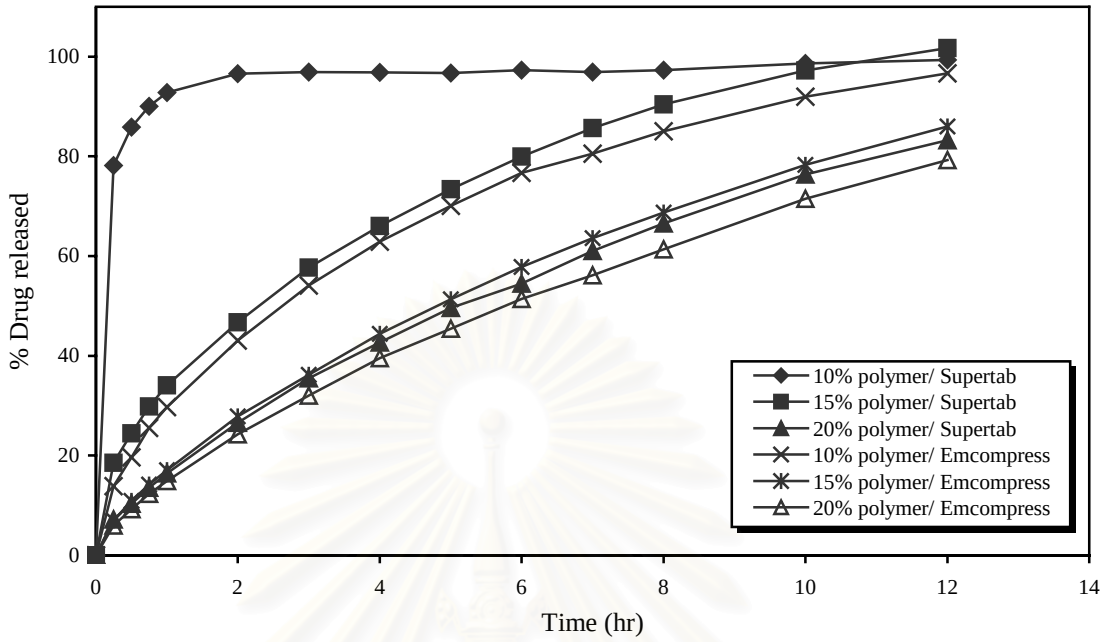


Figure 11 The release profiles of matrices containing different fillers and polymer concentrations in the HPMC:XG ratio of 10:0 in DI water

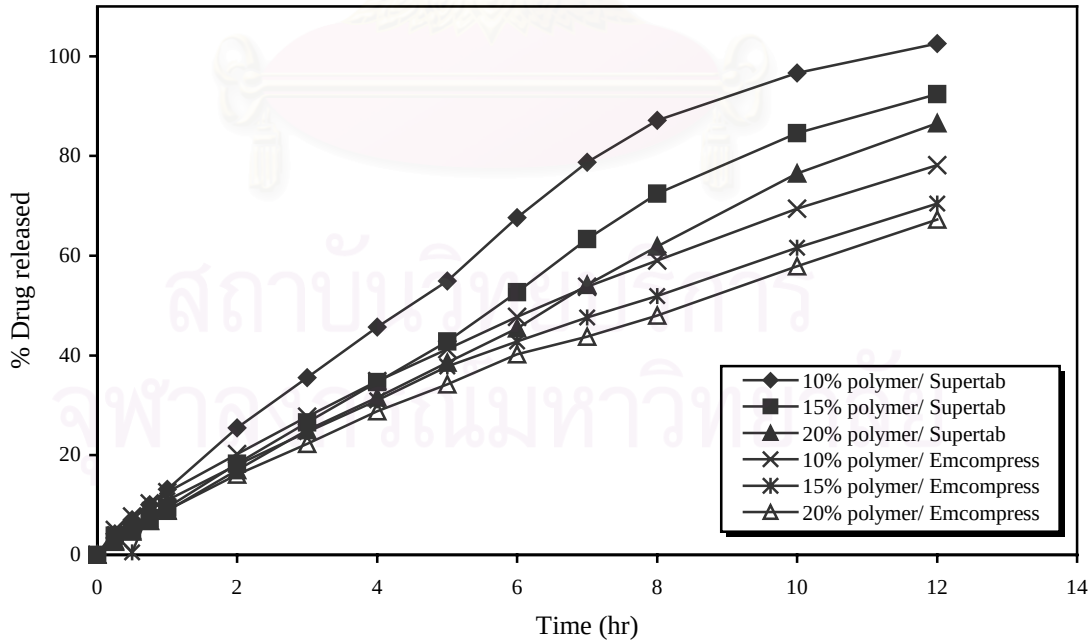


Figure 12 The release profiles of matrices containing different fillers and polymer concentrations in the HPMC:XG ratio of 7:3 in DI water

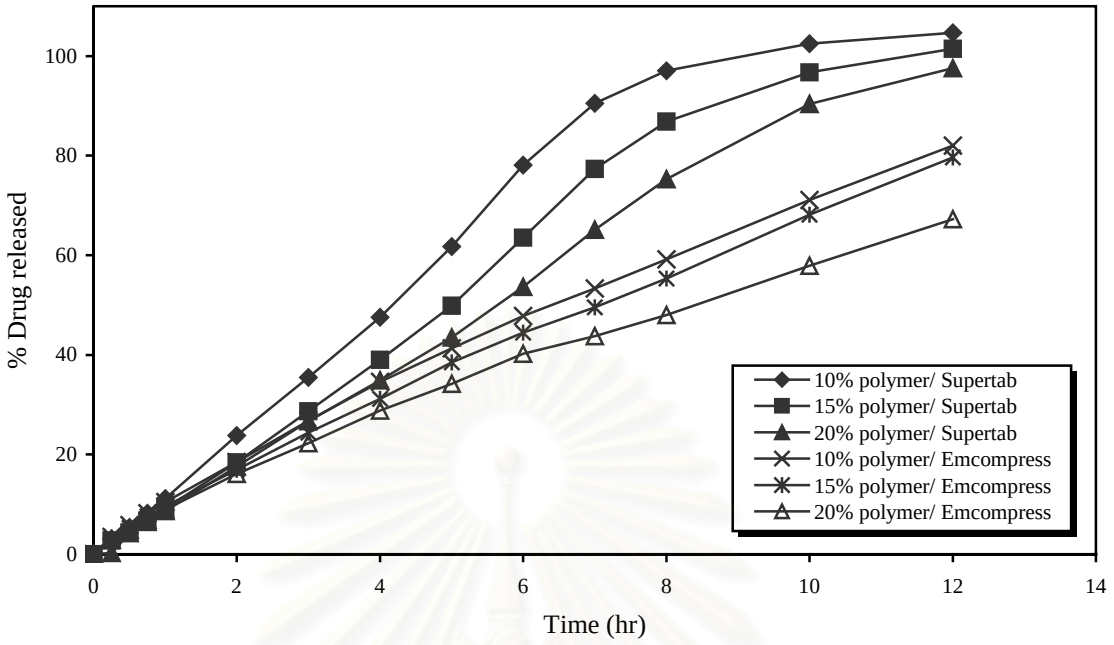


Figure 13 The release profiles of matrices containing different fillers and polymer concentrations in the HPMC:XG ratio of 5:5 in DI water

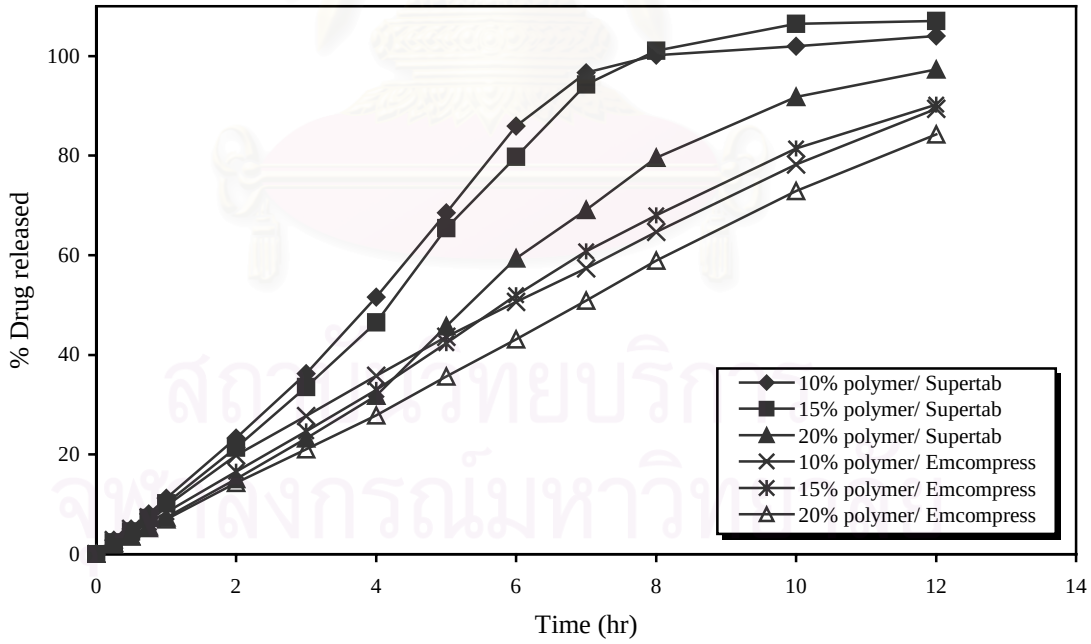


Figure 14 The release profiles of matrices containing different fillers and polymer concentrations in the HPMC:XG ratio of 3:7 in DI water

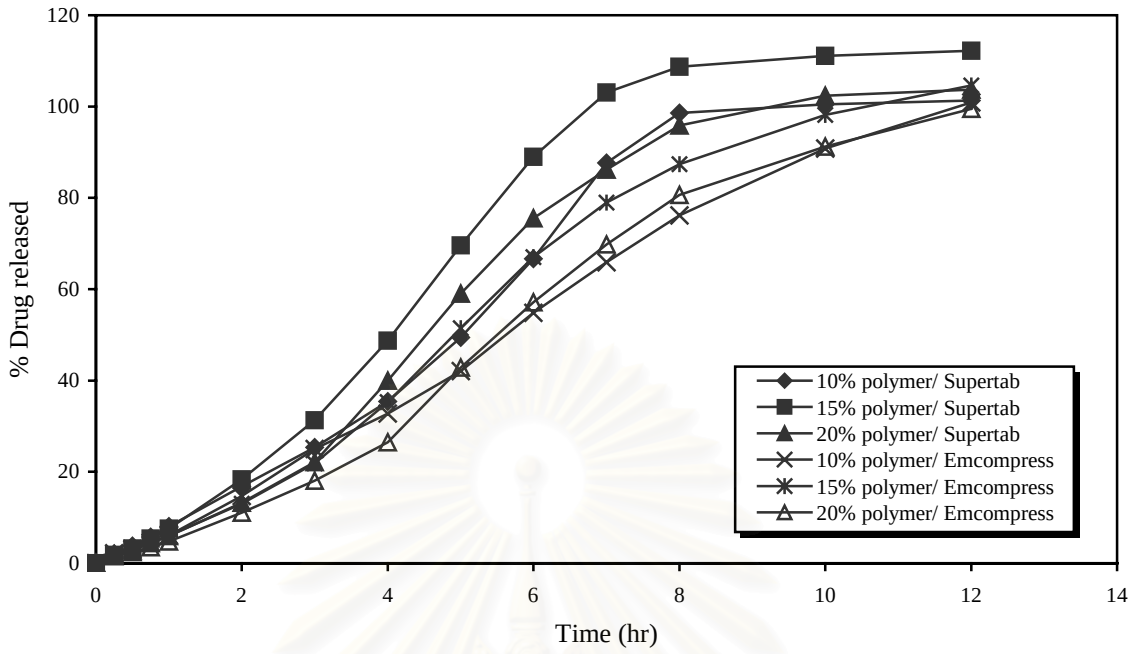


Figure 15 The release profiles of matrices containing different fillers and polymer concentrations in the HPMC:XG ratio of 0:10 in DI water

Moreover, other workers (Pillay and Fassihi,1998) studied the dissolution profiles from swellable floatable system of theophylline and diltiazem HCl. They found that the release profiles from swellable floatable tablet of theophylline was sensitive to its positioning in the dissolution vessel whereas that of diltiazem HCl did not show position sensitivity. This result was attributed to the different solubility of these drugs.

When compared the matrices containing equal polymer content with the same polymer ratio of HPMC:XG but different fillers (the Supertab® and the Emcompress®) the percent drug releases from matrices containing the Supertab® were much greater than those from matrices containing the Emcompress®(see Fig.11-15). Obviously, the diluent in the matrix played an important role on the drug release. The reason for this finding might be due to the different solubility of diluent. The Supertab® is the spray dried lactose used as a water-soluble excipient whereas the Emcompress® is the dibasic calcium phosphate used as a water-insoluble excipient. Therefore, when water penetrated into the matrix, the Supertab® in the matrix was readily dissloved which led to a

decrease in the tortuosity of matrix and hence, an increase in the amount of drug release. In contrast, the Emcompress® did not dissolve in the water and thus Emcompress® caused an increase in the tortuosity of matrix, presenting a reduction in the percent drug release. The more matrix integrity was observed in the matrix containing the Emcompress® than that containing the Supertab®. Thus, the higher erosion of matrix occurred in the matrix containing the Supertab®, resulting in the more percent drug release. This result agrees with previous studies by Ford et al. (1987); Efentakis et al. (1997); Vargas and Ghaly (1999); Zhang and Schwartz (2000). They concluded that the difference in drug release is due to variation in dissolution medium penetration. The soluble materials can produce faster release rate than the less soluble ones. In addition, the excipient characteristics in the matrix and their subsequent effects in matrix integrity were related to the drug release rate.

5.3 Effect of various polymer ratios on drug releases

The effect of different HPMC to XG ratios of 10:0, 7:3, 5:5, 3:7 and 0:10 at the polymer levels of 10%, 15% and 20% on drug releases from the Supertab® matrix or the Emcompress® matrix were displayed in Figures 16-21. The drug release experiments were performed using DI water as a dissolution medium.

For the Supertab® matrices (see Fig.16,18 and 20), the release profiles of matrix containing 10%, 15% and 20% HPMC exhibited the initial burst drug release and subsequent slow drug release during the course of dissolution process for 15% and 20% HPMC containing matrices. This result was probably attributed to the rapid disintegration at the matrix surface and then the formation of gel layer around the matrix. For partial substitution of HPMC with xanthan gum in the HPMC:XG ratio of 7:3 in the matrices containing 10%, 15% and 20% polymers, the initial burst drug releases were apparently reduced and afterwards the fast drug release were observed in the last period of release profiles.

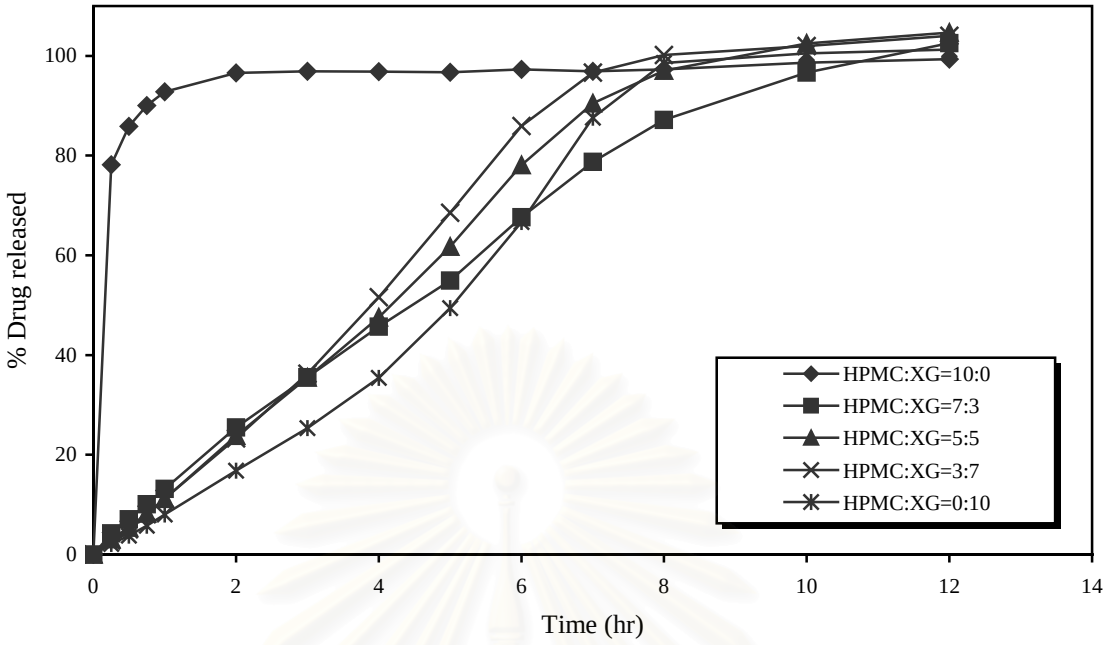


Figure 16 The release profiles of matrices containing spray dried lactose and 10% polymer in various HPMC:XG ratios in DI water

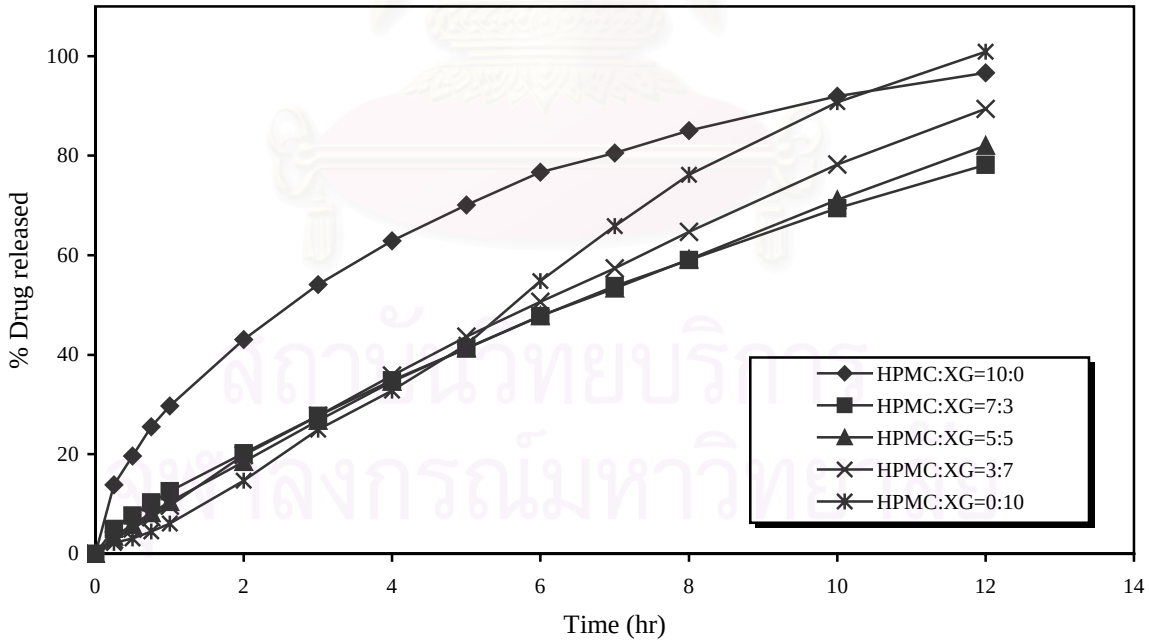


Figure 17 The release profiles of matrices containing dibasic calcium phosphate and 10% polymer in various HPMC:XG ratios in DI water

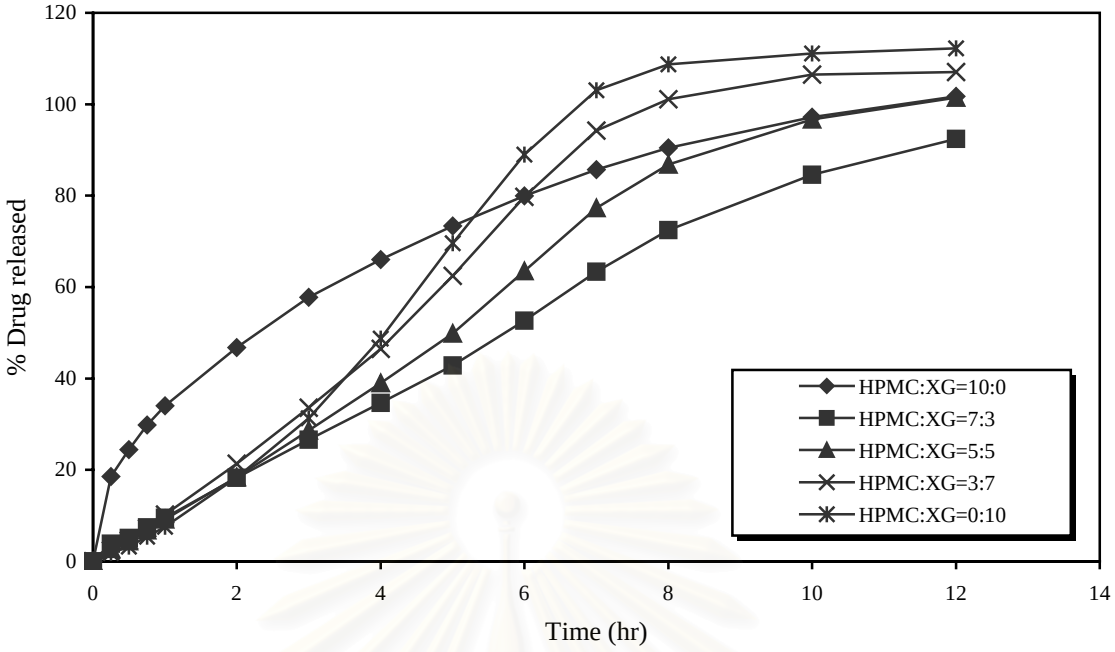


Figure 18 The release profiles of matrices containing spray dried lactose and 15% polymer in various HPMC:XG ratios in DI water

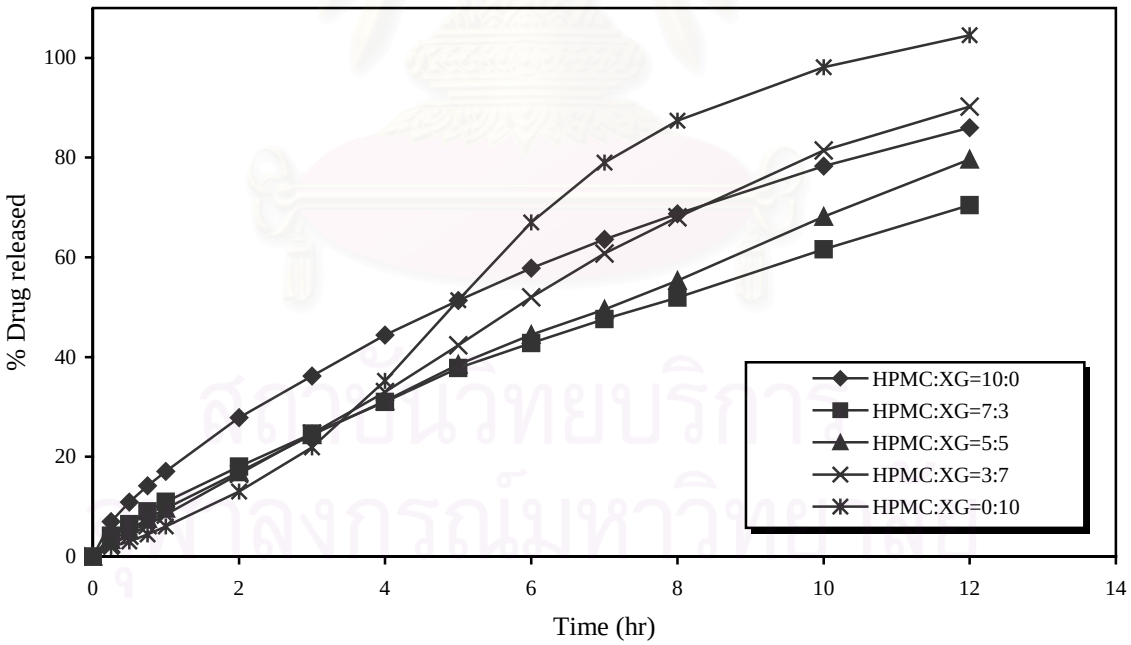


Figure 19 The release profiles of matrices containing dibasic calcium phosphate and 15% polymer in various HPMC:XG ratios in DI water

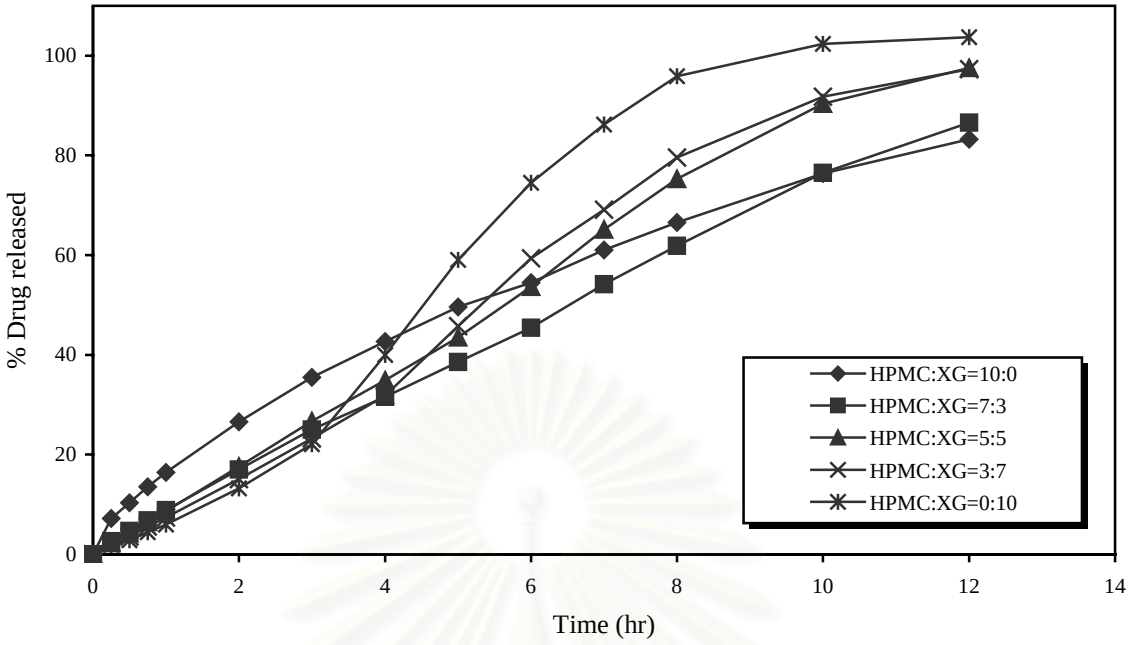


Figure 20 The release profiles of matrices containing spray dried lactose and 20% polymer in various HPMC:XG ratios in DI water

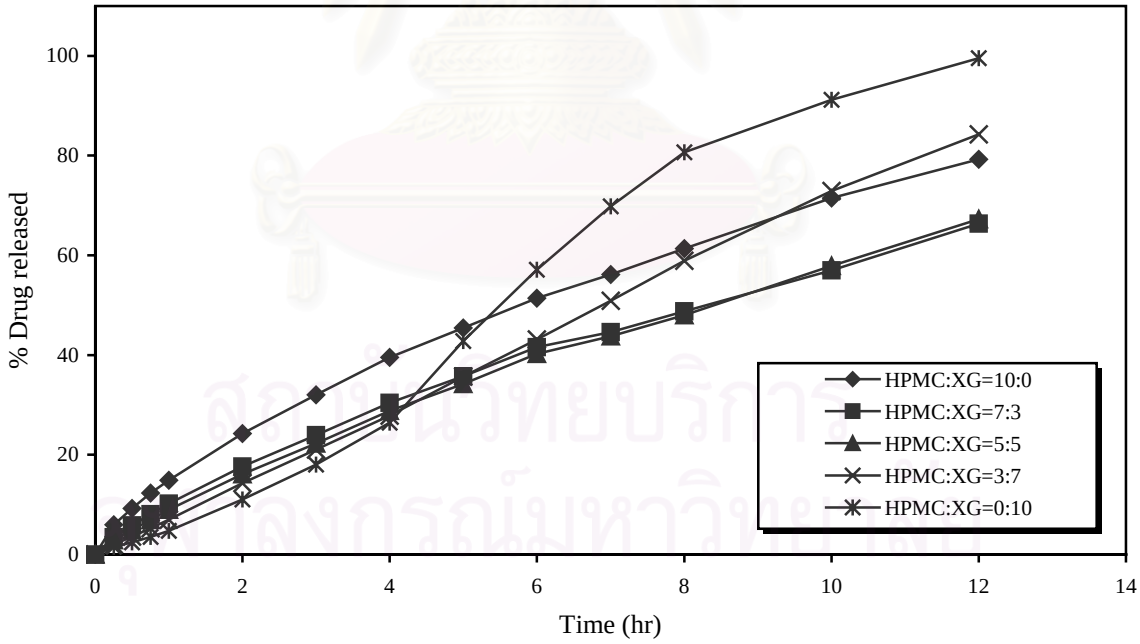


Figure 21 The release profiles of matrices containing dibasic calcium phosphate and 20% polymer in various HPMC:XG ratios in DI water

When the xanthan gum proportions of HPMC:XG at 5:5 and 3:7 in the matrices containing 10%,15% and 20% polymers were increased, the initial burst drug release were similar to that from matrices containing 10%,15% and 20% polymers in the HPMC:XG ratio of 7:3. On the other hand, during the late dissolution period, the drug release from matrix containing HPMC:XG ratio of 3:7 was more rapid than that from matrix containing HPMC:XG ratios of 5:5 and 7:3, respectively. Moreover, when HPMC was completely replaced with xanthan gum in the matrices containing 10%, 15% and 20% polymers, at the beginning of release profiles the percent drug releases were comparable to that from matrices containing 10%, 15% and 20% polymers in the HPMC:XG ratios of 7:3, 5:5 and 3:7. In contrast, during the late dissolution period the amount of drug release from matrix containing 15% and 20% polymers in the HPMC:XG ratio of 0:10 was markedly greater than that from matrices containing HPMC:XG ratios of 3:7, 5:5 and 7:3. Exceptionally, in the case of the matrix containing 10% polymer in the HPMC:XG ratio of 0:10, during the 3^{th}-6^{th} hours of dissolution, the amount of drug release was less than that from matrix containing HPMC:XG ratios of 7:3, 5:5 and 3:7, respectively. This result might be caused by the swelling and floatation of matrix containing HPMC:XG ratio of 0:10 at the surface of dissolution medium. The drug release of this matrix depended on its position in the dissolution vessel.

In conclusion, any degrees of HPMC substitution with xanthan gum in the matrices containing 10%, 15% and 20% polymers could minimize the initial burst drug release, resulting in more constant drug release. Conversely, an increase in replacement of HPMC with xanthan gum led to an augmentation of the percent drug release of matrices during the latter part of dissolution profiles. This might be caused by the property of polymer and the different amounts of HPMC and xanthan gum in the matrices. By visual inspection over the course of dissolution process, the matrices containing any amount of xanthan gum could maintain matrix integrity at the beginning of dissolution time. The matrix surface showed the strong gel-layer rather than the rapid disintegration. In addition, this result is also consistent with previous investigation and can be described according to Talukdar et al. (1996). Xanthan gum is hydrated quickly and then gel layer is formed immediately. Consequently, the matrix swells, the longer

diffusional path length required for the drug to leach out, result in decreasing drug release in the initial time of release profile from matrix containing xanthan gum. Furthermore, during the late dissolution profile, more amount of xanthan gum in the matrix was susceptible to more erosion of gel layer around the matrix, which observed visually. This result is similar to a previous study. Ranga Rao et al. (1988) studied the release profiles in DI water of matrices containing mixed polymers of hydroxypropylcellulose (HPC) and sodium carboxymethylcellulose (NaCMC) which are cellulose ether and semi-natural anionic polymer, respectively. Moreover, in this study the viscosity determinations of polymer gels that composed of various ratios of HPMC:XG (10:0, 7:3, 5:5, 3:7 and 0:10) in DI water may be substantial to verify the erosion of gel layer around the matrices containing the different polymer ratios of HPMC to XG. An increase in xanthan gum in the polymer ratio of HPMC:XG resulted in a decrease in viscosity of polymer gel. Consequently, a reduced viscosity of polymer gel in the matrix might cause the rapid erosion of gel layer around the matrix during the latter part of dissolution period, resulting in rapid drug release.

Furthermore, for the Emcompress® matrices (see Fig. 17, 19 and 21), the release profiles of matrices containing 10%, 15% and 20% HPMC also presented the typical dissolution performances. In addition, the initial burst drug release of matrix containing the Emcompress® and HPMC alone was reduced. This might be due to the important effect of the Emcompress® on encumbrance of dissolution medium penetration into the matrix. Consequently, the disintegration at the matrix surface was also decreased, resulting in slow initial drug release. Moreover, for the HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 at the polymer levels of 10%, 15% and 20%, the patterns of dissolution profiles from these matrices containing the Emcompress® were similar to those from matrices containing the Supertab® . In particular, an increase in amounts of xanthan gum in the matrix exhibited a greater rapid drug release during the latter portion of dissolution profiles.

5.4 Effect of various compression forces on drug releases

The matrices containing 15% mixed polymer of HPMC:XG ratios of 7:3 and 3:7 and different fillers (spray dried lactose and dibasic calcium phosphate) were chosen to investigate the effect of compression forces on drug release. The matrices were compressed at the forces of 1000, 2000 and 4000 lbs which approximately given the hardness of 7, 10 and 12 kp, respectively (Table 7). The determinations of percent drug content of matrices containing spray dried lactose and HPMC:XG ratios of 7:3 and 3:7 were 105.52 % and 106.111 %, respectively. The percent drug contents of matrices containing dibasic calcium phosphate and HPMC:XG ratios of 7:3 and 3:7 were 100.32 % and 104.91%, respectively. The influence of compression forces on drug release from matrices containing HPMC:XG ratios of 7:3 and 3:7 but different diluents were shown in Figures 22 and 23, respectively. An increase in compression forces caused a decrease in the percent drug release that markedly occurred during the last part of dissolution profiles. This was likely attributed to the different porosity within the matrix. At lower applied pressures, the more porosity within the matrix might allowed the greater dissolution medium penetration into the matrix, consequently increasing drug release.

Table 7 The physical properties of matrices containing different fillers (Supertab® or Emcompress®) with mixtures of xanthan gum and HPMC in the ratios of 7:3 and 3:7 at various compression forces

Matrix composition HPMC: XG: Filler	Compression forces (lbs)	Physical properties of matrices	
		Hardness [kp± (SD)] (n=3)	Thickness [mm± (SD)] (n=3)
7: 3 : Supertab®	1000	7.67 (0.61)	2.89 (0.01)
	2000	10.20 (0.29)	2.79 (0.01)
	4000	12.03 (0.25)	2.69 (0.02)
3: 7 : Supertab®	1000	7.30 (0.46)	2.89 (0.02)
	2000	10.03 (0.55)	2.75 (0.02)
	4000	11.47 (0.45)	2.68 (0.01)

Table 7 (Continued) The physical properties of matrices containing different fillers (Supertab® or Emcompress®) with mixtures of xanthan gum and HPMC in the ratios of 7:3 and 3:7 at various compression forces

Matrix composition HPMC: XG: Filler	Compression forces (lbs)	Physical properties of matrices	
		Hardness [kp± (SD)] (n=3)	Thickness [mm± (SD)] (n=3)
7: 3: Emcompress®	1000	8.53 (0.40)	2.78 (0.01)
	2000	10.50 (0.69)	2.66 (0.01)
	4000	11.83 (1.59)	2.59 (0.01)
3: 7: Emcompress®	1000	8.37 (0.35)	2.74 (0.01)
	2000	10.67 (0.59)	2.62 (0.02)
	4000	13.07 (0.45)	2.53 (0.01)

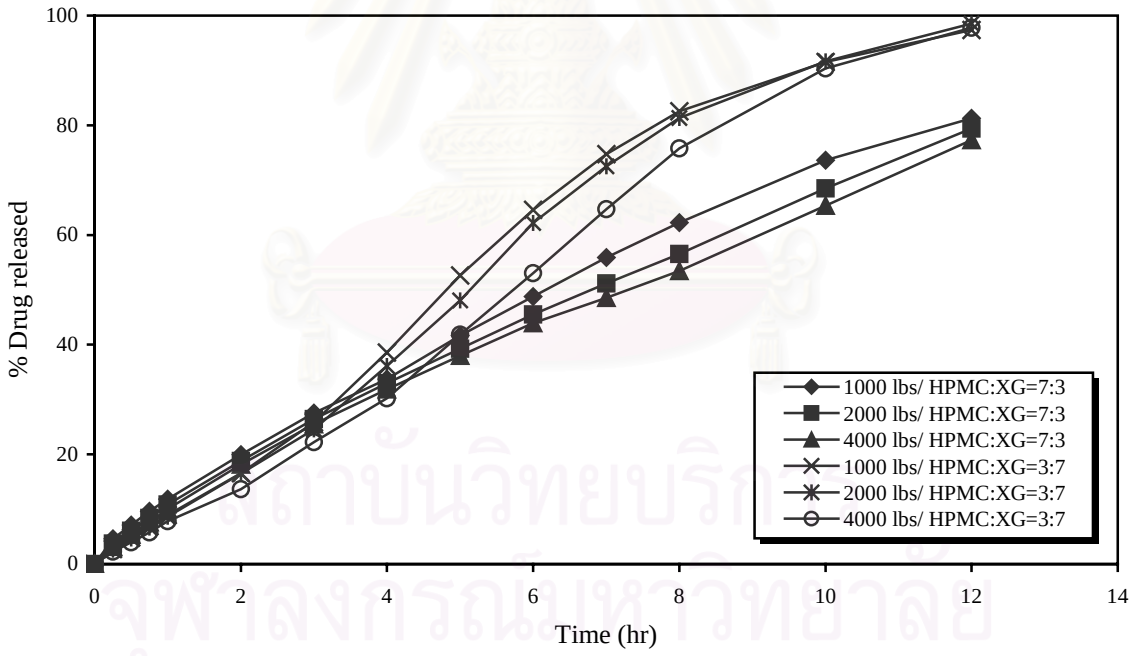


Figure 22 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratios of 7:3 and 3:7 at various compression forces in DI water

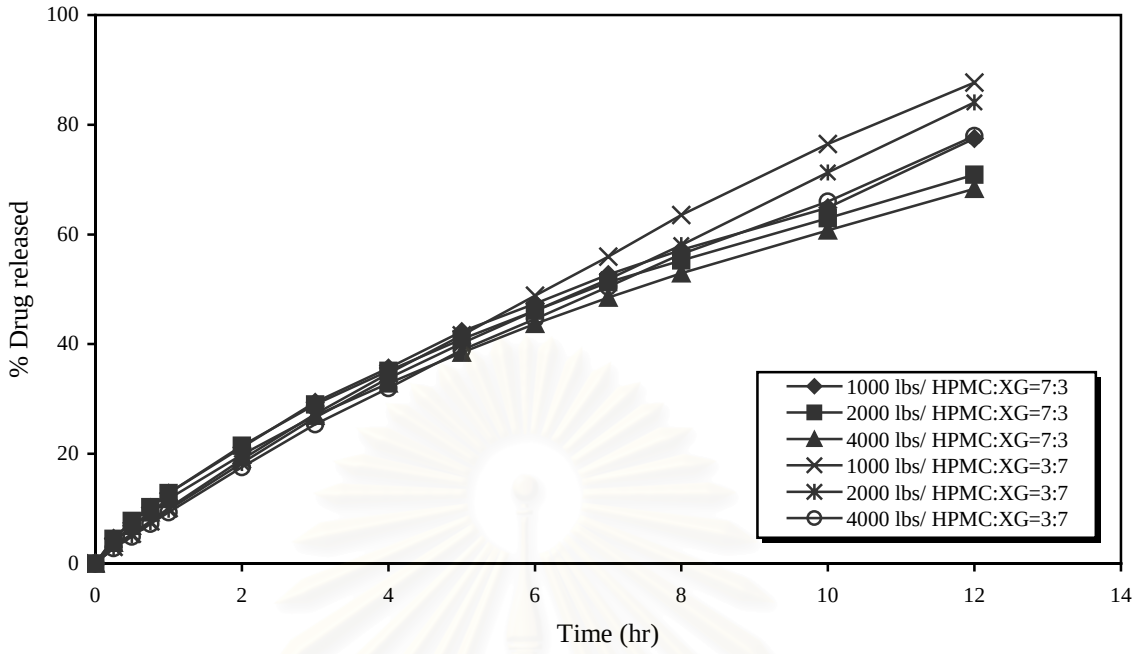


Figure 23 The release profiles of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratios of 7:3 and 3:7 at various compression forces in DI water

5.5 *Effect of various dissolution media on drug releases*

The matrices containing 15% polymer at various ratios of HPMC:XG; 10:0, 7:3, 5:5, 3:7 and 0:10 with different fillers; the Supertab® and the Emcompress® were investigated for the release profiles in different dissolution media as follows; DI water, 0.1 N HCl solution (pH 1.2), PBS pH 3, pH 6.8, pH 7.4, and NaCl solutions in the concentrations of 0.01 M , 0.05 M, 0.1 M and 0.2 M corresponding to the ionic strengths of 0.01, 0.05. 0.1 and 0.2, respectively.

5.5.1 Matrix containing the Supertab® and HPMC:XG ratio of 10:0

As displayed in Figures 24-25, the dissolution profiles of matrix containing HPMC:XG ratio of 10:0 and the Supertab® in different dissolution media were similar.

The initial rapid drug release was also observed in these dissolution media. In the case of different pH dissolution media (see Fig.24), during the first 4 hours of dissolution profiles, the percent drug releases in PBS pH 6.8 and pH 7.4 were greater than those in 0.1 N HCl solution and PBS pH 3. In addition, the percent drug releases were also greater than that in DI water.

In general, the drug solubility is one of the important factors that affected the drug release. In this study, the solubilities of theophylline in these dissolution media at 37 ^{O}C were similar. Therefore, the drug solubility might not be the essential factor for the difference in the percent drug release particularly during the beginning of dissolution period. Nonetheless, during the first 4 hours of dissolution period, the difference in the amount of drug release in these pH dissolution media is probably due to the effect of different dissolution media on the property of HPMC in the matrix. A previous study by Uko-Nne et al.(1989) may support the obtained result in that chloride and phosphate ions in dissolution media are known to cause dehydration of cellulose ether which could possibly impede the formation of gel network structure. This mention complies with the visual observation during dissolution test. During the initial dissolution period, it was observed that the rapid disintegration of the matrix surface occurred in 0.1 N HCl solution and phosphate buffer solution rather than that in DI water. Consequently, the percent drug release in DI water was less than that in the other dissolution media. However, at the last portion of dissolution profile, the percent drug releases in various pH dissolution media became closer to the complete dissolution of matrices.

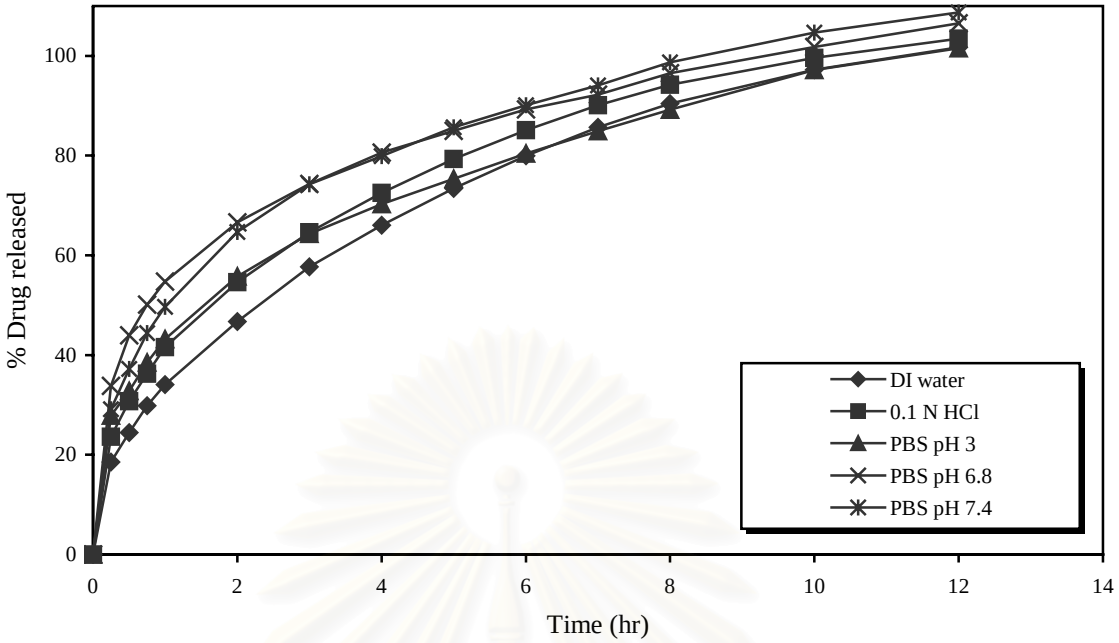


Figure 24 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 10:0 in various pH dissolution media

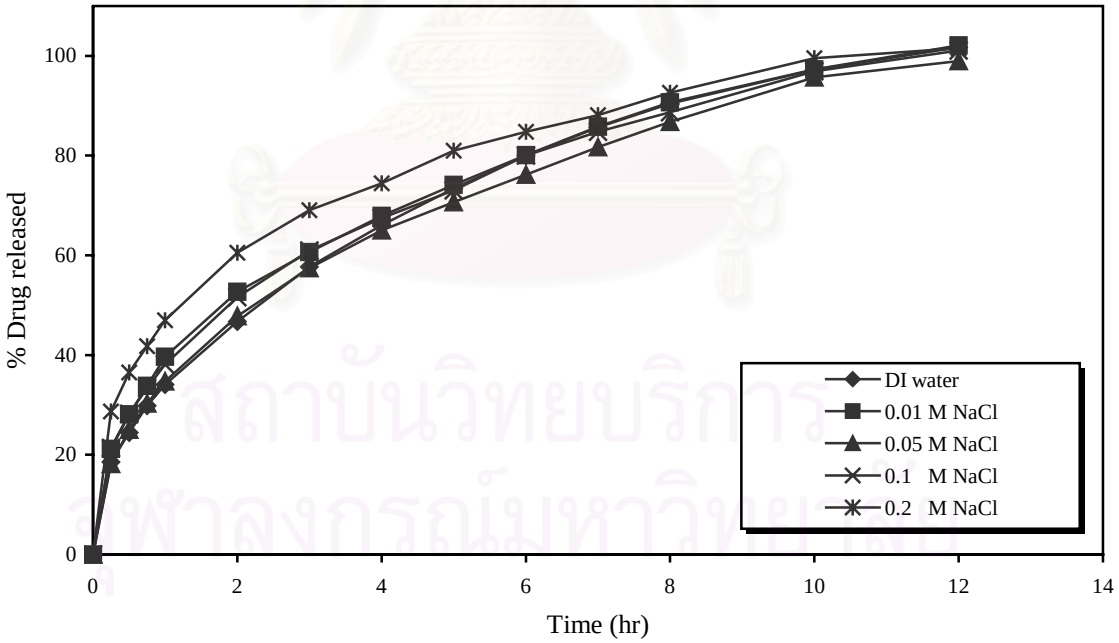


Figure 25 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 10:0 in various ionic strength dissolution media

At the different ionic strength of dissolution media (see Fig.25), during the first 6 hours of dissolution profile, the amount of drug release in 0.2 M NaCl solution was slightly greater than that in 0.01 M, 0.05 M and 0.1 M NaCl solutions. At the 12th hour of dissolution time, the percent drug release in these dissolution media was not different. As aforementioned, the chloride ion in dissolution medium might cause the dehydration of cellulose ether. Therefore, the HPMC in the matrix was also possibly affected by chloride ion in the NaCl solution, exhibiting a rapid drug release. In agreement with Jalil and Ferdous (1993), they found that an increase in theophylline release from matrix containing HPMC appeared with an increase in ionic strength in dissolution media (μ=0, 0.085, 0.17, 0.34, 0.51, 0.68 and 1.02) especially at very high ionic strength. The increased ionic strength in dissolution media may cause increased erosion and dissolution of polymer chain from the matrix surface. However, as the result of this study, the differences in the percent drug release in various ionic strengths in dissolution media (μ=0, 0.01, 0.05, 0.1 and 0.2) was not markedly observed. This finding might be due to the less different ionic strengths in dissolution media when compared with the experiment in the previous study.

5.5.2 Matrix containing the Supertab® and HPMC:XG ratio of 7:3

The dissolution profiles of matrices containing HPMC:XG ratio of 7:3 and the Supertab® in different dissolution media were illustrated in Figures 26-27. In the case of different ionic strengths in dissolution media (see Fig.27), the pattern of release profiles in DI water (μ=0) was slow drug release at the beginning of dissolution time and was rapid drug release at the end of dissolution period. On the contrary, the dissolution performances in the ionic strength media of 0.01, 0.05, 0.1 and 0.2 expressed the initial rapid drug release and subsequent slow drug release over the entire dissolution period. The ionic strength level of dissolution media affected the percent drug release. An increase in ionic strength in dissolution media led to an increase in the amount of drug release. This observation might be due to the effect of ionic strength on the hydration of polymer at the outer layer of matrix in particular xanthan gum.

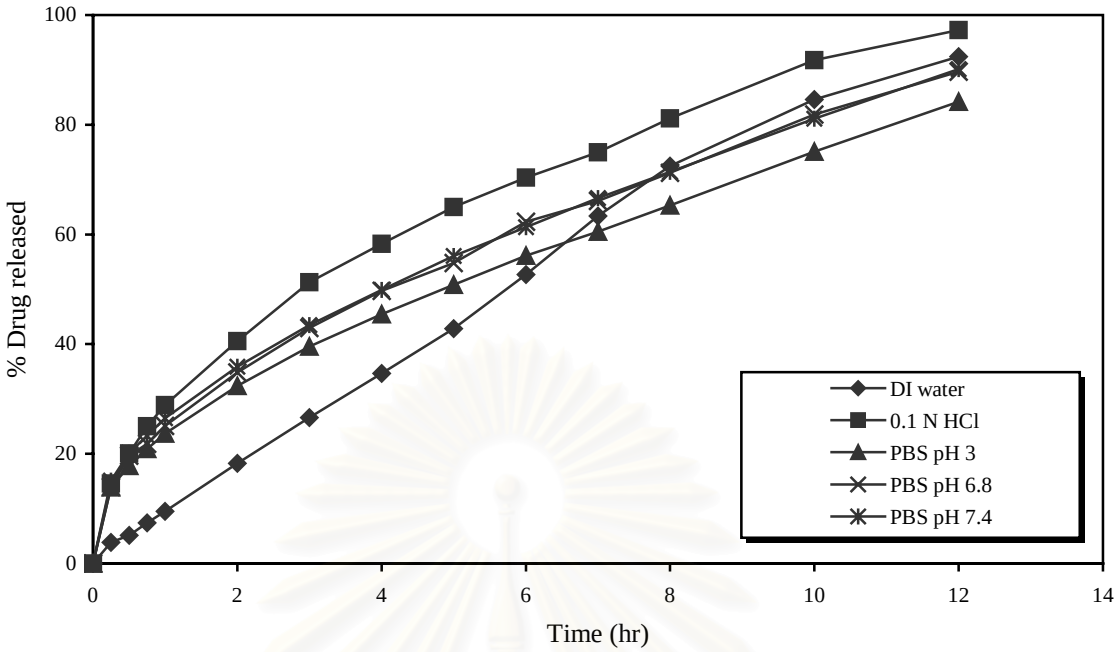


Figure 26 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 7:3 in various pH dissolution media

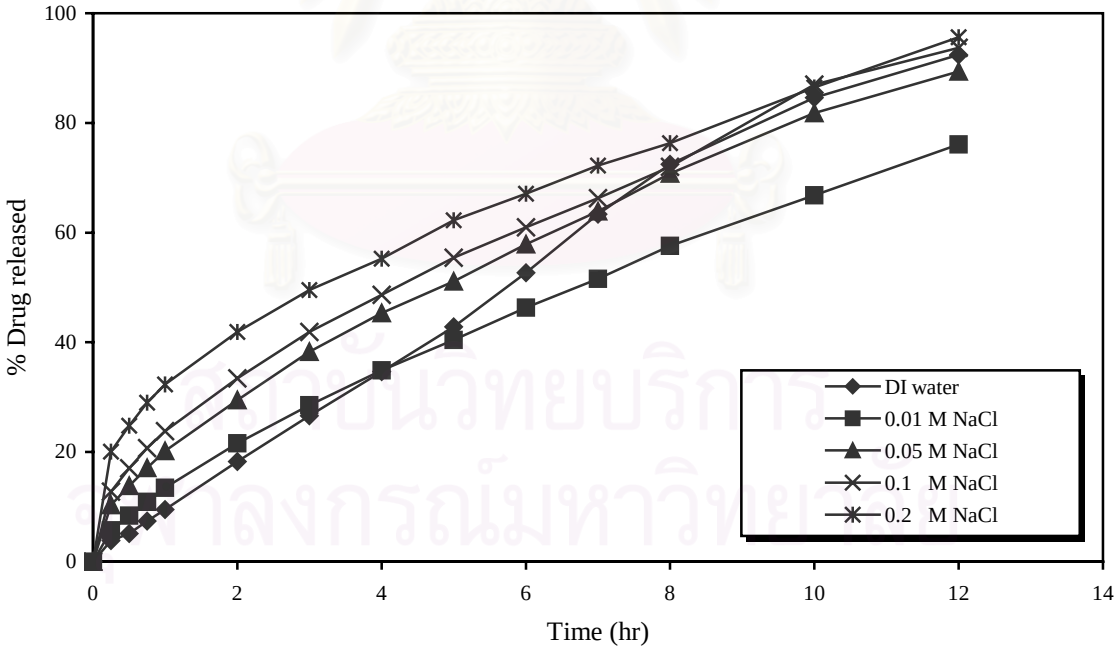


Figure 27 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 7:3 in various ionic strength dissolution media

In agreement with Talukdar and Kinget (1995), this investigation pointed out that an increase in ionic strength of dissolution media resulted in a decrease in swelling of matrix which containing only xanthan gum as a polymer. Thus, the reduced matrix swelling may imply the decreased hydration of polymer in the matrix and consequently increase the microvoids within the outer layer of matrix. Moreover, the increased microvoids within the outer layer of matrix is possible to facilitate the dissolution medium penetration, resulting in an increase in the disintegration at the matrix surface. Ultimately, it is possible to denote that more ionic strength in dissolution media led to more disintegration at the matrix surface, exhibiting more percent drug release.

In different pH dissolution media (see Fig.26), the pattern of release profile in DI water was different to that in 0.1 N HCl solution, PBS pH 3, pH 6.8 and pH 7.4. During the initial 6 hours of dissolution time, the release profile in DI water showed slow drug release whereas that in 0.1 N HCl solution, PBS pH 3, pH 6.8 and pH 7.4 manifested rapid drug release. The deviation in the amount of drug release during the beginning of the release profile may be due to the different properties of polymers in the matrix when exposed to different dissolution media. According to the visual observation during the dissolution test, when the matrix was immersed in DI water, the slight disintegration at the matrix surface and subsequent gel layer around the matrix were observed. In contrast, when the matrices were exposed to 0.1 N HCl solution, PBS pH 3, pH 6.8 and pH 7.4, the faster disintegration at the matrix surface and following gel layer at the boundary of matrix were seen. The different matrix disintegration in these dissolution media might be caused by the different ionic strength in these dissolution media that influenced the property of xanthan gum. In addition, during the late dissolution profile, the percent drug release in DI water was comparable to those in PBS pH 6.8 and pH 7.4 which due to the rapid erosion at the outer region of matrix in DI water.

The amount of drug release in 0.1 N HCl solution was greater than those in PBS pH 3, pH 6.8 and pH 7.4. In consideration of ionic strength, the ionic strengths of 0.1 N HCl solution and phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) were 0.1 and

more than 0.3, respectively. As previously mentioned, higher ionic strength in dissolution media caused more disintegration at the matrix surface. Therefore, the more matrix disintegration should occur in phosphate buffer solution (μ>0.3), when compared with 0.1 N HCl solution (μ=0.1). However, according to the result of this study, the more matrix disintegration in 0.1 N HCl solution was visually observed and consequently exhibited the more percent drug release. This result might be caused by the influence of different pH in dissolution medium on the matrix swelling. According to the previous study by other workers (Talukdar and Kinget,1995), it was found that the matrix containing xanthan gum in various dissolution media; NaCl solution, HCl solution and USP buffer pH 7.4 having equal ionic strength, showed the deviation in swelling rate. They concluded that the swelling rate in extremely acidic medium is significantly ($p<0.05$) lower than that in neutral or alkaline solutions. In addition, as the result of viscosity determination, the viscosity of polymer gel which composed of HPMC:XG ratio of 7:3 in 0.1N HCl solution was much less than that in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4). Therefore, the gel layer of matrix in 0.1N HCl solution might be more erosion than those in phosphate buffer solutions. Thus, the amount of drug release in 0.1N HCl solution was greater than that in phosphate buffer solutions over the entire dissolution period due to the less matrix swelling and more erosion of outer gel layer around the matrix in 0.1N HCl solution.

5.5.3 Matrix containing the Supertab® and HPMC:XG ratio of 5:5

The dissolution profiles of matrix containing the Supertab® and HPMC:XG in the ratio of 5:5 in different dissolution media were displayed in Figures 28-29. In the case of different pH dissolution media (see Fig.28), the release profile in DI water exhibited the slow drug release at the early dissolution period and the rapid drug release at the late dissolution period. This result might be due to the rapid formation of swollen gel layer at the matrix surface and then followed by the rapid depletion of swollen gel layer at the outer boundary of matrix. On the contrary, the release profiles in 0.1 N HCl solution and phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) showed the initial

rapid drug release and later slow drug release. This result might be caused by the more disintegration at matrix surface and following swollen gel layer surrounding the matrix. In addition, during the beginning of release profiles, the amounts of drug release in DI water, phosphate buffer solutions and 0.1 N HCl solution were the least, intermediate and the greatest, respectively. This result might be explained basing on the difference in swelling rate of polymer in the matrix. However, during the late dissolution profiles, the rate of drug release in DI water was the highest, that in 0.1 N HCl solution was intermediate and those in phosphate buffer solutions were the least. This result might be due to the difference in erosion of swollen gel layer at the outer region of matrix. The erosion rate of swollen gel layer might depend on the viscosity of swollen gel. As the result of viscosity measurement in this study, the viscosity in DI water, 0.1 N HCl solution and phosphate buffer solutions were the least, intermediate and the greatest, respectively (see Fig.6).

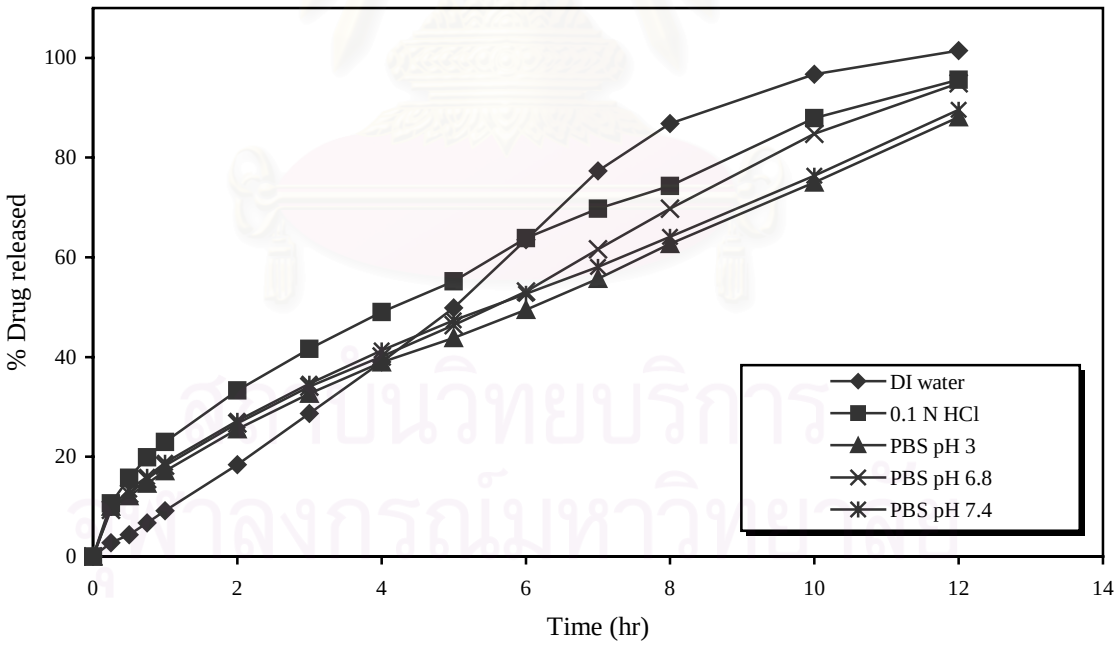


Figure 28 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 5:5 in various pH dissolution media

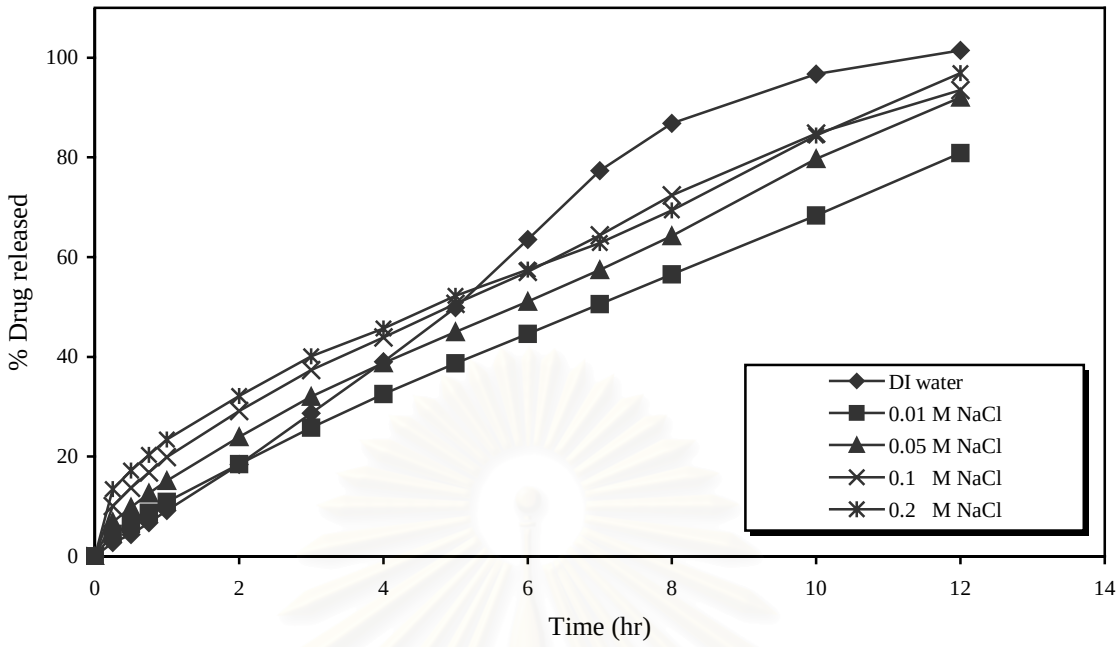


Figure 29 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 5:5 in various ionic strength dissolution media

Furthermore, for various ionic strengths of dissolution media (see Fig.29), by visual observation during the experiment, the matrices in different ionic strengths of dissolution media appeared to have disintegration and subsequent the swollen gel layer surrounding the matrix surface. The matrix in a lower ionic strength medium exhibited the swollen gel layer rather than the disintegration at the surface. Therefore, the matrix in 0.01 M NaCl solution (μ=0.01) showed the least disintegration and the greatest swollen gel layer. In contrast, the matrix in 0.2 M NaCl solution (μ=0.2) exhibited the greatest disintegration and the least swollen gel layer. It is important to denote that a decrease in ionic strength in dissolution medium led to a decrease in the percent drug release. This result is possibly attributed to the difference in matrix swelling in particular the swelling of xanthan gum in the various ionic strengths of dissolution media. The matrix in a decreased ionic strength medium presented an augmentation in the matrix swelling over the entire dissolution time, indicating an increased diffusional path length of drug and consequently a decreased percent drug release. Additionally, in this study the viscosity of polymer gel in the HPMC:XG ratio of 5:5 in ionic strength media of 0.05, 0.1 and 0.2 were similar but greater than that in ionic strength medium of

0.01 (see Fig.5). In consideration of difference in viscosity of these polymer gels, gel layer around the matrix in ionic strength medium of 0.01 might be eroded more than those in ionic strength media of 0.05, 0.1 and 0.2, resulting in the more percent drug release in ionic strength medium of 0.01. However, their viscosities in ionic strength media of 0.01, 0.05, 0.1 and 0.2 were somewhat high values. Therefore, the differences in erosion of gel layer around the matrix in varying ionic strength dissolution media were not apparently observed during the dissolution time. Consequently, the matrix swelling rather than the matrix erosion might affect the percent drug release rate.

5.5.4 Matrix containing the Supertab® and HPMC:XG ratio of 3:7

As illustrated in Figure 30, the dissolution performances of matrices containing the Supertab® and HPMC:XG ratio of 3:7 in 0.1 N HCl solution and phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) were closed to linear release profile. In contrast, the dissolution performance of this matrix in DI water was apparent to be sigmoid release profile. At the initial dissolution time, when the matrices were exposed to these dissolution media, the matrices exhibited the different expanding of gel layer around the matrices. The more expanding of gel layer around the matrix occurs, the less percent drug release was observed. The percent drug release was observed to be the greatest in 0.1 N HCl solution, the least in DI water and intermediate in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4).

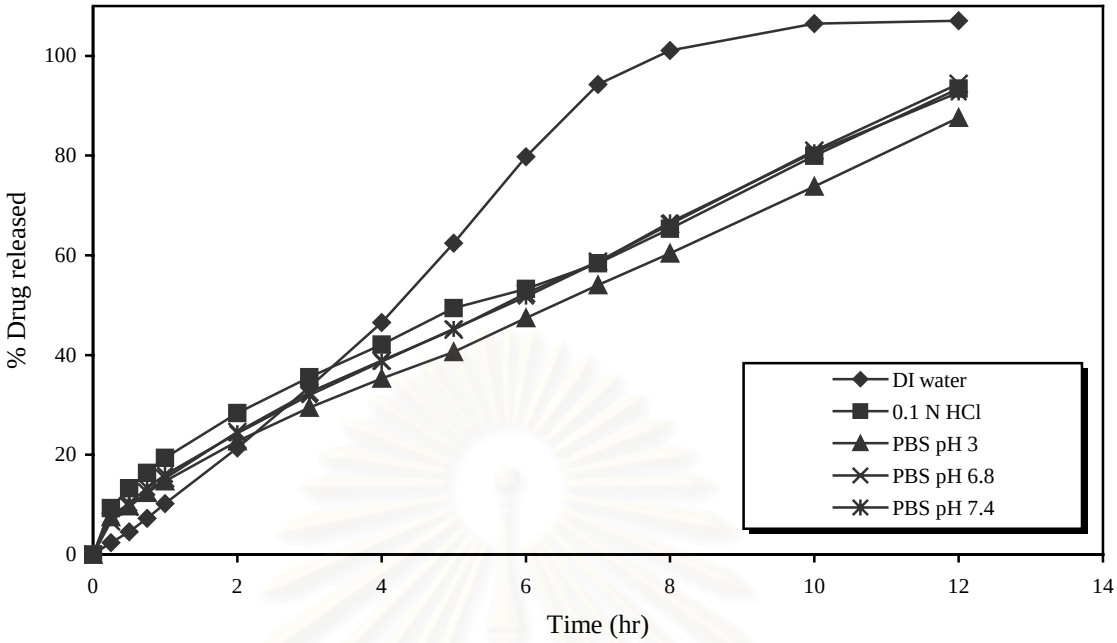


Figure 30 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 3:7 in various pH dissolution media

During the intermediate part of dissolution profiles, the release of the drug in DI water manifested the rapid drug release while that in 0.1 N HCl solution and phosphate buffer solutions displayed the slow drug release. This might be caused by the difference in erosion of gel layer boundary of the matrix. The erosion of gel layer might depend on the viscosity of polymer gel in the matrix. Thus, as the result of high viscosity of polymer gel in the HPMC:XG ratio of 3:7 in 0.1 N HCl solution and phosphate buffer solutions, the gel layer around the matrices in these dissolution media were not susceptible to erosion. The high viscosity of polymer gel in the matrix led to maintenance of matrix integrity, resulting in slow drug release. On the other hand, the viscosity of this polymer gel in DI water was rather low, thus, the outer gel layer of matrix was sensitive to erosion, resulting in rapid drug release.

In the case of different ionic strengths of dissolution media (see Fig.31), as anticipated, during the beginning of dissolution time, an increase in ionic strength in dissolution medium led to an increase in the amount of drug release. The matrix in increased ionic strength dissolution medium exhibited a decreased matrix swelling, resulting in a reduced diffusional path length of drug. Furthermore, in the presence of salt, the matrix could keep matrix integrity that might be due to the high viscosity of polymer gel in the matrix. Consequently, the matrix displayed the swelling rather than the dissolution of gel layer surrounding the matrix. Therefore, the difference in matrix swelling may cause the deviation in the percent drug release.

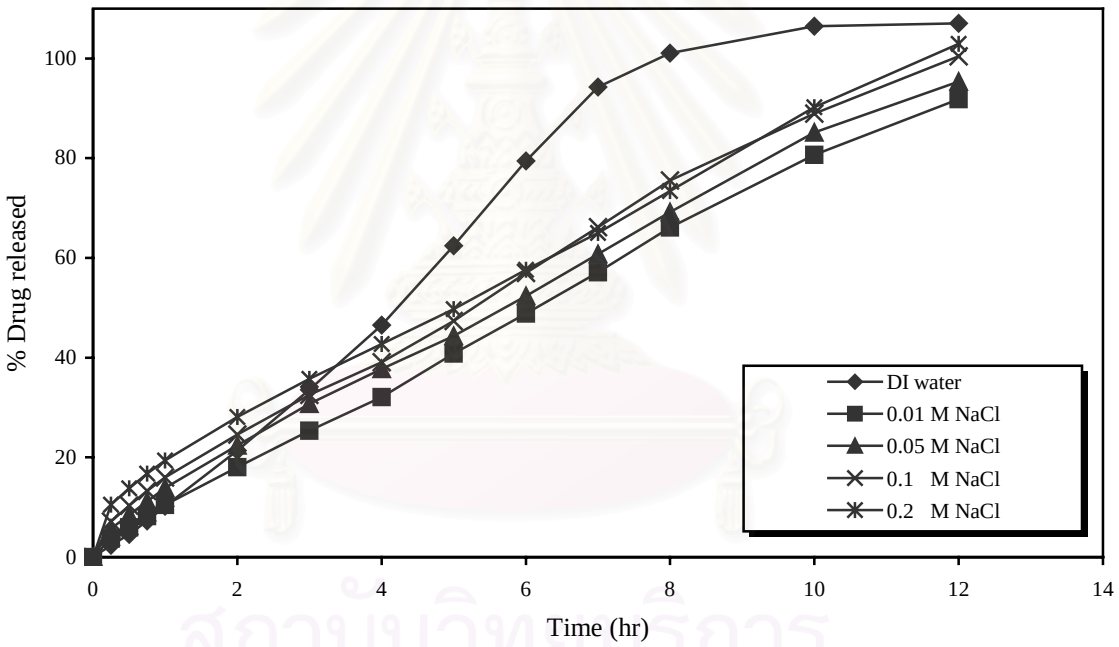


Figure 31 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 3:7 in various ionic strength dissolution media

5.5.5 Matrix containing the Supertab® and HPMC:XG ratio of 0:10

Figure 32 shows the release profiles in different pH of dissolution media, the pattern of dissolution profile in DI water was markedly different to that in 0.1 N HCl solution and phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4). The release profile in DI water was sigmoid profile whereas those in 0.1N HCl solution and phosphate buffer solutions approached linear profiles. During the initial dissolution time, the release profile in DI water, 0.1N HCl solution and phosphate buffer solutions were slow drug releases that might be due to the very rapid formation of swollen gel layer around the matrices. The initial percent drug releases on the first hour were observed to be the highest in 0.1N HCl solution, the least in DI water and intermediate in phosphate buffer solutions. As aforementioned, the deviation in matrix swelling might play an important factor on the difference in the percent drug release. In addition, by visual inspection during the intermediate dissolution time, the matrix in DI water lost its integrity, resulting in the rapid drug release. On the contrary, the matrices in 0.1N HCl solution and phosphate buffer solutions could maintain their integrities with the swollen gel layer, resulting in the slow drug release. This might be due to the different viscosities of polymer gel in these dissolution media. As the results of viscosity measurement in this study, the viscosity of polymer gel in the HPMC:XG ratio of 0:10 in DI water was much less than that those in 0.1 N HCl solution and phosphate buffer solutions. The less viscosity of polymer gel in the matrix might cause the more failure of matrix integrity.

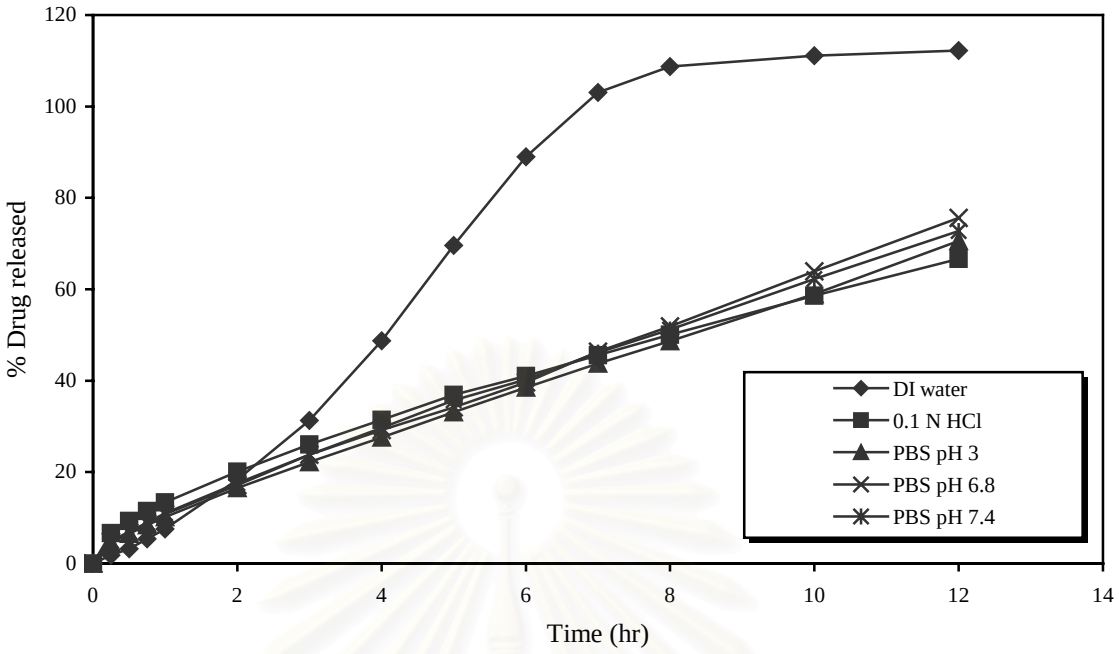


Figure 32 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 0:10 in various pH dissolution media

Furthermore, in the case of different ionic strengths of dissolution media, the release profiles in DI water, 0.01 M, 0.05 M, 0.1 M and 0.2 M NaCl solutions were displayed in Figure 33. As expected, during the initial dissolution period, an increase in the ionic strength of dissolution media resulted in an increase in the percent drug release. Surprisingly, during the intermediate dissolution time, the release profile in 0.01 M NaCl solution exhibited the rapid drug release. Consequently, the percent drug releases were observed to be the greatest in DI water, the least in 0.05 M, 0.1 M and 0.2 M NaCl solutions and intermediate in 0.01 M NaCl solution. The deviations in the percent drug releases might be the effect of the difference in erosion of outer gel layer of matrices. The erosion of gel layer might directly relate to the viscosity of polymer gel in the matrix.

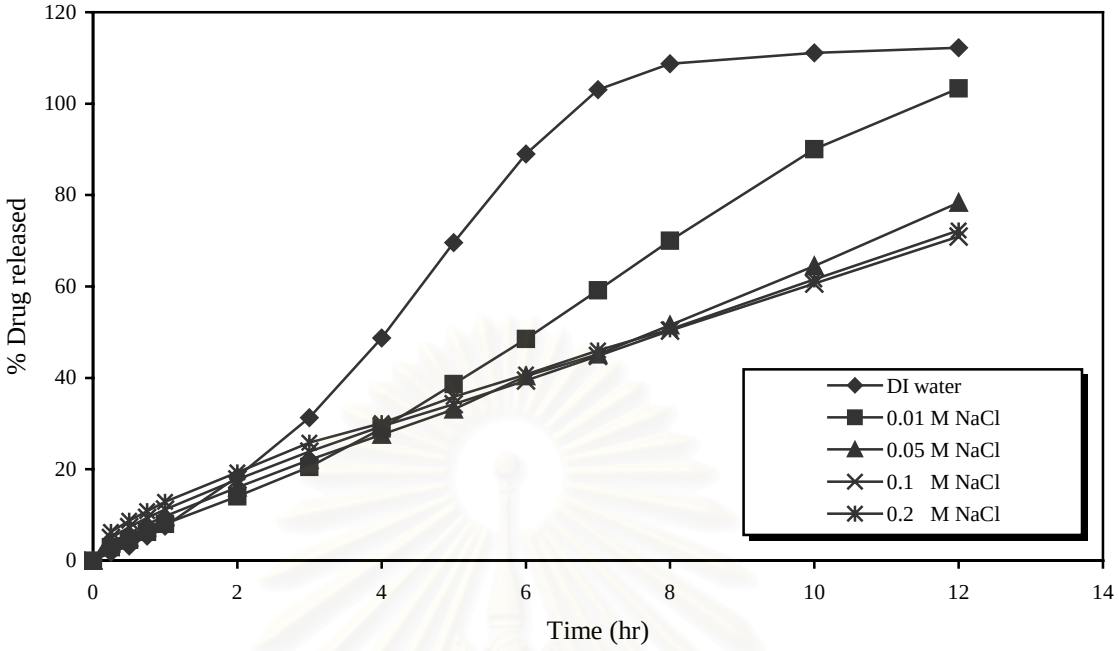


Figure 33 The release profiles of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 0:10 in various ionic strength dissolution media

5.5.6 Matrix containing the Emcompress® and HPMC:XG ratio of 10:0

The release profiles in varying pH of dissolution media were illustrated in Figure 34. The percent drug release in 0.1 N HCl solution was greater than that in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) and DI water. This result was possibly attributed to the different solubility of the Emcompress® in these dissolution media. The Emcompress® (dibasic calcium phosphate) was dissolved slowly in 0.1 N HCl solution but was not dissolved in phosphate buffer solutions and DI water. Consequently, the tortuosity of the matrix in 0.1 N HCl solution might be less than that in phosphate buffer solutions and DI water. This result might promote the drug release via diffusion. Additionally, the rates of drug release in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) were less than that in DI water. According to the previous study, Uko-Nne et al.(1989) mentioned that chloride and phosphate ions in dissolution

medium caused the dehydration of cellulose ether. Thus, the cause of this finding might be the difference in hydration rate of HPMC in phosphate buffer solutions and DI water. The hydration rate of HPMC in phosphate buffer solutions was less than that in DI water.

When the matrix was placed in the dissolution medium, the dissolution medium began to hydrate the matrix and swelling took place. As a consequence of the swelling process, chain relaxation of polymer occurred and the drug began to diffuse from the swollen gel layer (Heller,1987). Due to the hydration rate of HPMC in phosphate buffer solutions was less than that in DI water, the relaxation rate of HPMC chain and the diffusion rate of drug in phosphate buffer solutions might be less than those in DI water. Consequently, the percent drug release in phosphate buffer solutions was less than that in DI water.

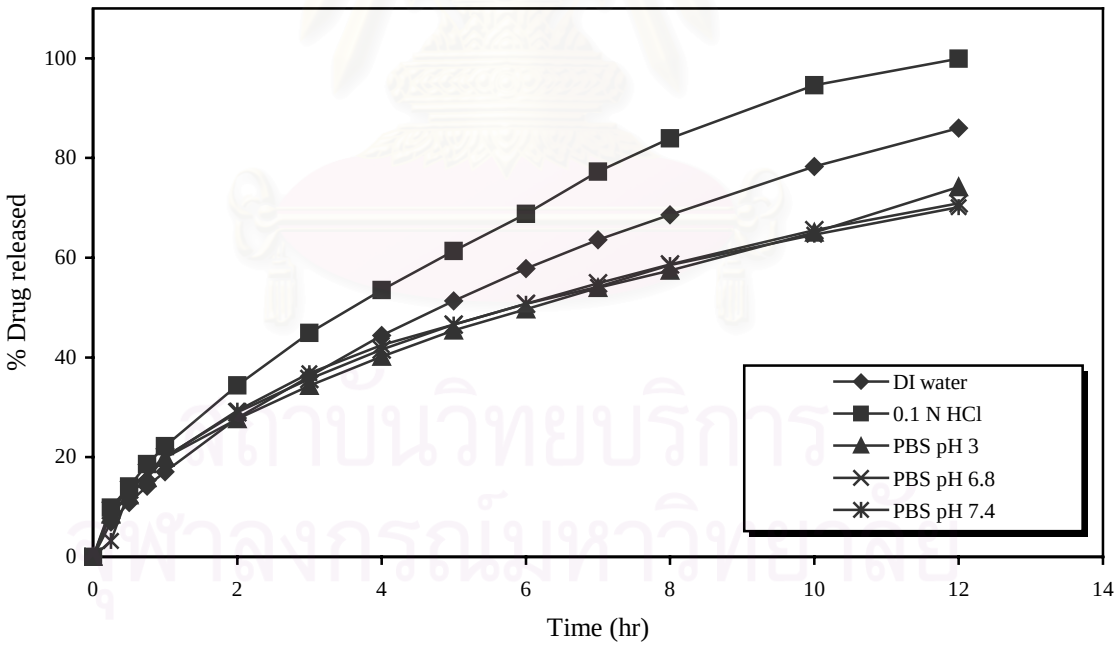


Figure 34 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 10:0 in various pH dissolution media

Furthermore, as displayed in Figure 35, the matrix containing Emcompress® and HPMC:XG ratio of 10:0 were also tested in various ionic strength of dissolution media. During the first 4 hours of dissolution time, the percent drug release in DI water, 0.01 M, 0.05 M, 0.1 M and 0.2 M NaCl solutions were comparable. Nevertheless, after the 4th hour of dissolution time, the percent drug release in DI water and 0.01 M NaCl solution were slightly greater than those in 0.05 M, 0.1 M and 0.2 M NaCl solutions. This might be due to the different swelling rate in these dissolution media. The relaxation rate of HPMC chain in DI water and 0.01 M NaCl solution might be greater that in 0.05 M, 0.1 M and 0.2 M NaCl solutions. Consequently, the drug liberation via diffusion in DI water and 0.01 M NaCl solution were faster than those in 0.05 M, 0.1 M and 0.2 M NaCl solutions.

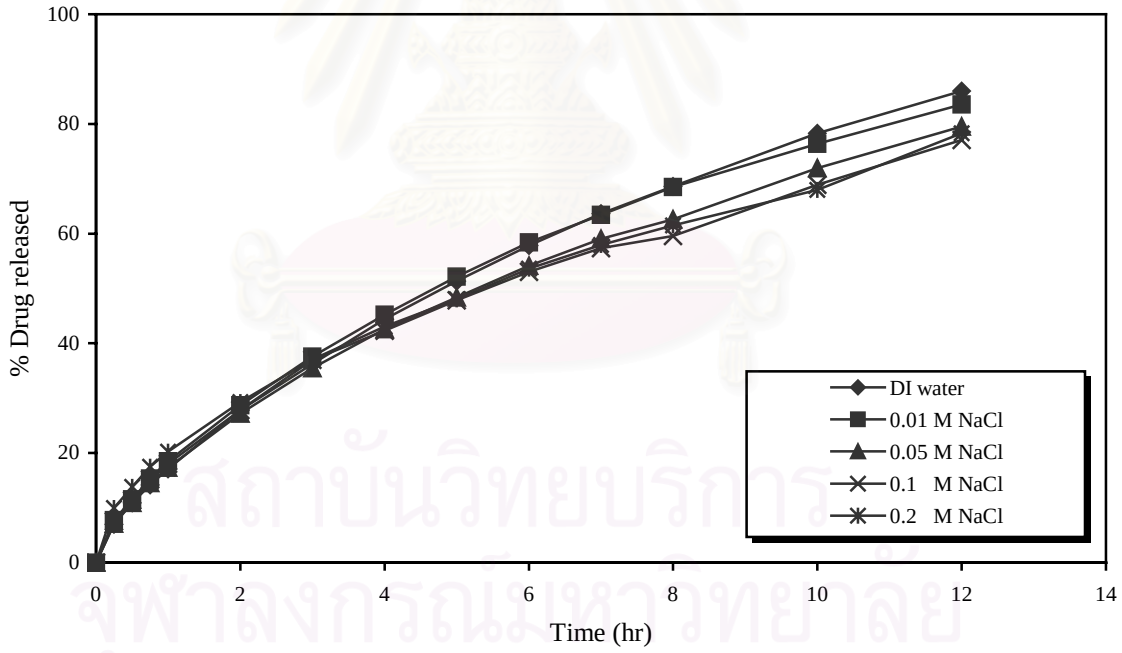


Figure 35 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 10:0 in various ionic strength dissolution media

5.5.7 Matrix containing the Emcompress® and HPMC:XG ratio of 7:3

As shown in Figure 36, the percent drug releases were observed to be the greatest in 0.1 N HCl solution, intermediate in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) and the least in DI water. The rate of drug release in 0.1 N HCl solution was the greatest that might be due to the slow dissolution of the Emcompress® in 0.1 N HCl solution. As a consequence of the Emcompress® dissolution, the higher porosity in the matrix occurred, the higher percent drug release was observed. In contrast, the Emcompress® does not dissolve in phosphate buffer solutions and DI water, the percent drug releases in these dissolution media were less than that in 0.1 N HCl solution. Moreover, the percent drug releases in phosphate buffer solutions were more than that in DI water. This is possibly attributed to the important effect of ionic strength in dissolution medium on the matrix swelling. The higher ionic strength in dissolution medium led to the less matrix swelling, resulting in the more percent drug release. The ionic strength of phosphate buffer solutions is more than 0.3 whereas that of DI water is zero. Thus, the matrix swelling in phosphate buffer solutions might be less than that in DI water. Although, for this matrix system, the swelling process led to the polymer chain disentanglement, the polymer dissolution and drug liberation, respectively, the more matrix swelling did not cause the more drug release. This might be explained by visual observation of the matrices in phosphate buffer solutions and DI water. During the dissolution period, the matrices in these dissolution media were swollen slowly and could maintain their integrities. The outer layer of matrices in these dissolution media exhibited the swelling rather than the erosion. Therefore, the rate of matrix swelling in DI water and phosphate buffer solutions might be different that resulted in different diffusional path length of drug.

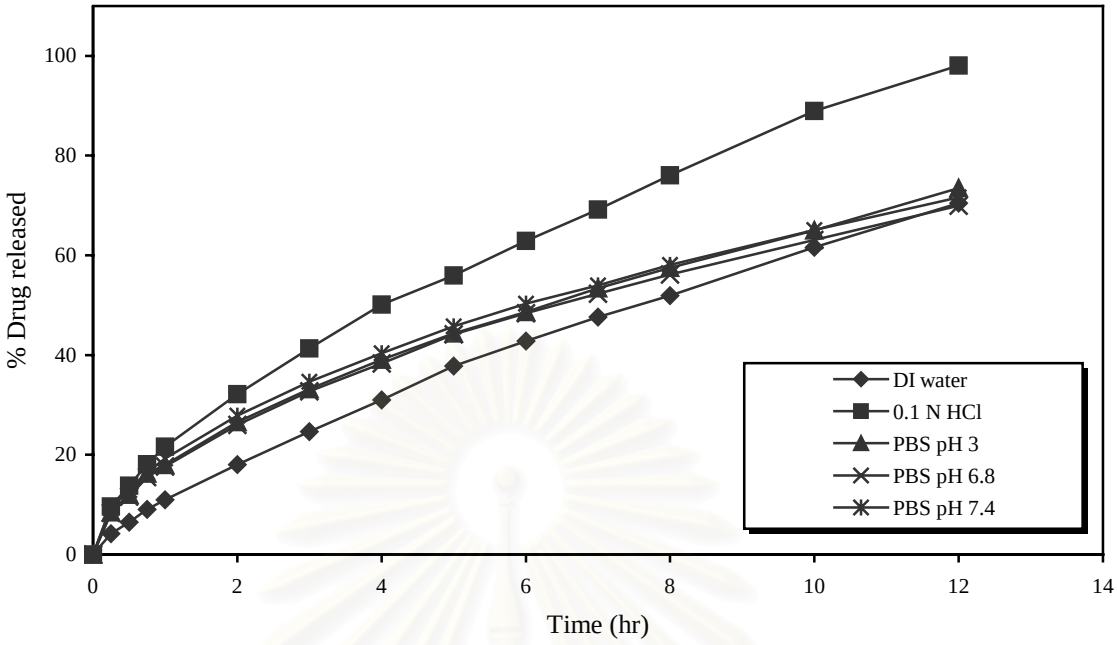


Figure 36 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 7:3 in various pH dissolution media

In addition, the release profiles of the matrix containing the Emcompress® and HPMC:XG ratio of 7:3 in various ionic strength of dissolution media were presented in Figure 37. When increased the ionic strength of dissolution medium, the percent drug release tended to be increased. The increased percent drug release with augmented ionic strength of dissolution medium might be due to the decreased matrix swelling. This is consistent with the dissolution profiles in phosphate buffer solutions and DI water (see Fig. 36). Moreover, the amount of drug releases in ionic strength dissolution media of 0.05, 0.1 and 0.2 were slightly increased. This is possibly attributed to slightly different swellings of HPMC in the matrix in these dissolution media, resulting in different diffusional path length of drug.

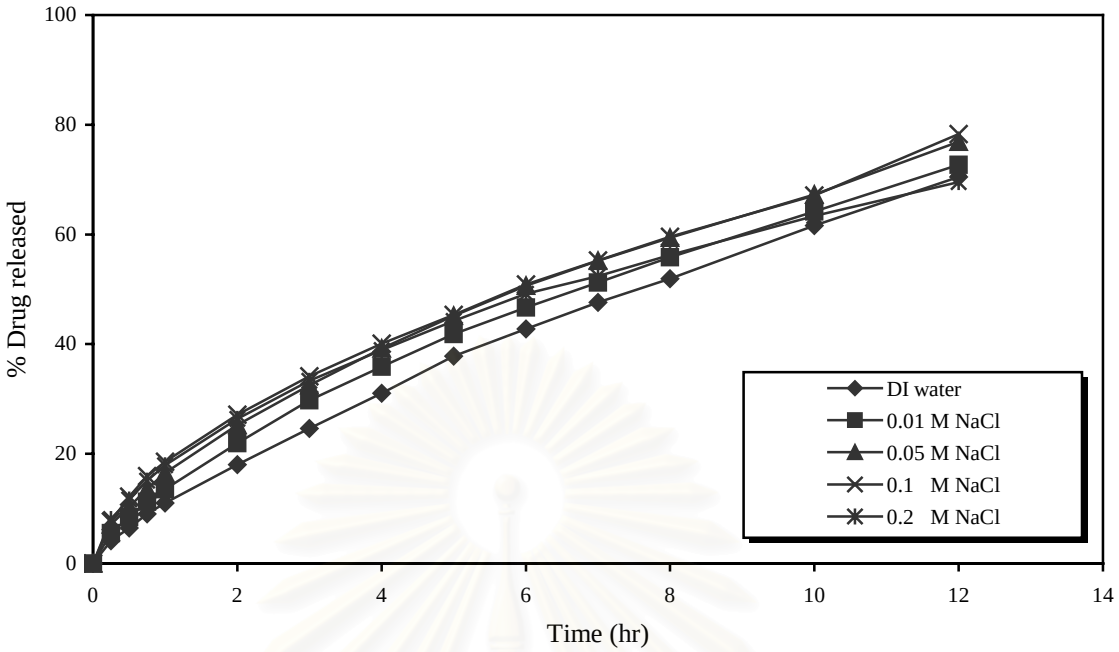


Figure 37 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 7:3 in various ionic strength dissolution media

5.5.8 Matrix containing the Emcompress® and HPMC:XG ratio of 5:5

The release profiles in different pH dissolution media were shown in Figure 38. During the first 8 hours of dissolution time, the rates of drug release were observed to be the greatest in 0.1 N HCl solution, the least in DI water and intermediate in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4). This result agreed with the release profiles from matrix containing the Emcompress® and HPMC:XG ratio of 7:3 in various pH dissolution media (see Fig. 36). This finding could be described by the same reason as mentioned previously. However, after the 8th hour of dissolution time, the rate of drug release in DI water was more rapid than that in phosphate buffer solutions. This is possibly due to the faster erosion of the swollen gel layer around the matrix in DI water.

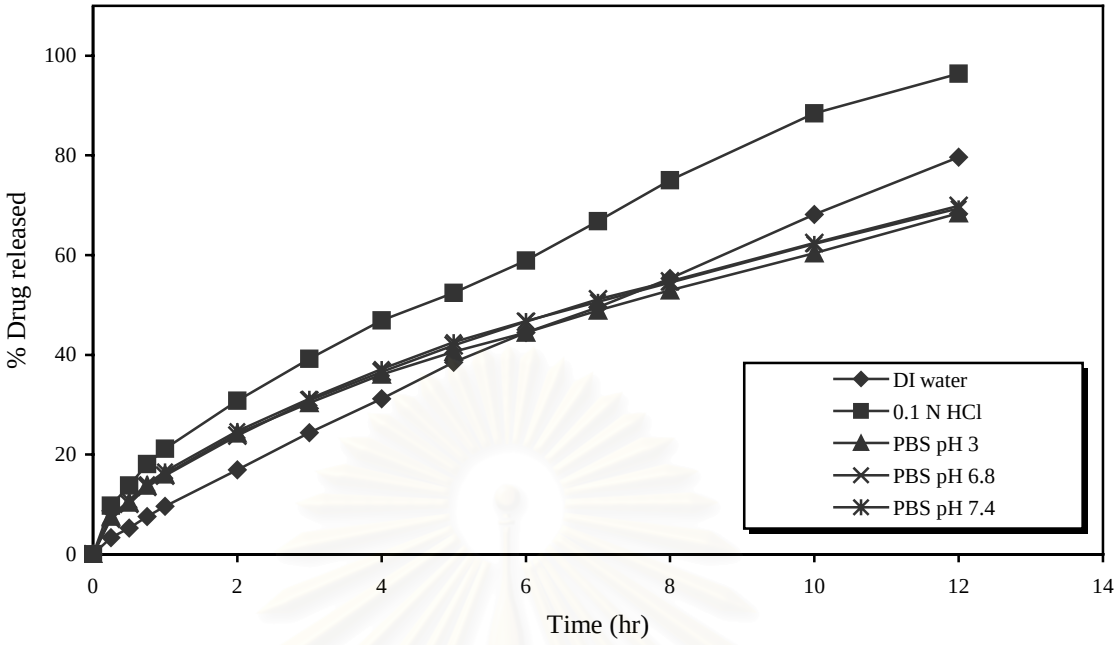


Figure 38 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 5:5 in various pH dissolution media

In the cases of the release profiles in various ionic strength of dissolution media (see Fig. 39), during the first 8 hours of dissolution time, an increase in the ionic strengths of dissolution medium caused an augmentation of the percent drug release because the ionic strength of dissolution medium reduced the matrix swelling. Thus, it is possible to indicate that the ionic strength of dissolution medium affects the swelling of polymer particularly xanthan gum in the matrix system. This result is also consistent with the release profiles of matrix the Emcompress® and HPMC:XG ratio of 7:3 (see Fig. 37). Nevertheless, after the 8th hour of dissolution time, the percent drug release in DI water was greater than that in higher ionic strength of dissolution media. The relation between the percent drug release during the 8th-12th hour of release profiles and the ionic strength of dissolution medium was not observed. The polymer erosion rather than the polymer swelling might cause the drug liberation from this matrix system during the late dissolution period.

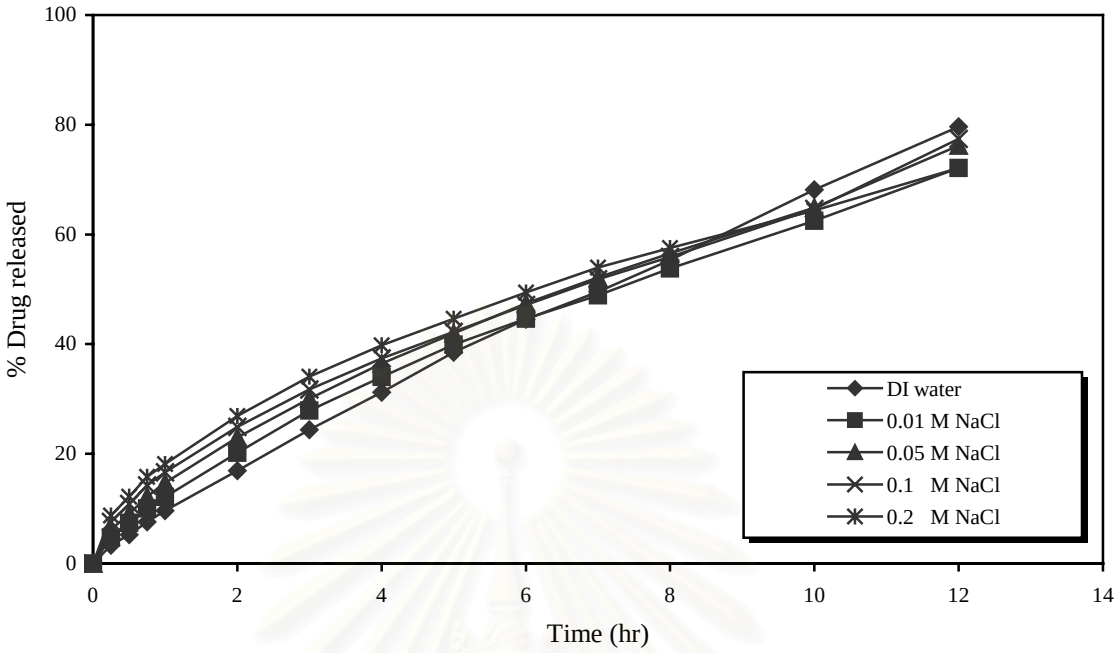


Figure 39 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 5:5 in various ionic strength dissolution media

5.5.9 Matrix containing the Emcompress® and HPMC:XG ratio of 3:7

The release profiles in different pH of dissolution media were displayed in Figure 40. As expected, during the beginning of dissolution time, the percent drug release in 0.1 N HCl solution, phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) and DI water were the greatest, intermediate and the least, respectively. This finding agreed with the release profiles from matrices containing the Emcompress® and HPMC:XG ratios of 7:3 and 5:5 (see Fig. 36 and 38). As discussed previously, the percent drug release in 0.1 N HCl solution was greater than that in phosphate buffer solutions and DI water due to the different solubility of the Emcompress® in dissolution media. In the cases of phosphate buffer solutions and DI water, the ionic strength of dissolution media may be a major factor that affected the percent drug release. However, during the late

dissolution period, the percent drug releases in 0.1 N HCl solution and DI water were comparable and were apparently greater than those in phosphate buffer solutions. In the case of DI water, the rate of drug release in this dissolution medium was markedly increased that is possibly due to the rapid erosion of the outer swollen gel layer of the matrix. On the other hand, for phosphate buffer solutions, the manifested erosion of the swollen gel layer were not observed. This might be caused by the slow swelling rate of matrix in phosphate buffer solutions. Consequently, the slow erosion rate of swollen gel layer might also take place in phosphate buffer solutions, leading to the slow drug release.

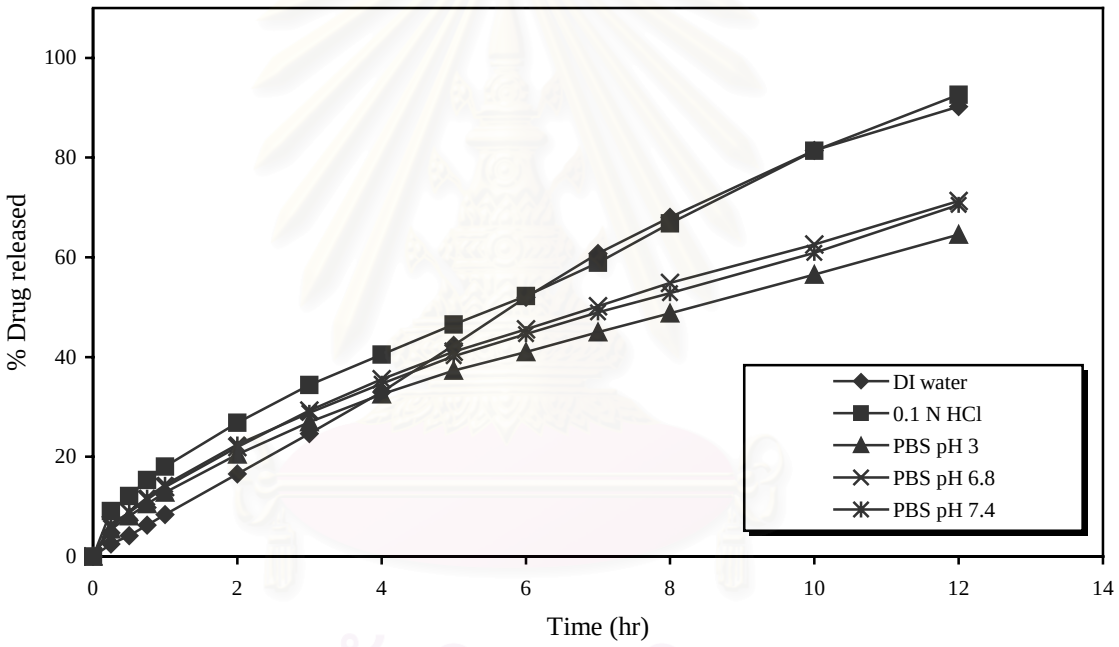


Figure 40 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 3:7 in various pH dissolution media

The release profiles in various ionic strengths of dissolution media were also presented in Figure 41. The pattern of release profile in DI water differed from those in various ionic strengths of dissolution media. During the first 4 hours of dissolution time, the drug liberation in DI water was slower than that in various ionic strengths of

dissolution media. This might be caused by the different swelling rate of the polymer in the matrix. The swelling rate in DI water might be faster than those in various ionic strengths of dissolution media. Additionally, in the cases of varying ionic strengths of dissolution media, the percent drug releases apparently increased as the ionic strength of dissolution media were increased. The increasing swelling rate of the matrix may occur in the decreased ionic strength of dissolution medium. This finding was still consistent with the release profiles from matrix the Emcompress® and HPMC:XG ratios of 7:3 and 5:5 (see Fig. 37 and 39). After the 4th hour, the drug release in DI water was greater than that in various ionic strengths of dissolution media. This might point out that the matrix swelling did not play an important role on the percent drug release. On contrary, during the late dissolution profile, the erosion of swollen polymer may be the major effect on the drug release. Thus, as a result of the late dissolution profile, the erosion of swollen polymer in DI water might be greater than that in various ionic strengths of dissolution media. In addition, the relationship between the percent drug releases after the 4th hour and the ionic strengths of dissolution media was not found.

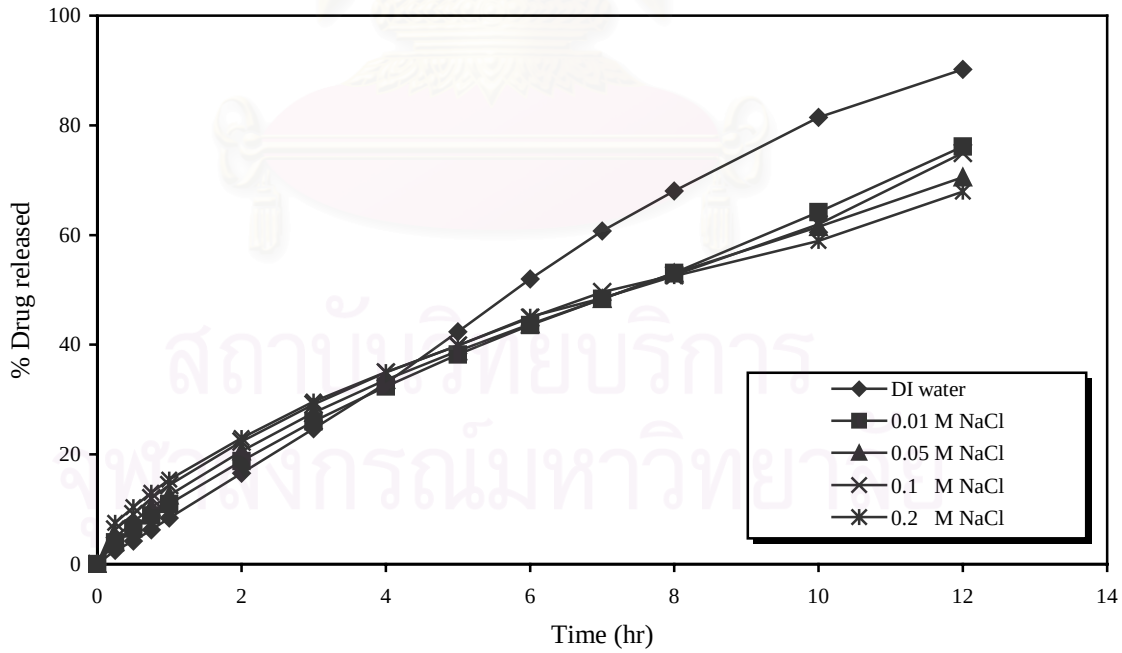


Figure 41 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 3:7 in various ionic strength dissolution media

5.5.10 Matrix containing the Emcompress® and HPMC:XG ratio of 0:10

As shown in Figure 42, the drug release was tested in different pH dissolution media. The initial drug releases were observed to be the greatest in 0.1 N HCl solution, the least in DI water and intermediate in phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4). This result is possibly attributed to the major effect of different matrix swelling. The matrix swelling might appear with the greatest in DI water, the least in 0.1 N HCl solution and the intermediate in phosphate buffer solutions. However, the percent drug releases in these dissolution media were not much different except when DI water was used. In addition, as unexpected, during the last part of dissolution profile, the percent drug release in 0.1 N HCl solution and phosphate buffer solutions were comparable. This finding might be caused by the formation of the strongly swollen gel layer around the matrix in these dissolution media. In the case of 0.1 N HCl solution, as the consequence of strongly swollen gel layer, the 0.1 N HCl solution could not penetrate readily to dissolve the Emcompress® in the matrix. Therefore, the Emcompress® was embeded in the strongly swollen gel layer of the matrix that might occur in both the 0.1 N HCl solution and phosphate buffer solutions. The strongly swollen gel layer may be caused by the ionic strength of dissolution medium. In addition, the percent drug release in DI water was apparently more than that in the 0.1 N HCl solution and phosphate buffer solutions. This is possibly due to the different dissolution rate of swollen gel layer in these dissolution media. According to the matrix containing xanthan gum only as a gel former, the gel strengths of xanthan gum in 0.1 N HCl solution and phosphate buffer solutions may be higher than that in DI water. Consequently, the swollen gel layer in 0.1 N HCl solution and phosphate buffer solutions might be less erosive than that in DI water. Furthermore, as the result of overall dissolution profiles, it is possible to denote that the pH of dissolution medium did not markedly affect the drug release from matrix containing xanthan gum only but the ionic strength of dissolution medium did.

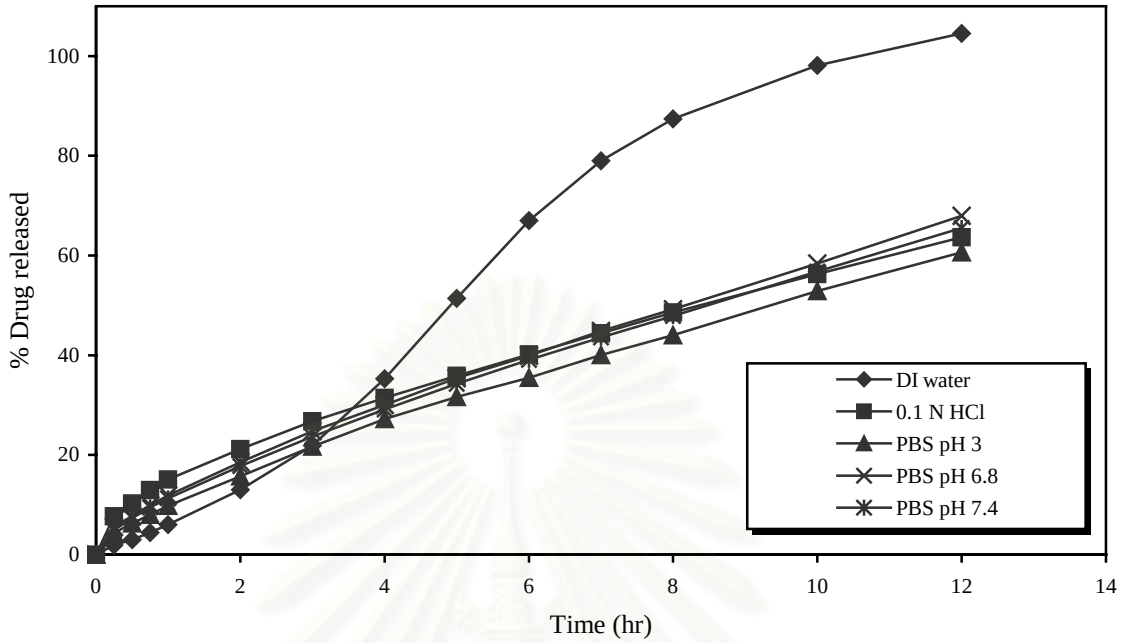


Figure 42 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 0:10 in various pH dissolution media

The release profiles in different ionic strength of dissolution media were also illustrated in Figure 43. As anticipated, during the initial release profiles, an increased ionic strength of dissolution medium led to an increased percent drug release. Thus the greatest drug release was observed in 0.2 M NaCl solution while the least percent drug release was founded in DI water. The different percent drug release in these dissolution media might be caused by the different swellings of xanthan gum gel in these dissolution media. The xanthan gum could be apparently swollen in DI water. In contrast, when increased ionic strength of dissolution medium, the swelling of xanthan gum gel was reduced. Consequently, the matrix in increased ionic strength of dissolution medium provided the decreased diffusional path length of drug, leading to the increased drug release. In addition, after the 6th hour of dissolution time, the percent drug release were observed to be the greatest in DI water, intermediate in 0.01 M NaCl

solution and the least in 0.05 M, 0.1 M and 0.2 M NaCl solutions. In the cases of 0.05 M, 0.1 M and 0.2 M NaCl solutions, the percent drug release at the 12th hour of dissolution time tended to increase with reducing ionic strength of dissolution medium. Therefore, as the result of the different drug release during the late dissolution time, it is possibly due to the different erosions of swollen xanthan gum gel in these dissolution media. The relation between the ionic strength of dissolution medium and the drug release via erosion of swollen polymer gel was observed. During the late dissolution time, the increased drug release occurred in the reduced ionic strength of dissolution medium that might be caused by the increased erosion of swollen polymer gel.

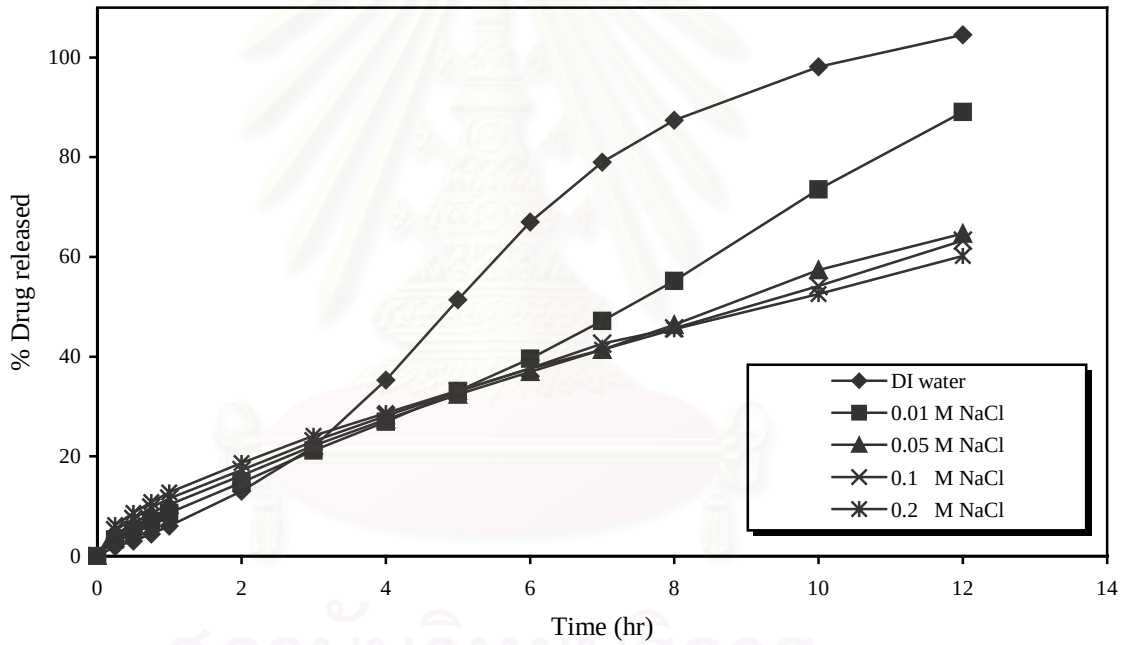


Figure 43 The release profiles of matrices containing dibasic calcium phosphate and 15%polymer in HPMC:XG ratio of 0:10 in various ionic strength dissolution media

6. The Swelling and Erosion of the Matrices

The swelling and erosion of the matrices were performed in various pH and ionic strength of dissolution media. The varying pH of dissolution media were 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8). The different ionic strength of dissolution media were DI water (μ=0), 0.01 M (μ=0.01), 0.2 M (μ=0.2) NaCl solutions. Nevertheless, the swelling profiles of matrix containing HPMC:XG ratio of 10:0 and the Supertab® or the Emcompress® were not shown due to the failure of matrix formation during testing. Therefore, it could not determine the dimensions and estimated the percent swelling of matrix. Therefore, only percent erosion of matrix containing HPMC:XG ratio of 10:0 with the Supertab® or the Emcompress® were investigated.

6.1 Matrix containing the Supertab® and HPMC:XG ratio of 10:0

As shown in Figures 44 and 45, the percent erosion of matrix in DI water, 0.1 N HCl solution, phosphate buffer solutions (pH 3 and pH 6.8), 0.01 M and 0.2 M NaCl solutions were not much different. The erosion profile corresponded to the drug release profile in the same dissolution medium (see Fig. 24 and 25). According to these erosion profiles, it is indicated that the matrix erosions were apparently rapid. This may lead to the fast drug release from matrix in the initial dissolution profile.

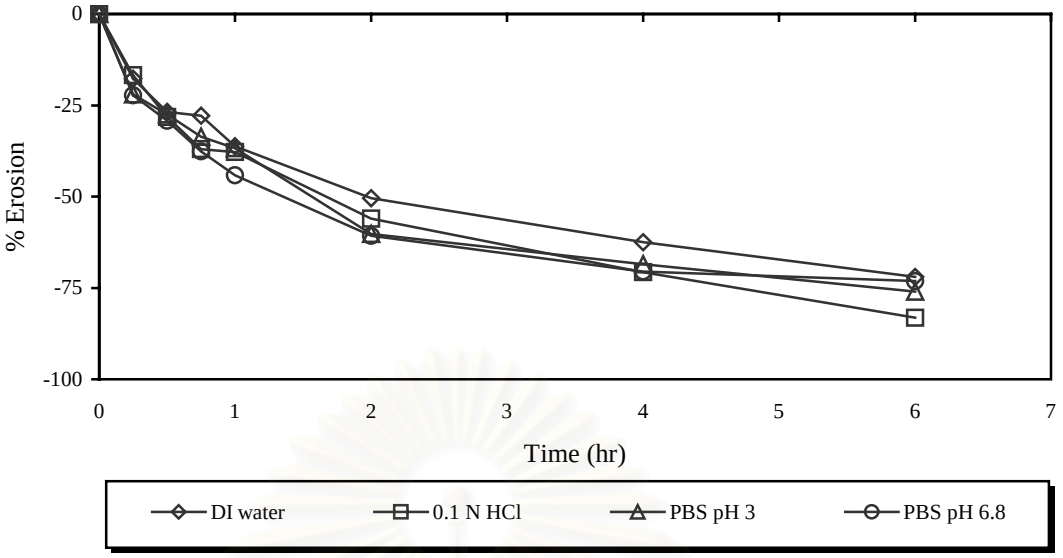


Figure 44 The percent erosion of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 10:0 in various pH dissolution media

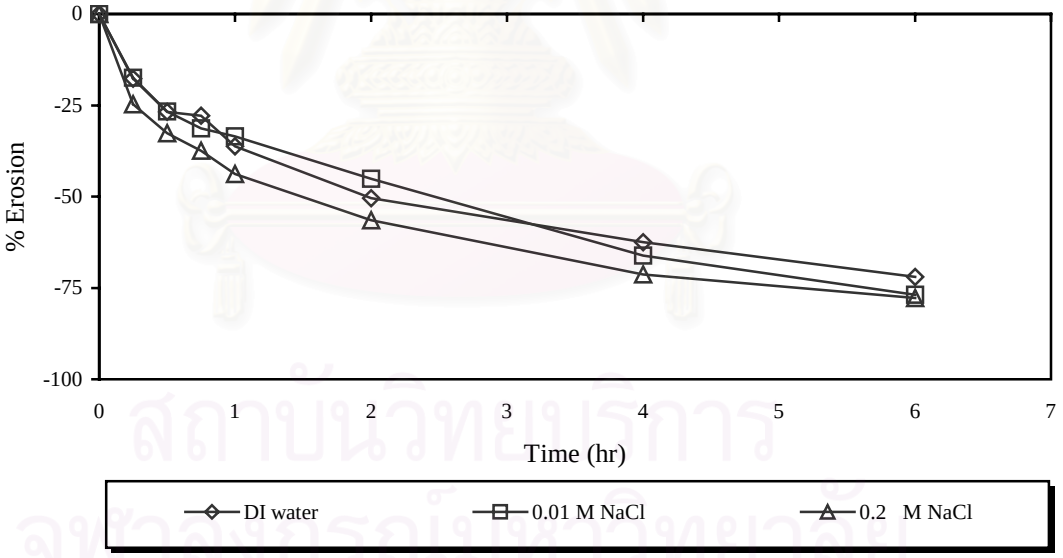


Figure 45 The percent erosion of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 10:0 in various ionic strength dissolution media

6.2 Matrix containing the Supertab® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10

The swelling and erosion profiles of matrix containing the Supertab® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in different pH dissolution media were illustrated in Figures 46-49, respectively. For all matrices in these dissolution media, the percent swellings were observed to be the greatest in DI water, the least in 0.1 N HCl solution and intermediate in phosphate buffer solutions (pH 3 and pH 6.8). In addition, for all matrices, the erosion profiles were inversely related to the swelling profiles. Therefore, the percent erosions were found to be the least in DI water, the greatest in 0.1 N HCl solution and intermediate in phosphate buffer solutions (pH 3 and pH 6.8). In accordance with the drug release profiles from matrix containing the Supertab® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 (see Fig. 26, 28, 30 and 32), during the first 4 hours, the percent drug releases were inversely correlated to the percent swellings. Due to the longer diffusional path length of drug, the more matrix swelling led to the less percent drug release. In contrast, the erosion profiles directly reflected the percent drug release. The more matrix erosion resulted in the more percent drug release. Thus, the swelling and erosion of matrix controlled the drug release from matrix.

Furthermore, during the 2^{th}-4^{th} hours of swelling profiles, the percent swelling of all matrices in DI water tended to decrease. On the other hand, during the 4^{th}-6^{th} hour of erosion profiles, the percent erosion of all matrices in DI water was markedly increased. Therefore, after the 4^{th} hour of dissolution profiles as shown in Fig. 26, 28, 30 and 32, the drug release of matrix containing HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in DI water were obviously increased. However, as the results of the erosion profiles of all matrices in 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8), during the 4^{th}-6^{th} hour, the percent erosions were not much increased. Therefore, after the 4^{th} hour of dissolution time, the release profiles of matrix containing HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8) exhibited slow drug releases.

For all of dissolution media, an increase in amount of xanthan gum in the matrix led to an increase in the percent swelling during 4 hours of the swelling profiles. On the contrary, during 6 hours of the erosion profiles, an augmentation of percent xanthan gum in the matrix resulted in a reduction of the percent erosion. This finding indicated that, for all dissolution media, the reduced initial burst drug releases were observed in the release profiles from matrices containing an increased amount of xnathan gum (see Fig. 26, 28, 30 and 32).

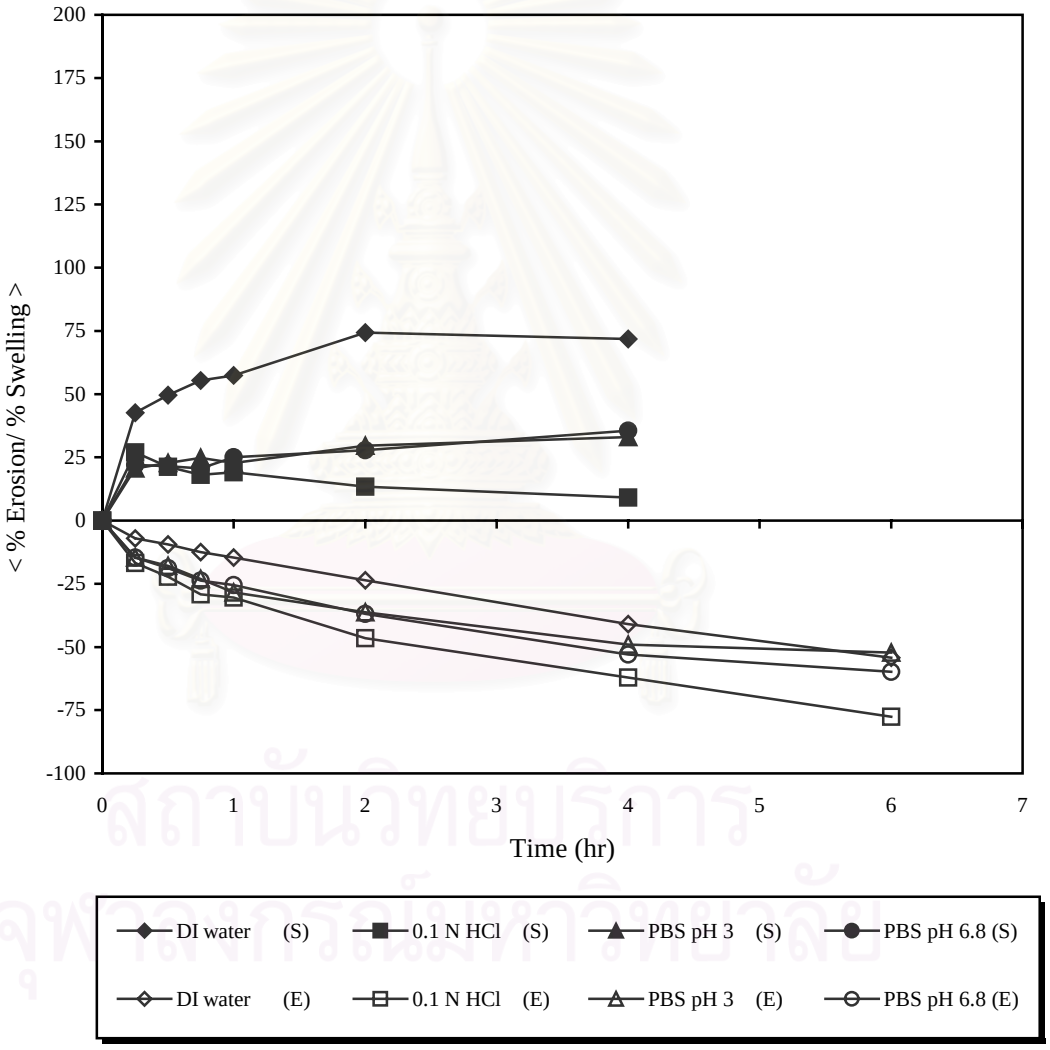


Figure 46 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 7:3 in various pH dissolution media

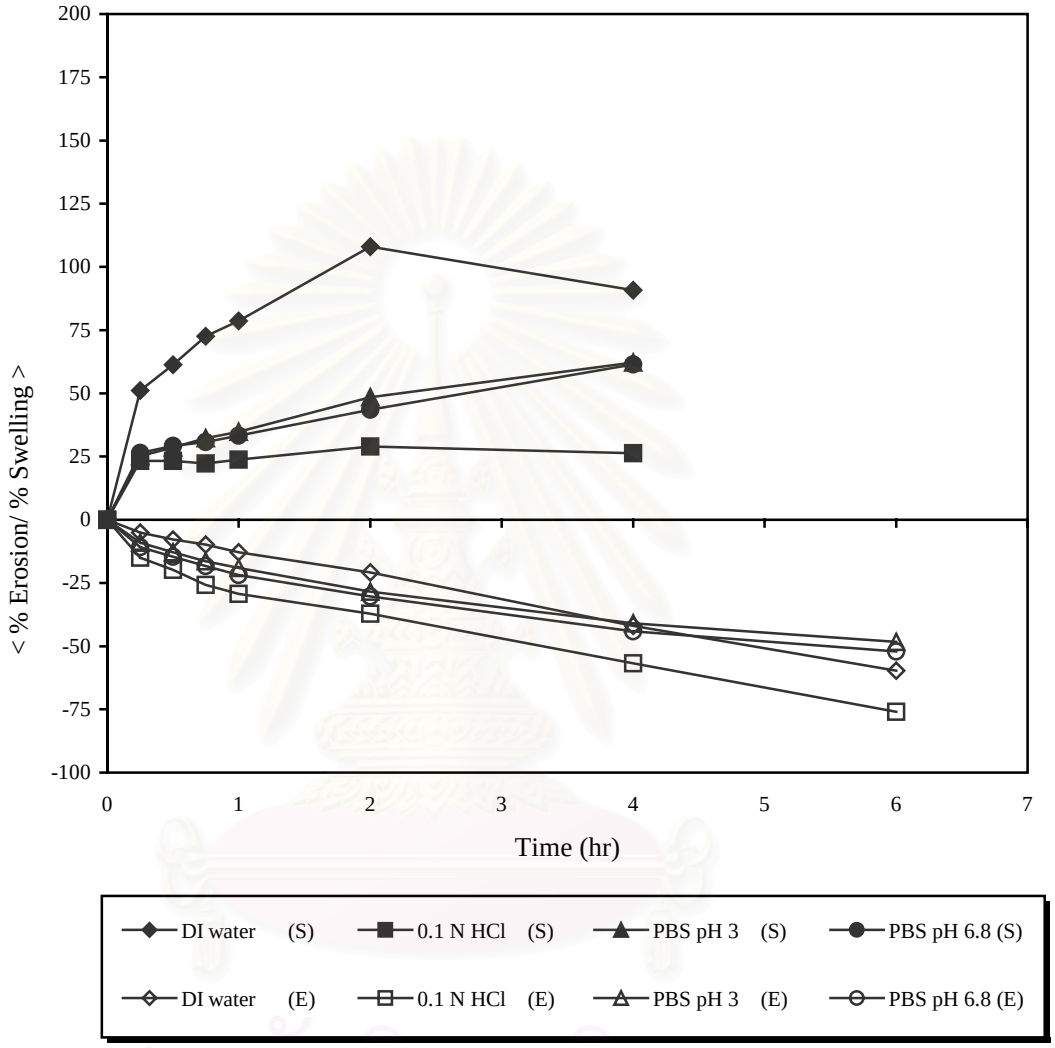


Figure 47 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 5:5 in various pH dissolution media

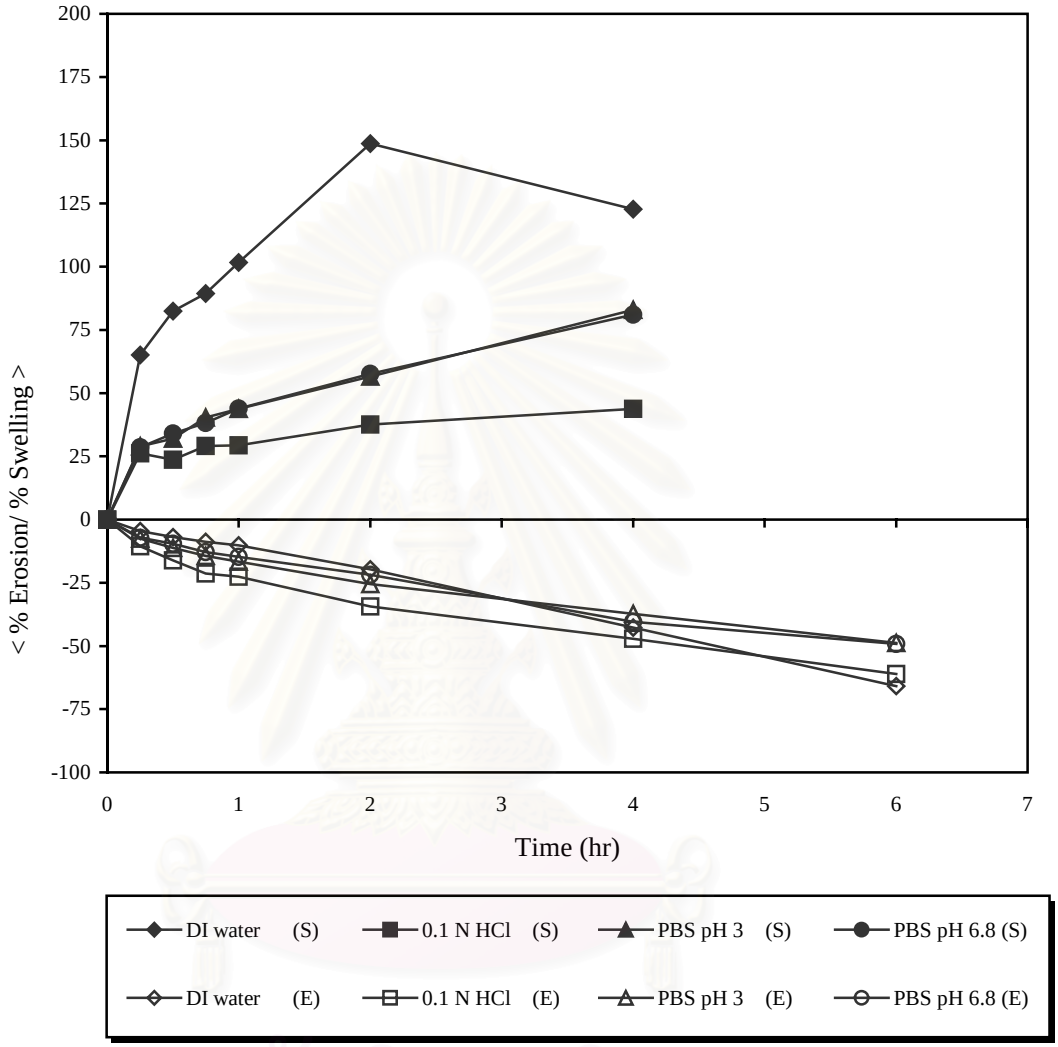


Figure 48 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 3:7 in various pH dissolution media

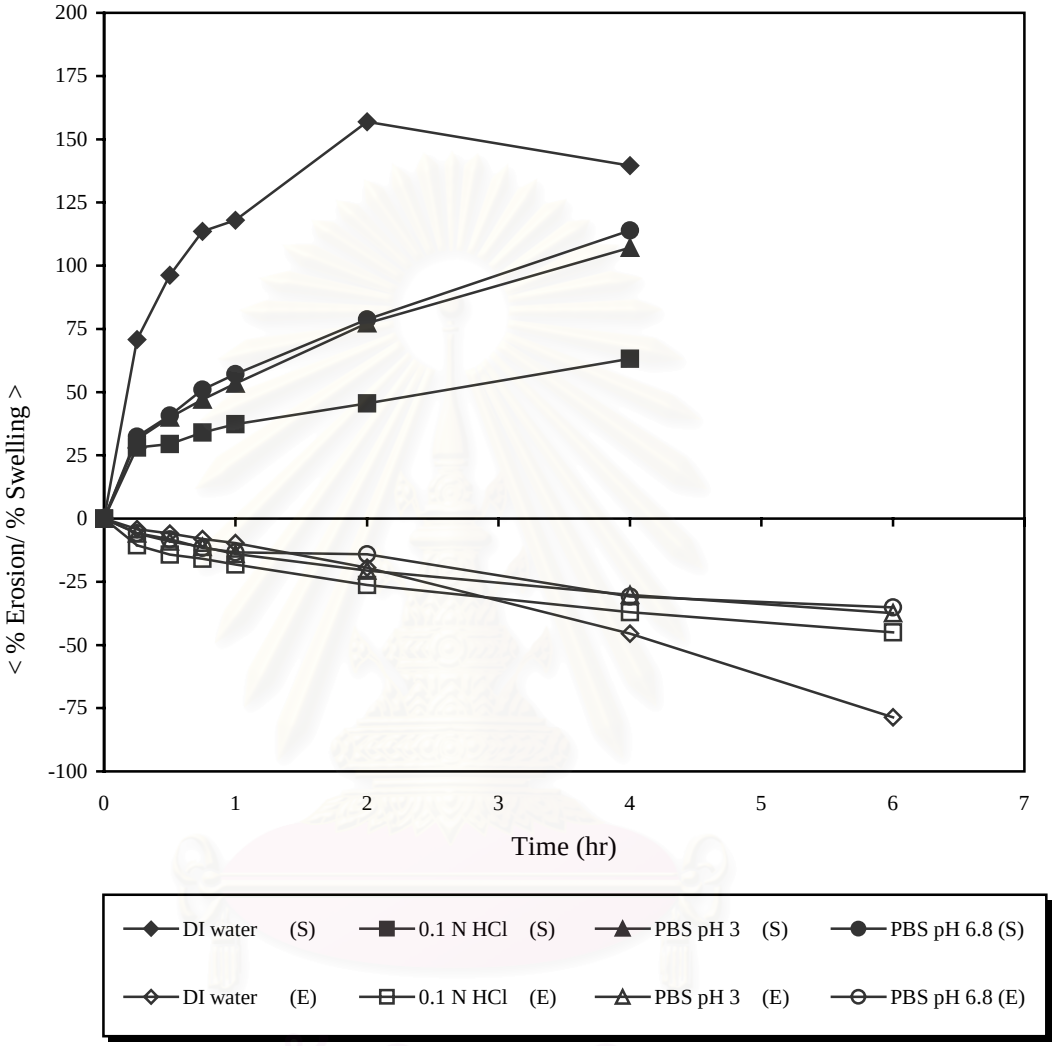


Figure 49 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 0:10 in various pH dissolution media

As illustrated in Figures 50-53, the swelling and erosion of matrix were also examined in different ionic strength of dissolution media (DI water, 0.01 M and 0.2 M NaCl solutions). As expected, for all matrices, during the first 2 hours of swelling profiles, the percent swellings were observed to be the greatest in DI water (μ=0), the least in 0.2 M NaCl solution (μ=0.2) and intermediate in 0.01 M NaCl solution (μ=0.01). The percent erosions were also founded to be the least in DI water, the greatest in 0.2 M NaCl solution and intermediate in 0.01 M NaCl solution. This result pointed out that, for all matrices, the increased ionic strength of dissolution medium caused the decreased matrix swelling but led to the increased matrix erosion during the beginning of release profiles.

As the result of matrix swelling, the thickness of swollen gel layer around the matrix occurred that led to the increased diffusional path length of drug. This caused the decreased percent drug release particularly at the beginning of dissolution time. Therefore, for all matrices in DI water, 0.01 M and 0.2 M NaCl solutions, the increased matrix swellings were observed in the decreased ionic strength of dissolution medium that resulted in the reduced percent drug releases. According to the release profiles in Figures 27, 29, 31 and 33, the initial drug releases of matrix HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in DI water, 0.01 M and 0.2 M NaCl solutions were corresponding to the percent swelling of matrix. Moreover, in the cases of all matrices in 0.01 M and 0.2 M NaCl solutions, during the early swelling and erosion profiles, an increase in amount of xanthan gum in the matrix presented an increase in the matrix swelling which in turn exhibited a decrease in the matrix erosion. It is indicated that at the initial dissolution period, the increased amount of xanthan gum in the matrix led to an increase in both of strong and swollen gel layer around the matrix simultaneously. Correspondingly, the initial drug release of matrix containing the increased amount of xanthan gum was also decreased (see Fig. 27, 29, 31 and 33).

In the case of matrix containing HPMC:XG ratio of 0:10 in different ionic strength of dissolution media (see Fig. 53), during the 4^{th}-6^{th} hour of erosion profile, the increasing erosion rate was observed in the decrease ionic strength of dissolution

medium. It is important to indicate that after the 6th hour of dissolution time, the increased percent drug release from matrix HPMC:XG ratio of 0:10 was also occurred in the decreased ionic strength of dissolution medium due to the greater erosion of swollen gel layer surrounding the matrix (see Fig. 33).

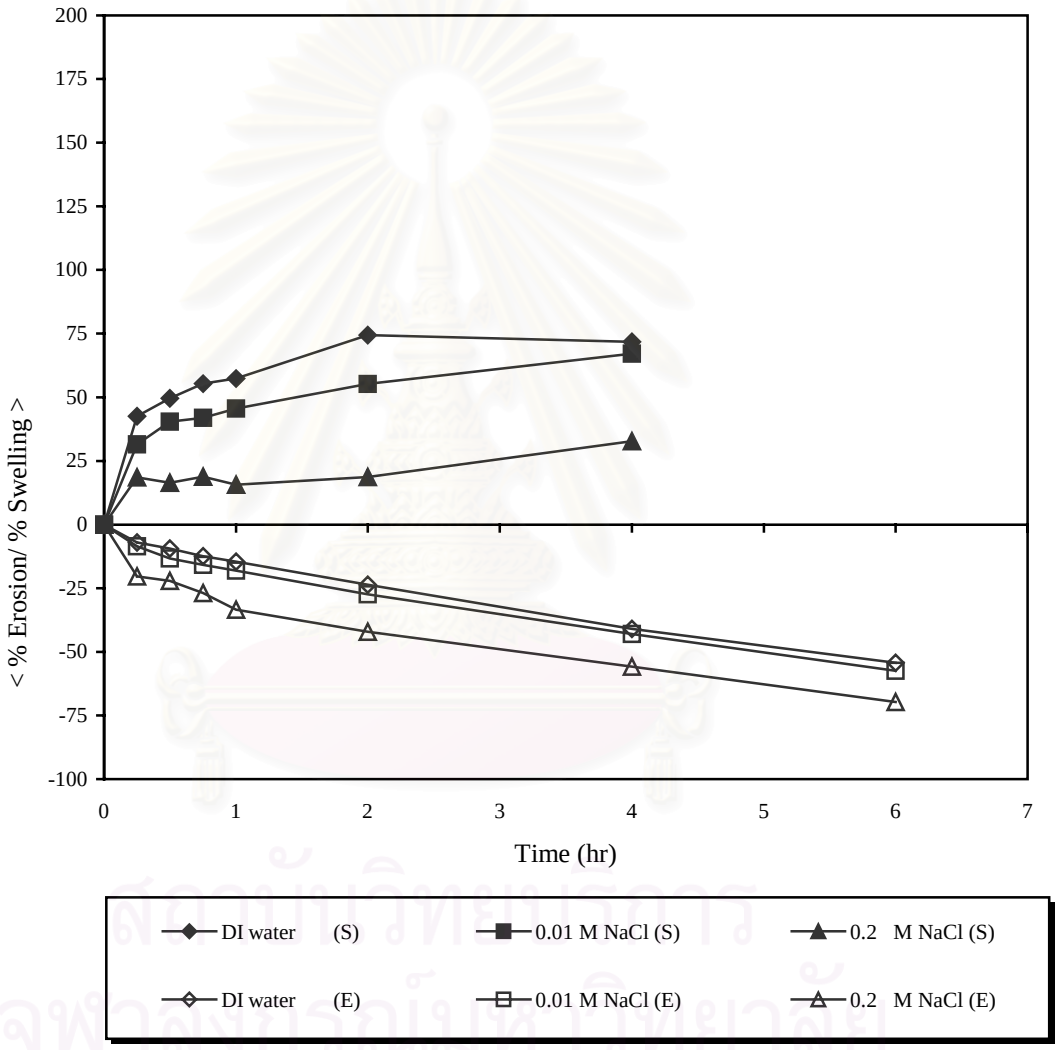


Figure 50 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 7:3 in various ionic strength dissolution media

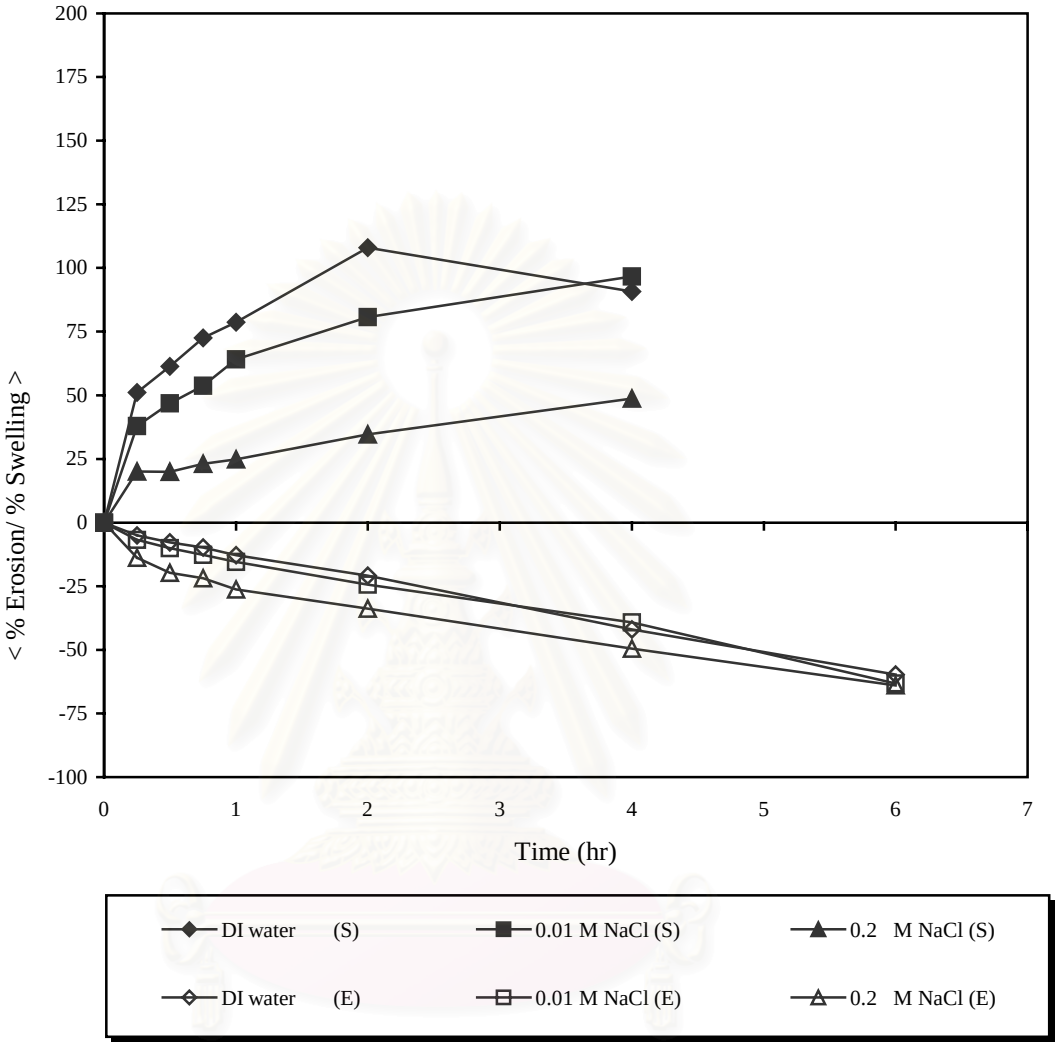


Figure 51 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 5:5 in various ionic strength dissolution media

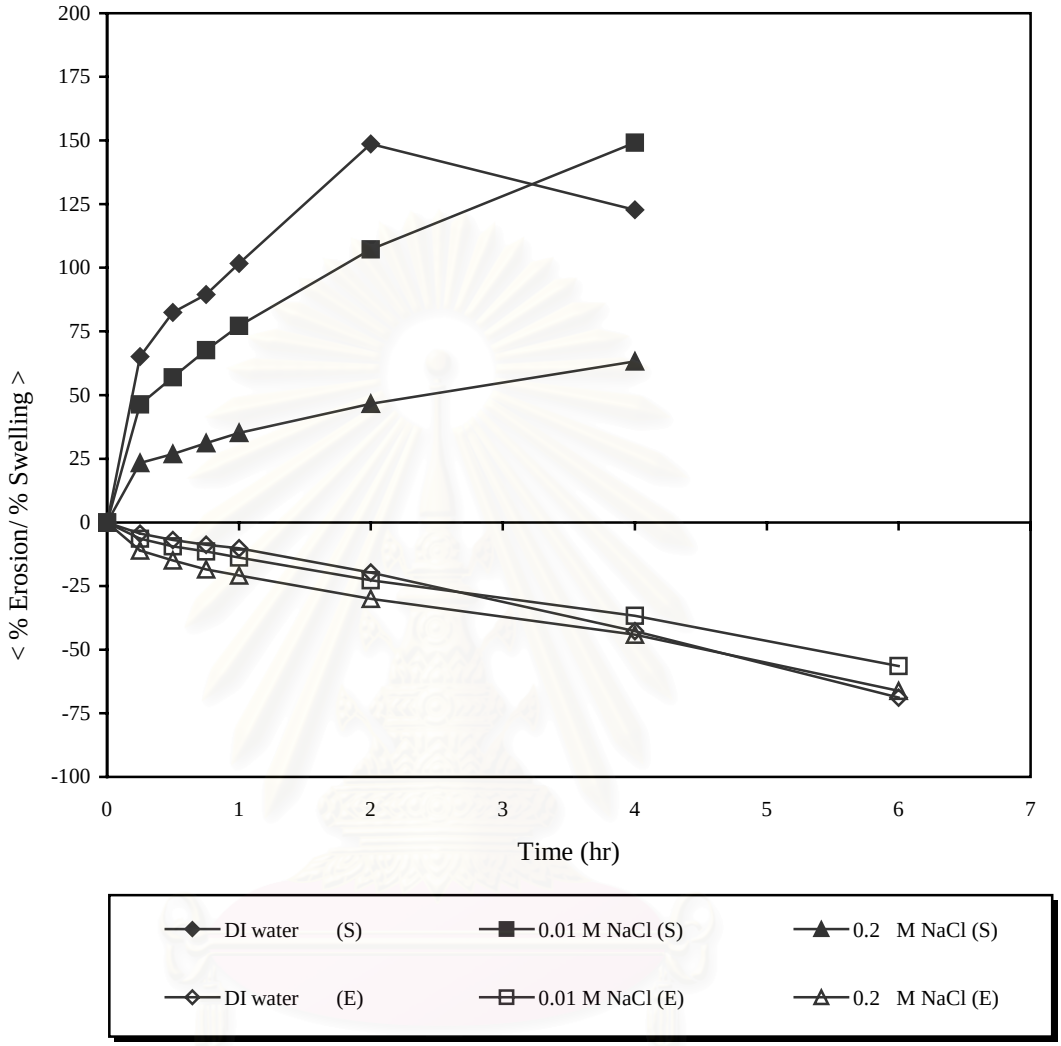


Figure 52 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 3:7 in various ionic strength dissolution media

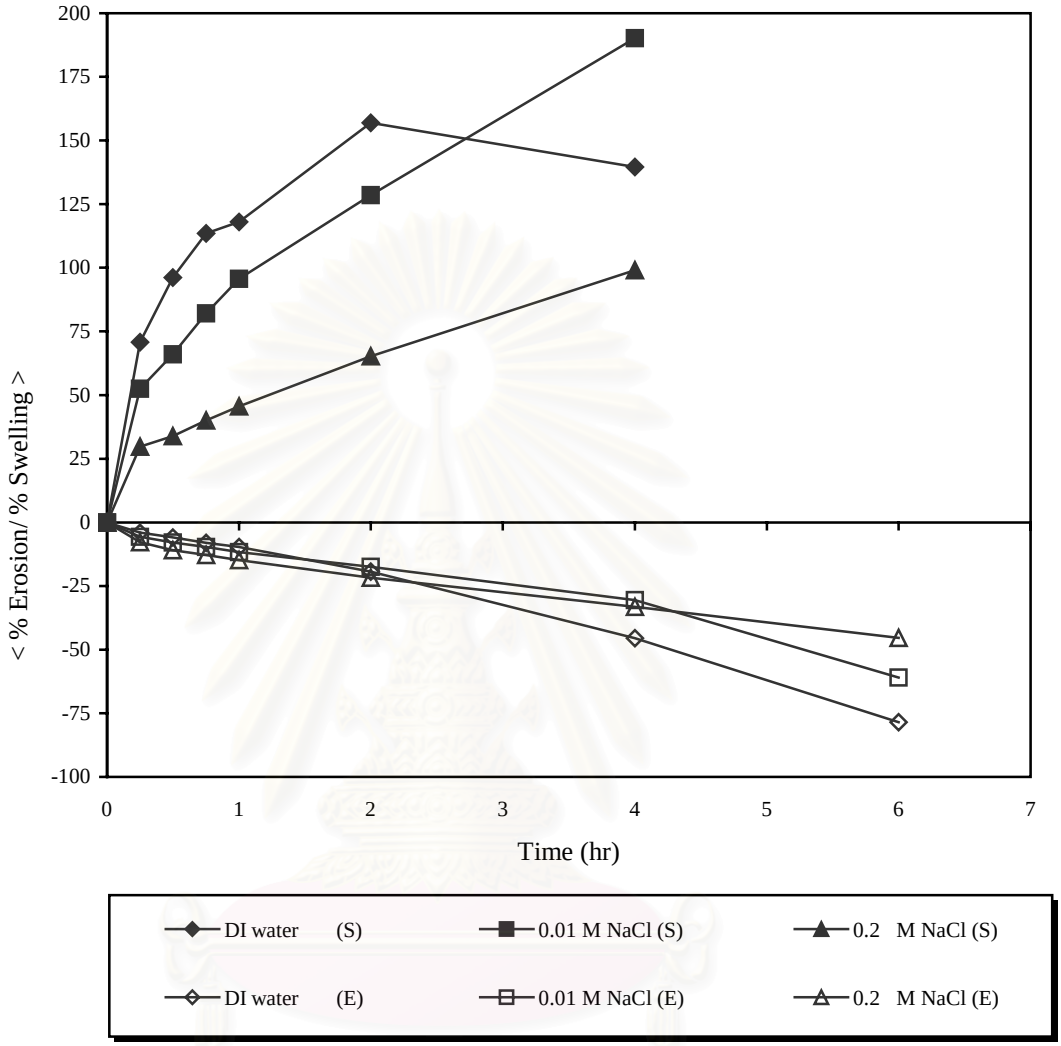


Figure 53 The percent swelling (S) and percent erosion (E) of matrices containing spray dried lactose and 15% polymer in HPMC:XG ratio of 0:10 in various ionic strength dissolution media

6.3 Matrix containing the Emcompress® and HPMC:XG ratio of 10:0

As displayed in Figure 54, the percent erosion of matrix in 0.1 N HCl solution was markedly greater than that in the other dissolution media. This is possibly attributed to the dissolution of the Emcompress® in 0.1 N HCl solution. As the result of erosion profile of matrix in these dissolution media, it could elucidate the dissolution performance of matrix in these dissolution media (see Fig. 34). The higher matrix erosion led to the greater percent drug release. In addition, the percent erosion of matrix was also determined in different ionic strength of dissolution media (see Fig. 55). The percent erosions of matrix in different ionic strength of dissolution media were not much different. This result corresponded to the amounts of drug release from the matrix (see Fig. 35).

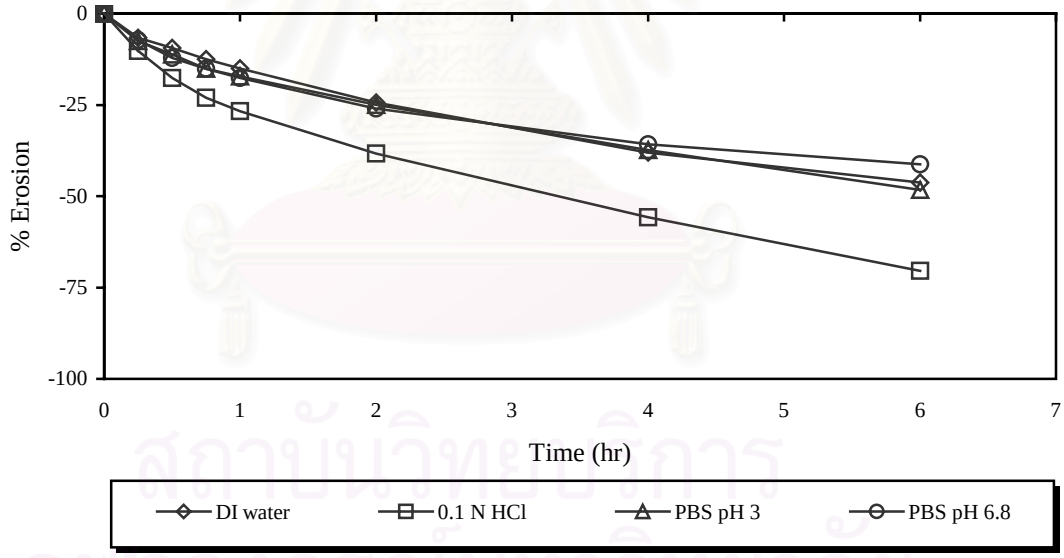


Figure 54 The percent erosion of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 10:0 in various pH dissolution media

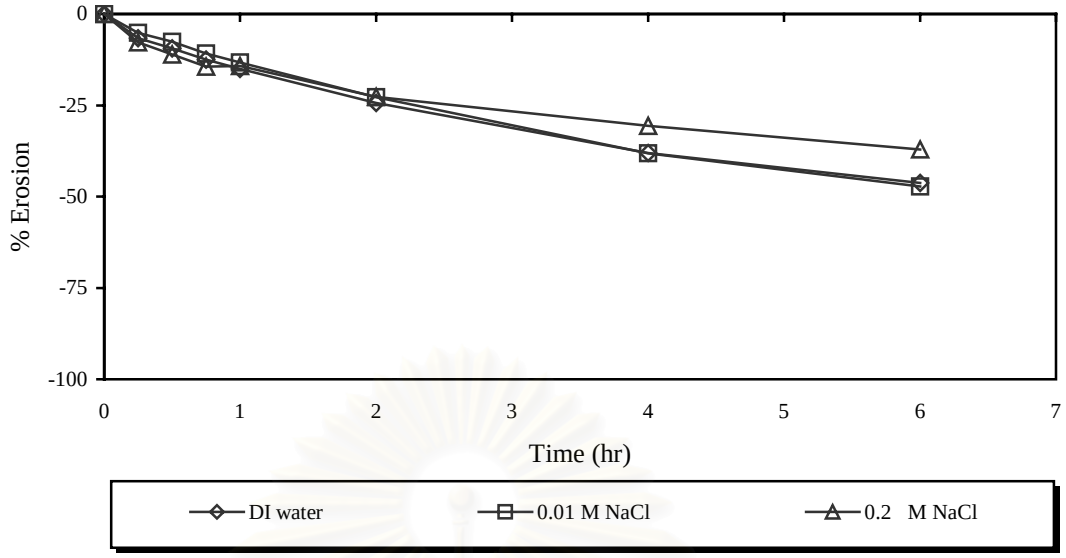


Figure 55 The percent erosion of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 10:0 in various ionic strength dissolution media

6.4 Matrix containing the Emcompress® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10

The swelling and erosion profiles of matrix containing Emcompress® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in different pH dissolution media were shown in Figures 56-59, respectively. For all matrices in DI water, 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8), the percent swellings were founded to be the greatest in DI water, intermediate in phosphate buffer solutions (pH 3 and pH 6.8) and the least in 0.1 N HCl solution. Moreover, the percent erosions of all matrices in 0.1N HCl solution were apparently greater than that in DI water and phosphate buffer solutions (pH 3 and pH 6.8) due to the dissolution of the Emcompress® in 0.1N HCl solution. According to the results of swelling and erosion of all matrices. The initial drug releases from matrices containing the Emcompress® and various HPMC:XG ratios in DI water, 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8) might be regulated by the matrix swelling rather than the matrix erosion. The higher matrix

swelling caused the lower initial drug release (see.Fig. 36, 38, 40 and 42). Additionally, in the case of matrix containing HPMC:XG ratio of 0:10 (see Fig. 59), during the 4^{th}-6^{th} hours of erosion profile, the erosion rate of swollen gel layer around the matrix in DI water was greater than that in 0.1 N HCl solution and phosphate buffer solutions (pH 3 and pH 6.8). This evidence may explain for the more drug liberation from the matrix in DI water during the late dissolution profile, when compared with 0.1 N HCl solution and phosphate buffer solutions (see Fig. 42).

Furthermore, for matrix containing HPMC:XG ratio of 7:3, 5:5, 3:7 and 0:10 in all dissolution media, an increase in amount of xanthan gum in the matrix led to an increase in the percent swelling of matrix. Thus, the higher xanthan gum in the matrix may cause the lower drug release during the beginning of dissolution period (see Fig. 36, 38, 40 and 42).

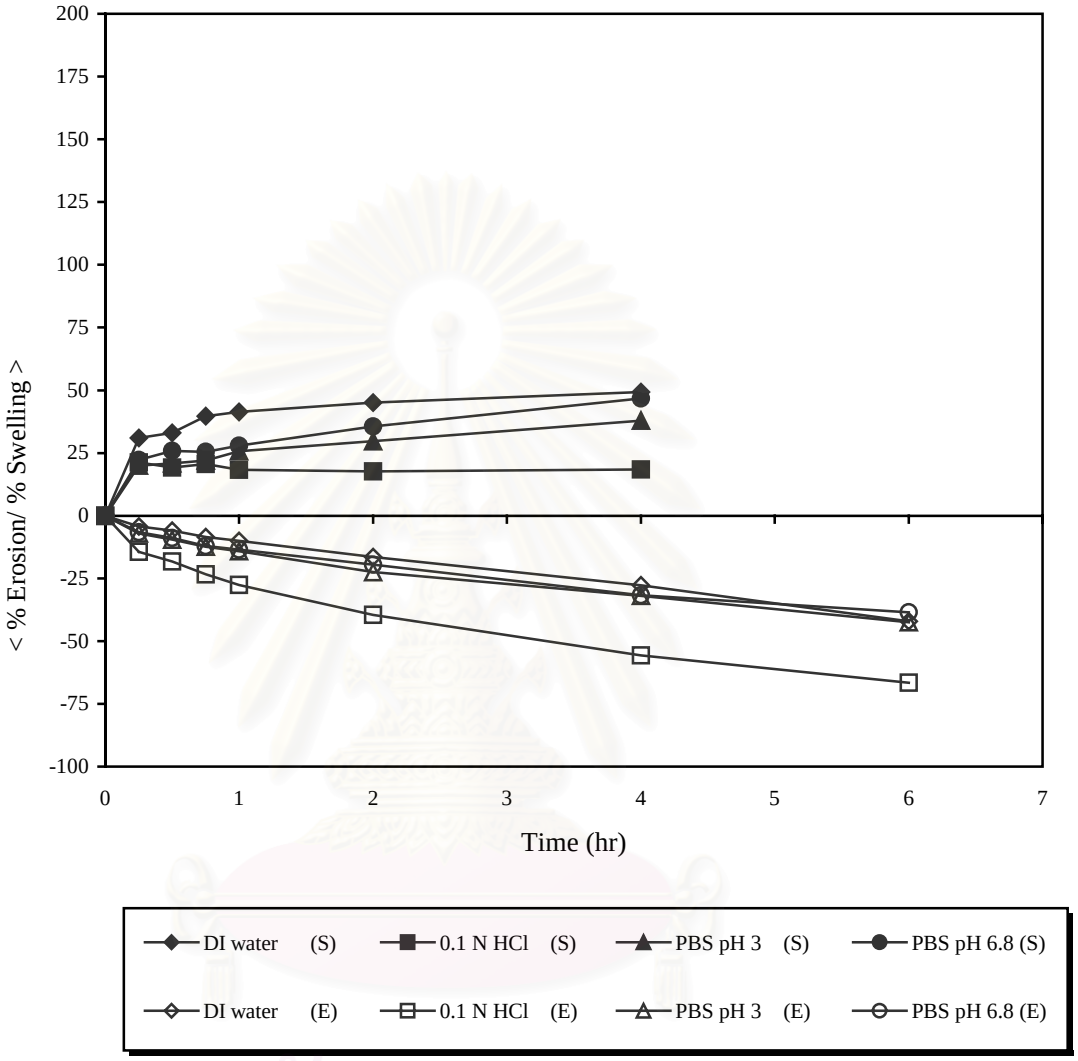


Figure 56 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 7:3 in various pH dissolution media

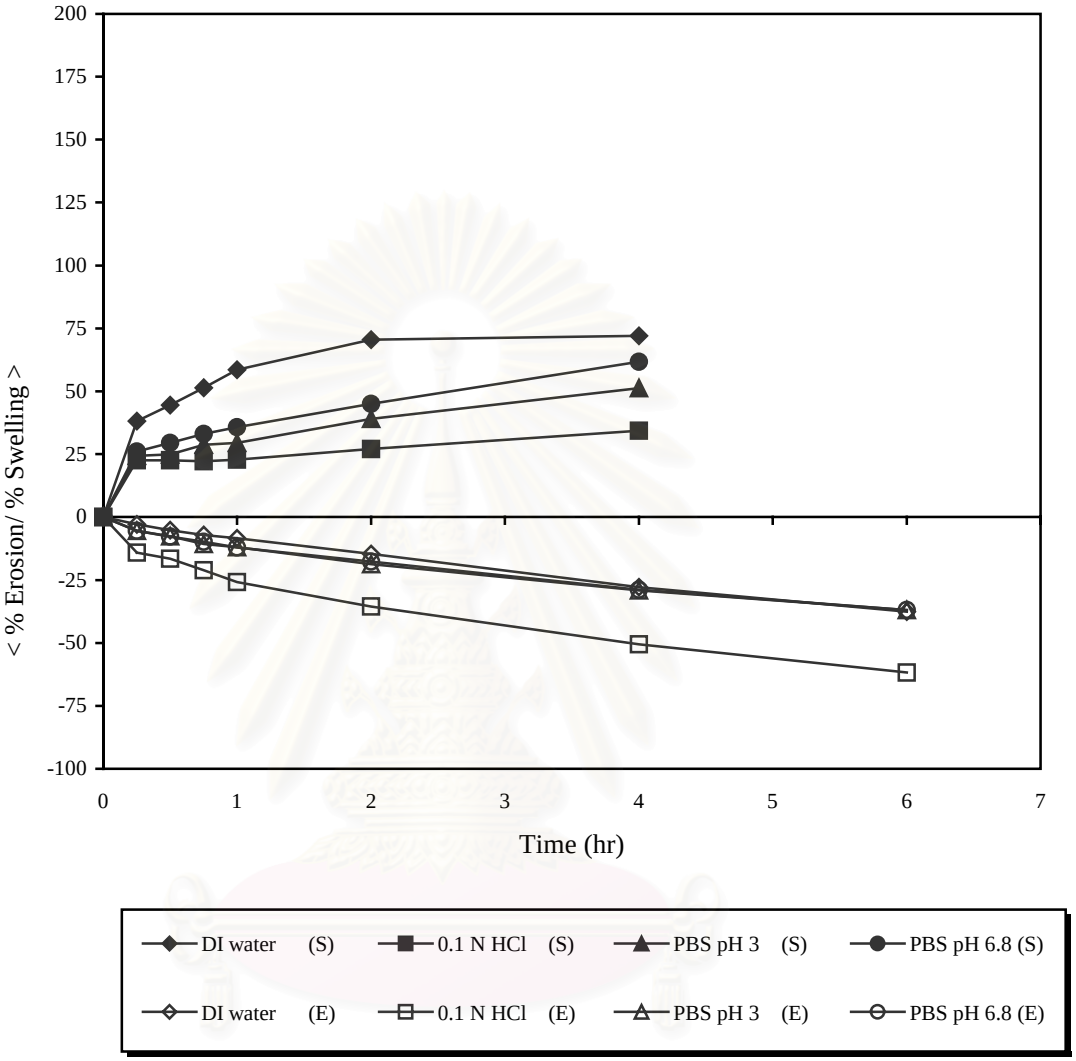


Figure 57 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 5:5 in various pH dissolution media

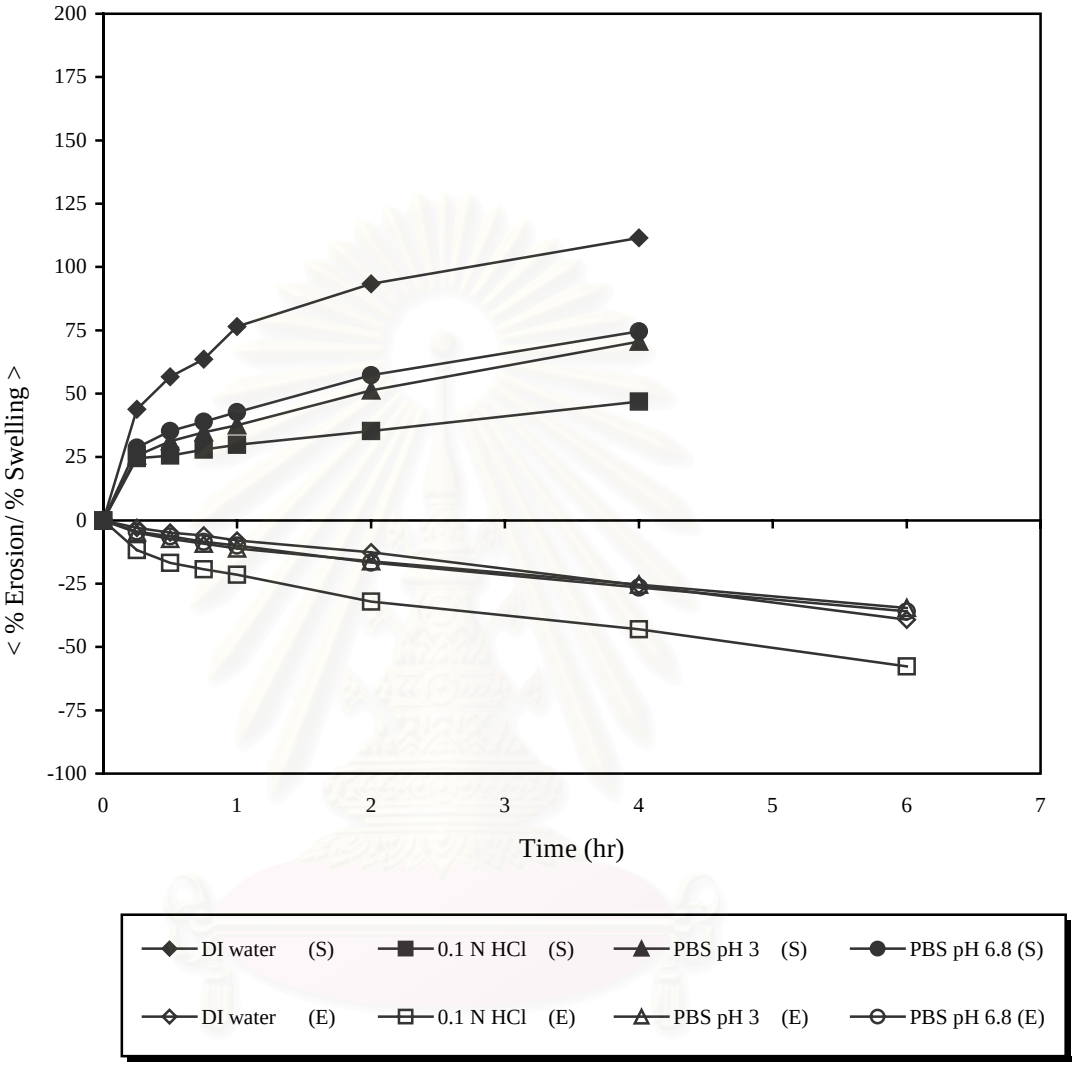


Figure 58 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 3:7 in various pH dissolution media

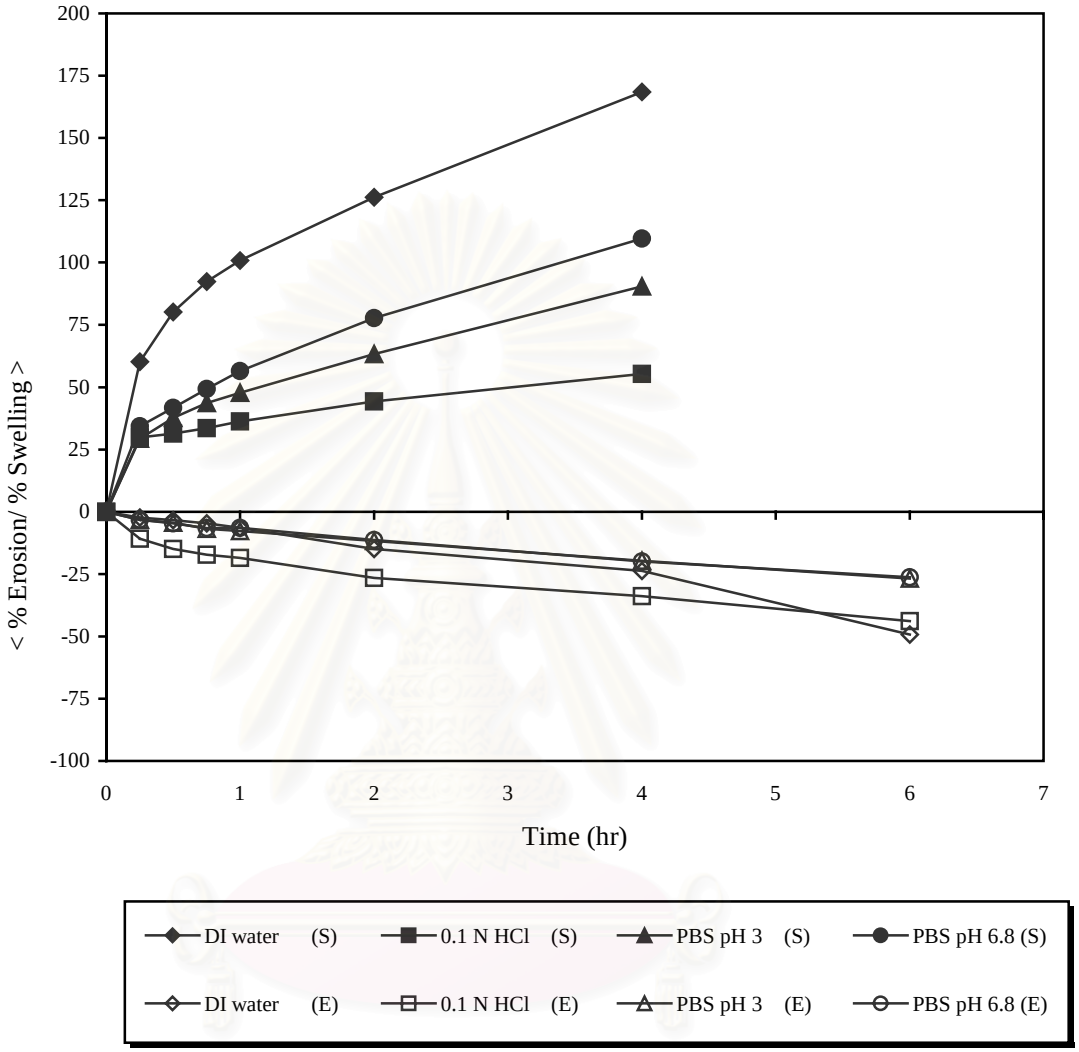


Figure 59 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 0:10 in various pH dissolution media

In the same way, the swelling and erosion profiles of matrix containing Emcompress® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in different ionic strength of dissolution media were presented in Figures 60-63, respectively. As the result of matrix swelling, the ionic strength of dissolution medium affected obviously to the polymer swelling. An increase in ionic strength of dissolution medium allowed a decrease in polymer swelling. The greater polymer swelling resulted in the longer diffusional path length of drug, thus reducing initial drug release (see Fig. 37, 39, 41 and 43). Furthermore, for all matrices (see Fig. 60-63), during the first 4 hours of erosion profiles, the percent erosion of matrix in DI water, 0.01 M and 0.2 M NaCl solutions were not much different. This indicated that the integrities of all matrices in these dissolution media could be maintained by formation of swollen gel layer at the matrix surface.

Furthermore, in the case of matrix containing HPMC:XG ratio of 0:10 (see Fig. 63), after the 4^{th} hour of erosion profile, the percent erosions of matrix were observed to be the greatest in DI water, intermediate in 0.01 M NaCl solution and the least in 0.2 M NaCl solution. This finding also correlated to the percent drug release after the 4^{th} hour of dissolution profile (see Fig .43).

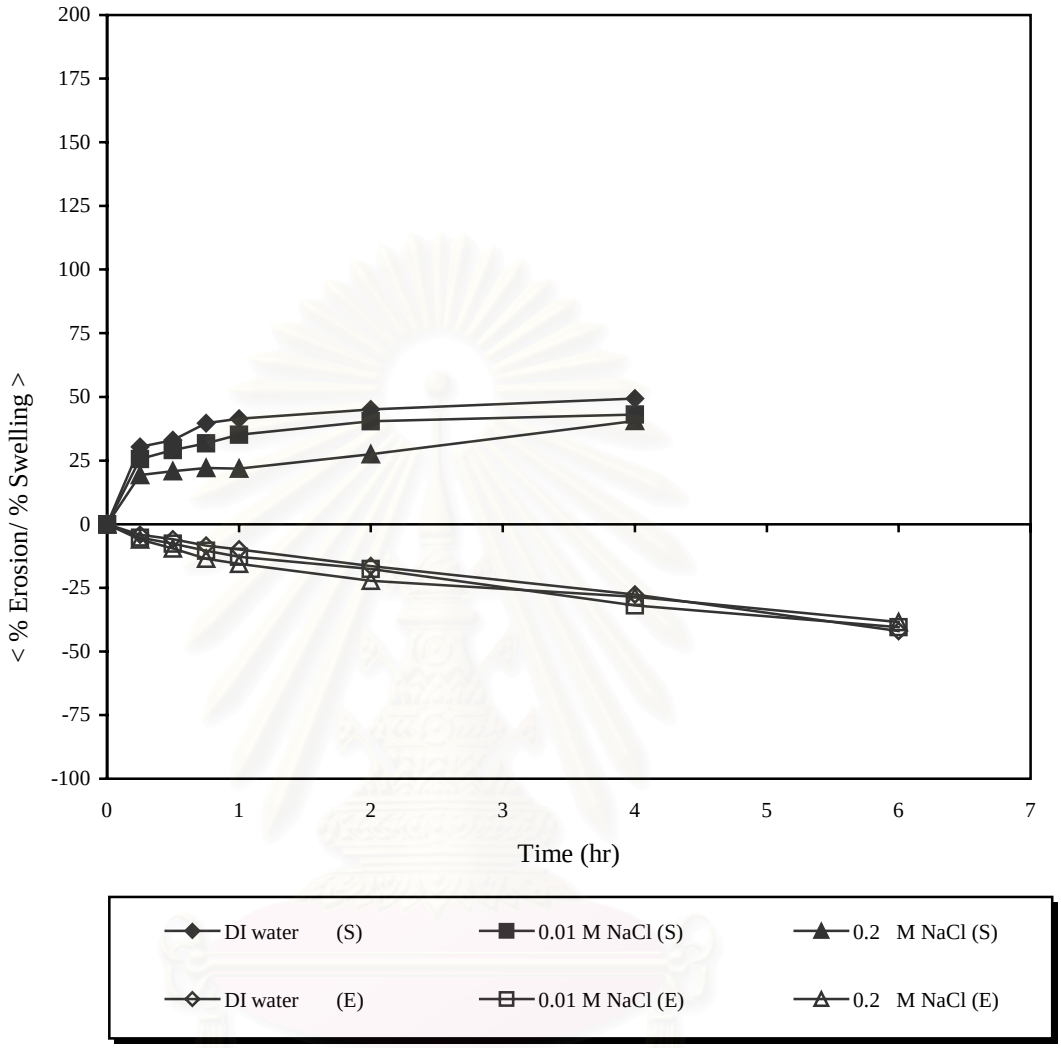


Figure 60 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 7:3 in various ionic strength dissolution media

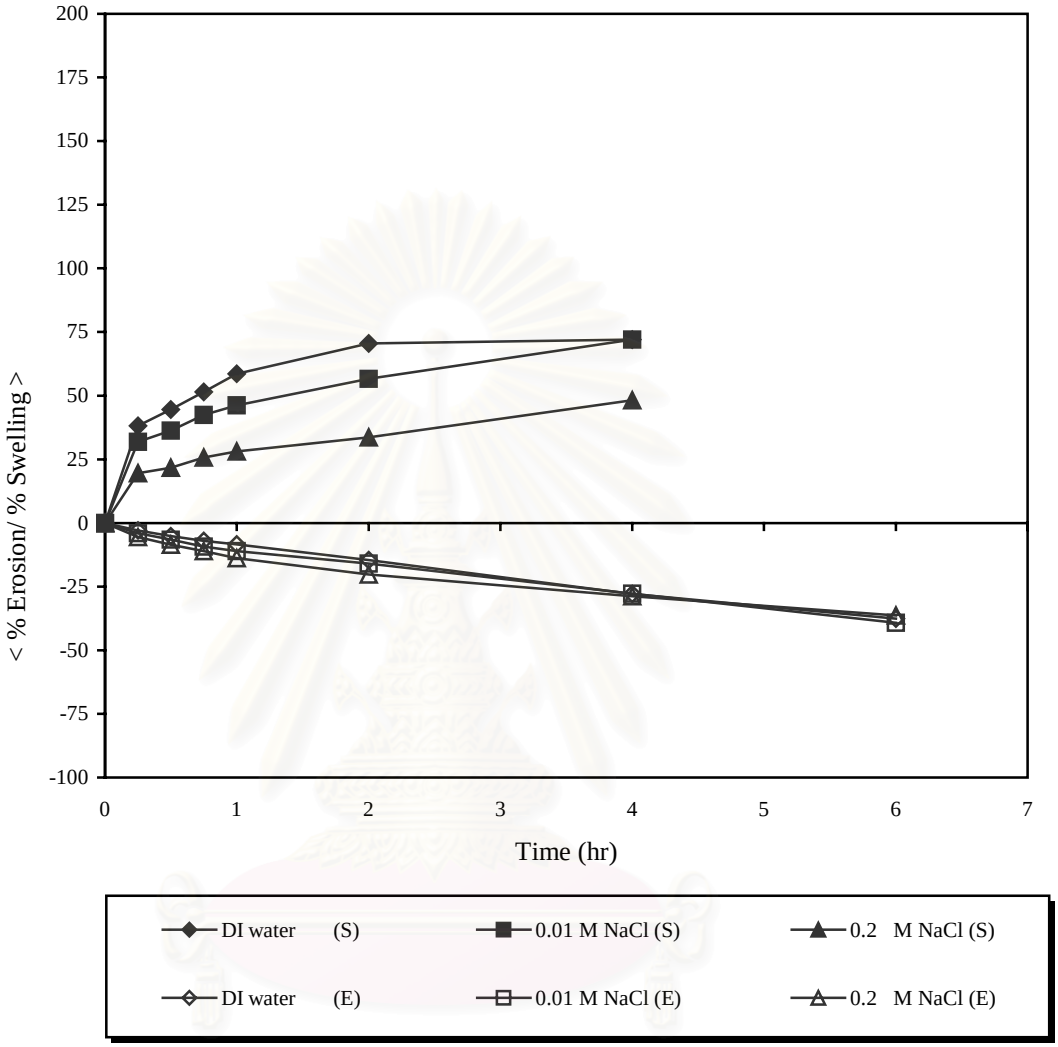


Figure 61 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 5:5 in various ionic strength dissolution media

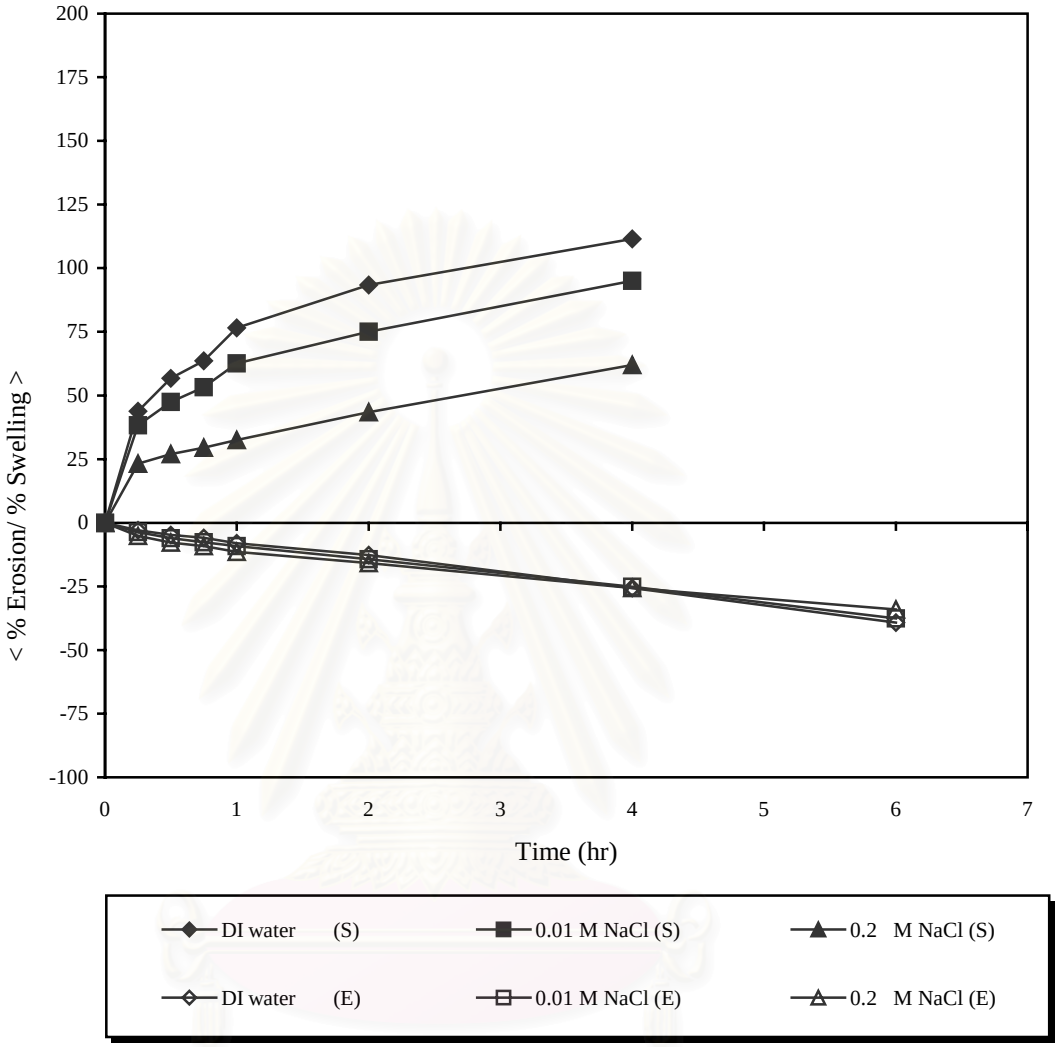


Figure 62 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 3:7 in various ionic strength dissolution media

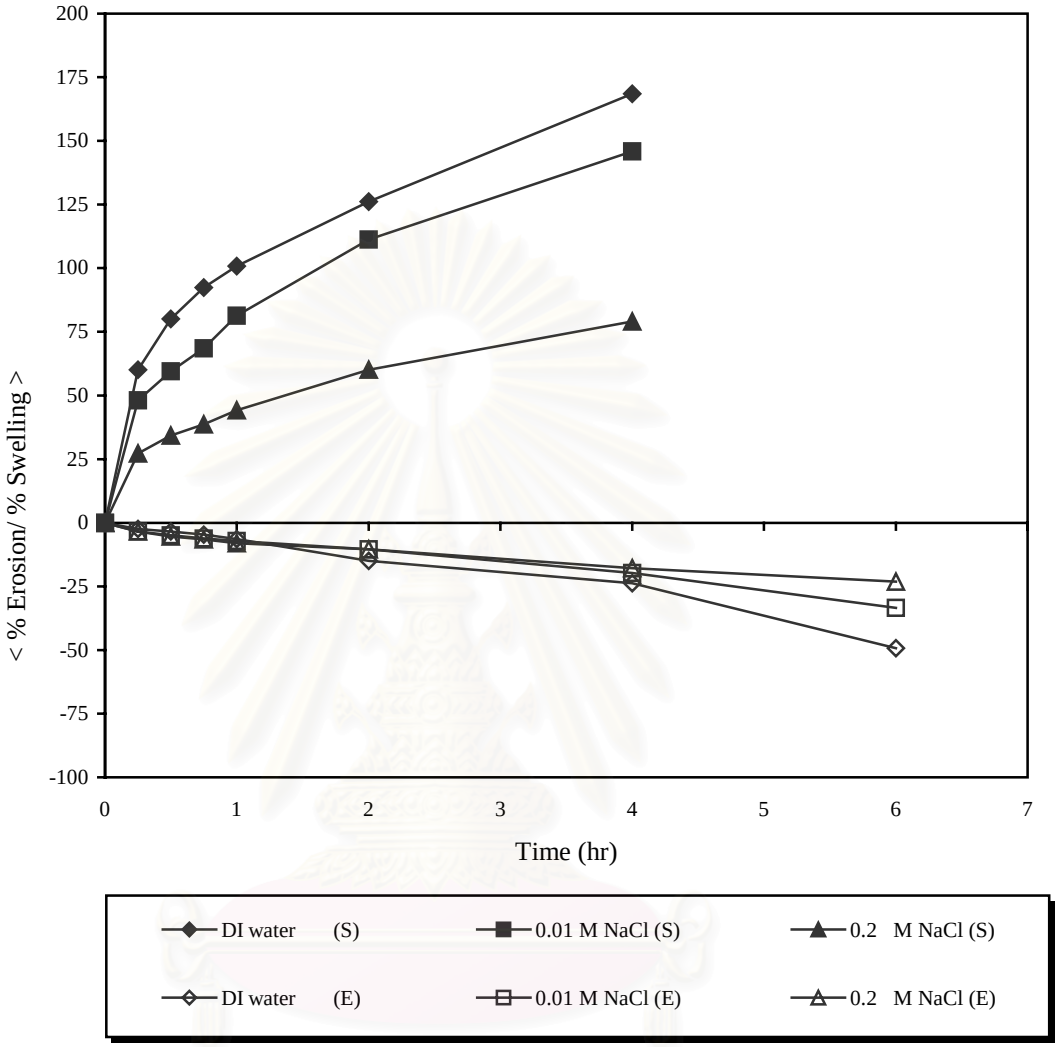


Figure 63 The percent swelling (S) and percent erosion (E) of matrices containing dibasic calcium phosphate and 15% polymer in HPMC:XG ratio of 0:10 in various ionic strength dissolution media

7. Morphology of hydrated matrices

The morphology of hydrated matrices containing the spray dried lactose (Supertab®) or the dibasic calcium phosphate (Emcompress®) and HPMC:XG ratios of 10:0, 5:5 and 0:10 in DI water, 0.1 N HCl solution and phosphate buffer solution pH 6.8 and 0.2 M NaCl solutions were performed by cryoelectron microscope. The photomicrographs of the internal morphology of hydrated matrices after 2 hours hydration in these dissolution media were shown in Figures 64-75. These illustrated the microscopic structure of outer and inner regions of hydrated matrices. For all matrices in all dissolution media, the overall structure of the gel layer at the outer region of hydrated matrix was less porous than that of the inner region of the same matrix. This indicated that the formation of swollen gel layer around the matrix might reduce the porosity of matrix, resulted in the retardation of drug release.

However, for all matrices, the photomicrographs of the outer region of hydrated matrix did not obviously shown the distinction in different dissolution media. Due to all matrices containing drug 66.67 % and swellable polymer only 15 %, thus it is difficult to discriminate the morphology of swollen gel in hydrated matrices in different dissolution media. Furthermore, some photomicrographs, for instances in Fig. 65 (C), 69 (C), 71 (C) and 75 (A,C), illustrated the large holes or cracks that might result from the preparation of fractured specimens.

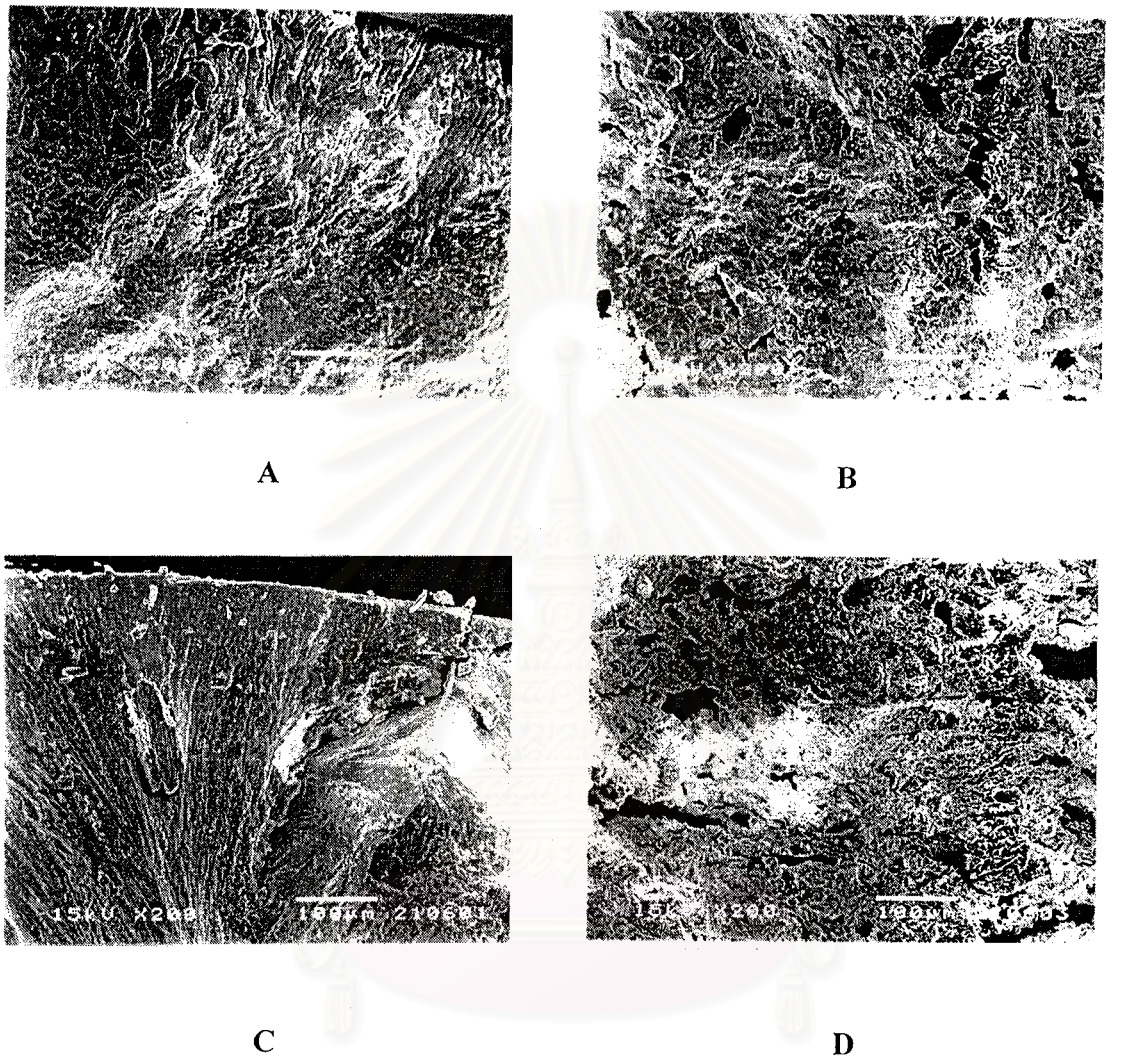


Figure 64 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 10:0 and different fillers, hydrated for 2 hr in DI water, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

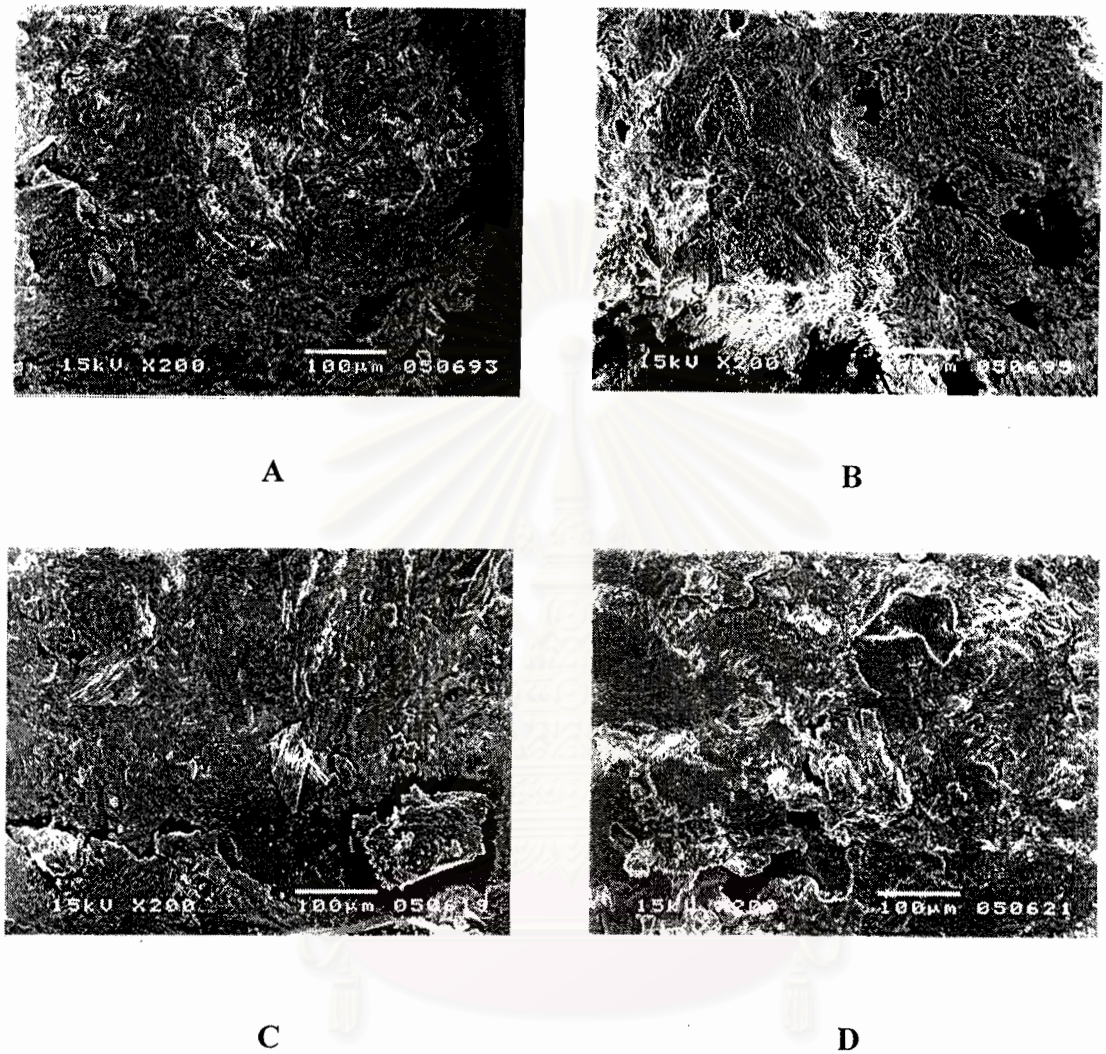


Figure 65 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 10:0 and different fillers, hydrated for 2 hr in 0.1 N HCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

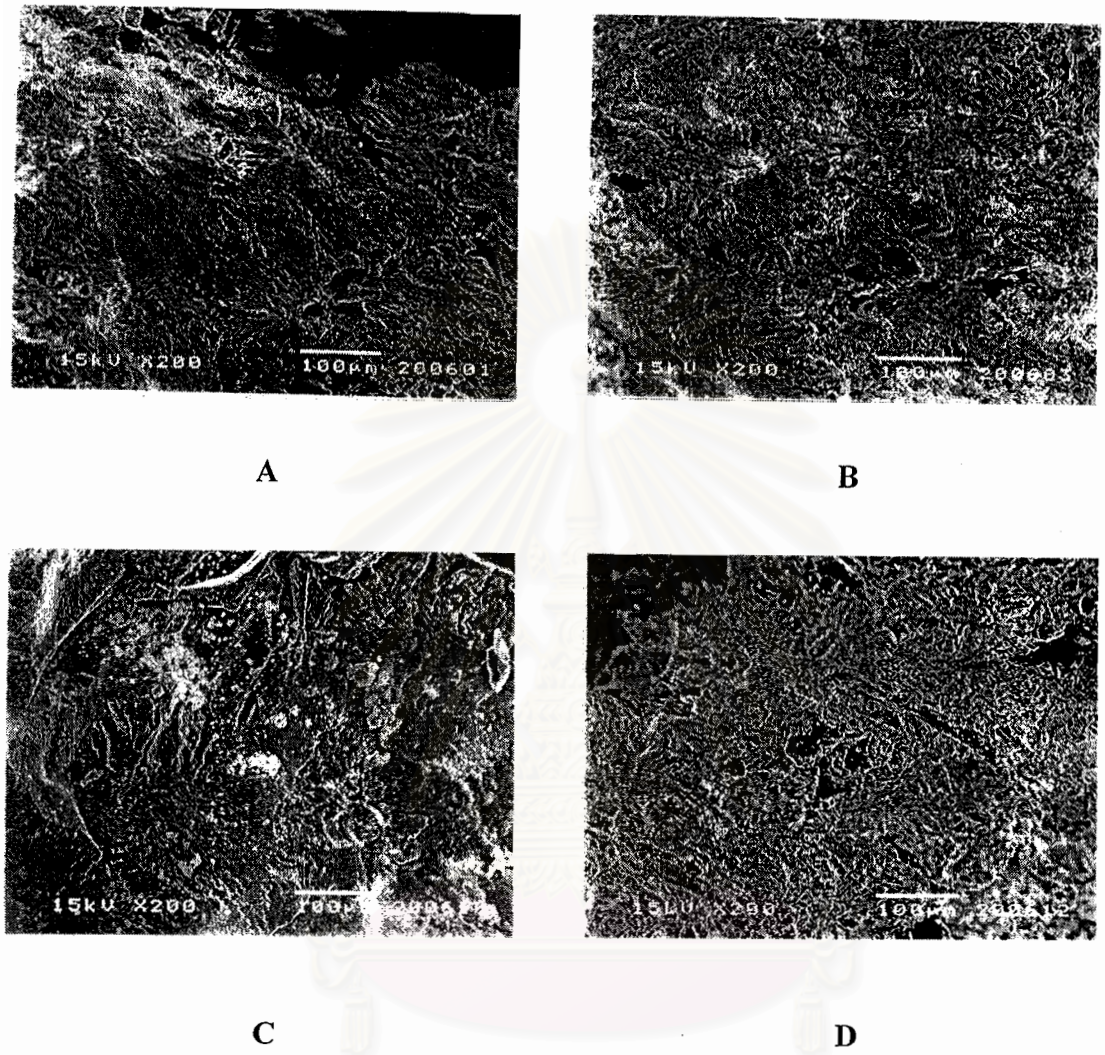


Figure 66 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 10:0 and different fillers, hydrated for 2 hr in PBS pH 6.8, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

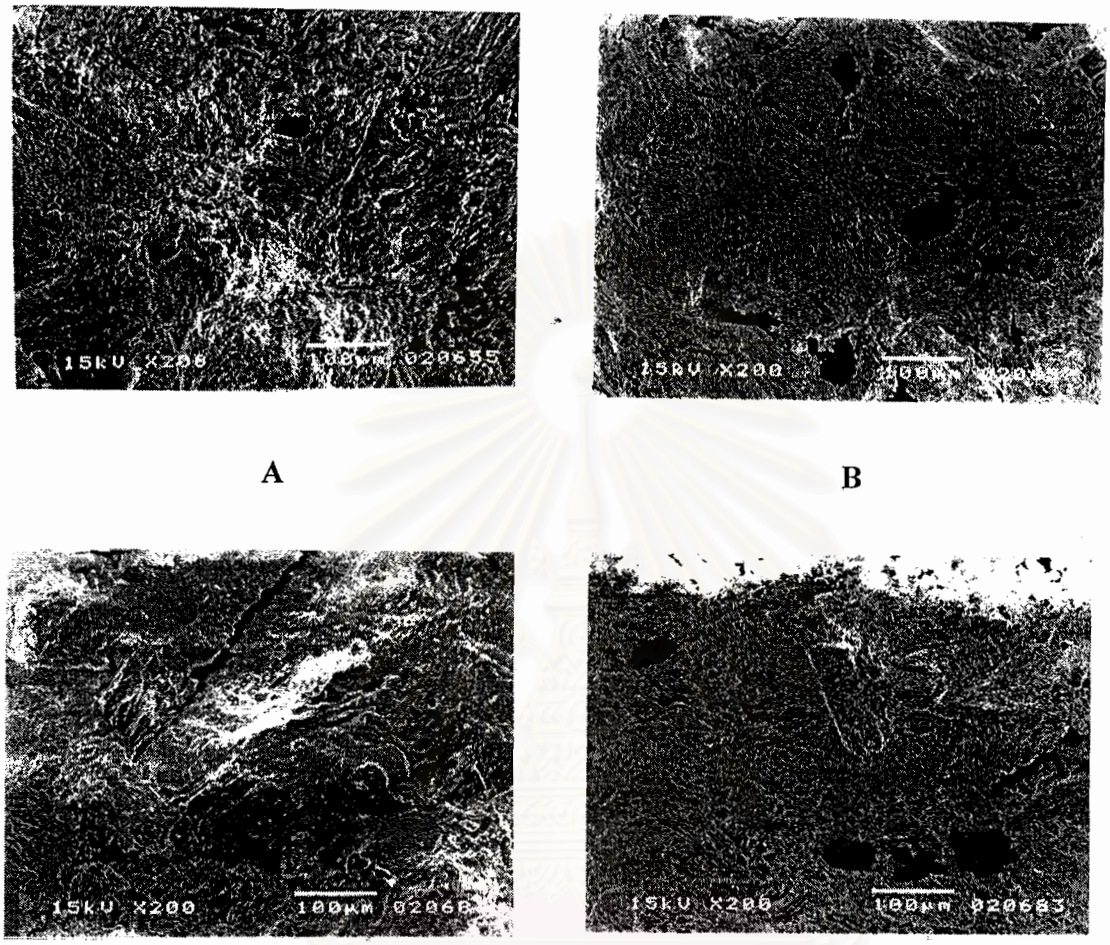


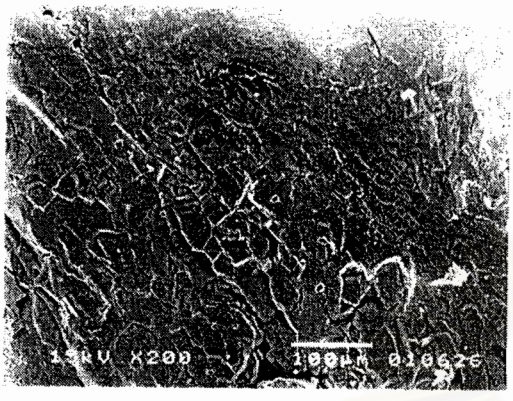
Figure 67 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 10:0 and different fillers, hydrated for 2 hr in 0.2 M NaCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

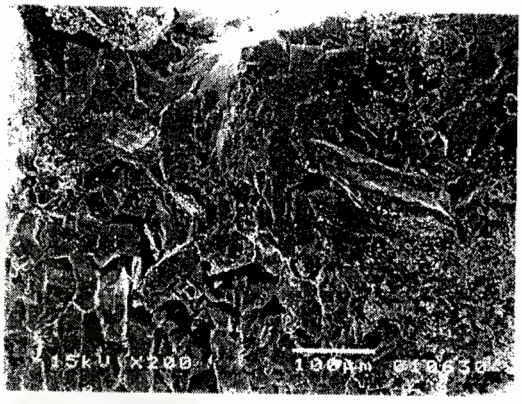
(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

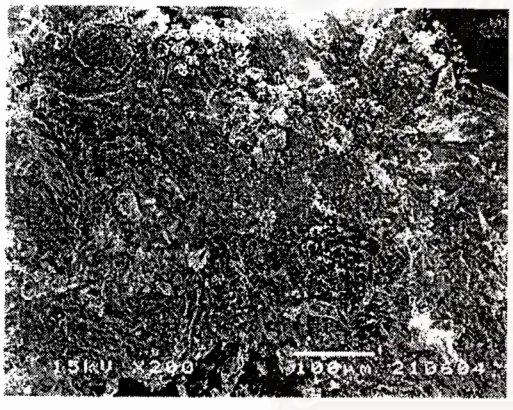
(D) the inner region of hydrated matrix containing dibasic calcium phosphate



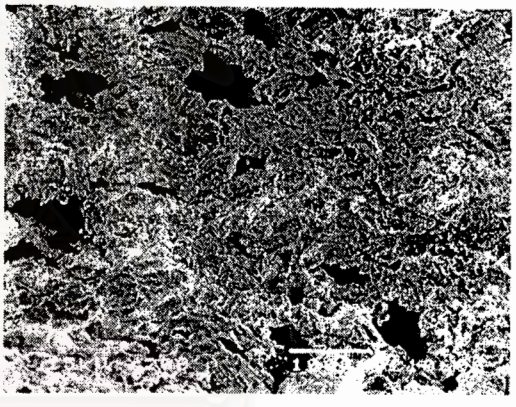
A



B



C



D

Figure 68 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 5:5 and different fillers, hydrated for 2 hr in DI water, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

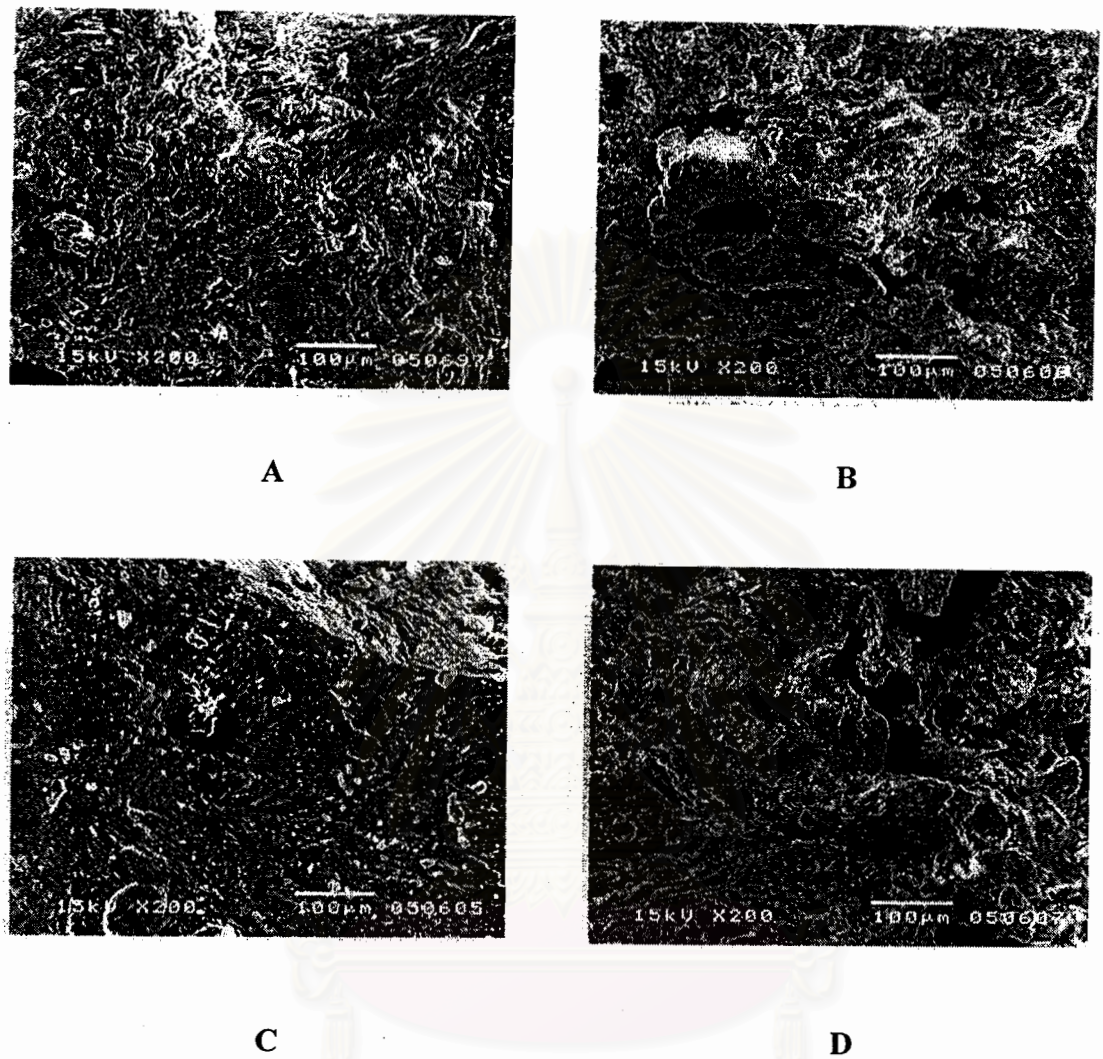


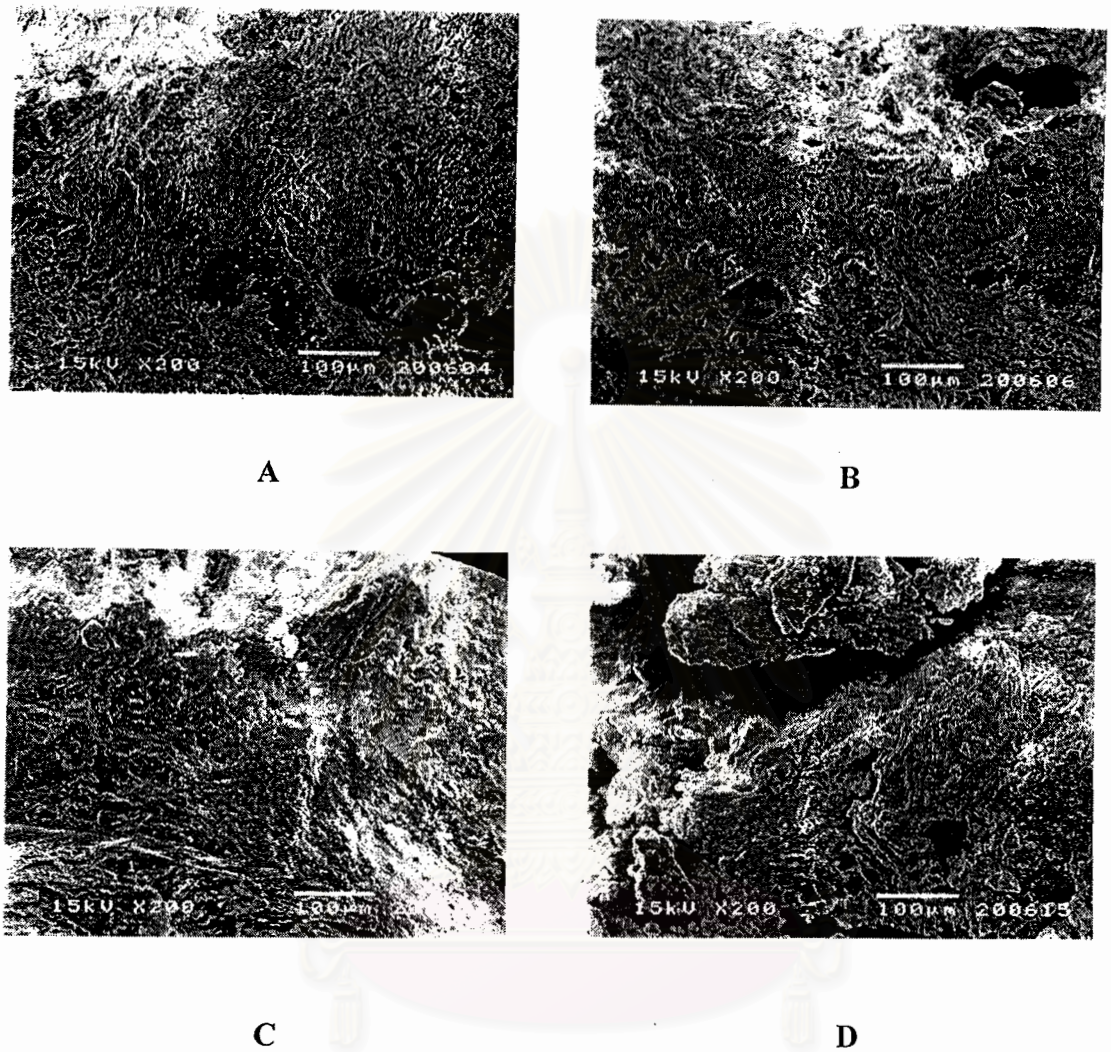
Figure 69 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 5:5 and different fillers, hydrated for 2 hr in 0.1 N HCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate



A B

C D

Figure 70 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 5:5 and different fillers, hydrated for 2 hr in PBS pH 6.8, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

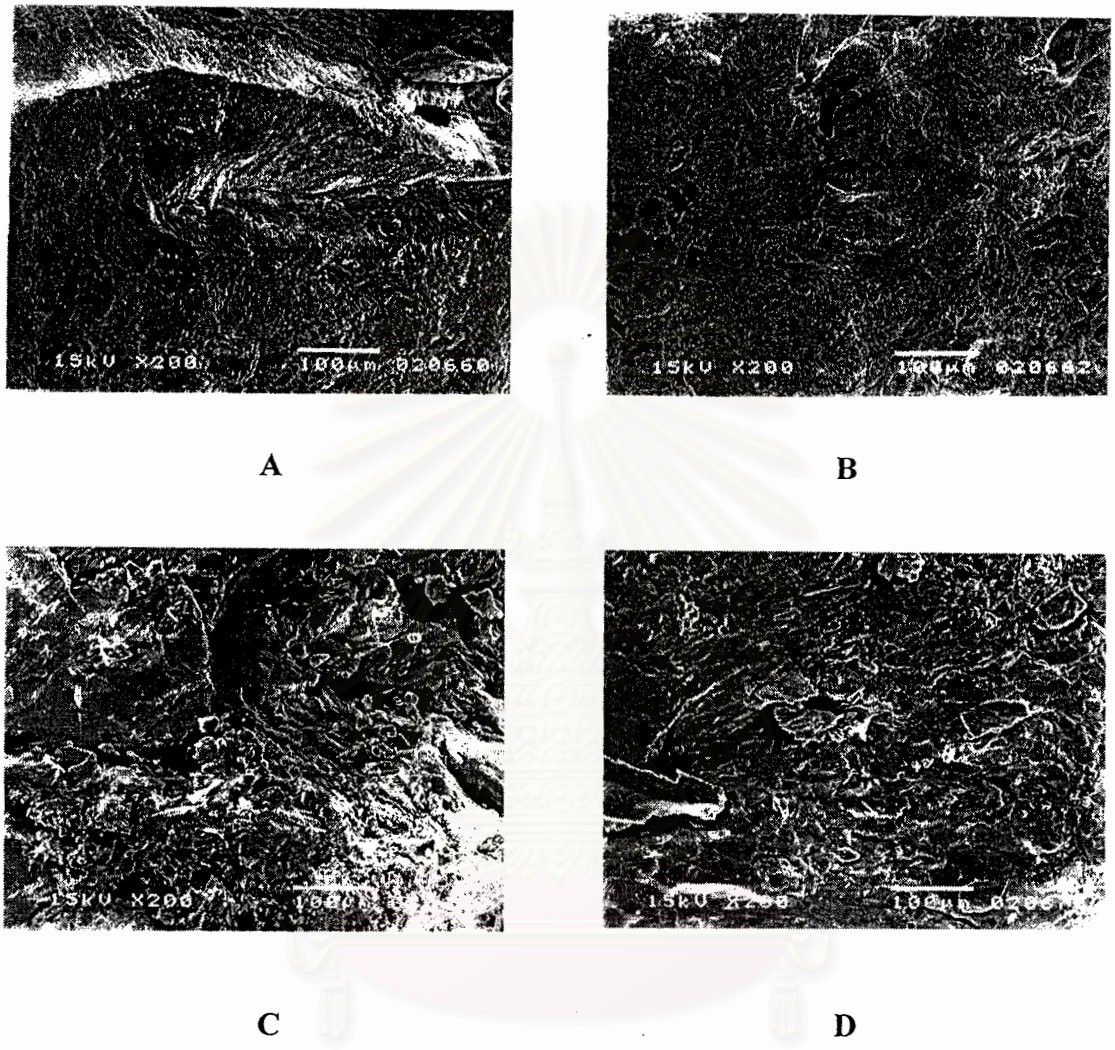


Figure 71 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 5:5 and different fillers, hydrated for 2 hr in 0.2 M NaCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

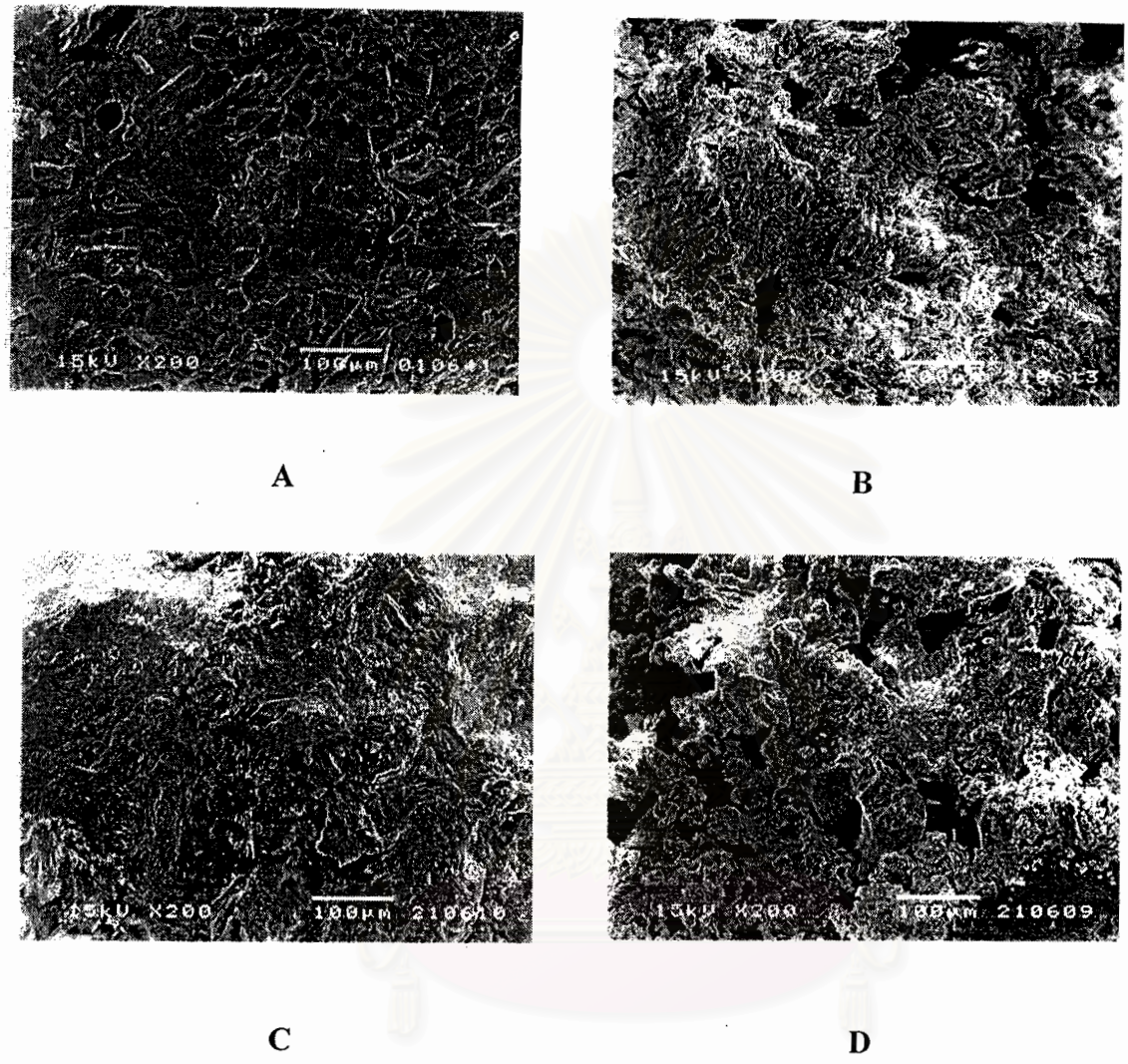


Figure 72 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 0:10 and different fillers, hydrated for 2 hr in DI water, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

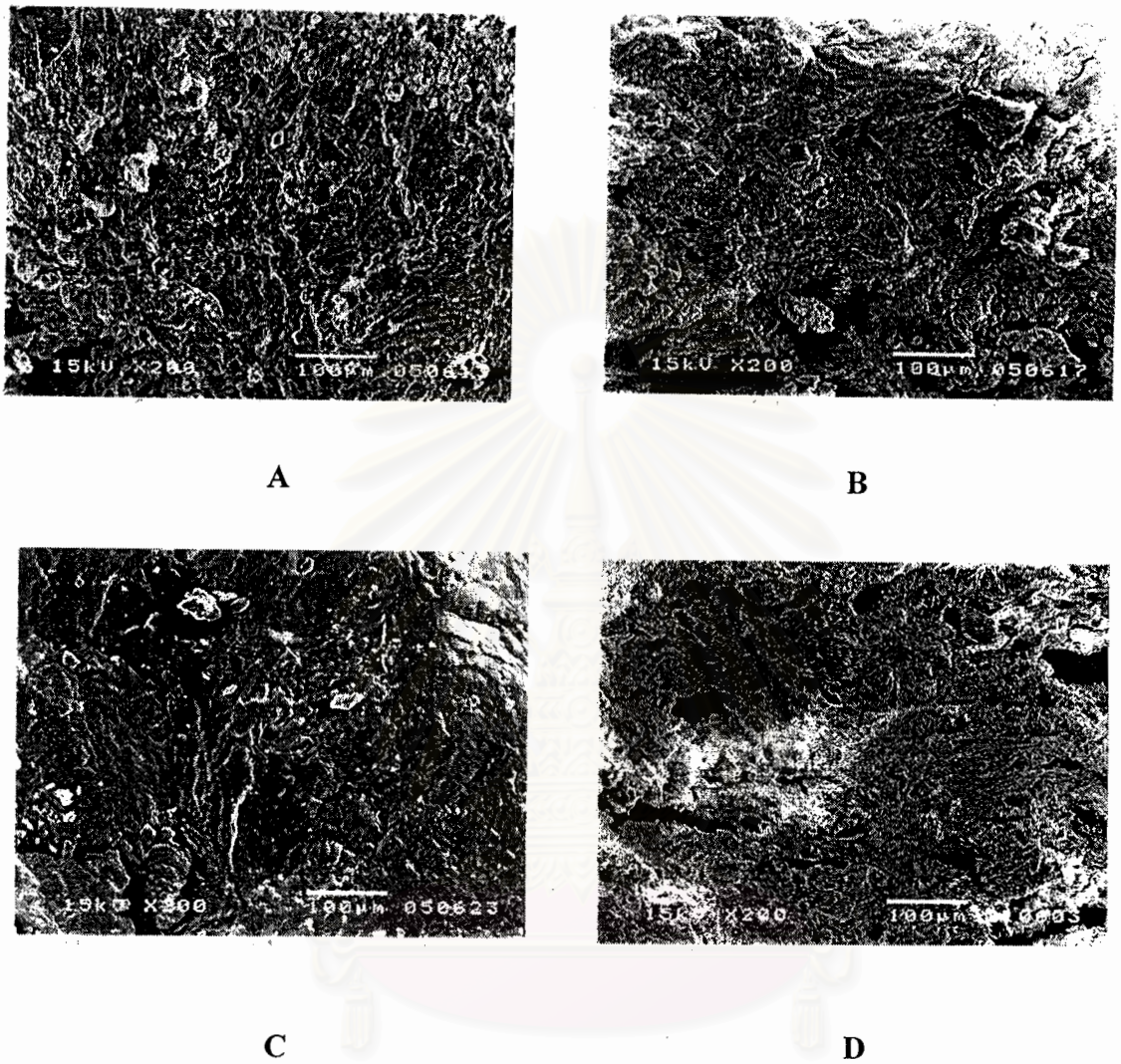


Figure 73 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 0:10 and different fillers, hydrated for 2 hr in 0.1 N HCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

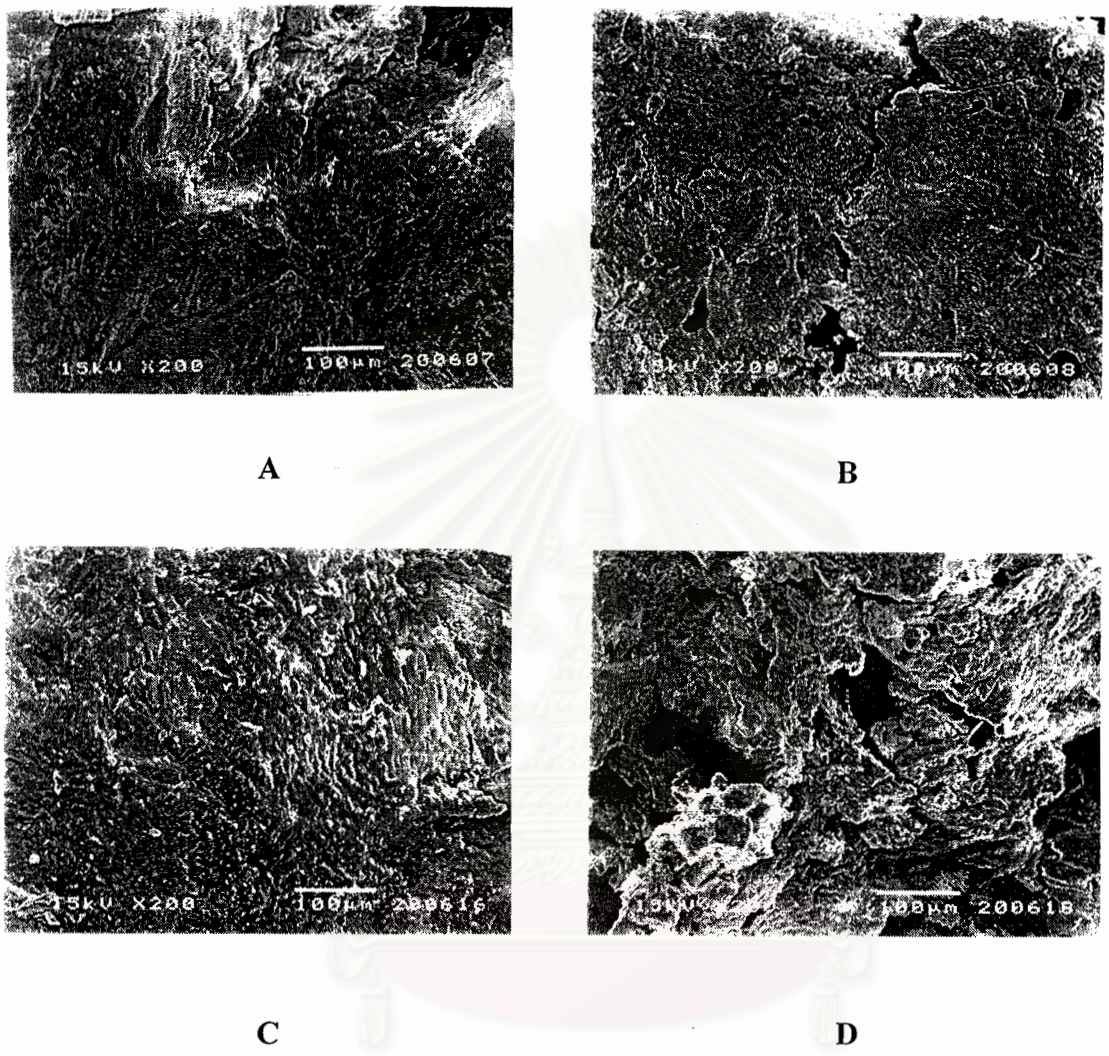


Figure 74 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 0:10 and different fillers, hydrated for 2 hr in PBS pH 6.8, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

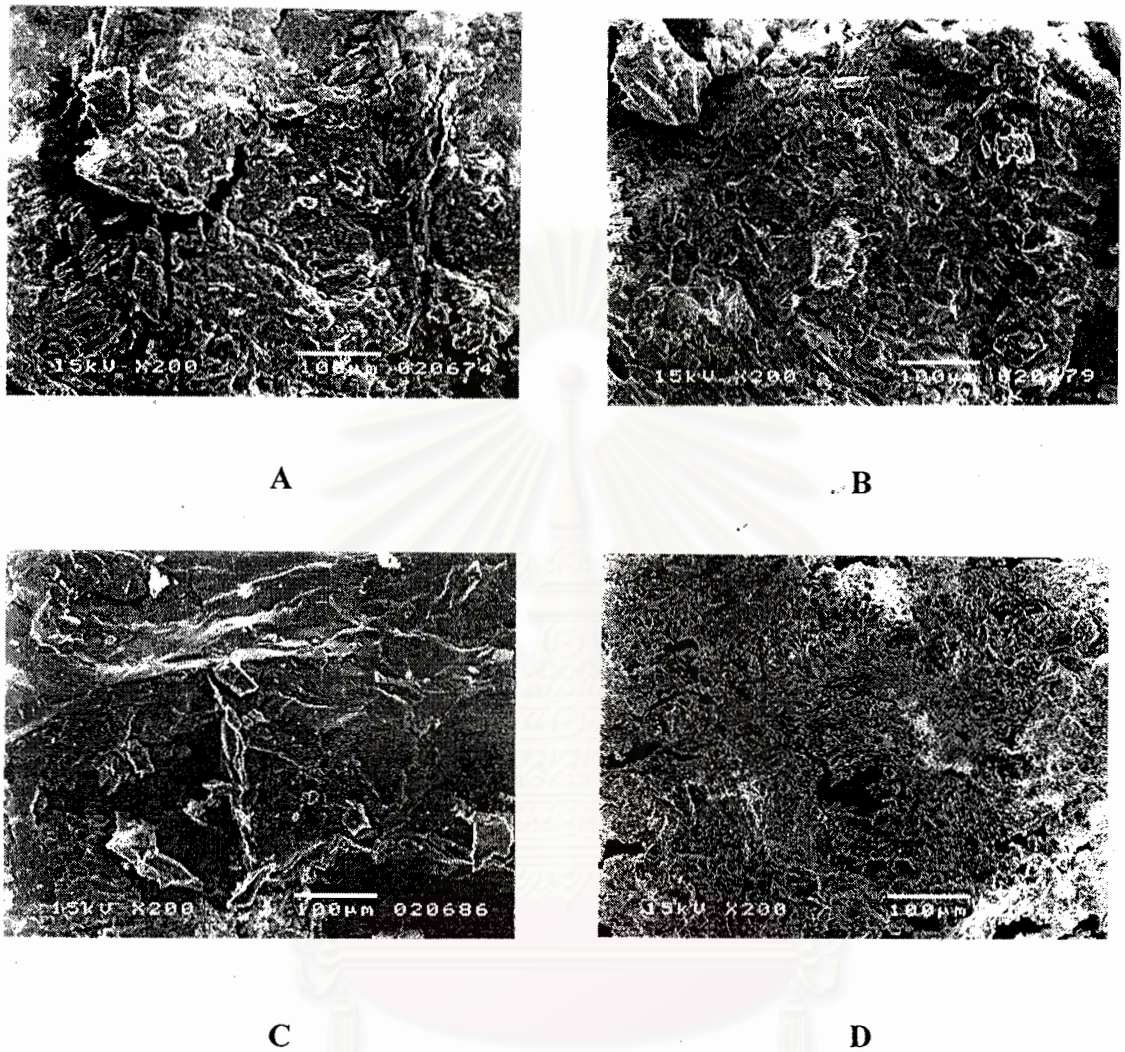


Figure 75 Photomicrographs of hydrated theophylline matrices containing HPMC:XG ratio of 0:10 and different fillers, hydrated for 2 hr in 0.2 M NaCl solution, 37±0.5 °C (x 200, cross-section)

(A) the outer region of hydrated matrix containing spray dried lactose

(B) the inner region of hydrated matrix containing spray dried lactose

(C) the outer region of hydrated matrix containing dibasic calcium phosphate

(D) the inner region of hydrated matrix containing dibasic calcium phosphate

8. Release mechanism analysis

The mechanism of drug release from polymeric matrix was investigated by fitting the release data into the exponent equation, given below.

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fractional release of drug (0.1-0.6), t is the release time, k is a constant incorporating structural and geometric characteristics of release device and n is the release exponent indicative of mechanism of release. For example, in the case of a tablet, n=0.45 for case I or Fickian diffusion, n=0.89 for case II transport, 0.45<n< 0.89 for anomalous transport, and n> 0.89 for super case II transport (Ritger and Peppas, 1987)

In addition, Peppas and Sahlin (1989) proposed a model and derived the equation which quantifying the appropriate amount of drug release by Fickian diffusion and by polymer relaxation as follows.

$$M_t/M_\infty = k_1t^{1/2} + k_2t$$

In here, the first and second terms on the right hand side represent the Fickian diffusion and the case II relaxation contributions.

The mechanism of drug release for matrices containing spray dried lactose (Supertab®) or dibasic calcium phosphate (Emcompress®) and 15% polymer in the HPMC:XG ratios of 10:0, 7:3, 5:5, 3:7 and 0:10 in various dissolution media were investigated by fitting the dissolution data into the equations of Ritger and Peppas (1987) and Peppas and Sahlin (1989). The values of n, correlation coefficient (r), k_1 and k_2 following linear regression of dissolution data were given in Table 8.

Table 8 Values of release exponent (n), correlation coefficient (r) obtained from equation of Ritger and Peppas (1987) and diffusional (k_1) and relaxational (k_2) constants obtained from equation of Peppas and Sahlin (1989)

Matrix composition HPMC: XG: Filler	Dissolution medium	Release exponent (n)	Correlation coefficient (r)	Diffusional constant (k_1) ($hr^{-1/2}$)	Relaxational constant (k_2) (hr^{-1})
10: 0: Supertab®	DI water	0.4580	0.9991	0.886	0.115
	0.1 N HCl	0.4082	0.9996	*	*
	PBS pH 3	0.3471	0.9963	*	*
	PBS pH 6.8	0.3495	0.9987	*	*
	PBS pH 7.4	0.3873	0.9994	*	*
	0.01 M NaCl	0.4446	0.9990	*	*
	0.05 M NaCl	0.4639	0.9999	1.111	-
	0.1 M NaCl	0.4255	0.9998	*	*
	0.2 M NaCl	0.3585	0.9996	*	*
7: 3: Supertab®	DI water	0.9533	0.9993	*	*
	0.1 N HCl	0.5052	0.9996	0.940	0.060
	PBS pH 3	0.4461	0.9982	*	*
	PBS pH 6.8	0.4571	0.9983	0.891	0.109
	PBS pH 7.4	0.4366	0.9990	*	*
	0.01 M NaCl	0.6950	0.9998	0.381	0.623
	0.05 M NaCl	0.5536	0.9983	0.664	0.339
	0.1 M NaCl	0.4941	0.9989	0.763	0.240
	0.2 M NaCl	0.3706	0.9990	*	*

* Not applicable due to the mechanism of drug release was not the anomalous transport.

Table 8 (Continued) Values of release exponent (n), correlation coefficient (r) obtained from equation of Ritger and Peppas (1987) and diffusional (k_1) and relaxational (k_2) constants obtained from equation of Peppas and Sahlin (1989)

Matrix composition HPMC: XG: Filler	Dissolution medium	Release exponent (n)	Correlation coefficient (r)	Diffusional constant (k_1) ($hr^{-1/2}$)	Relaxational constant (k_2) (hr^{-1})
5: 5: Supertab®	DI water	1.0528	0.9997	*	*
	0.1 N HCl	0.5457	0.9998	0.895	0.106
	PBS pH 3	0.5791	0.9992	0.603	0.399
	PBS pH 6.8	0.5753	0.9993	0.550	0.453
	PBS pH 7.4	0.5628	0.9991	0.647	0.356
	0.01 M NaCl	0.7917	0.9999	0.357	0.645
	0.05 M NaCl	0.6778	0.9998	0.551	0.452
	0.1 M NaCl	0.5734	0.9995	0.643	0.360
	0.2 M NaCl	0.4873	0.9992	0.776	0.225
3: 7: Supertab®	DI water	1.0936	0.9998	*	*
	0.1 N HCl	0.5629	0.9998	0.780	0.222
	PBS pH 3	0.6378	0.9995	0.486	0.516
	PBS pH 6.8	0.6805	0.9997	0.557	0.444
	PBS pH 7.4	0.6531	0.9995	0.427	0.576
	0.01 M NaCl	0.9236	0.9985	*	*
	0.05 M NaCl	0.7338	0.9996	0.341	0.661
	0.1 M NaCl	0.6528	0.9994	0.388	0.614
	0.2 M NaCl	0.5535	0.9988	0.493	0.509

* Not applicable due to the mechanism of drug release was not the anomalous transport.

Table 8 (Continued) Values of release exponent (n), correlation coefficient (r) obtained from equation of Ritger and Peppas (1987) and diffusional (k_1) and relaxational (k_2) constants obtained from equation of Peppas and Sahlin (1989)

Matrix composition HPMC: XG: Filler	Dissolution medium	Release exponent (n)	Correlation coefficient (r)	Diffusional constant (k_1) ($hr^{-1/2}$)	Relaxational constant (k_2) (hr^{-1})
0: 10: Supertab®	DI water	1.3306	0.9993	*	*
	0.1 N HCl	0.6373	0.9995	0.564	0.438
	PBS pH 3	0.7835	0.9995	0.185	0.816
	PBS pH 6.8	0.7867	0.9988	-	1.020
	PBS pH 7.4	0.7739	0.9996	0.267	0.734
	0.01 M NaCl	1.1614	0.9977	*	*
	0.05 M NaCl	0.8428	0.9988	-	1.066
	0.1 M NaCl	0.7432	0.9994	0.163	0.837
	0.2 M NaCl	0.6904	0.9989	0.269	0.731
10: 0: Emcompress®	DI water	0.6765	0.9999	0.663	0.339
	0.1 N HCl	0.6372	0.9999	0.781	0.221
	PBS pH 3	0.5511	0.9996	1.042	-
	PBS pH 6.8	0.5274	0.9997	1.075	-
	PBS pH 7.4	0.5340	0.9988	1.243	-
	0.01 M NaCl	0.6491	0.9999	0.734	0.268
	0.05 M NaCl	0.6398	0.9997	0.863	0.138
	0.1 M NaCl	0.6127	0.9990	1.196	-
	0.2 M NaCl	0.5658	0.9996	1.020	-

* Not applicable due to the mechanism of drug release was not the anomalous transport.

Table 8 (Continued) Values of release exponent (n), correlation coefficient (r) obtained from equation of Ritger and Peppas (1987) and diffusional (k_1) and relaxational (k_2) constants obtained from equation of Peppas and Sahlin (1989)

Matrix composition HPMC: XG: Filler	Dissolution medium	Release exponent (n)	Correlation coefficient (r)	Diffusional constant (k_1) ($hr^{-1/2}$)	Relaxational constant (k_2) (hr^{-1})
7: 3: Emcompress®	DI water	0.7569	0.9996	0.561	0.442
	0.1 N HCl	0.6064	0.9996	0.830	0.171
	PBS pH 3	0.5533	0.9993	0.871	0.130
	PBS pH 6.8	0.5618	0.9995	0.936	0.065
	PBS pH 7.4	0.5388	0.9998	1.000	-
	0.01 M NaCl	0.6843	0.9996	0.810	0.192
	0.05 M NaCl	0.6307	0.9998	0.817	0.185
	0.1 M NaCl	0.5649	0.9997	0.844	0.157
	0.2 M NaCl	0.5412	0.9998	0.933	0.068
5: 5: Emcompress®	DI water	0.8494	0.9996	0.414	0.588
	0.1 N HCl	0.5753	0.9997	0.822	0.179
	PBS pH 3	0.5698	0.9998	0.857	0.145
	PBS pH 6.8	0.5982	0.9998	0.840	0.162
	PBS pH 7.4	0.5761	0.9998	0.933	0.068
	0.01 M NaCl	0.7180	0.9995	0.780	0.222
	0.05 M NaCl	0.6519	0.9999	0.731	0.271
	0.1 M NaCl	0.5799	0.9999	0.817	0.184
	0.2 M NaCl	0.5571	0.9997	0.955	0.046

* Not applicable due to the mechanism of drug release was not the anomalous transport.

Table 8 (Continued) Values of release exponent (n), correlation coefficient (r) obtained from equation of Ritger and Peppas (1987) and diffusional (k_1) and relaxational (k_2) constants obtained from equation of Peppas and Sahlin (1989)

Matrix composition HPMC: XG: Filler	Dissolution medium	Release exponent (n)	Correlation coefficient (r)	Diffusional constant (k_1) ($hr^{-1/2}$)	Relaxational constant (k_2) (hr^{-1})
3: 7: Emcompress®	DI water	1.0447	0.9995	*	*
	0.1 N HCl	0.5918	0.9996	0.605	0.398
	PBS pH3	0.6476	0.9994	0.871	0.130
	PBS pH 6.8	0.6602	0.9998	0.782	0.220
	PBS pH 7.4	0.6309	0.9998	0.815	0.187
	0.01 M NaCl	0.7608	0.9996	0.659	0.343
	0.05 M NaCl	0.6947	0.9998	0.738	0.264
	0.1 M NaCl	0.6301	0.9998	0.835	0.166
	0.2 M NaCl	0.5893	0.9998	0.917	0.084
0: 10: Emcompress®	DI water	1.5166	0.9983	*	*
	0.1 N HCl	0.5539	0.9988	0.544	0.458
	PBS pH 3	0.7334	0.9997	0.436	0.567
	PBS pH 6.8	0.6931	0.9997	0.460	0.543
	PBS pH 7.4	0.7031	0.9997	0.463	0.540
	0.01 M NaCl	0.9395	0.9983	*	*
	0.05 M NaCl	0.7538	0.9998	0.463	0.538
	0.1 M NaCl	0.7092	0.9998	0.573	0.429
	0.2 M NaCl	0.6512	0.9996	0.512	0.490

* Not applicable due to the mechanism of drug release was not the anomalous transport.

In the case of matrix containing HPMC:XG ratio of 10:0 and the Supertab® in various dissolution media, the values of release exponent (n) were in the range of 0.3873-0.4639 that indicated closely Fickian diffusion. The values of diffusional constant (k_1) were paramount. Thus, the release exponent data was corresponding to the diffusional constant data. The eminent mechanism of drug release from matrix was Fickian diffusion.

In the cases of matrices containing the Supertab® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 , the release exponent (n) values in DI water was greater than 0.89, indicating Super case II transport. This indicated that when these matrices exposed to DI water, the polymer in the matrices could swell fully. Consequently, the water-filled pores within the matrices were reduced, resulting in opposed diffusion mechanism. Therefore, the chief mechanism of drug release from these matrices in DI water could be explained on the polymer relaxation, erosion and drug dissolution. The release mechanisms of these matrices with increased ionic strength of dissolution medium were shifted from anomalous transport to Fickian diffusion, Super case II transport to anomalous transport or no deviation from anomalous transport, depending on the ratio of HPMC:XG in the matrix. This indicated that the ionic strength of dissolution medium and the ratio of HPMC:XG affected the release mechanism. In consideration with the values of diffusional (k_1) and relaxational (k_2) constants, the $k_1$values increased with the increased ionic strength of dissolution medium (μ=0.01, 0.05, 0.1 and 0.2) which in turn the k_2 values decreased. This implied that at the higher ionic strength of dissolution medium, the mechanism of drug release might involve in the diffusion partially through swollen matrix and partially through solvent-filled pores rather than the polymer relaxation and erosion. In addition, the mechanism of drug release from matrices containing the Supertab® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in different pH dissolution media were also investigated. According to the n, k_1 and k_2 data, the release mechanism of matrices containing HPMC:XG ratios of 7:3 and 5:5 in 0.1 N HCl solution and phosphate buffer solutions pH 3, pH 6.8 and pH 7.4 were anomalous transport that may be controlled by the diffusional transport rather than the polymer erosion.

Moreover, in the case of matrix containing the Supertab® and HPMC:XG ratio 3:7, the mechanism of drug release in 0.1 N HCl solution and phosphate buffer solutions pH 3, pH 6.8 and pH 7.4 was also anomalous transport because the n values were in the range of 0.45-0.89. When considered the values of k_1 and k_2 , the k_1 values were much greater than the k_2 values. Therefore, the drug release from this matrix may be predominantly controlled by diffusional mechanism. Additionally, the k_1 and k_2 values in phosphate buffer solution pH 3, pH 6.8 and pH 7.4 were comparable. Thus, this pointed out that the mechanism of drug release in phosphate buffer solutions may be equally regulated by diffusion and polymer erosion.

For matrix containing the Supertab® and HPMC:XG ratio of 0:10, the obtained n values in 0.1 N HCl solution and phosphate buffer solutions pH 3, pH 6.8 and pH 7.4 expressed the anomalous transport. The k_1 and k_2 values in 0.1 N HCl solution were not much different. Thus, the couple of diffusion and polymer relaxation was equally important to the drug release in 0.1 N HCl solution. Nevertheless, the drug releases in phosphate buffer solutions were dominated by polymer relaxation/ erosion.

In consideration with different filler in the matrix, the release mechanisms of matrices containing the Emcompress® and HPMC:XG ratios of 10:0, 7:3, 5:5, 3:7 and 0:10 were studied. For matrix containing the Emcompress® and HPMC:XG ratio of 10:0, as expected, the release mechanisms in all dissolution media were anomalous transport ($0.45<n<0.89$). The contribution of Fickian diffusion was preponderant release mechanism due to the eminent k_1 values. Besides, it is important to note that the release mechanism of this matrix was changed from Fickion diffusion to anomalous transport when replaced the Supertab® with the Emcompress®. This finding is possibly attributed to the different tortuosity with the matrix. Due to matrix containing the soluble diluent (Supertab®), the higher porosity and then the more rapid drug diffusion may occur. On the other hand, the insoluble diluent (Emcompress®) did not diffuse outward but became entrapped in the matrix. Consequently, the matrix containing the Emcompress® had the more tortuosity that impeded drug diffusion.

Furthermore, according to n, k_1 and k_2 values, the mechanism of drug release from matrices containing the Emcompress® and HPMC:XG ratios of 7:3 and 5:5 in DI water were anomalous transport that was equally controlled by diffusion and polymer relaxation. However, the release mechanism of matrices containing the Emcompress® and HPMC:XG ratios of 3:7 and 0:10 were Super case II transport, having the polymer relaxation as an important process. These results indicated that the different ratio of HPMC:XG affected the mechanism of drug release. Moreover, in the cases of matrices containing the Emcompress® and HPMC:XG ratios of 7:3, 5:5 and 3:7 in different ionic strength of dissolution media (μ=0.01, 0.05, 0.1 and 0.2), with increased ionic strength of dissolution medium, the release mechanism was anomalous transport ($0.45<n<0.89$). When k_1 and k_2 values of these matrices in different ionic strength of dissolution media were compared, the k_1 values were greater than the k_2 values, indicating the prominent diffusion-controlled release. Additionally, with increasing ionic strength of dissolution medium, the predominant diffusion releases of these matrices were slightly increased.

Nevertheless, for matrix containing the Emcompress® and HPMC:XG ratio of 0:10, the release exponent (n) value in 0.01 M NaCl solution (μ=0.01) was 0.9395, expressing release mechanism of Super case II transport. When the ionic strengths of dissolution medium were to 0.05, 0.1 and 0.2, the n values of matrix in these dissolution media were in the range of 0.7538-0.6512, indicating to the release mechanism of anomalous transport. The values of k_1 and k_2 of matrix in ionic strength dissolution media of 0.05, 0.1 and 0.2 were comparable. This result pointed out that the drug releases in these dissolution media were equally governed by diffusion and polymer relaxation. According to the obtained result, the release mechanism of matrix containing xanthan gum alone depended on the ionic strength level of dissolution medium.

According to n, k_1 and k_2 data in different pH of dissolution media, the release mechanisms of matrices containing the Emcompress® and HPMC:XG ratios of 7:3, 5:5 and 3:7 were anomalous transport that were prominently controlled by diffusion transport. In contrast, the release mechanism of matrix containing the Emcompress® and

HPMC:XG ratio of 0:10 was anomalous transport that was equally dominated by diffusion and polymer relaxation.

Moreover, in comparison with the Supertab® as a filler, the k_1 values of matrices containing the Emcompress® and HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10 in all dissolution media except 0.1 N HCl solution were increased. This finding was observed considerably in the cases of increased proportional xanthan gum in the matrix. Thus, it could be noted that the type of diluent involved in the dominant release mechanism. The Emcompress® in the matrix did not dissolve in all dissolution media except 0.1 N HCl solution but it was embeded within the matrices. Consequently, the porosity within the matrices may be inadequate for the polymer relaxation to be taken place. Therefore, the decreasing relaxational constant (k_2) which in turn the increasing diffusional constant (k_1) were observed in the matrices containing the Emcompress® , when compared with the matrices containing the Supertab®.

CHAPTER IV

CONCLUSIONS

In the present study, the hydrophilic matrix composed of drug, hydrophilic polymers and filler. Theophylline was used as a model drug. The mixtures of hydrophilic polymers (xanthan gum and hydroxypropyl methylcellulose) were employed in various proportions. The drug release was controlled by diffusion and polymer relaxation/ erosion. The important factors such as polymer loading, proportional polymers of xanthan gum and hydroxypropyl methylcellulose, type of filler, compression forces and conditions of dissolution media were investigated. An increase in polymer loading (10%, 15% and 20%) allowed a decrease in drug release. Additionally, at the same polymer loading of matrix in DI water, the increased amount of xanthan gum in the matrix could reduce the initial burst drug release due to the more rapid polymer swelling and then the greater swollen gel layer around the matrix, leading to reduction of drug diffusion. However,during the late dissolution period, the increased portion of xanthan gum in the matrix caused the greater erosion of swollen gel layer at the matrix surface, resulting in the more rapid drug release.

Furthermore, the type of filler in the matrix affected the release characteristics. The soluble filler (spray dried lactose) was essential to augment porosity of the matrix, causing the increased drug release. On the contrary, the insoluble filler (dibasic calcium phosphate) led to the increased tortuosity of the matrix, resulting in the decreased drug release. In addition, the different compression forces (1000, 2000 and 4000 lbs) slightly effected the drug release. An increase in compression forces to make the matrix allowed a decrease in drug release. This result is possibly due to the reduced porosity of the matrix.

Moreover, the various dissolution media as follows: DI water, 0.01, 0.05, 0.1 and 0.2 M NaCl solutions, 0.1 N HCl solution and phosphate buffer solution pH 3, pH 6.8 and pH 7.4 were used to investigate the effect of dissolution media on release

characteristics. The dissolution media affected the properties of hydrophilic polymers and diluents in the matrices, leading to alteration of release properties and their mechanisms. The dissolution media having different pHs or ionic strengths affected the drug release behaviors that could be explained in terms of matrix swelling and matrix erosion. For matrix containing HPMC alone, the drug releases in these dissolution media were comparable. In the cases of matrices containing HPMC:XG ratios of 7:3, 5:5, 3:7 and 0:10, the drug releases were increased with the increased ionic strength of dissolution medium, owing to the reduced matrix swelling which in turn the increased matrix erosion. Additionally, when compared among DI water, 0.1 N HCl solution and phosphate buffer solutions, the drug releases were found to be the greatest in 0.1 N HCl solution, intermediate in phosphate buffer solutions and the least in DI water. The difference in drug release of these matrices was attributed to the different matrix swelling. Indeed, the pH and ionic strength of dissolution media mostly affected the swelling of xanthan gum in the matrices.

In the case of matrix containing dibasic calcium phosphate, the greatest drug release was observed in 0.1N HCl solution, when compared with the other dissolution media. This evidence indicated that the type of dissolution medium affected the property of filler in the matrix. The obtained result may be caused by the increased porosity within the matrix due to the dissolution of dibasic calcium phosphate in 0.1N HCl solution.

Moreover, as the result of photomicrographs of hydrophilic matrices, the porosity at the outer region of hydrated matrix was less than that at the inner region of the same matrix. Therefore, it indicated that the swelling process of hydrated matrices in these dissolution media could sustain drug releases.

Eventually, the mechanisms of drug release from the matrices depended on the type of fillers, the amount and kind of hydrophilic polymers and the condition of dissolution media.

REFERENCES

Alderman, D.A., 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Tech. Prod. Mfr. 5:1-9.

Baveja, S.K., Ranga Rao, K.V., and Padmalatha, D. 1987. Zero-order release hydrophilic matrix tablets of β-adrenergic blockers. Int. J. Pharm. 39: 39-45.

Bonferoni, M.C., Rossi, S., Tamayo, M., Pedraz, J.L., Dominguez-Gil, A., and Caramella, C. 1993. On the employment of λ-carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with Na carboxymethylcellulose and xanthan gum. J. Control. Release 26: 119-127.

Callet, F., Milas, M., and Rinaudo, M. 1987. Influence of acetyl and pyruvate contents on rheological properties of xanthan gum in dilute solution. Int. J. Biol. Macromol. 9: 291-293.

Colombo, P., et al. 1997. The important of drug diffusion front in drug delivery kinetics from swellable matrices. Pharm. Res. 14: p. S532 cited in Colombo, P., Bettini, R., Santi, P., and Peppas, N.A. 2000. Swellable matrices for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance. PSTT 3(6): p. 201.

Colombo, P., Bettini, R., Massimo, G., Catellani, P.L., Santi, P., and Peppas, N.A. 1995. Drug diffusion front movement is important in drug release control from swellable matrix tablets. J. Pharm. Sci. 84(8): 991-997.

Colombo, P., Bettini, R., Santi, P., De Ascentiis, A., and Peppas, N.A. 1996. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. J. Control. Release. 39: 231-237.

Colombo, P., Bettini, R., Santi, P., and Peppas, N.A. 2000. Swellable matrices for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance. PSTT 3(6): 198-204.

Colombo, P., Gazzaniga, A., Caramelle, C., Conte, U., and La Manna, A. 1987. In vitro programmable zero-order release drug delivery system. Acta Pharm. Technol. 33: 15-20.

Cottrell, I.W., Kang, K.S., and Kovacs, P. Xanthan gum. 1980. In R.L. Davidson (ed.), Handbook of water-soluble gums and resins, pp.24-1−24-31. New York: McGraw-Hill.

Dortung, B., and Gunal, N. 1997. Release of acetazolamide from swellable hydroxypropylmethylcellulose matrix tablets. Drug Dev. Ind. Pharm. 23(12): 1245-1249.

Dhopeshwarkar, V., and Zatz, J.L. 1993. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Dev. Ind. Pharm. 19(9): 999-1017.

Efentakis, M., Vlachou, M., and Choulis, N.H. 1997. Effect of excipients on swelling and drug release from compressed matrices. Drug Dev. Ind. Pharm. 23(1):107-112.

Feely, L.C., and Davis, S.S. 1988a. Influence of surfactant on drug release from hydroxypropylmethylcellulose matrices. Int. J. Pharm. 41: 83-90.

Feely, L.C., and Davis, S.S. 1988b. The influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices. Int. J. Pharm. 44: 131-139.

Ford, J.L., Rubinstein, M.H., and Hogan, J.E. 1985. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. Int. J. Pharm. 24: 339-350.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E., and Edgar, P.J. 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Int. J. Pharm. 40: 223-234.

Fu Lu, M., Woodward, L., and Borodkin, S. 1991. Xanthan gum and alginate based controlled release theophylline formulations. Drug Dev. Ind. Pharm. 17(14): 1987-2004.

Greminger, G.K., Jr., Krumel, K.L. 1980. Alkyl and hydroxyalkylalkylcelulose. In R.L. Davidson (ed.), Handbook of water-soluble gums and resins, pp.3-1−3-25. New York: McGraw-Hill.

Heller, J. 1987. Use of polymers in controlled release of active agents. In J.R. Robinson and Vincent H.L. Lee (eds.),Control drug delivery 29 vols.2nd ed, pp. 190-191. New York: Marcel Dekker.

Higuchi, T. 1963. Mechanism of sustained-action medication. Theorectical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52:1145-1149.

Hodsdon, A.C., Mitchell, J.R., Davies, M., and Melia, C.D. 1995. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 3. The influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. . J. Control. Release. 33: 143-152.

Jalil, R., and Ferdous, A.J. 1993. Effect of viscosity increasing agent and electrolyte concentration on the release of theophylline from a HPMC cased sustained release capsules. Drug Dev. Ind. Pharm. 19(19): 2637-2643.

Khan, G.M., and Zhu, J.B. 1998. Formulation and in vitro evaluation of ibuprofen-carbopol® 974P-NF controlled release matrix tablets III: influence of co-excipients on release rate of the drug. J. Control. Release. 54:185-190.

Khan, G.M., and Zhu, J.B. 1999. Studies on drug release kinetics from ibuprofen-carbomer hydrophilic matrix tablets: influence of co-excipients on release rate of the drug. J. Control. Release. 57:197-203.

Kim, H., and Fassihi, R. 1997a. Application of binary polymer system in drug release rate modulation. 1. Characterization of release mechanism. J. Pharm. Sci. 86(3): 316-322.

Kim, H., and Fassihi, R. 1997b. Application of binary polymer system in drug release rate modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. J. Pharm. Sci. 86(3): 323-328.

Kurahashi, H., Kami, H., and Sunada, H. 1996. Influence of physicochemical properties on drug release rate from hydroxypropylmethylcellulose matrix tablets. Chem. Pharm. Bull. 44(4): 829-832.

Mitchell, K., Ford, D.J., Armstrong, D.J., Elliott, P.N.C., Rostron, C., and Hogan, J.E. 1993. The influence of concentration on the release of drugs from gels and matrices containing Methocel®. Int. J. Pharm. 100: 155-163.

Mocker, J.E. ,and Lippold, B.C. 1993. Zero-order drug release from hydrocollid matrices. Pharm. Res. 10(7): 1066-1070.

Nakano, M., and Ogata, A. 1984. Examination of natural gums as matrices for sustained release of theophylline. Chem. Pharm.Bull. 32(2): 782-785.

Nakano, M., Ohmori, N., Ogata, A., Sugimoto, K., Tobino, Y., Iwaoku, R., and Juni, K. 1983. Sustained release of theophylline from hydroxypropylmethylcellulose tablets. J. Pharm. Sci. 72(4): 378-380.

Nokhodchi, A., Farid, D., Nafafi, M., and Adrangui, M. 1997. Studies on controlled-release formulations of diclofenac sodium. Drug Dev. Ind. Pharm. 23(11): 1019-1023.

Peppas, N.A. 1985. Analysis of Fickian and non- Fickian drug release from polymers. Pharm. Acta. Helv. 60(4): 110-111.

Peppas, N.A., and Peppas, L.B. 1994. Water diffusion and sorption in amorphous macromolecular system and food. J. Food. Eng. 22:189-210.

Peppas, N.A., and Sahlin, J. J. 1989. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int. J. Pharm. 57: 169-172.

Perez-Marcos, B., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C., and Hogan, J.E. 1996. Influence of pH on the release of propranolol hydrochloride from matrices containing hydroxypropylmethylcellulose K4M and carbopol 974. J. Pharm. Sci. 85(3): 330-334.

Pillay, V., and Fassihi, R. 1998. Evaluation and comparison of dissolution data derived from different modified release dosage formed: an alternative method. J. Control. Release. 55: 45-55.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P. 1988. Cellulose matrices for zero-order release of soluble drugs. Drug Dev. Ind. Pharm. 14(15-17): 2299-2320.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P. 1990. Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J. Control. Release. 12: 133-141.

Ritger, P.L., and Peppas, N.A. 1987. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J. Control. Release. 5: 37-42.

Salsa, T., Veiga, F., and Pina, M.E. 1997. Oral controlled-release dosage forms. I. cellulose ether polymers in hydrophilic matrices. Drug Dev. Ind. Pharm. 23(9): 929-938.

Sarisuta, N., and Mahahpunt, P. 1994. Effects of compression force and type of fillers on release of diclofenac sodium from matrix tablets. Drug Dev. Ind. Pharm. 20 (6): 1049-1061.

Sheu, M.T., Chou, H.L., Kao, C.C., Liu, C.H., and Sokoloski, T.D. 1992. Dissolution of diclofenac sofium from matrix tablets. Int. J. Pharm. 85: 57-63.

Sujja-areevath, J., Munday, D.L., Cox, P.J., and Khan, K.A. 1996. Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations. Int. J. Pharm. 139: 53-62.

Sung, K.C., Nixon, P.R., Skoug, J.W., Ju, T.R., Gao, P., Topp, E.M., and Patel, M.V. 1996. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. Int. J. Pharm. 142: 53-60.

Talukdar, M.M., Kinget, R. 1995. Swelling and drug release behaviour of xanthan gum matrix tablets. Int. J. Pharm. 120: 63-72.

Talukdar, M.M., Kinget, R. 1997. Comparative study on xanthan gum and hydroxypropylmethylcellulose as matrices for controlled-release drug delivery II. Drug diffusion in hydrated matrices. Int. J. Pharm. 151: 99-107.

Talukdar, M.M., Michoel, A., Rombaut, P., and Kinget, R. 1996. Comparative study on xanthan gum and hydroxypropylmethylcellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour. Int. J. Pharm. 129: 233-241.

Talukdar, M.M., and Plaizier-Vercammen, J. 1993. Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparation. Drug Dev. Ind. Pharm. 19(9): 1037-1046.

Talukdar, M.M., Vinckier, I., Moldenaers, P., and Kinget, R. 1996. Rheological characterization of xanthan gum and hydroxypropylmethylcellulose with respect to controlled-release drug delivery. J. Pharm Sci. 85(5): 537-540.

Tros de IIarduya, M.C., Martin, C., Goni, M.M. and Martinez-Oharriz, M.C. 1997. Oxazepam dissolution rate from hydroxypropylmethylcellulose matrices. Drug Dev. Ind. Pharm. 23(4): 393-396.

Uko-Nne, S.D., Mendes, R.W., and Jamhekar, S.S. 1989. Dried molasses as a direct compression matrix for oral controlled release drug delivery II: Release mechanism and characteristics of theophylline from a molasses-HPMC matrix. Drug Dev. Ind. Pharm. 15(5): 719-741.

Vargas, C.I., and Ghaly, E.S. 1999. Kinetic release of theophylline from hydrophilic swellable matrices. Drug Dev. Ind. Pharm. 25(9): 1045-1050.

Vazquez, M.J., Casalderrey, M., Duro, R., Gomez-Amoza, J.L., Matinez-Pacheco, R., Souto, C., and Concheiro, A. 1996. Atenolol release from hydrophilic matrix tablets with hydroxypropylmethylcellulose (HPMC) mixtures as gelling agent: effects of viscosity of the HPMC mixture. Eur. J. Pharm. Sci. 4: 39-48.

Vazquez, M.J., Gomez-Amoza, J.L., Matinez-Pacheco, R., Souto, C., and Concheiro, A. 1995. Relationships between drug dissolution profile and gelling agent viscosity in tablets prepared with hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) mixtures. Drug Dev. Ind. Pharm. 21(16): 1859-1874.

Vazquez, M.J., Perez-Marcos, B., Gomez-Amoza, J.L., Matinez-Pacheco, R., Souto, C., and Concheiro, A. 1992. Influence of technological variables on release of drugs from hydrophilic matrices. Drug Dev. Ind. Pharm. 18(11-12): 1355-1375.

Velasco, M.V., Ford, J.L., Rowe, P., and Rajabi-Siahboomi, A.R. 1999. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J. Control. Release. 57: 75-85.

Waaler, P.J., Andersen, M., Graffner, C., and Muller, B.W. 1992. Influence of compaction pressure on the properties of xanthan/guar gum matrix tablets. Acta Pharm. Nord. 4(3): 167-170.

Wade, A., and Weller, P.J. 1994. Hanbook of pharmaceutical excipients 2nd ed. pp. 229-231, 562-563. Washington,DC: American Parmaceutical Association: The Pharmaceutical Press.

Xu, G., and Sunada, H. 1995. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Chem. Pharm. Bull. 43(3): 483-487.

Zatz,J.L., and Knapp, S. 1984. Viscosity of xanthan gum solutions at low shear rates. J. Pharm. Sci. 73(4): 468-471.

Zhang, Y.E., and Schwartz, J.B. 2000. Effect of diluents on tablet integrity and controlled drug release. Drug Dev. Ind. Pharm. 26(7): 761-765.

APPENDICES

Appendix A

The UV/visible spectrophotometer was used to determine the amount of theophylline. The λ_{max} of drug absorbances in DI water, phosphate buffer solutions (pH 3, pH 6.8 and pH 7.4) and NaCl solutions (0.01, 0.05, 0.1 and 0.2 M) was identical (272 nm). The λ_{max} of drug absorbance in 0.1 N HCl solution was 270 nm. The absorbance spectra in these media were illustrated in Figures 76-84. In addition, the absorbance spectra of polymers (HPMC and xanthan gum) and fillers (spray dried lactose and dibasic calcium phosphate) without drug were shown in Figures 85-88 that verified no interferences in the drug absorbances.

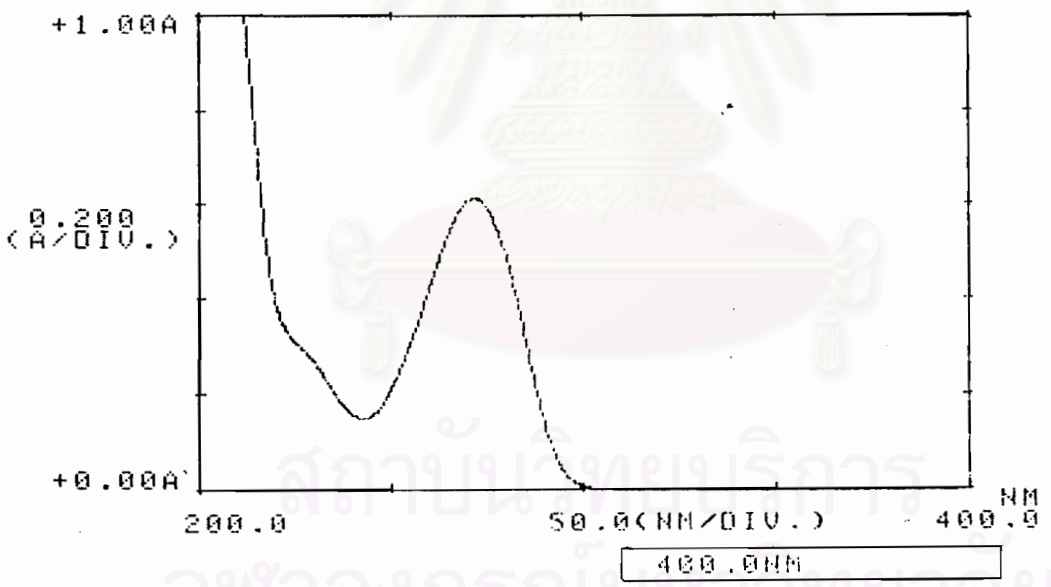


Figure 76 The UV spectrum of theophylline in DI water

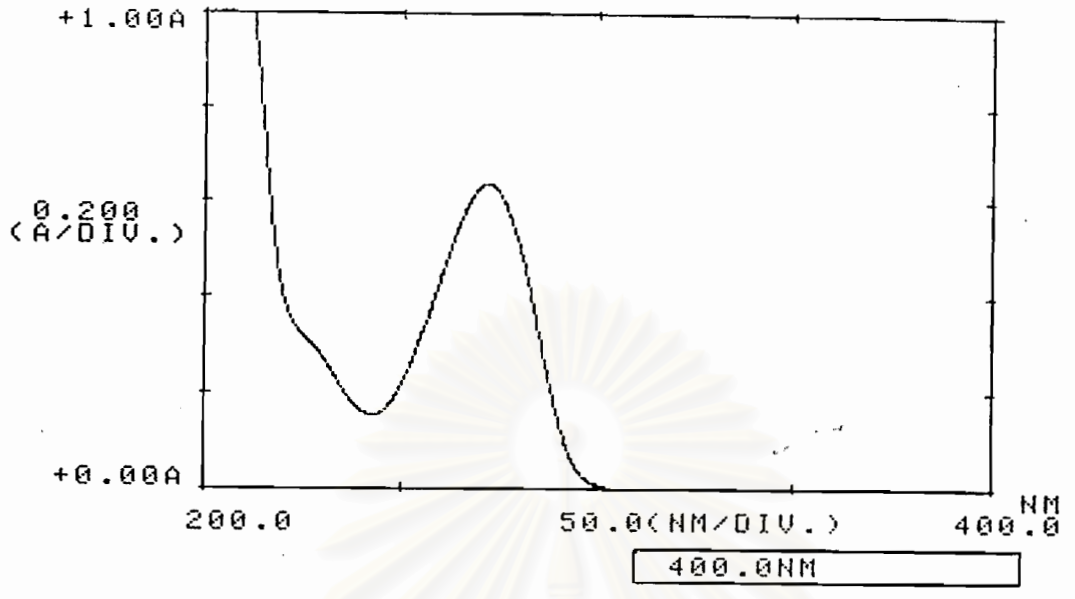


Figure 77 The UV spectrum of theophylline in 0.1 N HCl

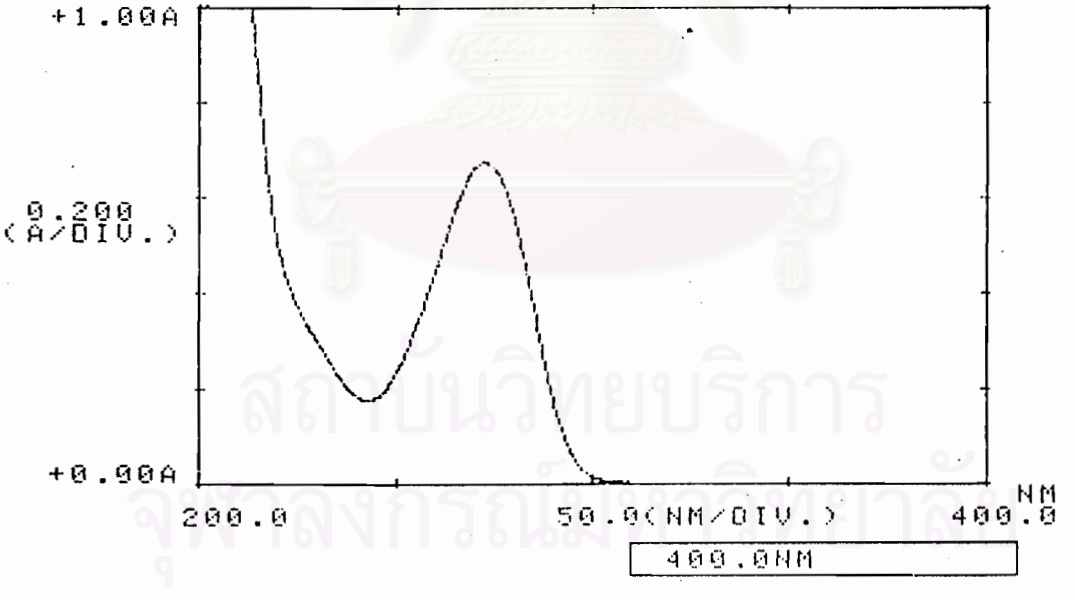


Figure 78 The UV spectrum of theophylline in phosphate buffer pH 3

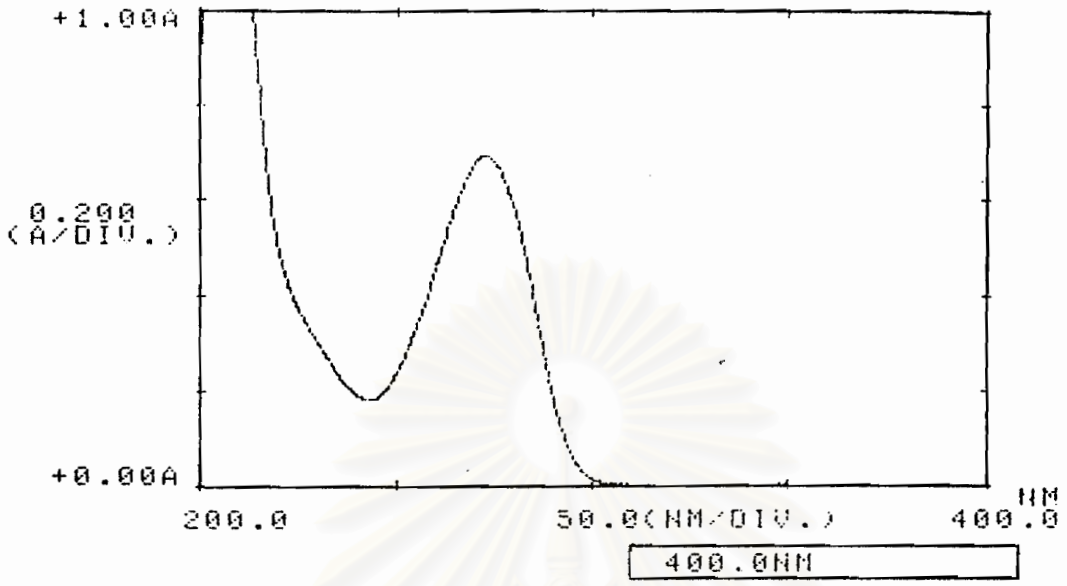


Figure 79 The UV spectrum of theophylline in phosphate buffer pH 6.8

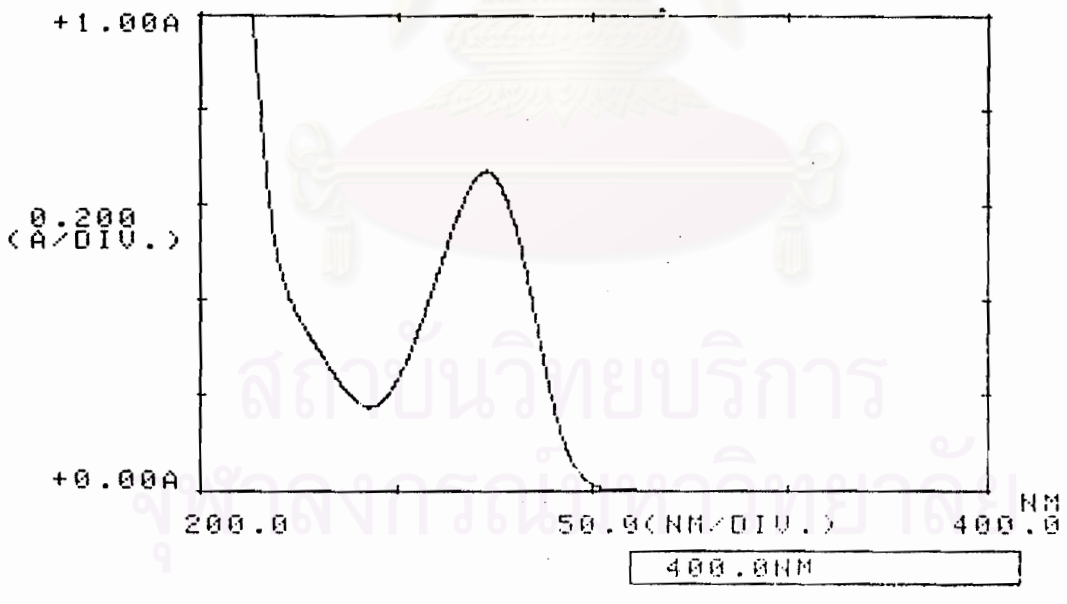


Figure 80 The UV spectrum of theophylline in phosphate buffer pH 7.4

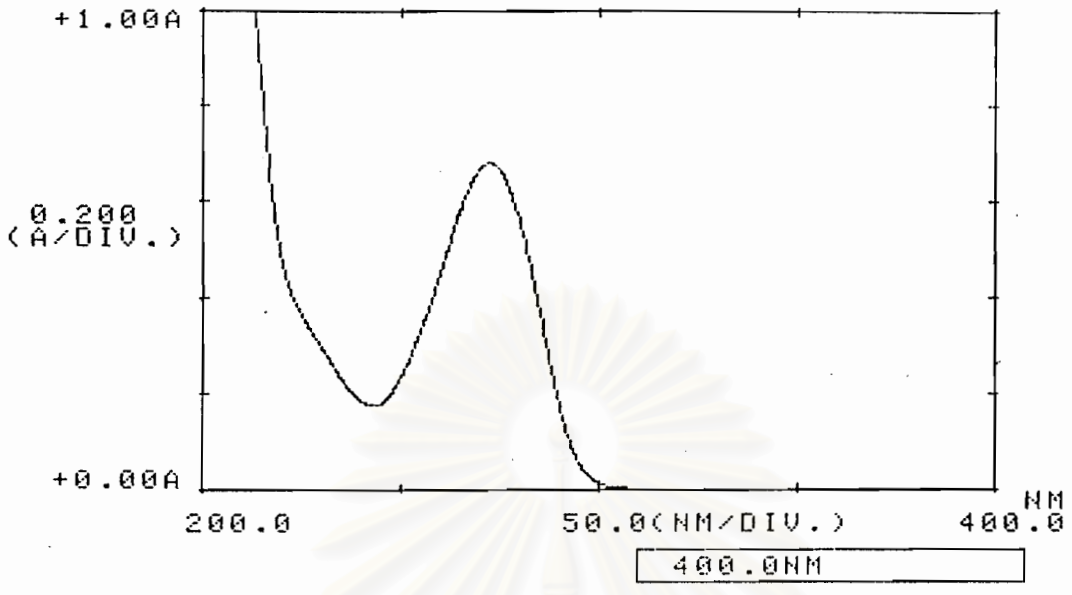


Figure 81 The UV spectrum of theophylline in 0.01 M NaCl

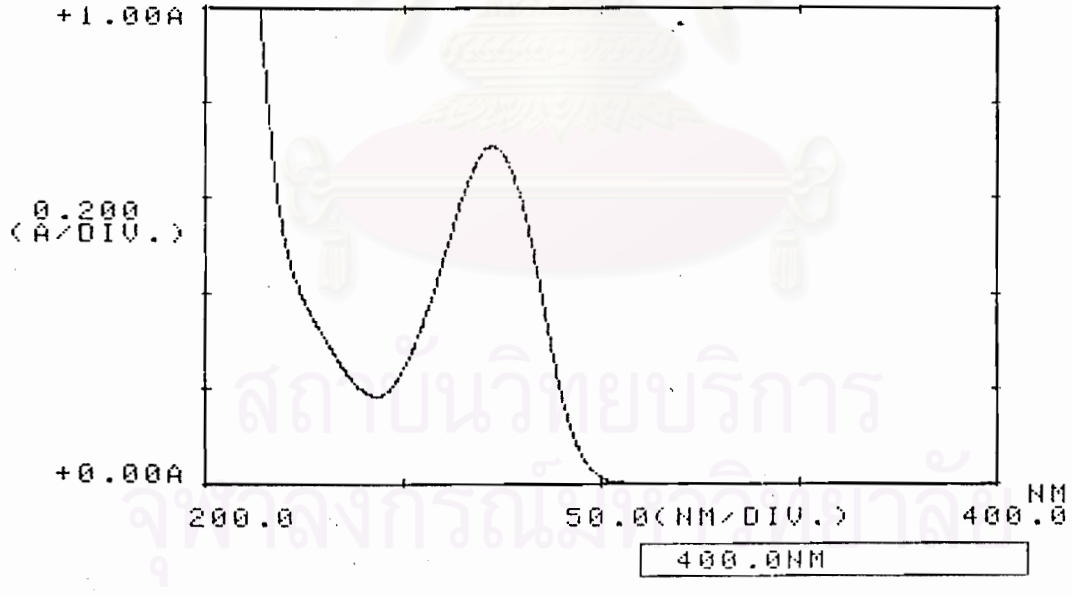


Figure 82 The UV spectrum of theophylline in 0.05 M NaCl

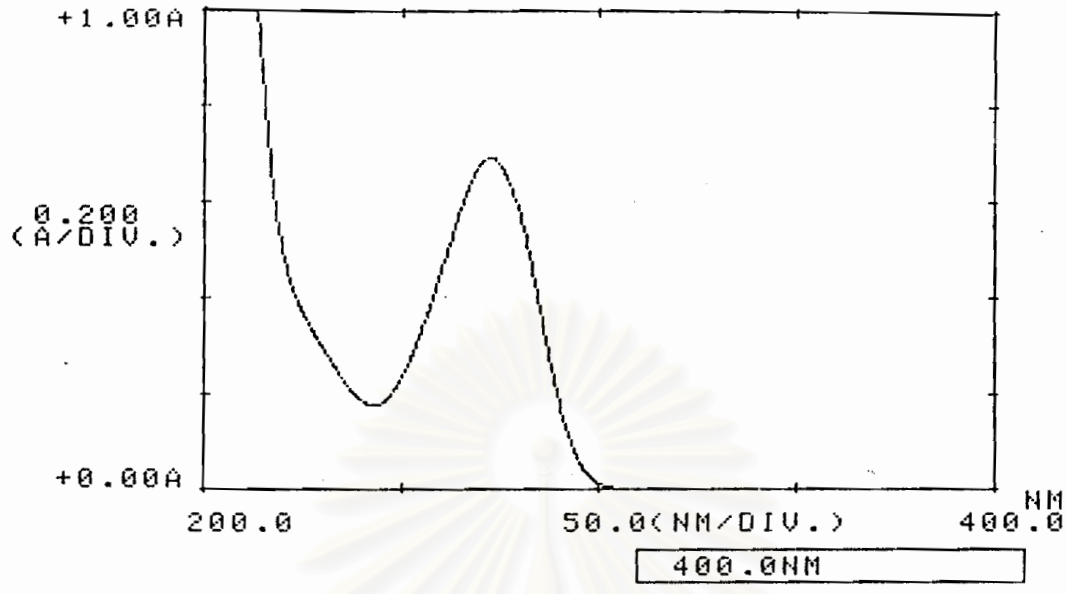


Figure 83 The UV spectrum of theophylline in 0.1 M NaCl

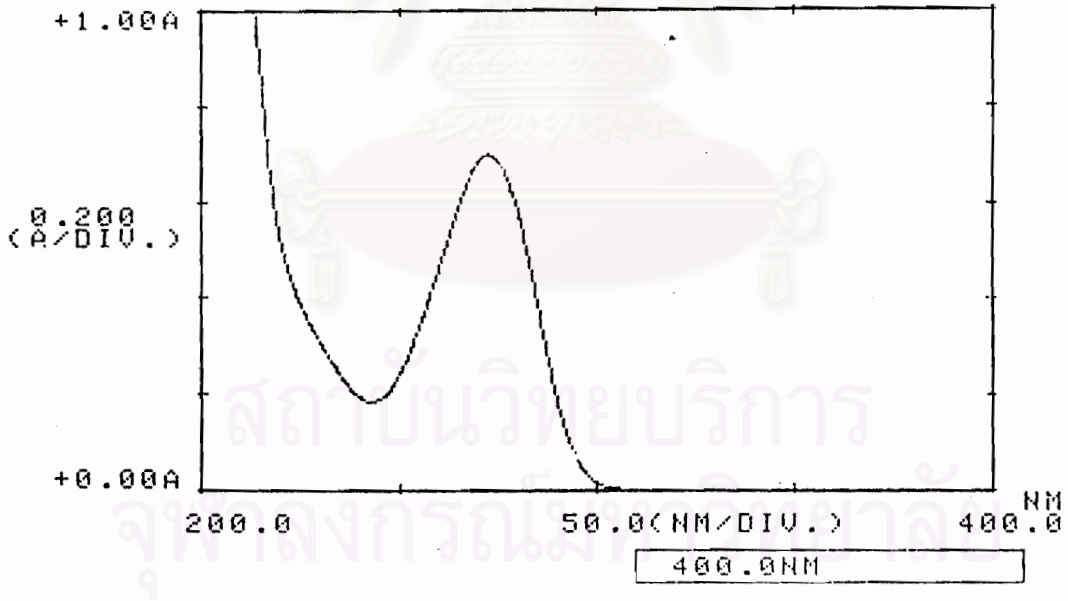


Figure 84 The UV spectrum of theophylline in 0.2 M NaCl

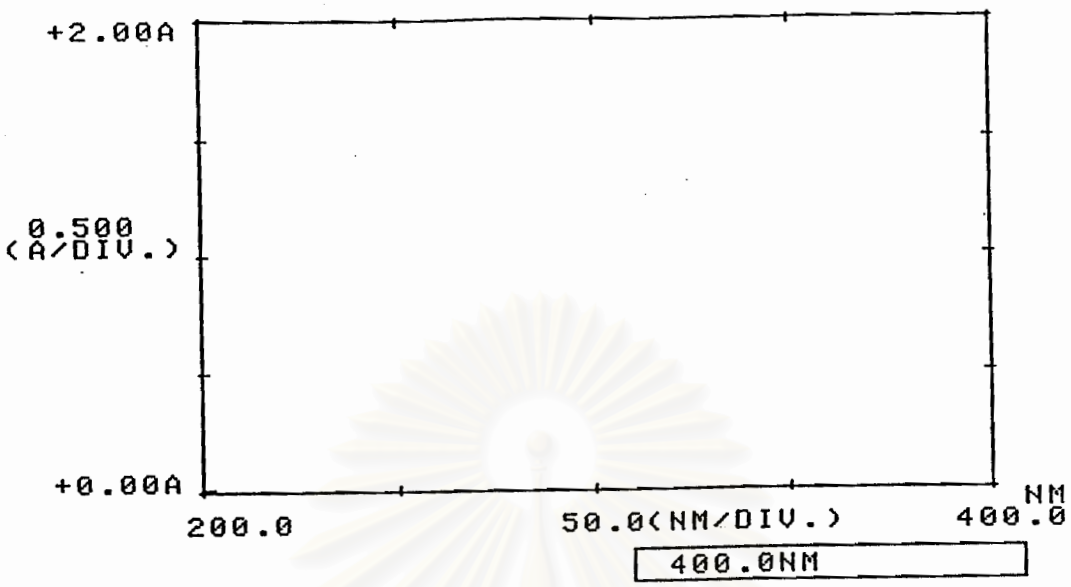


Figure 85 The UV spectrum of HPMC and spray dried lactose mixture in DI water

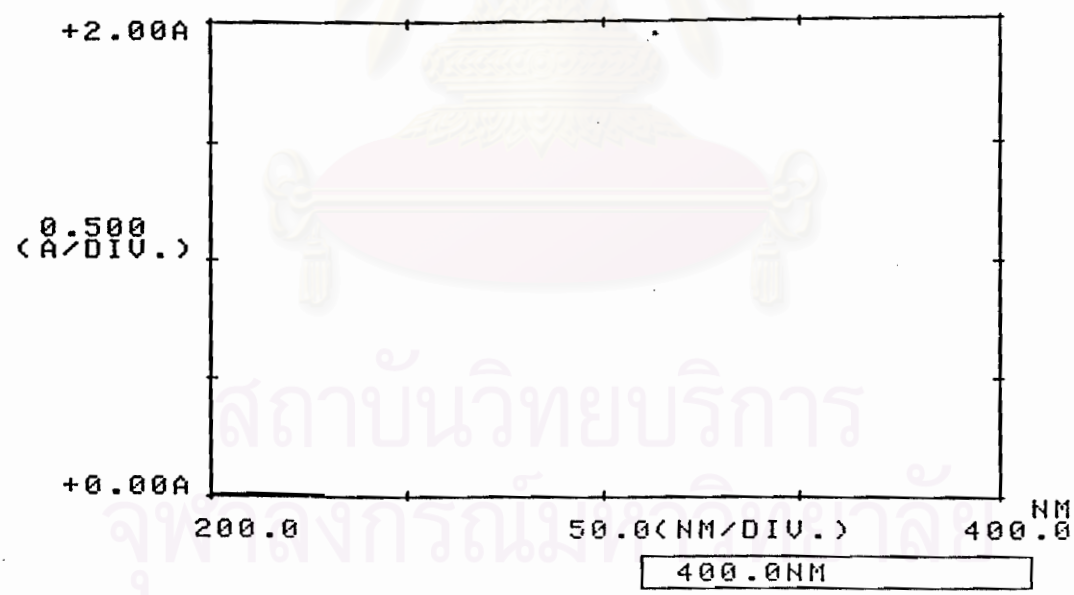


Figure 86 The UV spectrum of HPMC and dibasic calcium phosphate mixture in DI water

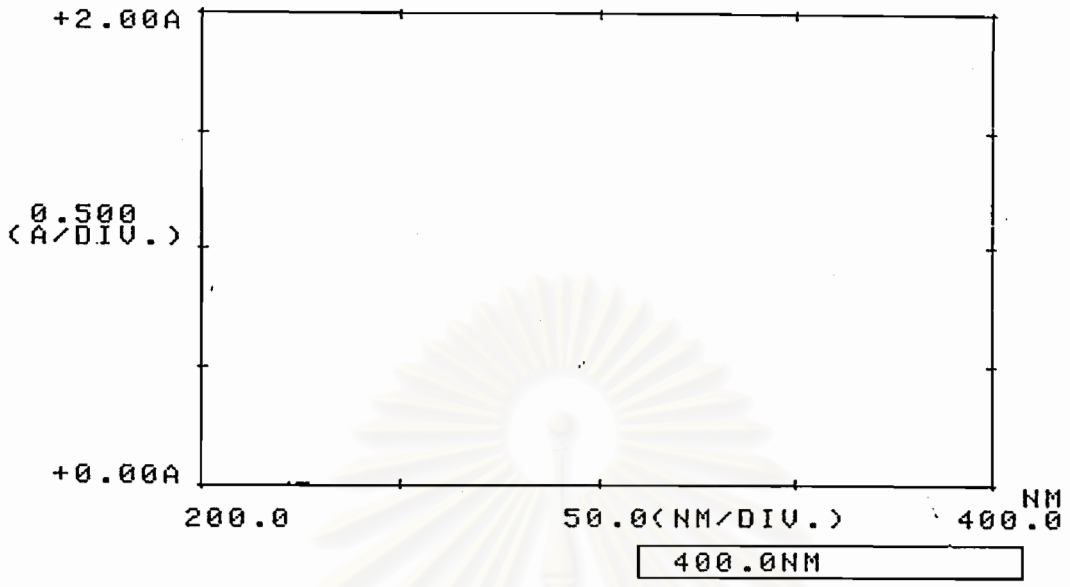


Figure 87 The UV spectrum of xanthan gum and spray dried lactose mixture in DI water

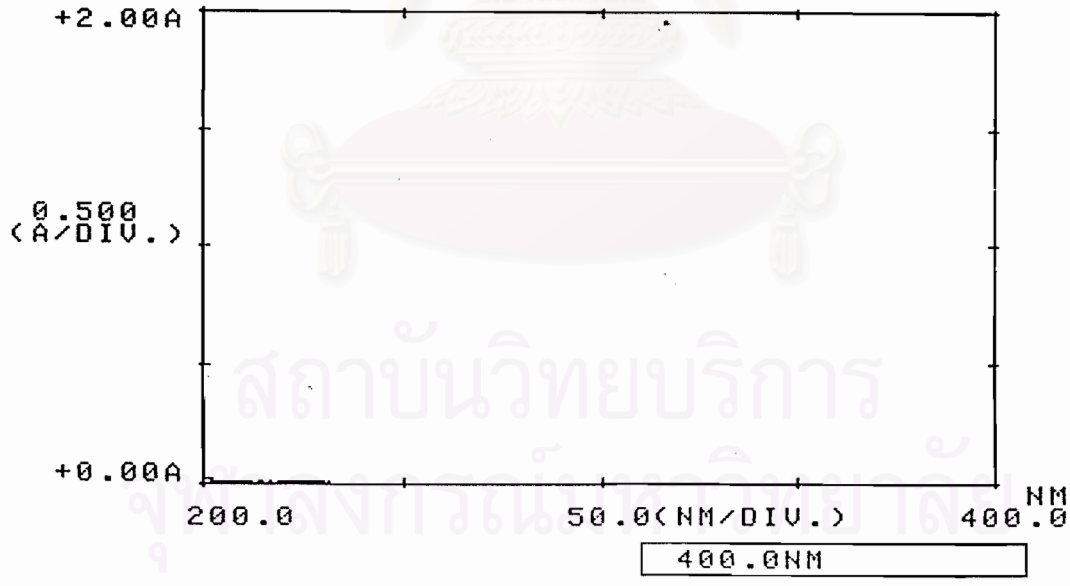


Figure 88 The UV spectrum of xanthan gum and dibasic calcium phosphate mixture in DI water

Appendix B

The concentrations versus absorbances of theophylline in various media were presented in Tables 9-17. The calibration curves of theophylline and a linear relationship with the correlation of determination were also in Figures 89-97.

Table 9 Absorbances of theophylline in DI water at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.618	0.093
3.236	0.187
6.471	0.371
9.707	0.556
12.943	0.740
16.179	0.925
19.414	1.111

Table 10 Absorbances of theophylline in 0.1 N HCl at 270 nm

Concentration (mcg/ml)	Absorbance
0	0
1.623	0.089
3.246	0.179
6.491	0.356
9.737	0.530
12.983	0.705
16.228	0.884
19.474	1.060

Table 11 Absorbances of theophylline in phosphate buffer pH 3 at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.668	0.096
3.335	0.193
6.671	0.385
10.006	0.575
13.341	0.765
16.676	0.957
20.012	1.148

Table 12 Absorbances of theophylline in phosphate buffer pH 6.8 at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.633	0.093
3.266	0.185
6.531	0.363
9.797	0.540
13.062	0.732
16.328	0.903
19.593	1.086

Table 13 Absorbances of theophylline in phosphate buffer pH 7.4 at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.633	0.092
3.266	0.185
6.531	0.368
9.797	0.550
13.062	0.734
16.328	0.913
19.593	1.099

Table 14 Absorbances of theophylline in 0.01 M NaCl at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.608	0.093
3.216	0.187
6.432	0.371
9.647	0.556
12.863	0.737
16.079	0.922
19.295	1.108

Table 15 Absorbances of theophylline in 0.05 M NaCl at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.618	0.094
3.236	0.189
6.471	0.375
9.707	0.561
12.943	0.747
16.179	0.932
19.414	1.121

Table 16 Absorbances of theophylline in 0.1 M NaCl at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.628	0.095
3.256	0.190
6.511	0.374
9.767	0.559
13.022	0.745
16.278	0.929
19.534	1.113

Table 17 Absorbances of theophylline in 0.2 M NaCl at 272 nm

Concentration (mcg/ml)	Absorbance
0	0
1.623	0.093
3.246	0.185
6.491	0.364
9.737	0.542
12.983	0.720
16.228	0.900
19.474	1.078

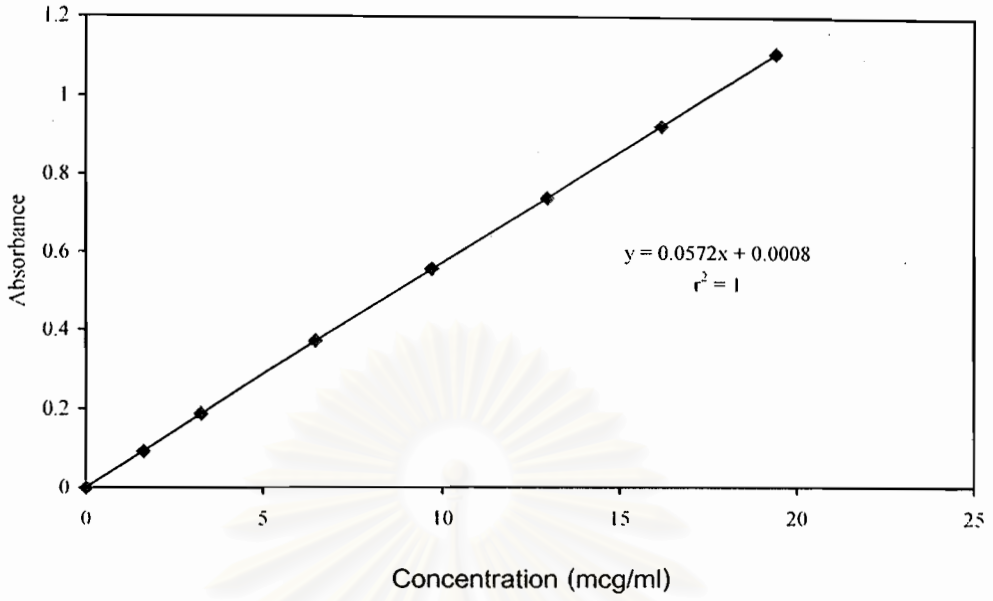


Figure 89 Calibration curve of theophylline in DI water at 272 nm

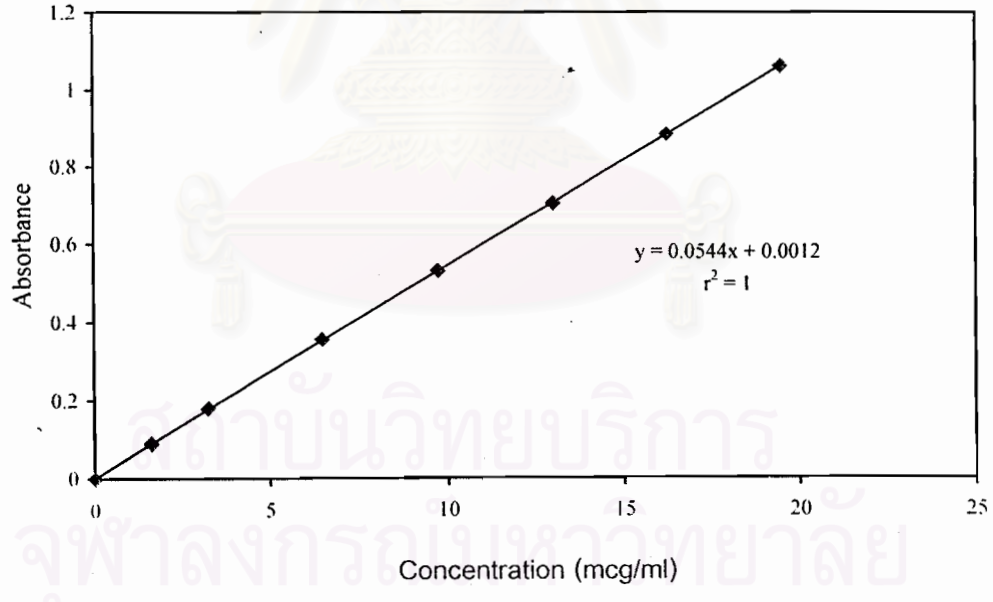


Figure 90 Calibration curve of theophylline in 0.1 N HCl at 270 nm

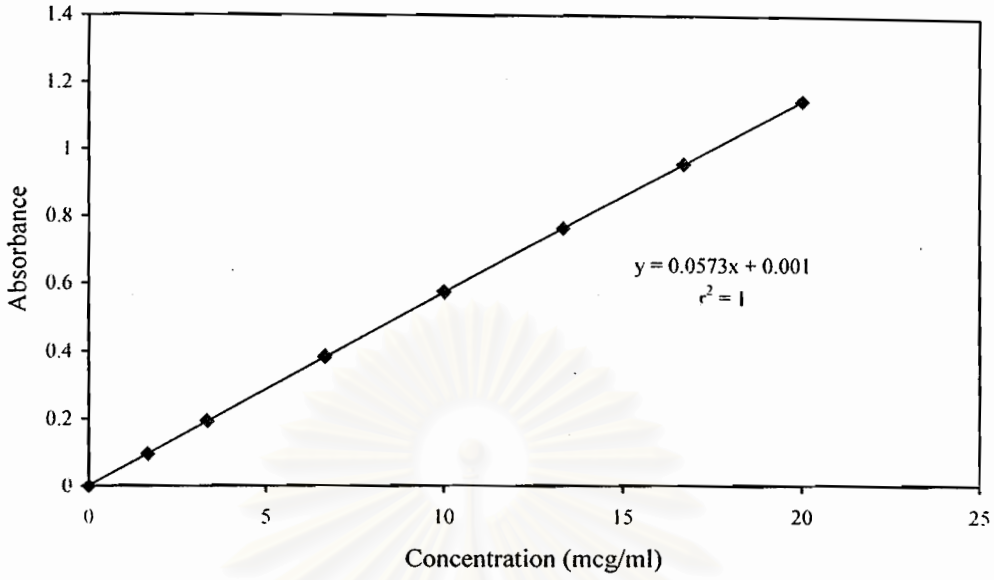


Figure 91 Calibration curve of theophylline in PBS pH 3 at 272 nm

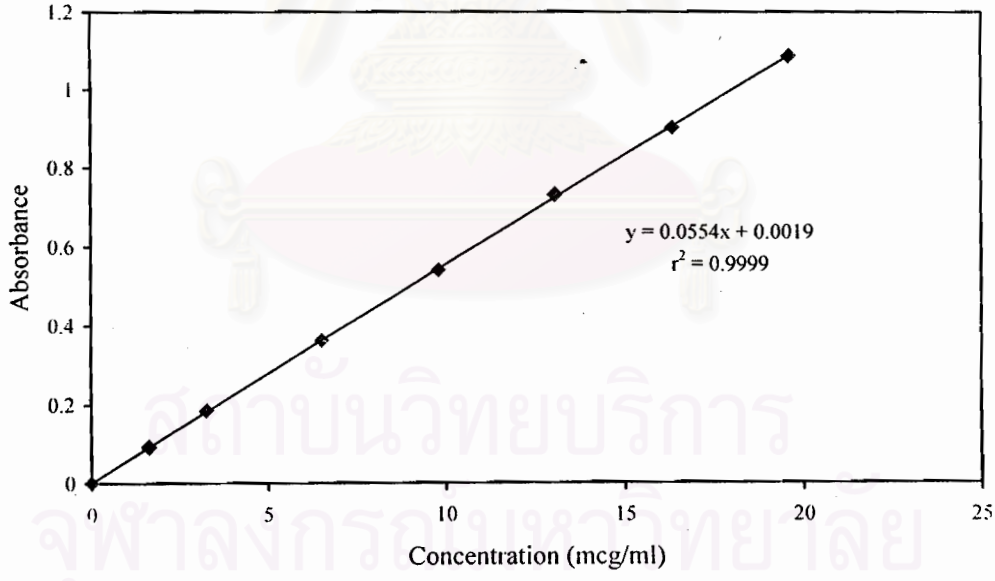


Figure 92 Calibration curve of theophylline in PBS pH 6.8 at 272 nm

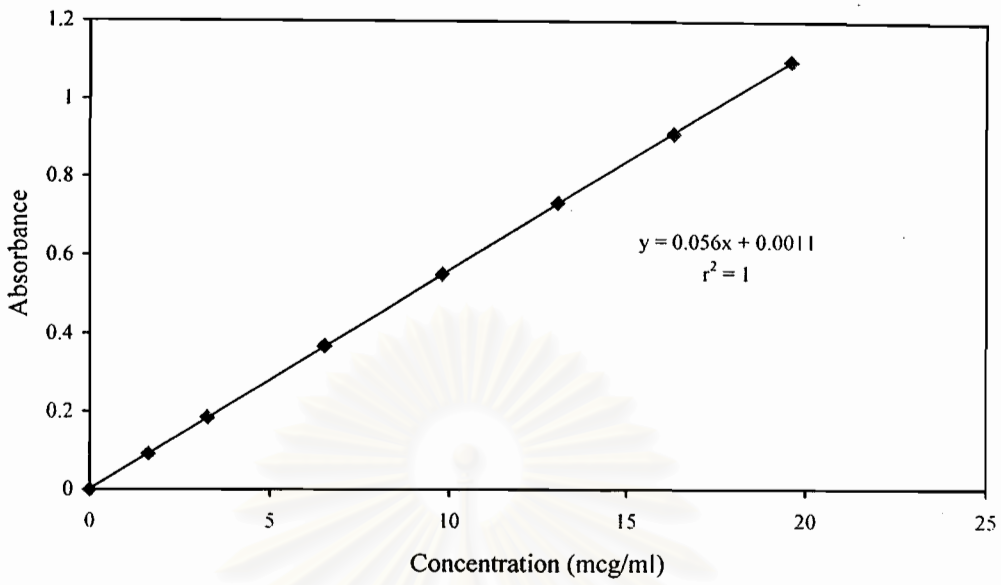


Figure 93 Calibration curve of theophylline in PBS pH 7.4 at 272 nm

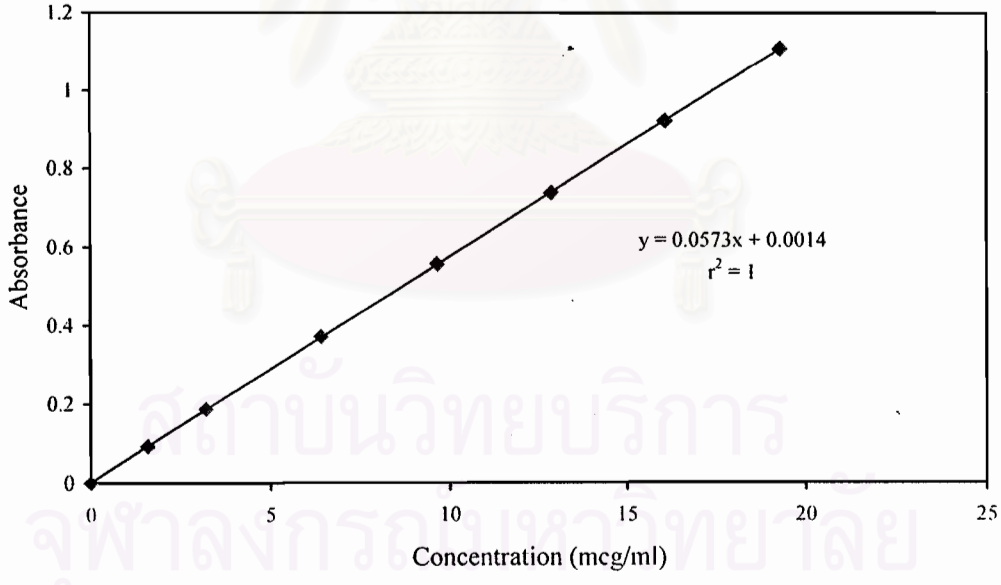


Figure 94 Calibration curve of theophylline in 0.01 M NaCl at 272 nm

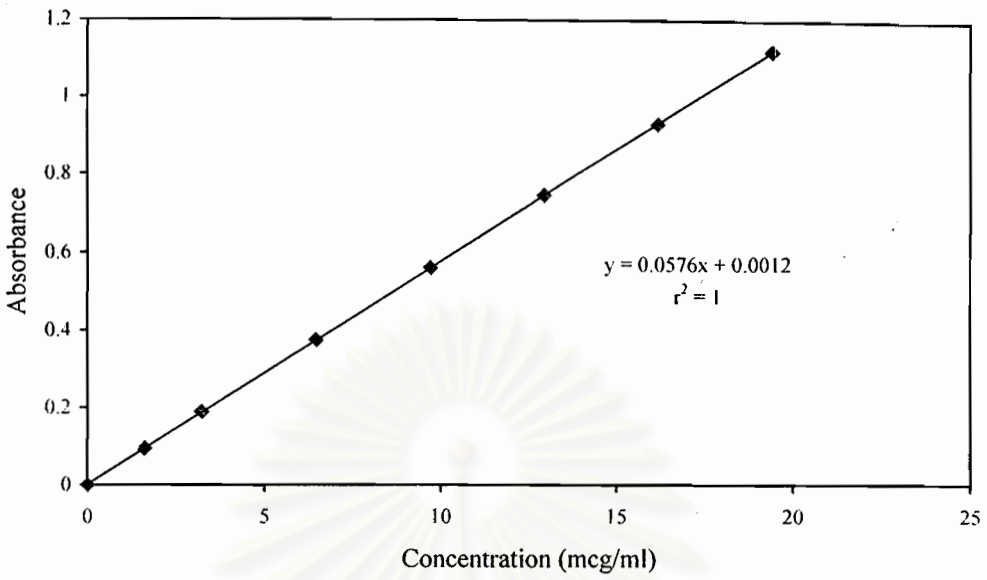


Figure 95 Calibration curve of theophylline in 0.05 M NaCl at 272 nm

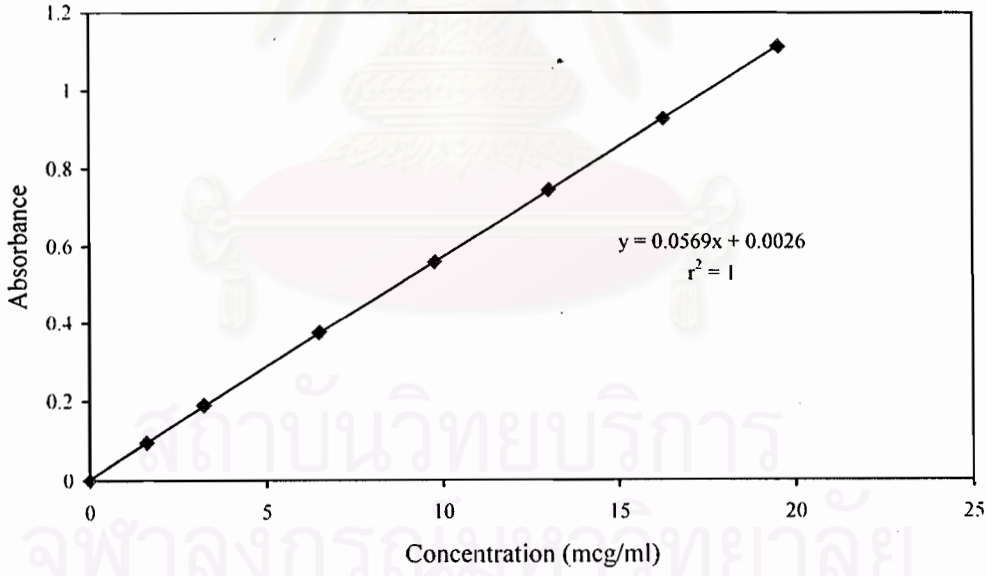


Figure 96 Calibration curve of theophylline in 0.1 M NaCl at 272 nm

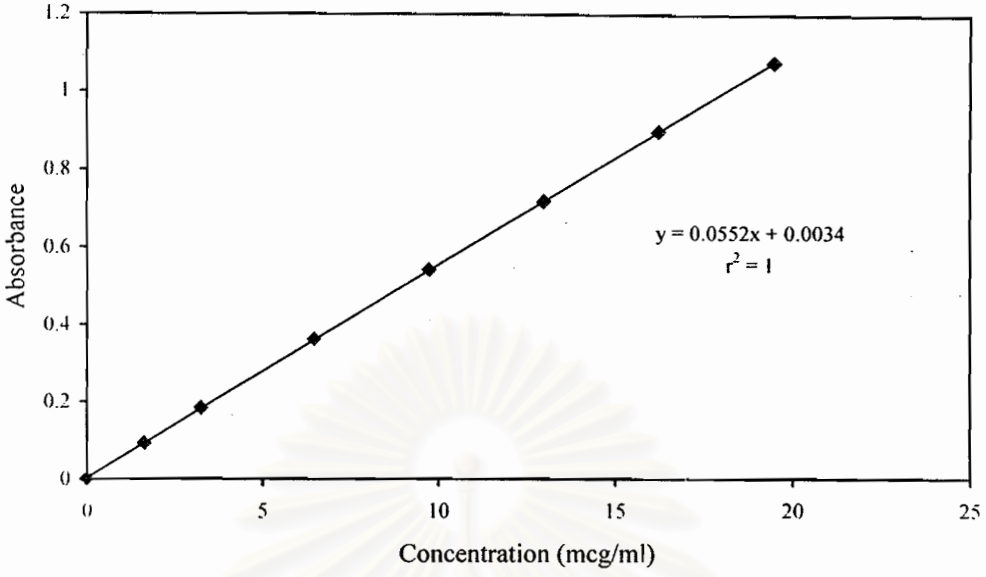


Figure 97 Calibration curve of theophylline in 0.2 M NaCl at 272 nm

Appendix C

Viscosity

The gel viscosities composed various HPMC to xanthan gum ratios in different media at 37 ^{O}C and shear rate of 100 rpm were presented in Tables 18-26.

Table 18 The gel viscosities of various HPMC to xanthan gum ratios in DI water

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1146.32	1158.90	1150.33	1151.85	6.43	0.56
7 : 3	1128.33	1215.25	1230.57	1224.72	8.27	0.68
5 : 5	994.13	1000.90	982.88	992.64	9.10	0.92
3 : 7	718.82	720.71	733.04	724.19	7.72	1.07
0 : 10	523.13	536.36	520.76	527.76	7.91	1.50

Table 19 The gel viscosities of various HPMC to xanthan gum ratios in 0.1 N HCl

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	855.12	849.27	842.50	848.96	6.32	0.74
7 : 3	749.83	760.44	745.24	751.84	7.80	1.04
5 : 5	1130.09	1125.81	1113.72	1123.21	8.49	0.76
3 : 7	1439.19	1440.07	1430.55	1436.60	5.26	0.37
0 : 10	1754.90	1750.67	1761.22	1755.60	5.31	0.30

Table 20 The gel viscosities of various HPMC to xanthan gum ratios in phosphate buffer pH 3

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	899.05	880.52	890.22	889.93	9.27	1.04
7 : 3	1668.02	1658.51	1666.84	1664.46	5.18	0.31
5 : 5	1830.25	1822.89	1835.08	1829.41	6.41	0.34
3 : 7	1767.85	1773.92	1777.40	1773.06	4.83	0.27
0 : 10	1844.17	1830.77	1840.24	1839.39	6.89	0.37

Table 21 The gel viscosities of various HPMC to xanthan gum ratios in phosphate buffer pH 6.8

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	999.51	1004.82	1010.27	1004.87	5.38	0.54
7 : 3	1456.45	1465.93	1450.60	1457.66	7.74	0.53
5 : 5	1555.35	1564.96	1559.22	1559.84	4.84	0.31
3 : 7	1566.03	1574.20	1579.38	1573.20	6.73	0.43
0 : 10	1715.17	1700.27	1711.82	1709.09	7.82	0.46

Table 22 The gel viscosities of various HPMC to xanthan gum ratios in phosphate buffer pH 7.4

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1128.54	1134.09	1139.02	1133.88	5.24	0.46
7 : 3	1515.11	1509.98	1512.04	1512.38	2.58	0.17
5 : 5	1600.06	1610.21	1598.73	1603.00	6.28	0.39
3 : 7	1661.47	1659.39	1651.88	1657.58	5.04	0.30
0 : 10	1790.12	1782.72	1785.90	1786.25	3.71	0.21

Table 23 The gel viscosities of various HPMC to xanthan gum ratios in 0.01 M NaCl

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1078.05	1080.47	1071.13	1076.55	4.85	0.45
7 : 3	1121.99	1129.38	1133.85	1128.41	5.99	0.53
5 : 5	1142.35	1130.31	1136.73	1136.46	6.02	0.53
3 : 7	1168.20	1177.41	1165.39	1170.33	6.29	0.54
0 : 10	960.71	965.10	958.83	961.55	3.22	0.33

Table 24 The gel viscosities of various HPMC to xanthan gum ratios in 0.05 M NaCl

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1206.71	1198.96	1200.26	1201.98	4.15	0.35
7 : 3	1348.86	1357.53	1345.79	1350.73	6.09	0.45
5 : 5	1568.24	1553.47	1570.18	1563.96	9.14	0.58
3 : 7	1590.99	1593.29	1601.17	1595.15	5.34	0.33
0 : 10	1687.97	1702.61	1700.23	1696.94	7.86	0.46

Table 25 The gel viscosities of various HPMC to xanthan gum ratios in 0.1 M NaCl

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1199.03	1188.40	1200.82	1196.08	6.71	0.56
7 : 3	1359.44	1345.21	1348.52	1351.06	7.45	0.55
5 : 5	1536.14	1547.09	1534.73	1539.32	6.77	0.44
3 : 7	1641.22	1629.74	1635.88	1635.61	5.74	0.35
0 : 10	1905.95	1890.26	1900.34	1898.85	7.95	0.42

Table 26 The gel viscosities of various HPMC to xanthan gum ratios in 0.2 M NaCl

Polymer composition HPMC : XG	Viscosity (mPas)					
	1	2	3	Mean	SD	% CV
10 : 0	1170.26	1174.26	1168.65	1171.06	2.89	0.25
7 : 3	1220.24	1228.47	1224.70	1224.47	4.12	0.34
5 : 5	1450.66	1442.19	1445.11	1445.99	4.30	0.30
3 : 7	1651.88	1662.35	1659.29	1657.84	5.38	0.32
0 : 10	1829.06	1837.37	1833.99	1833.47	4.18	0.23

Appendix D

Percentage Amount of Drug Releases

Table 27 Percentage amounts of theophylline from matrices containing spray dried lactose (Formulation blank1) in various dissolution media

Time (hr)	Percentage amount of drug release									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	15.16	15.10	16.21	15.49	0.62	15.45	14.78	14.68	14.97	0.42
0.50	23.86	23.79	24.13	13.93	0.18	26.13	25.40	24.52	25.35	0.80
0.75	34.03	33.44	33.85	33.77	0.30	33.97	33.34	32.29	33.20	0.84
1	42.08	41.74	42.29	42.04	0.27	42.01	41.57	40.51	41.36	0.76
2	67.63	69.38	69.61	68.87	1.08	66.64	66.82	64.72	66.06	1.16
3	87.65	87.86	88.67	88.06	0.53	83.51	88.11	83.11	84.91	2.78
4	99.62	100.22	100.85	100.23	0.61	96.83	99.01	96.64	97.50	1.31
5	103.06	103.27	103.71	103.35	0.33	101.19	100.91	100.38	100.83	0.41
6	104.75	103.79	104.23	104.25	0.48	102.68	101.37	102.08	102.04	0.65
7	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-
Time (hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	14.81	13.78	13.98	14.19	0.54	16.37	16.57	16.67	16.54	0.15
0.50	24.35	22.47	22.82	23.21	0.99	28.03	28.90	29.41	28.78	0.69
0.75	33.50	30.96	31.07	31.84	1.43	37.79	38.57	38.73	38.36	0.49
1	42.11	39.15	39.11	40.12	1.71	47.96	48.74	49.16	18.62	0.60
2	67.39	63.96	62.99	64.78	2.31	78.10	79.14	78.75	78.66	0.52
3	84.81	83.11	80.75	82.89	2.03	100.29	98.70	95.66	98.22	2.35
4	96.52	96.37	94.18	95.69	1.30	104.22	104.45	104.22	104.30	0.13
5	99.91	100.75	99.91	100.19	0.48	105.14	104.15	104.12	104.47	0.58
6	101.96	102.22	101.76	101.98	0.22	106.26	104.65	105.02	105.31	0.84
7	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-

Table 27 (Continued) Percentage amounts of theophylline from matrices containing spray dried lactose (Formulation blank1) in various dissolution media

Time (hr)	Percentage amount of drug release									
	PBS pH 7.4					0.01 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	16.27	16.01	16.12	16.13	0.12	14.36	14.95	16.42	15.24	1.06
0.50	26.89	26.69	26.49	26.69	0.20	23.55	24.68	26.66	24.96	1.57
0.75	38.34	38.08	38.23	38.22	0.12	33.43	34.77	37.21	35.14	1.91
1	51.92	49.90	48.90	50.24	1.53	44.30	45.71	48.13	46.04	1.93
2	79.20	77.36	76.35	77.64	1.44	73.24	74.47	74.56	74.09	0.73
3	99.35	98.49	97.47	98.44	0.94	94.46	96.09	94.61	95.05	0.90
4	102.43	102.98	101.94	102.45	0.51	100.39	101.06	102.12	101.19	0.86
5	102.93	102.88	103.64	103.15	0.42	101.08	101.76	103.02	101.95	0.98
6	104.43	104.37	104.94	104.58	0.31	102.16	102.64	103.33	102.71	0.58
7	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-
Time (hr)	0.05 M NaCl					0.1 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	15.27	14.88	14.97	15.04	0.20	13.76	15.59	14.55	14.63	0.91
0.50	25.64	215.64	26.27	25.85	0.36	24.29	26.19	24.94	25.14	0.96
0.75	35.59	36.27	37.06	36.31	0.73	34.59	36.41	35.59	35.53	0.91
1	44.15	46.11	47.10	45.79	1.50	44.01	45.45	45.41	44.95	0.82
2	70.22	73.56	76.71	73.50	3.24	71.56	71.83	75.36	72.92	2.11
3	89.14	96.82	94.73	93.57	3.97	92.10	89.42	94.36	91.96	2.47
4	98.70	100.02	99.47	99.40	0.66	100.22	100.07	102.30	100.84	1.24
5	101.13	102.07	101.71	101.64	0.47	102.09	102.14	103.80	102.68	0.97
6	102.60	103.35	103.19	103.05	0.39	102.98	102.83	104.31	103.37	0.81
7	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-

Table 27 (Continued) Percentage amounts of theophylline from matrices containing spray dried lactose (Formulation blank1) in various dissolution media

Time (hr)	Percentage amount of drug release				
	0.2 M NaCl				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	14.44	14.44	14.29	14.39	0.08
0.50	23.77	24.02	23.82	23.87	0.13
0.75	35.03	33.66	34.37	34.35	0.68
1	48.42	45.35	45.97	46.58	1.62
2	82.35	72.52	74.57	76.48	5.18
3	98.93	93.68	98.81	97.14	2.99
4	103.87	103.46	103.95	103.76	0.26
5	104.38	104.37	104.67	104.47	0.16
6	105.29	104.87	105.37	105.18	0.26
7	-	-	-	-	-
8	-	-	-	-	-
10	-	-	-	-	-
12	-	-	-	-	-

Table 28 Percentage amounts of theophylline from matrices containing dibasic calcium phosphate (Formulation blank2) in various dissolution media

Time (hr)	Percentage amount of drug release									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	12.60	12.74	12.15	12.50	0.31	15.40	15.66	15.97	15.68	0.28
0.50	16.88	16.88	16.41	16.72	0.26	24.27	25.10	25.00	24.79	0.45
0.75	21.20	21.40	20.66	21.08	0.37	32.35	33.45	33.40	33.06	0.62
1	24.84	24.98	24.30	24.70	0.35	39.74	41.31	41.47	40.84	0.95
2	36.29	36.49	36.07	36.28	0.21	64.51	67.03	65.17	65.57	1.30
3	46.13	45.74	45.52	45.80	0.31	83.84	86.26	84.81	84.97	1.21
4	54.11	53.13	53.09	53.44	0.57	96.55	98.79	97.32	97.55	1.13
5	60.60	60.00	58.78	59.79	0.92	103.17	104.21	103.76	103.71	0.51
6	66.16	66.35	65.51	66.01	0.43	103.66	104.91	104.25	104.27	0.60
7	71.59	71.58	69.75	70.97	1.05	-	-	-	-	-
8	75.89	75.68	74.46	75.46	0.56	-	-	-	-	-
10	83.77	83.16	82.68	83.20	0.54	-	-	-	-	-
12	89.17	89.93	88.66	89.25	0.63	-	-	-	-	-
Time (hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	11.43	10.94	11.43	11.26	0.28	11.44	11.49	11.64	11.53	0.10
0.50	16.56	16.45	16.95	16.65	0.26	16.04	16.29	16.30	16.21	0.14
0.75	21.40	21.79	22.29	21.83	0.44	19.98	20.33	20.29	20.20	0.19
1	25.22	25.61	26.31	25.71	0.55	23.70	24.42	24.32	24.15	0.38
2	35.70	35.06	35.33	35.36	0.31	35.59	36.67	36.27	36.18	0.54
3	46.14	45.74	46.95	46.28	0.61	45.73	46.16	46.77	46.22	0.52
4	55.47	55.66	57.07	56.07	0.87	54.76	58.24	56.21	56.41	1.75
5	64.70	65.68	66.71	65.70	1.01	62.05	65.99	63.93	63.99	1.96
6	72.66	73.05	74.49	73.40	0.96	69.02	72.59	70.92	70.84	1.78
7	79.52	79.92	81.18	82.20	0.86	74.43	78.44	77.97	76.95	2.19
8	86.25	86.45	87.33	86.68	0.57	79.89	83.94	82.86	82.23	2.10
10	95.98	96.19	97.08	96.42	0.58	89.67	94.58	92.88	92.37	2.49
12	100.72	101.32	101.43	101.16	0.38	98.53	102.07	100.55	100.39	1.77

Table 28 (Continued) Percentage amounts of theophylline from matrices containing dibasic calcium phosphate (Formulation blank2) in various dissolution media

Time (hr)	Percentage amount of drug release									
	PBS pH 7.4					0.01 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	11.70	12.00	11.04	11.58	0.48	11.02	11.76	11.46	11.41	0.37
0.50	16.75	17.35	15.99	16.70	0.68	15.71	16.55	16.25	16.17	0.42
0.75	22.21	22.27	20.28	21.58	1.12	19.61	20.61	20.26	20.16	0.50
1	26.11	25.87	23.77	25.25	1.29	23.11	24.32	23.97	23.80	0.62
2	35.44	35.19	33.87	34.83	0.84	34.31	36.21	36.00	35.51	1.04
3	46.82	45.62	41.72	44.72	2.66	42.49	44.51	44.50	43.83	1.16
4	57.97	55.15	50.81	54.64	3.60	50.01	52.26	52.24	51.50	1.29
5	67.24	64.58	59.79	63.87	3.77	55.85	58.32	57.91	57.36	1.32
6	74.18	72.31	67.26	71.25	3.58	61.75	65.22	65.01	63.99	1.94
7	80.00	78.70	73.80	77.50	3.26	68.29	71.60	71.58	70.49	1.90
8	84.86	85.36	79.61	83.28	3.18	71.57	75.50	74.89	73.99	2.11
10	92.58	93.29	89.05	91.65	2.25	78.79	83.75	82.54	81.70	2.58
12	98.17	99.69	95.44	97.76	2.15	84.91	89.73	88.71	87.78	2.53
Time(hr)	0.05 M NaCl					0.1 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	11.02	10.24	10.68	10.64	0.39	11.04	10.55	10.85	10.81	0.24
0.50	16.02	15.09	15.29	15.47	0.49	15.47	15.16	15.27	15.30	0.15
0.75	20.59	19.84	19.80	20.08	0.44	19.88	19.63	19.73	19.75	0.12
1	24.48	23.58	23.58	23.88	0.52	23.41	23.11	23.56	23.36	0.23
2	37.01	35.65	35.80	36.15	0.74	34.38	34.57	34.73	34.76	0.20
3	48.60	45.62	46.22	46.81	1.57	45.73	44.72	44.16	44.86	0.80
4	57.92	54.71	54.92	55.85	1.79	53.74	53.31	52.13	53.06	0.83
5	65.96	61.94	62.35	63.42	2.21	61.43	60.41	59.02	60.28	1.21
6	73.11	67.88	68.09	69.69	2.96	68.02	66.39	65.38	66.60	1.33
7	78.38	73.48	74.48	74.45	2.59	73.09	72.43	70.42	71.98	1.38
8	84.49	78.36	82.88	81.91	3.17	77.82	78.14	74.53	76.83	1.99
10	92.79	86.60	87.27	88.89	3.39	86.93	87.26	83.81	86.05	1.90
12	98.45	93.75	94.43	95.54	2.53	92.98	93.91	89.62	92.17	2.25

Table 28 (Continued) Percentage amounts of theophylline from matrices containing dibasic calcium phosphate (Formulation blank2) in various dissolution media

Time (hr)	Percentage amount of drug release				
	0.2 MNaCl				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	11.44	11.08	11.19	11.24	0.18
0.50	16.05	15.48	15.54	15.69	0.31
0.75	20.09	19.83	19.37	19.77	0.36
1	23.88	23.81	23.35	23.68	0.28
2	36.46	36.04	35.11	35.87	0.68
3	44.72	45.11	43.46	44.43	0.86
4	53.55	53.33	51.87	52.92	0.91
5	60.64	60.22	59.35	60.07	0.65
6	68.01	66.98	66.51	67.17	0.77
7	74.24	73.19	72.51	73.31	0.87
8	78.89	77.22	77.15	77.75	0.98
10	88.07	85.36	85.90	86.44	1.43
12	96.52	92.77	92.91	94.07	2.13

Table 29 Percentage amounts of theophylline from matrices containing 10% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F1-F5) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	79.21	87.68	67.61	78.17	10.07	4.22	4.12	4.26	4.20	0.06
0.50	86.35	92.71	78.49	85.85	7.12	7.24	6.92	7.05	7.07	0.16
0.75	91.54	94.46	84.14	90.05	5.31	10.31	9.87	10.12	10.10	0.22
1	94.19	95.12	89.11	92.81	3.23	13.57	12.88	13.09	13.18	0.35
2	96.68	96.33	96.70	96.57	0.20	25.05	26.25	25.20	25.50	0.65
3	97.90	96.80	96.08	96.93	0.91	35.87	36.10	34.73	35.56	0.73
4	97.27	96.72	96.45	96.69	0.28	46.20	46.65	44.21	45.69	1.30
5	97.00	96.62	96.45	96.69	0.28	55.83	55.83	53.13	54.93	1.55
6	98.55	96.51	96.71	97.26	1.12	68.76	68.01	66.22	67.66	1.30
7	97.16	96.76	96.78	96.90	0.22	80.12	79.35	76.80	78.76	1.74
8	97.78	96.81	97.21	97.26	0.48	88.37	87.41	85.58	87.12	1.41
10	98.94	98.33	98.55	98.60	0.30	96.71	97.44	95.79	96.65	0.83
12	99.73	99.30	98.98	99.33	0.37	102.09	103.22	102.30	102.54	0.59
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.04	3.00	3.20	3.08	0.10	2.90	2.73	2.73	2.79	0.09
0.50	5.25	5.30	5.54	5.36	0.15	5.29	5.00	5.00	5.09	0.16
0.75	8.16	8.08	8.35	8.20	0.13	8.36	7.90	7.94	8.07	0.25
1	11.12	10.95	11.37	11.14	0.21	11.79	11.33	10.63	11.25	0.58
2	24.30	22.71	24.38	23.80	0.94	24.64	23.41	21.82	23.29	1.41
3	36.03	33.97	36.49	35.49	1.34	38.42	36.66	33.61	36.23	2.43
4	48.64	45.73	48.35	47.57	1.60	55.91	50.57	48.33	51.60	3.89
5	63.56	59.14	62.44	61.71	2.29	74.70	66.67	64.32	68.56	5.44
6	80.27	75.25	78.76	78.09	2.57	90.05	84.76	82.95	85.92	3.68
7	92.07	89.07	90.36	90.50	1.50	97.63	97.19	95.17	96.66	1.30
8	97.40	96.44	97.18	97.01	0.50	99.43	101.44	99.60	100.16	1.11
10	102.58	102.56	102.36	102.50	0.12	100.86	103.28	101.79	101.98	1.21
12	103.48	106.47	104.01	104.65	1.59	102.11	106.07	103.81	104.00	1.98

Table 29 (Continued) Percentage amounts of theophylline from matrices containing 10% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F1-F5) in DI water

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	2.08	2.04	2.13	2.09	0.04
0.50	3.73	3.76	3.82	3.77	0.04
0.75	5.81	5.14	6.28	5.74	0.57
1	7.23	8.12	8.71	8.02	0.74
2	17.18	16.21	17.01	16.80	0.51
3	26.01	24.73	25.28	25.34	0.63
4	36.71	34.45	35.16	35.44	1.15
5	50.78	45.90	51.52	49.40	3.05
6	69.75	62.58	67.71	66.68	3.69
7	88.74	83.91	90.21	87.62	3.29
8	98.26	98.21	99.18	98.55	0.54
10	99.51	100.75	101.18	100.48	0.87
12	100.18	100.90	102.81	101.30	1.35

Table 30 Percentage amounts of theophylline from matrices containing 10% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F6-F10) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	12.51	14.78	14.23	13.84	1.18	5.54	4.59	4.78	4.97	0.50
0.50	17.73	20.96	20.17	19.62	1.68	8.28	7.26	7.51	7.68	0.53
0.75	24.01	27.00	25.61	25.54	1.49	11.05	9.83	10.12	10.33	0.64
1	27.98	31.39	29.80	29.73	1.70	13.41	12.06	12.32	12.60	0.72
2	40.40	45.41	43.41	43.07	2.52	21.53	19.38	19.70	20.21	1.16
3	50.99	56.65	54.62	54.09	2.86	29.48	26.68	27.01	27.72	1.53
4	59.55	65.66	63.42	62.88	3.08	36.96	33.82	33.84	34.88	1.80
5	67.23	71.44	71.52	70.07	2.45	43.85	39.82	40.03	41.23	2.26
6	73.81	76.89	79.32	76.67	2.76	49.97	46.28	46.89	47.71	1.97
7	78.30	80.64	82.70	80.55	2.20	55.76	53.01	52.65	53.80	1.70
8	83.42	85.01	86.70	85.04	1.63	60.44	58.83	57.88	59.05	1.29
10	90.74	91.94	93.27	91.99	1.26	70.62	69.19	68.42	69.41	1.11
12	95.79	97.59	96.58	96.65	0.89	79.73	78.68	76.15	78.19	1.84
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.30	3.58	3.57	3.48	0.15	2.94	2.77	2.77	2.83	0.09
0.50	5.66	5.94	5.83	5.81	0.14	4.95	5.08	5.10	5.04	0.08
0.75	7.98	8.27	8.33	8.19	0.18	7.23	7.40	7.46	7.36	0.11
1	10.25	10.43	10.62	10.43	0.18	9.42	9.76	9.88	9.69	0.24
2	18.31	18.24	18.86	18.47	0.34	19.35	19.82	20.28	19.82	0.46
3	26.23	26.48	27.49	26.73	0.66	27.00	27.77	28.39	27.72	0.69
4	33.86	34.49	35.44	34.60	0.79	35.18	35.81	36.52	35.84	0.66
5	40.39	41.76	41.79	41.32	0.81	43.32	43.54	43.95	43.60	0.31
6	47.01	48.78	47.65	47.81	0.89	50.11	50.91	50.93	50.65	0.46
7	53.11	53.75	53.18	53.35	0.34	56.59	58.73	56.84	57.39	1.17
8	58.90	60.11	58.58	59.20	0.81	64.47	67.02	62.62	64.70	2.20
10	71.30	72.53	69.44	71.09	1.55	79.14	81.52	74.01	78.22	3.83
12	83.07	84.31	78.67	82.02	2.96	90.13	93.11	84.94	89.39	4.13

Table 30 (Continued) Percentage amounts of theophylline from matrices containing 10% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F6-F10) in DI water

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	2.31	2.05	2.15	2.17	0.13
0.50	3.03	3.09	3.04	3.05	0.03
0.75	4.52	4.40	4.48	4.46	0.05
1	6.20	5.97	6.02	6.06	0.12
2	14.94	14.48	14.59	14.67	0.24
3	24.71	25.08	25.16	24.98	0.23
4	32.11	33.47	32.72	32.77	0.68
5	41.97	43.50	40.65	42.04	1.42
6	54.19	58.77	51.52	54.82	3.66
7	64.83	69.84	62.89	65.85	3.58
8	75.58	78.56	74.38	76.17	2.14
10	90.62	91.73	89.97	90.77	0.88
12	101.83	99.54	101.37	100.91	1.21

Table 31 Percentage amounts of theophylline from matrices containing 15% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F11-F15) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	16.44	18.24	21.04	18.57	2.31	3.24	4.06	4.17	3.82	0.50
0.50	21.62	24.04	27.67	24.44	3.04	4.93	5.18	5.26	5.13	0.16
0.75	27.46	28.91	33.18	29.85	2.97	7.22	7.44	7.55	7.40	0.16
1	31.36	33.02	37.74	34.04	3.31	9.26	9.59	9.68	9.51	0.22
2	43.30	45.58	51.35	46.75	4.14	17.78	18.17	18.85	18.27	0.53
3	53.97	55.88	63.31	57.72	4.93	25.72	26.86	27.17	26.59	0.76
4	62.56	64.28	71.19	66.01	4.57	33.68	34.68	35.51	34.62	0.91
5	70.23	71.77	78.16	73.39	4.20	41.74	42.71	44.04	42.83	1.15
6	76.38	79.54	83.99	79.97	3.82	50.38	51.93	55.69	52.67	2.72
7	83.19	85.38	88.48	85.68	2.65	60.42	62.73	66.90	63.35	3.28
8	88.67	90.68	92.01	90.45	1.68	70.19	71.59	75.63	72.47	2.82
10	95.99	98.43	97.16	97.19	1.21	83.60	83.71	86.49	84.60	1.63
12	100.99	102.25	101.96	101.74	0.65	91.94	91.49	93.74	92.39	1.18
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	2.78	2.68	2.72	2.73	0.05	2.28	2.39	2.37	2.34	0.05
0.50	4.29	4.40	4.49	4.39	0.09	4.37	4.71	4.49	4.52	0.16
0.75	6.59	6.80	6.87	6.75	0.14	6.95	7.55	7.19	7.23	0.30
1	9.02	9.23	9.27	9.17	0.13	9.86	10.60	10.10	10.19	0.37
2	18.63	18.64	17.96	18.41	0.38	20.76	22.04	21.32	21.37	0.64
3	29.38	29.16	27.42	28.65	1.07	32.37	34.54	33.81	33.58	1.10
4	39.64	39.34	38.04	39.01	0.85	45.31	47.74	46.44	46.50	1.21
5	50.75	51.50	47.32	49.86	2.22	62.08	61.97	63.31	62.45	0.74
6	63.92	65.24	61.39	63.52	1.95	79.96	78.85	80.41	79.74	0.80
7	77.03	78.56	76.36	77.32	1.12	94.47	93.55	94.73	94.25	0.61
8	86.90	88.07	85.47	86.81	1.30	100.63	101.08	101.48	101.07	0.42
10	96.68	97.67	95.80	96.71	0.93	106.25	106.91	106.32	106.50	0.35
12	102.03	101.72	100.58	101.44	0.76	107.18	107.45	106.46	107.03	0.51

Table 31 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F11-F15) in DI water

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	1.83	1.82	1.72	1.79	0.06
0.50	3.21	3.24	3.23	3.23	0.01
0.75	5.31	5.19	5.61	5.37	0.21
1	7.64	7.37	7.70	7.57	0.17
2	18.06	19.02	17.98	18.35	0.58
3	30.67	33.02	30.10	31.26	1.55
4	47.87	51.40	46.82	48.70	2.39
5	69.64	72.55	66.58	69.59	2.98
6	88.44	92.81	85.76	89.01	3.55
7	103.20	104.56	101.49	103.08	1.53
8	108.57	108.73	108.88	108.72	0.15
10	110.13	111.31	111.87	111.10	0.88
12	110.49	112.29	113.86	112.21	1.68

Table 32 Percentage amounts of theophylline from matrices containing 15% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F16-F20) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	7.12	7.14	6.81	7.02	0.18	4.12	4.23	4.10	4.15	0.06
0.50	11.04	11.19	10.45	10.89	0.39	6.45	6.73	6.32	6.50	0.20
0.75	14.24	14.44	13.78	14.15	0.33	8.91	9.38	8.82	9.04	0.30
1	17.17	17.39	16.63	17.06	0.38	10.91	11.35	10.73	10.99	0.31
2	28.25	28.26	26.99	27.83	0.73	18.00	18.64	17.45	18.03	0.59
3	36.62	36.94	35.04	36.20	1.01	24.47	25.59	23.84	24.64	0.89
4	44.47	45.72	42.94	44.38	1.39	30.71	32.46	29.90	31.02	1.31
5	51.22	53.37	49.40	51.33	1.98	38.44	38.88	36.06	37.79	1.51
6	57.78	60.15	55.56	57.83	2.29	42.78	44.21	41.35	42.78	1.42
7	63.44	65.65	61.78	63.62	1.94	47.75	49.19	45.91	47.62	1.64
8	68.77	70.41	67.09	68.76	1.66	52.18	53.25	50.33	51.92	1.47
10	77.83	80.85	76.13	78.27	2.39	61.36	63.62	59.88	61.62	1.88
12	85.43	88.49	84.11	86.01	2.24	70.05	73.31	67.97	70.45	2.69
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.43	3.34	3.20	3.32	0.11	2.49	2.53	2.48	2.50	0.02
0.50	5.31	5.36	5.01	5.23	0.18	4.15	4.15	4.29	4.20	0.07
0.75	7.70	7.70	7.34	7.58	0.20	6.13	6.36	6.28	6.26	0.11
1	9.82	9.87	9.23	9.64	0.35	8.24	8.34	8.57	8.38	0.16
2	17.28	16.96	16.55	16.93	0.36	16.52	16.38	16.76	16.55	0.19
3	24.97	24.49	23.76	24.41	0.60	24.36	24.59	25.04	24.66	0.34
4	31.72	31.39	30.50	31.20	0.63	32.73	32.81	33.42	32.99	0.37
5	39.23	38.83	37.41	38.49	0.95	42.53	42.34	42.17	42.35	0.17
6	44.79	45.17	43.54	44.50	0.85	52.74	52.00	51.26	52.00	0.74
7	50.41	49.80	48.35	49.52	1.05	61.94	60.44	59.88	60.75	1.06
8	56.27	55.27	54.39	55.31	0.94	69.55	67.27	67.28	68.03	1.31
10	69.71	68.49	66.22	68.14	1.76	82.11	80.94	81.31	81.45	0.59
12	81.50	79.09	78.38	79.66	1.63	92.17	88.74	89.68	90.20	1.77

Table 32 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F16-F20) in DI water

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	1.95	1.95	1.84	1.91	0.05
0.50	3.02	3.01	2.98	3.01	0.02
0.75	4.44	4.40	4.44	4.42	0.02
1	5.96	5.94	6.10	6.00	0.08
2	12.84	13.00	13.15	13.00	0.15
3	21.71	22.50	21.40	21.87	0.56
4	35.79	36.42	33.66	35.29	1.44
5	52.28	52.30	49.70	51.43	1.49
6	65.43	67.81	67.74	66.99	1.35
7	78.92	79.95	78.11	78.99	0.92
8	85.87	89.07	87.21	87.38	1.60
10	96.81	99.46	98.17	98.15	1.32
12	103.94	104.25	105.51	104.57	0.83

Table 33 Percentage amounts of theophylline from matrices containing 20% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F21-F25) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	7.36	7.36	6.87	7.20	0.28	2.64	2.59	2.68	2.63	0.04
0.50	10.42	10.61	9.97	10.33	0.32	4.69	1.65	1.65	1.66	0.02
0.75	13.55	13.87	13.18	13.53	0.34	6.76	6.78	6.80	6.78	0.01
1	16.33	16.85	16.02	16.40	0.41	8.79	8.91	8.86	8.85	0.06
2	26.37	27.11	26.13	26.54	0.51	16.89	17.19	16.97	17.02	0.15
3	35.34	36.24	34.95	35.51	0.66	24.58	25.47	25.10	25.05	0.44
4	42.27	43.70	42.10	42.69	0.87	31.08	31.99	31.61	31.56	0.45
5	49.16	50.31	49.31	49.59	0.62	38.38	39.15	38.21	38.58	0.49
6	53.73	55.26	54.44	54.48	0.76	43.62	47.74	44.93	45.43	2.10
7	60.75	61.01	61.28	61.01	0.26	51.15	57.53	53.77	54.15	3.21
8	66.54	66.43	66.72	66.56	0.14	58.37	65.76	61.40	61.84	3.71
10	76.08	76.33	76.62	76.34	0.27	73.66	78.90	76.90	76.49	2.64
12	83.13	83.39	83.13	83.22	0.15	85.39	88.09	86.26	86.58	1.37
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	2.22	2.21	2.29	2.24	0.04	2.21	2.25	2.47	2.31	0.13
0.50	4.19	4.13	4.30	4.21	0.08	3.57	3.63	3.63	3.61	0.03
0.75	6.50	6.31	6.67	6.49	0.17	5.54	5.58	5.64	5.59	0.04
1	8.72	8.51	8.76	8.66	0.13	7.38	7.31	7.35	7.35	0.03
2	17.58	17.35	17.74	17.56	0.19	15.10	15.03	15.03	15.05	0.04
3	26.97	26.29	26.75	26.67	0.34	23.33	23.19	23.19	23.24	0.08
4	35.41	34.27	35.11	34.93	0.58	32.09	32.02	31.36	31.82	0.40
5	44.48	42.59	43.36	43.48	0.95	46.65	46.10	44.45	45.73	1.14
6	53.93	52.20	54.85	53.66	1.34	60.73	59.98	57.40	59.37	1.74
7	65.72	63.60	66.09	65.14	1.34	70.37	69.25	67.73	69.12	1.32
8	75.95	73.99	75.95	75.30	1.13	80.47	79.16	79.10	79.58	0.77
10	91.52	89.54	90.03	90.36	1.03	92.34	91.74	91.31	91.80	0.51
12	97.91	97.41	97.34	97.55	0.31	97.35	97.30	97.23	97.30	0.06

Table 33 (Continued) Percentage amounts of theophylline from matrices containing 20% polymer in various ratios of HPMC:XG and spray dried lactose (Formulation F21-F25) in DI water Percentage amounts

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	1.79	1.80	2.05	1.88	0.14
0.50	2.85	2.67	2.91	2.81	0.12
0.75	4.56	4.20	4.47	4.41	0.18
1	6.14	5.78	6.01	5.97	0.18
2	13.37	12.99	13.29	13.22	0.20
3	22.16	22.14	22.01	22.10	0.08
4	34.92	36.47	48.63	40.01	7.50
5	53.69	56.68	66.70	59.02	6.81
6	70.11	72.38	81.02	74.51	5.75
7	82.98	85.09	90.47	86.18	3.86
8	93.19	95.33	99.09	95.87	2.98
10	101.27	101.94	103.87	102.36	1.35
12	102.91	103.21	104.97	103.70	1.11

Table 34 Percentage amounts of theophylline from matrices containing 20% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F26-F30) in DI water

Time (hr)	Percentage amount of drug release									
	HPMC:XG=10:0					HPMC:XG=7:3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	6.36	5.78	5.72	5.95	0.35	3.44	3.40	3.55	3.46	0.07
0.50	9.80	9.02	8.98	9.27	0.46	5.75	5.77	6.04	5.85	0.15
0.75	12.82	11.97	12.15	12.31	0.44	8.00	7.98	8.27	8.08	0.16
1	15.42	14.67	14.63	14.91	0.44	10.12	10.10	10.45	10.22	0.19
2	24.93	23.89	23.97	24.27	0.57	17.76	17.46	17.77	17.67	0.17
3	32.60	31.86	31.56	32.01	0.53	24.12	23.59	24.14	23.95	0.30
4	40.04	39.53	38.99	39.52	0.52	30.48	30.25	30.49	30.41	0.13
5	45.89	45.45	44.87	45.40	0.51	36.10	35.15	35.92	35.72	0.50
6	51.59	51.14	51.51	51.42	0.23	41.94	40.98	41.76	41.56	0.51
7	56.57	56.12	55.73	56.14	0.42	45.21	43.68	44.84	44.58	0.80
8	61.41	61.92	60.75	61.36	0.58	48.89	48.09	49.27	48.75	0.60
10	71.50	72.01	72.02	71.51	0.49	55.99	56.50	58.44	56.98	1.29
12	79.96	79.52	78.32	79.26	0.84	65.23	65.55	68.27	66.35	1.67
Time(hr)	HPMC:XG=5:5					HPMC:XG=3:7				
0	0	0	0	0	0	0	0	0	0	0
0.25	2.83	2.91	2.84	2.86	0.04	1.98	1.98	2.04	2.00	0.03
0.50	4.92	5.03	4.92	4.96	0.06	3.61	3.53	3.55	3.56	0.03
0.75	6.91	7.04	6.91	6.95	0.07	5.19	5.34	5.21	5.25	0.08
1	8.88	9.07	8.92	8.96	0.10	7.01	7.04	6.98	7.01	0.02
2	16.06	16.37	15.83	16.09	0.26	14.49	14.49	13.90	14.29	0.34
3	22.48	22.48	21.87	22.28	0.35	21.50	21.35	20.22	21.02	0.69
4	28.96	29.20	28.28	28.81	0.47	28.58	28.13	26.77	27.82	0.94
5	34.30	34.87	33.34	34.17	0.77	36.83	35.34	34.93	35.70	1.00
6	40.68	40.33	39.72	40.24	0.48	45.60	42.42	41.26	43.10	2.24
7	44.32	44.52	42.40	43.74	1.16	53.91	49.94	48.78	50.88	2.68
8	48.17	48.19	17.55	17.97	0.36	62.30	58.11	56.37	58.93	3.04
10	57.52	58.28	57.83	57.88	0.38	76.92	71.38	70.36	72.89	3.52
12	66.21	67.92	67.65	67.26	0.92	86.85	83.48	82.46	84.27	2.29

Table 34 (Continued) Percentage amounts of theophylline from matrices containing 20% polymer in various ratios of HPMC:XG and dibasic calcium phosphate (Formulation F26-F30) in DI water

Time (hr)	Percentage amount of drug release				
	HPMC:XG=0:10				
	1	2	3	Mean	SD
0	0	0	0	0	0
0.25	1.50	1.50	1.50	1.50	0.00
0.50	2.45	2.42	2.41	2.43	0.02
0.75	3.57	3.38	3.53	3.50	0.09
1	4.86	4.64	4.81	4.77	0.11
2	11.30	10.93	10.93	11.05	0.21
3	18.00	18.58	17.55	18.04	0.51
4	25.80	26.10	27.42	26.44	0.86
5	39.92	48.23	40.30	42.82	4.69
6	54.58	63.17	53.67	57.14	5.24
7	68.65	74.93	65.88	69.82	4.63
8	79.92	84.24	77.86	80.67	3.25
10	91.86	91.05	90.70	91.21	0.59
12	100.79	98.67	99.06	99.51	1.12

Table 35 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and spray dried lactose (Formulation F11) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	22.46	24.35	23.93	23.58	0.99	26.52	23.93	33.10	27.85	4.72
0.50	28.81	32.19	31.14	30.71	1.73	30.61	28.58	39.25	32.81	5.66
0.75	34.17	37.39	37.16	36.24	1.79	35.33	33.88	46.27	38.49	6.77
1	39.80	42.84	42.19	41.61	1.59	40.70	39.04	49.77	43.17	5.77
2	52.44	56.14	55.27	54.61	1.93	53.91	51.43	61.87	55.74	5.45
3	63.31	65.79	64.70	64.60	1.24	61.27	61.96	69.72	64.32	4.69
4	71.14	73.44	72.97	72.52	1.21	67.31	68.21	75.25	70.26	3.43
5	79.06	80.53	78.38	79.32	1.10	72.22	73.33	80.44	75.33	4.46
6	85.15	86.23	83.84	85.07	1.19	76.38	78.69	86.08	80.38	5.06
7	90.26	91.13	88.93	90.11	1.11	81.57	53.11	89.97	84.88	4.47
8	94.99	93.77	93.85	94.20	0.68	86.01	87.57	94.10	89.22	4.29
10	99.56	99.36	99.87	99.60	0.25	94.88	96.85	99.65	97.13	2.40
12	103.32	102.70	104.27	103.43	0.79	99.64	101.85	103.7	101.52	1.73
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	31.04	27.11	43.22	33.79	8.40	25.51	27.96	33.88	29.12	4.30
0.50	44.19	36.91	50.72	43.94	6.90	33.35	35.62	42.63	37.20	4.83
0.75	51.08	44.34	55.00	50.14	5.38	40.66	43.16	49.43	44.42	4.51
1	55.56	48.96	59.73	54.75	5.43	45.60	48.94	54.46	49.67	4.47
2	66.90	62.29	70.70	66.63	4.21	62.01	62.33	69.75	64.70	4.37
3	74.44	70.82	77.66	74.30	3.42	70.65	72.40	79.69	74.24	4.79
4	80.40	77.57	83.86	80.61	3.15	77.53	77.87	84.22	79.87	3.76
5	84.97	83.14	86.81	84.98	1.83	84.28	83.40	89.40	85.69	3.24
6	89.79	86.91	91.03	89.24	2.11	88.24	88.57	93.41	90.07	2.89
7	92.59	90.51	93.63	92.24	1.58	92.43	92.36	97.45	94.08	2.91
8	97.68	94.34	97.49	96.50	1.87	97.07	98.22	100.91	98.73	1.97
10	101.99	100.69	102.62	101.76	0.98	103.59	103.11	107.26	104.65	2.26
12	106.75	106.06	106.76	106.52	0.40	107.71	108.66	109.78	108.72	1.03

Table 35 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and spray dried lactose (Formulation F11) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	17.92	23.31	22.21	21.14	2.84	19.52	16.85	18.14	18.17	1.34
0.50	24.87	30.32	29.11	28.10	2.85	26.77	23.56	24.77	25.03	1.61
0.75	30.13	36.64	34.62	33.79	3.32	32.27	28.46	30.06	30.26	1.91
1	35.45	42.62	40.98	39.68	3.75	36.60	32.94	34.56	34.70	1.83
2	48.40	56.25	53.39	52.68	3.97	50.49	45.40	47.44	47.78	2.56
3	56.71	63.44	61.75	60.63	3.50	60.17	55.02	57.09	57.43	2.58
4	64.90	69.51	69.20	67.87	2.57	66.38	63.16	65.44	64.99	1.65
5	71.58	75.24	75.52	74.11	2.20	72.05	69.00	70.91	70.65	1.54
6	78.33	80.43	81.51	80.09	1.61	76.79	74.50	77.22	76.17	1.46
7	83.54	86.46	87.36	85.79	1.99	82.56	79.46	83.01	81.67	1.93
8	88.41	91.75	91.86	90.68	1.96	87.20	84.86	88.24	86.77	1.73
10	96.11	97.29	98.40	97.27	1.14	95.85	93.88	97.30	95.68	1.71
12	101.90	101.89	102.61	102.13	0.41	99.82	97.44	99.70	98.99	1.34
Time (hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	20.74	20.95	22.35	21.35	0.87	25.12	28.23	32.78	28.71	3.85
0.50	27.26	27.87	29.49	28.21	1.15	32.31	36.90	40.26	36.49	3.99
0.75	33.19	33.20	34.64	33.67	0.83	38.05	41.66	45.68	41.79	3.81
1	37.37	37.78	39.23	38.13	0.98	43.44	46.46	50.93	46.94	3.77
2	50.43	52.05	52.31	51.60	1.02	57.15	60.41	63.90	60.49	3.37
3	59.81	61.25	61.92	60.99	1.07	65.64	68.93	72.67	69.08	3.51
4	66.68	67.13	68.61	67.47	1.01	71.93	74.02	77.38	74.44	2.74
5	72.62	72.47	73.96	73.02	0.82	78.08	80.81	84.00	80.96	2.96
6	80.02	77.86	82.18	80.02	2.16	82.43	84.35	87.57	84.78	2.60
7	84.88	82.90	86.46	84.75	1.78	86.19	86.27	91.80	88.09	3.21
8	88.98	86.98	90.18	88.71	1.61	89.16	92.35	96.28	92.59	3.56
10	97.94	94.71	98.15	96.93	1.92	96.70	99.30	102.65	99.55	2.98
12	101.17	100.11	101.97	101.08	0.93	102.87	104.67	105.98	104.51	1.55

Table 36 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and spray dried lactose (Formulation F12) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	15.42	14.05	14.25	14.58	0.74	13.51	13.97	14.11	13.86	0.31
0.50	21.27	19.50	19.50	20.09	1.02	17.60	17.68	18.05	17.77	0.24
0.75	26.21	24.21	24.61	25.01	1.05	20.61	20.99	21.00	20.87	0.21
1	30.21	28.20	28.21	28.87	1.16	23.29	23.82	23.97	23.69	0.35
2	42.49	39.86	39.28	40.54	1.70	31.93	32.62	32.55	32.37	0.37
3	53.72	50.87	49.30	51.29	2.23	38.89	39.58	40.18	39.55	0.64
4	60.76	57.49	56.69	58.31	2.15	44.43	45.80	46.18	45.47	0.92
5	67.09	64.17	63.76	65.01	1.81	49.59	51.49	51.32	50.80	1.05
6	72.70	69.17	69.14	70.33	2.04	54.57	57.05	56.70	56.11	1.34
7	77.77	74.01	73.20	74.99	2.44	58.68	61.93	60.82	60.48	1.65
8	83.49	80.27	79.65	81.13	2.06	63.94	66.85	64.99	65.26	1.47
10	93.37	91.10	90.86	91.77	1.38	73.14	77.02	75.14	75.10	1.93
12	98.45	96.55	96.70	97.23	1.05	81.71	84.69	86.13	84.18	2.25
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	12.23	14.86	14.73	13.94	1.48	16.21	14.97	14.11	15.10	1.05
0.50	17.61	20.68	20.68	19.65	1.77	21.61	19.93	19.08	20.21	1.28
0.75	19.88	22.71	22.79	21.79	1.65	24.51	23.26	22.10	23.29	1.20
1	23.18	26.04	26.11	25.11	1.67	27.52	26.48	25.39	26.46	1.06
2	33.04	35.70	35.78	34.84	1.55	36.94	35.89	34.86	35.89	1.03
3	41.17	43.70	43.86	42.91	1.51	44.56	43.65	42.15	43.45	1.21
4	48.45	50.25	50.41	49.70	1.08	50.59	49.90	49.07	49.85	0.75
5	53.12	55.44	55.83	54.80	1.46	57.13	55.91	55.07	56.04	1.03
6	63.50	61.79	61.61	62.30	1.03	62.11	61.44	60.41	61.32	0.85
7	67.25	64.95	66.11	66.10	1.15	69.04	66.09	64.66	66.59	2.23
8	73.15	70.44	70.07	71.22	1.68	74.14	70.96	69.14	71.41	2.59
10	84.11	81.36	80.03	81.83	2.07	83.65	81.01	78.60	81.09	2.52
12	91.14	89.90	87.98	89.67	1.59	92.13	89.08	89.11	90.11	1.74

Table 36 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and spray dried lactose (Formulation F12) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	5.76	5.65	5.73	5.72	0.05	10.21	9.69	11.11	10.34	0.72
0.50	8.45	8.43	8.28	8.39	0.09	13.80	12.92	14.71	13.81	0.89
0.75	10.95	10.92	10.90	10.92	0.02	17.10	16.05	18.15	17.10	1.05
1	13.28	13.21	13.89	13.46	0.37	20.02	19.10	21.38	20.17	1.14
2	21.12	21.34	22.24	21.57	0.59	29.03	27.88	31.51	29.48	1.85
3	28.41	28.70	28.42	28.51	0.16	37.84	36.02	41.02	38.29	2.53
4	34.70	35.07	34.90	34.89	0.18	44.95	42.67	48.39	45.34	2.87
5	40.27	40.28	40.66	40.41	0.22	51.54	48.30	53.53	51.12	2.63
6	45.91	47.21	45.93	46.35	0.74	59.29	54.92	59.46	57.89	2.57
7	51.78	51.06	51.80	51.55	0.42	65.28	61.41	64.89	63.86	2.13
8	57.53	56.80	58.48	57.61	0.84	72.99	67.61	71.68	70.76	2.80
10	67.05	66.32	67.09	66.82	0.43	83.93	79.03	82.41	81.79	2.50
12	76.86	74.63	76.71	76.07	1.24	90.91	87.25	90.11	89.42	1.91
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	12.50	13.97	11.83	12.77	1.09	20.03	19.06	21.10	20.06	1.02
0.50	16.65	18.42	16.02	17.03	1.23	24.87	23.55	26.01	24.81	1.22
0.75	20.26	22.16	19.72	20.71	1.28	29.15	27.58	30.25	28.99	1.34
1	23.32	25.32	22.78	23.81	1.34	32.86	30.66	33.35	32.29	1.43
2	32.70	35.10	32.45	33.42	1.46	42.54	40.08	43.04	41.89	1.58
3	40.83	44.08	40.80	41.91	1.88	50.47	47.68	50.44	49.53	1.60
4	47.70	50.83	47.48	48.67	1.87	56.46	53.64	55.55	55.22	1.43
5	54.19	57.55	54.54	55.43	1.84	63.43	60.77	62.50	62.23	1.34
6	60.38	62.65	59.80	60.94	1.50	67.57	66.42	67.21	67.07	0.58
7	64.76	68.73	65.29	66.26	2.15	72.71	71.36	72.54	72.20	0.73
8	71.06	74.13	70.84	72.01	1.84	77.13	75.01	76.77	76.30	1.13
10	83.39	89.12	88.41	86.98	3.12	86.80	84.84	87.78	86.47	1.49
12	93.24	94.54	93.27	93.69	0.74	95.79	95.36	95.62	95.59	0.22

Table 37 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and spray dried lactose (Formulation F13) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	10.81	10.75	10.40	10.65	0.22	10.22	9.47	10.24	9.98	0.43
0.50	15.94	15.86	15.62	15.80	0.16	11.84	12.07	12.51	12.14	0.34
0.75	20.23	19.91	19.51	19.88	0.36	14.26	14.63	14.98	14.63	0.36
1	23.06	22.98	22.89	22.98	0.08	16.73	17.10	17.53	17.12	0.40
2	32.90	33.52	33.43	33.28	0.33	25.58	25.51	25.60	25.56	0.05
3	42.12	41.49	41.24	41.62	0.45	33.07	32.77	32.11	32.65	0.48
4	49.44	49.04	48.63	49.04	0.40	39.13	39.69	38.02	38.95	0.85
5	55.32	55.11	55.09	55.17	0.12	44.43	44.25	42.74	43.81	0.92
6	64.23	63.42	64.00	63.88	0.41	51.10	49.79	47.52	49.47	1.81
7	71.05	68.45	69.82	69.77	1.29	57.47	57.45	52.15	55.69	3.06
8	75.36	73.73	73.93	74.34	0.89	64.83	64.82	58.52	62.73	3.63
10	91.01	85.79	86.98	87.92	2.73	78.09	76.96	70.03	75.03	4.36
12	96.71	94.60	95.61	95.64	1.05	90.37	89.03	84.84	88.08	2.88
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	9.24	9.84	8.93	9.34	0.46	9.33	9.81	10.12	9.76	0.39
0.50	12.56	12.88	12.25	12.56	0.31	12.93	13.32	13.94	13.40	0.50
0.75	15.34	15.67	15.49	15.50	0.16	16.61	16.16	16.09	15.96	0.29
1	18.39	18.40	17.92	18.24	0.27	18.40	18.95	18.96	18.77	0.32
2	26.68	27.47	25.97	26.70	0.75	26.90	27.46	27.24	27.20	0.28
3	34.04	34.22	33.87	34.04	0.17	34.18	34.90	34.91	34.67	0.41
4	40.39	40.22	39.79	40.13	0.31	41.05	41.85	41.09	41.33	0.45
5	46.08	46.10	47.02	46.40	0.53	47.06	47.68	47.30	47.35	0.31
6	51.62	52.81	54.91	53.11	1.66	52.95	52.42	52.61	52.66	0.26
7	59.17	60.57	65.02	61.59	3.05	58.31	58.16	57.78	58.08	0.27
8	67.77	68.59	72.91	69.76	2.75	64.50	63.78	63.96	64.08	0.37
10	81.89	84.09	88.26	84.75	3.23	77.29	76.17	75.58	76.35	0.86
12	92.48	93.73	98.52	94.91	3.19	90.40	89.65	88.68	89.57	0.86

Table 37 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and spray dried lactose (Formulation F13) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.17	4.12	5.19	4.49	0.60	6.94	6.69	7.04	6.89	0.17
0.50	6.44	6.33	6.64	6.47	0.15	9.86	9.60	10.06	9.84	0.22
0.75	8.69	8.56	8.96	8.74	0.19	12.73	12.35	12.81	12.63	0.24
1	10.92	10.76	11.11	10.93	0.17	15.18	14.85	15.36	15.13	0.25
2	18.63	18.32	18.57	18.51	0.16	23.86	23.84	24.09	23.93	0.13
3	26.12	25.58	25.61	25.77	0.30	31.59	32.47	31.97	32.01	0.44
4	32.87	32.48	32.31	32.55	0.28	38.60	39.34	38.42	38.79	0.48
5	39.42	38.65	38.11	38.72	0.65	44.80	45.18	45.01	45.00	0.18
6	44.91	44.70	44.15	44.59	0.39	50.70	51.46	51.09	51.08	0.37
7	51.59	49.87	50.26	50.57	0.90	56.66	59.48	56.12	57.42	1.80
8	57.58	55.85	56.24	56.56	0.91	63.24	67.21	62.32	64.26	2.60
10	69.27	67.52	68.29	68.36	0.88	78.48	82.87	77.36	79.57	2.91
12	81.46	80.81	80.28	80.8	0.59	91.45	94.77	89.57	91.93	2.63
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	9.94	10.09	10.19	10.08	0.12	13.86	12.92	13.70	13.49	0.50
0.50	13.61	13.73	13.94	13.76	0.16	17.52	16.49	17.52	17.18	0.59
0.75	16.66	16.73	16.99	16.79	0.17	20.56	19.79	20.67	20.34	0.47
1	19.69	19.85	20.08	19.87	0.19	23.62	22.81	23.93	23.45	0.57
2	28.68	29.21	29.45	29.11	0.39	32.29	31.55	32.52	32.12	0.50
3	36.85	37.47	37.63	37.32	0.41	39.96	39.29	40.98	40.08	0.85
4	43.26	44.41	44.04	43.90	0.58	45.40	44.95	46.78	45.71	0.95
5	50.91	50.94	50.01	50.61	0.53	52.51	51.08	53.12	52.24	1.04
6	59.20	56.59	55.26	57.02	2.01	57.35	56.89	58.17	57.47	0.64
7	69.48	62.29	61.33	64.37	4.45	62.05	60.80	65.60	62.82	2.49
8	77.78	70.89	68.41	72.36	4.85	68.55	65.73	73.89	69.39	4.14
10	89.57	83.55	81.23	84.78	4.30	84.07	80.44	88.70	84.40	4.13
12	96.75	91.61	92.10	93.49	2.83	97.03	95.31	98.40	96.91	1.54

Table 38 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and spray dried lactose (Formulation F14) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	9.52	9.34	9.01	9.29	0.26	7.38	7.84	7.25	7.49	0.30
0.50	13.57	13.39	12.93	13.30	0.32	9.59	9.70	9.81	9.70	0.10
0.75	16.63	16.50	16.02	16.38	0.32	12.35	12.39	12.39	12.38	0.02
1	19.62	19.55	18.94	19.37	0.37	14.67	14.68	14.73	17.70	0.03
2	28.74	28.40	27.88	28.34	0.43	22.48	22.81	22.80	22.70	0.18
3	36.13	35.62	34.93	35.56	0.60	29.20	29.44	29.75	29.46	0.27
4	42.51	42.74	41.04	42.10	0.91	35.35	35.36	35.12	35.28	0.13
5	48.97	48.75	47.45	48.39	0.82	41.05	40.28	40.47	40.60	0.40
6	53.44	53.43	52.95	53.27	0.28	47.41	47.81	47.02	47.41	0.39
7	59.21	58.36	57.67	58.41	0.77	54.03	54.63	53.43	54.03	0.59
8	67.32	64.39	64.31	65.34	1.71	60.32	61.12	59.72	60.39	0.70
10	84.25	78.99	76.63	79.96	3.90	73.97	74.59	72.77	73.78	0.92
12	95.12	93.76	91.37	93.42	1.89	87.77	87.21	87.74	87.57	0.31
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.51	6.90	6.66	6.69	0.19	7.26	7.96	8.04	7.75	0.42
0.50	9.43	9.86	9.53	9.60	0.22	10.17	10.09	10.42	10.23	0.16
0.75	12.25	12.76	12.41	12.47	0.26	12.94	13.19	13.84	13.33	0.46
1	15.03	15.58	15.22	15.28	0.27	15.51	15.76	16.58	15.95	0.55
2	24.59	24.85	24.35	24.60	0.25	24.15	24.08	24.75	24.33	0.36
3	32.45	33.21	31.97	32.54	0.62	31.60	32.10	32.21	31.97	0.32
4	38.93	39.45	38.36	38.91	0.54	38.81	38.74	38.61	38.72	0.10
5	45.06	45.51	44.85	45.14	0.33	45.12	45.34	45.36	45.27	0.13
6	51.47	52.33	53.30	52.36	0.91	51.25	51.88	52.11	51.75	0.44
7	57.33	58.19	60.60	58.71	1.69	58.46	58.28	59.12	58.62	0.44
8	64.88	64.94	68.80	66.21	2.24	64.73	66.37	67.62	66.24	1.44
10	78.84	79.71	84.44	81.00	3.01	79.55	81.01	81.46	80.67	0.99
12	93.35	94.03	95.75	94.38	1.23	91.89	92.96	93.22	92.69	0.70

Table 38 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and spray dried lactose (Formulation F14) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.60	3.76	3.72	3.69	0.08	5.66	5.68	5.82	5.72	0.08
0.50	5.87	6.01	5.95	5.94	0.07	8.35	8.39	8.65	8.47	0.16
0.75	8.10	8.40	8.18	8.23	0.15	11.11	11.02	11.34	11.16	0.16
1	10.28	10.58	10.54	10.47	0.16	13.83	13.83	14.00	13.89	0.09
2	17.71	18.27	18.03	18.01	0.28	22.62	21.99	22.63	22.41	0.36
3	25.48	25.42	25.09	25.33	0.20	31.03	30.31	30.80	30.71	0.36
4	31.87	31.89	32.47	32.08	0.34	38.44	37.45	37.27	37.72	0.63
5	39.32	42.29	40.91	40.84	1.48	45.53	43.54	43.96	44.34	1.04
6	47.63	49.26	49.64	48.84	1.06	54.26	51.08	51.69	52.34	1.69
7	55.05	57.48	58.85	57.13	1.92	63.28	59.28	59.70	60.75	2.20
8	63.92	66.58	67.76	66.09	1.96	72.01	67.36	68.18	69.18	2.47
10	78.80	81.29	81.90	80.66	1.63	87.29	83.97	84.21	85.16	1.84
12	89.90	92.41	93.22	91.84	1.73	96.85	94.08	95.11	95.35	1.39
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.21	6.97	7.11	7.10	0.11	10.33	9.89	11.42	10.55	0.78
0.50	10.36	10.23	10.44	10.35	0.10	13.53	13.14	14.77	13.81	0.84
0.75	13.34	13.12	13.31	13.26	0.11	16.57	15.99	17.60	16.72	0.81
1	16.03	15.87	15.95	15.95	0.08	19.17	18.58	20.43	19.39	0.94
2	24.79	24.38	24.55	24.57	0.20	27.89	27.21	29.25	28.12	1.03
3	32.76	32.03	32.76	32.52	0.41	36.05	34.38	36.77	35.73	1.22
4	39.58	38.77	38.98	39.11	0.42	43.25	40.75	42.91	42.30	1.35
5	47.56	47.92	46.55	47.34	0.71	51.49	47.94	49.72	49.71	1.77
6	58.39	59.36	53.21	56.99	3.30	63.09	53.77	55.98	57.61	4.87
7	68.55	69.73	60.13	66.14	5.23	74.00	59.66	61.28	64.98	7.85
8	78.02	79.61	68.91	75.51	5.77	84.40	67.66	68.27	73.45	9.49
10	88.98	90.58	87.32	88.96	1.63	99.83	85.97	84.95	90.25	8.31
12	101.24	101.27	98.77	100.43	1.43	107.02	101.41	100.37	102.94	3.57

Table 39 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and spray dried lactose (Formulation F15) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	6.68	6.57	6.75	6.67	0.09	4.70	4.41	4.33	4.48	0.19
0.50	9.28	9.22	9.39	9.29	0.08	6.70	6.47	6.35	6.50	0.17
0.75	11.41	11.34	11.60	11.45	0.13	8.65	8.39	8.12	8.39	0.26
1	13.36	13.26	13.56	13.39	0.15	10.39	10.14	10.01	10.18	0.19
2	20.04	19.87	20.31	20.07	0.21	16.69	16.31	16.57	16.52	0.19
3	25.89	25.97	26.33	26.06	0.23	22.35	21.93	22.33	22.20	0.23
4	31.29	31.63	31.47	31.46	0.16	27.61	27.59	27.51	27.57	0.05
5	36.85	36.85	37.08	36.92	0.13	33.61	32.58	33.18	33.12	0.51
6	41.29	40.87	40.89	41.02	0.24	38.22	38.39	39.01	38.53	0.41
7	46.00	45.35	45.37	45.58	0.36	44.29	43.25	43.66	43.73	0.52
8	50.11	49.89	50.12	50.04	0.13	49.81	48.16	47.97	48.65	1.01
10	58.74	57.88	59.18	58.60	0.66	60.86	58.17	57.78	58.94	1.67
12	67.04	65.95	67.05	66.68	0.63	73.84	68.29	69.51	70.55	2.91
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.13	4.54	4.61	4.76	0.32	5.07	5.09	4.84	5.00	0.13
0.50	6.89	6.62	6.70	6.74	0.14	6.96	7.03	6.84	6.94	0.09
0.75	8.97	8.77	8.77	8.84	0.11	9.07	9.03	8.80	8.97	0.14
1	10.93	10.65	10.67	10.75	0.15	11.03	11.03	10.80	10.95	0.13
2	17.27	17.17	17.05	17.16	0.11	17.65	17.65	17.48	17.59	0.10
3	24.01	23.66	23.66	23.78	0.20	23.80	23.64	23.96	23.80	0.15
4	29.05	29.45	29.11	29.20	0.21	29.53	29.53	29.93	29.66	0.23
5	33.63	34.45	34.45	34.17	0.47	35.06	35.48	36.51	35.68	0.74
6	39.22	39.85	39.84	39.64	0.35	39.79	40.62	40.42	40.27	0.43
7	45.51	47.18	46.34	46.34	0.83	45.18	46.85	46.44	46.16	0.86
8	50.81	52.29	52.49	51.86	0.92	50.42	51.90	52.52	51.61	1.07
10	62.86	64.57	64.35	63.93	0.93	60.68	62.59	63.43	62.23	1.40
12	74.21	76.15	76.55	75.64	1.25	71.26	72.78	74.24	72.76	1.49

Table 39 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and spray dried lactose (Formulation F15) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.01	2.86	3.03	2.96	0.08	3.91	3.95	4.01	3.96	0.04
0.50	4.48	4.46	4.61	4.52	0.08	5.96	6.02	6.07	6.02	0.05
0.75	6.27	6.30	6.41	6.33	0.07	7.91	7.99	8.02	7.97	0.05
1	7.96	8.07	8.21	8.08	0.12	9.60	9.69	9.79	9.69	0.09
2	14.12	13.80	14.21	14.05	0.21	16.14	15.90	16.06	16.03	0.12
3	20.35	19.86	21.41	20.54	0.79	22.11	22.03	22.11	22.08	0.04
4	28.46	28.25	30.10	28.94	1.01	28.04	27.23	27.44	27.57	0.41
5	37.26	37.86	40.74	38.62	1.85	32.77	33.16	33.37	33.10	0.30
6	47.38	47.37	50.89	48.55	2.02	42.18	39.15	39.77	40.37	1.59
7	58.01	58.40	61.15	59.18	1.71	44.84	45.21	45.42	45.16	0.29
8	69.55	68.74	71.72	70.01	1.54	51.16	51.32	52.15	51.54	0.53
10	88.90	88.89	92.31	90.03	1.96	64.18	63.74	65.38	64.43	0.84
12	101.79	101.98	106.24	103.33	2.51	78.74	77.50	78.75	78.33	0.72
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.03	4.98	4.98	5.00	0.03	6.28	6.31	6.28	6.29	0.01
0.50	7.43	7.29	7.34	7.35	0.06	8.82	8.76	8.65	8.74	0.08
0.75	9.44	9.30	9.30	9.34	0.07	10.93	10.87	10.81	10.87	0.05
1	11.30	11.16	11.19	11.22	0.07	12.90	12.87	12.86	12.88	0.01
2	17.76	17.92	17.59	17.76	0.16	19.38	19.21	19.37	19.32	0.09
3	23.82	24.06	23.73	23.87	0.17	26.13	25.54	25.79	25.82	0.29
4	29.65	29.04	29.44	29.37	0.31	30.04	29.82	30.46	30.11	0.32
5	34.54	34.24	34.03	34.24	0.20	36.03	35.81	35.61	35.82	0.21
6	40.11	39.09	39.08	39.43	0.59	41.46	41.02	39.77	40.75	0.87
7	45.23	44.61	44.59	44.81	0.36	45.47	46.71	45.86	46.01	0.63
8	51.01	50.16	49.75	50.31	0.63	49.93	52.03	49.91	50.63	1.21
10	61.73	60.47	59.64	60.61	1.04	61.37	63.49	59.67	61.51	1.91
12	72.77	70.48	69.44	70.89	1.70	72.51	75.07	69.12	72.23	2.98

Table 40 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and dibasic calcium phosphate (Formulation F16) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	10.00	10.46	9.26	9.91	0.60	8.83	7.88	8.91	8.54	0.57
0.50	14.25	14.73	13.33	14.10	0.71	12.93	11.65	12.55	12.38	0.66
0.75	18.85	19.26	17.69	18.60	0.81	15.71	16.61	15.16	15.83	0.73
1	22.56	22.90	21.06	22.17	0.97	19.67	18.03	19.04	18.91	0.82
2	35.04	35.06	33.12	34.41	1.11	29.24	26.89	26.90	27.68	1.35
3	45.70	45.56	43.59	44.95	1.17	35.90	33.83	33.31	34.35	1.37
4	54.52	53.55	52.47	53.51	1.02	41.86	39.77	38.93	40.19	1.51
5	62.61	61.49	59.74	61.38	1.58	47.61	45.19	43.45	45.41	2.09
6	70.32	69.29	66.70	68.77	1.86	51.79	49.34	47.78	49.64	2.02
7	79.02	78.39	74.35	77.25	2.53	56.21	53.73	51.96	53.97	2.13
8	85.36	84.52	81.86	83.92	1.82	59.70	57.01	55.60	57.44	2.08
10	96.46	94.18	93.13	94.59	1.70	67.68	64.37	63.14	65.07	2.34
12	101.55	98.84	99.41	99.93	1.43	78.05	72.59	71.93	74.19	3.36
Time (hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	9.53	8.89	9.65	9.36	0.40	9.01	9.73	8.82	9.19	0.48
0.50	14.06	12.84	13.75	13.55	0.63	13.06	13.86	12.82	13.25	0.54
0.75	17.18	16.44	17.18	16.93	0.42	16.47	17.28	16.15	16.63	0.58
1	20.41	19.50	20.25	20.06	0.48	19.74	20.71	19.49	19.98	0.64
2	29.45	28.45	29.20	29.03	0.52	29.37	29.97	28.57	29.30	0.69
3	36.01	35.08	36.01	35.70	0.53	36.90	37.57	35.93	36.80	0.82
4	41.93	40.83	42.01	41.59	0.65	42.84	42.97	41.62	42.48	0.74
5	47.34	45.67	46.74	46.58	0.84	47.54	46.99	45.32	46.62	1.15
6	51.25	49.76	51.24	50.75	0.85	51.81	51.06	49.36	50.74	1.25
7	55.20	53.89	55.59	54.89	0.88	54.93	54.77	52.86	54.18	1.15
8	58.98	58.07	58.98	58.68	0.52	59.27	59.10	57.17	58.52	1.16
10	65.41	64.48	66.60	65.50	1.06	65.63	65.07	63.12	64.60	1.31
12	71.10	69.96	71.70	70.92	0.88	71.06	70.49	68.92	70.16	1.11

Table 40 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and dibasic calcium phosphate (Formulation F16) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	7.84	7.65	7.76	7.75	0.09	7.15	7.03	7.15	7.11	0.06
0.50	11.66	11.45	11.55	11.55	0.11	11.04	10.79	10.81	10.88	0.13
0.75	15.58	15.19	15.99	15.32	0.22	14.88	14.49	14.26	14.55	0.31
1	18.69	18.38	18.46	18.51	0.16	17.82	17.27	16.96	17.35	0.43
2	28.80	28.56	28.79	28.72	0.13	27.86	27.16	26.61	27.21	0.62
3	37.63	37.22	37.77	37.54	0.28	36.33	35.30	34.75	35.46	0.79
4	45.31	44.67	45.61	45.19	0.48	43.80	42.31	41.60	42.57	1.12
5	52.61	51.42	52.41	52.15	0.63	49.58	48.30	47.28	48.39	1.15
6	58.78	57.77	58.58	58.38	0.53	55.33	53.92	53.11	54.12	1.12
7	63.66	62.26	64.24	63.39	1.01	59.96	59.30	57.91	59.06	1.04
8	68.98	67.37	69.17	68.51	0.99	64.25	63.39	60.06	62.57	2.21
10	77.64	75.04	76.48	76.38	1.30	73.78	71.95	70.12	71.95	1.82
12	85.80	82.21	82.69	83.57	1.94	82.63	78.48	77.40	79.50	2.76
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.56	7.29	7.74	7.53	0.22	8.36	7.51	8.42	8.09	0.51
0.50	11.39	11.07	11.60	11.35	0.26	11.78	11.17	11.96	11.64	0.41
0.75	15.21	14.73	15.52	15.16	0.39	15.45	14.55	15.30	15.10	0.48
1	18.02	17.70	18.42	18.05	0.36	18.19	17.36	18.19	17.92	0.47
2	27.72	27.32	28.44	27.83	0.56	26.74	25.90	26.42	26.35	0.42
3	39.56	35.02	36.46	37.01	2.31	33.61	33.17	33.21	33.33	0.24
4	42.24	41.40	43.16	42.27	0.88	39.43	38.66	38.70	38.93	0.43
5	47.76	46.91	48.85	47.84	0.97	44.75	43.81	44.02	44.19	0.49
6	53.41	51.96	53.81	53.06	0.97	50.18	48.90	48.54	49.21	0.86
7	57.29	56.02	58.66	57.32	1.32	53.32	52.02	51.86	52.40	0.79
8	58.87	58.95	60.84	59.55	1.11	57.08	55.97	55.61	56.22	0.76
10	68.64	67.74	70.24	68.87	1.26	63.69	62.37	64.01	63.36	0.86
12	75.97	76.83	78.38	77.06	1.21	69.77	68.23	70.69	69.56	1.78

Table 41 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and dibasic calcium phosphate (Formulation F17) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	9.87	9.52	9.48	9.62	0.21	7.00	9.95	8.54	8.50	1.47
0.50	14.38	13.59	13.36	13.78	0.53	10.93	13.27	11.81	12.01	1.18
0.75	18.90	17.89	17.48	18.09	0.72	14.43	16.68	17.59	16.24	1.62
1	22.57	21.47	20.89	21.64	0.85	16.78	19.37	17.78	17.98	1.30
2	33.29	31.77	31.43	32.16	0.99	25.26	27.95	26.43	26.55	1.35
3	42.90	41.03	40.10	41.34	1.42	31.72	34.91	32.97	33.20	1.60
4	51.63	50.11	48.64	50.13	1.49	37.73	41.04	38.42	39.06	1.74
5	57.55	55.81	54.53	55.96	1.51	42.05	46.56	44.50	44.37	2.25
6	64.97	63.01	60.68	62.59	2.14	46.41	50.78	48.69	48.63	2.18
7	72.68	68.43	66.49	69.20	3.16	50.82	56.01	53.32	53.38	2.59
8	80.46	74.51	73.17	76.05	3.88	54.88	60.32	57.21	57.47	2.73
10	92.04	87.26	87.56	88.95	2.67	62.10	67.60	65.24	64.98	2.75
12	98.37	97.87	97.97	98.07	0.26	69.99	79.07	71.40	73.49	4.88
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	9.08	8.08	7.88	8.35	0.63	9.83	8.46	9.55	9.28	0.71
0.50	12.50	11.17	11.09	11.59	0.79	13.66	11.98	13.02	12.89	0.84
0.75	16.46	14.90	15.22	15.53	0.82	17.39	15.52	16.58	16.50	0.94
1	18.83	16.92	17.17	17.64	1.03	20.31	18.25	19.25	19.27	1.02
2	27.30	24.97	25.78	26.02	1.83	29.02	26.78	27.78	27.86	1.12
3	34.08	31.32	32.71	32.70	1.38	35.82	33.40	34.74	34.65	1.21
4	39.88	36.68	38.33	38.29	1.59	41.49	38.97	40.64	40.37	1.28
5	45.73	42.74	44.01	44.16	1.50	45.66	44.51	47.01	45.73	1.24
6	50.07	46.64	48.52	48.41	1.71	50.96	48.79	51.11	50.29	1.29
7	53.64	50.78	52.48	52.30	1.43	54.70	52.71	54.45	53.96	1.08
8	57.44	54.76	56.28	56.16	1.34	58.28	56.87	59.03	58.06	1.09
10	64.53	61.82	62.95	63.10	1.36	65.30	64.08	65.86	65.08	0.91
12	71.48	68.95	69.48	69.97	1.33	71.18	70.95	72.75	71.63	0.97

Table 41 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and dibasic calcium phosphate (Formulation F17) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	5.43	5.56	5.56	5.52	0.07	6.38	7.87	7.04	7.10	0.75
0.50	8.42	8.54	8.41	8.46	0.07	9.41	11.25	10.25	10.30	0.92
0.75	11.20	11.38	11.18	11.25	0.11	12.61	14.67	13.49	13.59	1.03
1	13.47	13.64	13.40	13.50	0.12	15.48	17.72	16.28	16.49	1.13
2	22.00	22.24	21.60	21.95	0.31	23.90	26.78	25.02	25.23	1.45
3	29.51	30.23	29.51	29.75	0.41	30.70	33.93	32.77	32.47	1.63
4	35.39	36.58	35.62	35.86	0.63	37.18	40.52	39.82	39.18	1.76
5	41.33	42.69	41.48	41.83	0.74	42.72	47.35	45.31	45.13	2.31
6	45.57	48.55	45.97	46.70	1.61	48.22	52.74	50.87	50.61	2.27
7	50.56	52.40	50.76	51.24	1.01	53.02	57.00	55.51	55.17	2.01
8	55.01	57.06	55.41	55.83	1.08	57.47	60.91	59.79	59.39	1.75
10	63.42	65.49	63.62	64.18	1.14	65.47	68.75	67.62	67.28	1.65
12	70.93	75.77	71.34	72.68	2.68	72.97	79.40	78.26	76.88	3.42
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.65	7.38	7.83	7.62	0.22	9.07	9.80	11.10	9.99	1.02
0.50	11.95	11.73	12.84	12.17	0.58	12.84	13.62	14.97	13.81	1.07
0.75	15.63	15.46	16.74	15.94	0.69	16.70	17.29	18.62	17.54	0.98
1	18.56	17.92	19.21	18.56	0.64	19.16	20.00	21.50	20.22	1.18
2	26.72	26.54	28.09	27.12	0.84	28.22	29.06	30.59	29.29	1.19
3	33.55	33.69	35.17	34.14	0.89	35.43	37.18	38.55	37.05	1.56
4	39.35	39.73	41.15	40.07	0.94	42.06	43.26	43.76	43.03	0.87
5	44.18	45.36	46.47	45.34	1.14	46.90	48.52	48.69	48.04	0.98
6	49.73	50.52	52.40	50.89	1.37	52.11	54.26	54.56	53.64	1.33
7	53.81	55.01	56.90	55.24	1.55	56.51	58.48	58.78	57.92	1.23
8	57.92	58.93	61.83	59.56	2.03	59.94	62.13	62.44	61.50	1.36
10	65.62	66.45	69.18	67.08	1.86	66.49	68.68	68.78	67.98	1.29
12	77.34	77.39	80.15	78.29	1.60	76.69	78.72	79.43	78.28	1.42

Table 42 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and dibasic calcium phosphate (Formulation F18) in various dissolution media

Time (hr)	Percentage amount of drug releases									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	9.46	10.23	9.58	9.76	0.41	7.16	7.87	7.59	7.54	0.35
0.50	13.49	14.22	13.74	13.82	0.37	9.98	10.67	10.57	10.41	0.37
0.75	17.67	18.60	17.93	18.07	0.48	13.49	13.98	13.90	13.79	0.26
1	20.86	21.55	21.11	21.17	0.34	15.37	16.42	16.26	16.02	0.56
2	30.47	30.92	31.06	30.81	0.30	23.42	24.86	24.46	24.25	0.74
3	39.10	39.22	39.37	39.23	0.13	29.26	30.96	30.87	30.37	0.95
4	47.06	47.10	46.66	46.94	0.24	35.13	36.57	36.56	36.09	0.83
5	52.34	52.59	52.35	52.43	0.13	39.84	41.30	40.70	40.61	0.73
6	58.92	59.17	58.73	58.94	0.22	43.61	45.09	44.67	44.46	0.76
7	66.19	67.27	67.03	66.83	0.56	47.82	49.50	49.28	48.87	0.91
8	74.78	75.25	75.01	75.01	0.23	51.87	53.37	53.54	52.93	0.92
10	88.23	88.09	88.88	88.40	0.42	59.10	61.22	60.80	60.37	1.11
12	94.77	96.07	98.33	96.39	1.80	65.63	71.11	68.52	68.42	2.74
Time (hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.20	6.85	7.34	7.13	0.25	7.73	7.65	7.51	7.63	0.11
0.50	10.27	9.76	10.32	10.12	0.30	10.82	10.76	10.66	10.75	0.08
0.75	13.91	13.33	13.34	13.53	0.33	14.14	13.98	13.98	14.04	0.09
1	15.94	15.35	16.10	15.80	0.39	16.72	16.55	16.55	16.61	0.09
2	24.27	23.19	23.94	23.80	0.55	25.04	24.55	24.55	24.71	0.28
3	31.30	30.37	30.89	30.85	0.46	31.76	30.78	31.10	31.22	0.49
4	37.27	35.92	36.60	36.60	0.67	37.91	36.52	37.01	37.14	0.70
5	42.56	41.89	41.32	41.92	0.62	43.27	41.83	42.44	42.51	0.72
6	47.50	46.01	46.45	46.65	1.64	47.97	45.90	46.52	46.80	1.06
7	52.08	50.78	50.61	51.16	0.80	51.30	50.22	50.44	50.65	0.57
8	55.69	54.37	54.20	54.76	0.81	55.27	53.97	54.20	54.48	0.69
10	63.21	62.28	61.91	62.47	0.66	63.30	61.58	61.82	62.24	0.92
12	71.41	69.87	68.47	69.92	1.47	69.81	69.29	68.91	69.34	0.45

Table 42 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and dibasic calcium phosphate (Formulation F18) in various dissolution media

Time (hr)	Percentage amount of drug releases									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.81	4.79	4.64	4.74	0.09	6.06	5.99	6.44	6.16	0.24
0.50	7.49	7.47	7.23	7.39	0.14	8.99	8.85	9.33	9.06	0.24
0.75	10.15	10.15	9.79	10.03	0.21	12.21	11.90	12.38	12.16	0.24
1	12.27	12.27	11.79	12.11	0.27	14.70	14.38	14.94	14.67	0.28
2	20.44	20.36	19.71	20.17	0.39	23.24	22.53	23.10	22.96	0.37
3	28.14	28.22	27.33	27.90	0.49	30.39	29.36	30.32	30.02	0.57
4	34.12	34.51	33.46	34.03	0.53	36.68	35.63	37.08	36.46	0.74
5	39.92	40.24	39.57	39.91	0.33	42.40	41.11	42.34	41.95	0.72
6	44.37	45.37	44.14	44.63	0.65	47.51	46.85	47.90	47.42	0.52
7	48.79	49.59	48.35	48.91	0.63	52.70	51.08	52.72	52.17	0.94
8	53.44	54.25	53.59	53.76	0.43	56.79	55.54	57.20	56.51	0.86
10	61.68	63.10	62.62	62.47	0.71	64.44	64.15	66.03	64.87	1.01
12	70.60	73.61	72.14	72.12	1.50	74.32	76.78	77.50	76.20	1.66
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.50	7.80	7.50	7.60	0.17	8.74	9.08	8.45	8.76	0.31
0.50	10.72	11.00	10.74	10.82	0.15	12.26	12.41	11.89	12.19	0.26
0.75	14.12	14.37	14.12	14.21	0.14	15.49	16.07	15.89	15.82	0.29
1	16.66	16.83	16.42	16.63	0.20	18.20	18.29	17.95	18.14	0.17
2	25.01	25.18	24.53	24.91	0.33	26.89	27.15	26.56	26.87	0.29
3	31.62	32.27	31.30	31.73	0.49	34.46	33.98	33.71	34.05	0.37
4	37.28	37.86	37.03	37.39	0.42	39.82	39.83	39.64	39.76	0.10
5	42.20	42.78	41.79	42.26	0.49	44.98	44.75	44.07	44.60	0.47
6	47.13	47.75	46.51	47.13	0.62	49.84	49.64	48.77	49.42	0.56
7	52.19	51.63	51.57	51.80	0.34	54.65	54.24	52.96	53.95	0.88
8	55.91	56.14	55.68	55.91	0.23	57.88	57.87	56.78	57.51	0.63
10	63.84	64.47	65.59	64.63	0.88	64.60	64.60	63.91	64.37	0.40
12	74.02	78.43	79.76	77.40	3.00	71.61	73.03	71.72	72.12	0.79

Table 43 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and dibasic calcium phosphate (Formulation F19) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	9.12	9.09	9.06	9.09	0.02	5.29	5.49	5.48	5.42	0.11
0.50	12.08	12.19	12.06	12.11	0.06	7.98	8.17	8.08	8.08	0.09
0.75	15.33	15.53	15.17	15.35	0.17	10.45	10.57	10.51	10.51	0.05
1	17.91	18.23	17.97	18.03	0.17	12.75	12.83	12.83	12.80	0.04
2	26.46	27.09	26.85	26.80	0.32	20.15	20.68	20.53	20.45	0.27
3	34.16	34.65	34.40	34.40	0.24	26.58	27.41	26.81	26.93	0.43
4	40.29	40.78	40.38	40.48	0.26	32.10	33.17	32.41	32.56	0.54
5	46.49	46.75	46.25	46.50	0.24	36.79	36.02	37.03	37.28	0.65
6	52.03	52.85	51.80	52.23	0.55	40.74	41.72	40.57	41.01	0.62
7	58.66	59.57	58.51	58.91	0.57	44.54	45.91	44.56	45.01	0.78
8	66.64	67.67	66.05	66.78	0.82	48.19	49.57	48.58	48.78	0.71
10	80.95	82.19	80.94	81.36	0.71	55.99	57.58	56.01	56.53	0.91
12	92.26	93.32	92.25	92.61	0.61	63.69	66.60	63.34	64.54	1.79
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.45	6.47	6.10	6.34	0.20	5.70	5.64	5.99	5.78	0.18
0.50	8.91	8.91	8.73	8.86	0.11	8.79	8.71	9.18	8.89	0.24
0.75	11.50	11.56	11.23	11.43	0.17	11.78	11.70	12.00	11.82	0.15
1	13.95	14.05	13.69	13.90	0.18	14.40	14.26	14.54	14.40	0.14
2	22.01	22.32	21.45	21.92	0.43	22.73	22.19	22.43	22.45	0.27
3	29.76	29.46	28.66	29.29	0.56	29.18	28.79	28.50	28.82	0.34
4	36.13	35.90	34.63	35.55	0.81	35.09	34.61	34.32	34.67	0.38
5	41.94	41.63	39.57	41.05	1.28	41.02	40.04	39.48	40.18	0.77
6	46.34	46.34	44.02	45.57	1.33	45.67	44.30	43.73	44.57	0.99
7	50.87	50.71	48.91	50.16	1.08	49.60	48.98	48.22	48.94	0.69
8	55.24	55.23	54.15	54.87	0.62	53.77	52.76	51.98	52.84	0.89
10	63.18	62.98	61.50	62.55	0.91	61.42	61.74	59.61	60.92	1.14
12	71.98	72.55	69.31	71.28	1.72	71.06	71.96	68.47	70.50	1.81

Table 43 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and dibasic calcium phosphate (Formulation F19) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.88	4.02	4.00	3.97	0.07	4.94	4.77	4.80	4.84	0.09
0.50	6.43	6.55	6.47	6.48	0.05	7.79	7.60	7.73	7.71	0.09
0.75	8.78	8.86	8.96	8.87	0.08	10.39	10.20	10.29	10.29	0.09
1	10.90	10.96	11.07	10.98	0.08	12.74	12.13	12.70	12.52	0.33
2	18.79	18.72	18.79	18.77	0.04	20.63	20.46	20.62	20.57	0.09
3	26.03	25.81	26.18	26.01	0.18	27.85	27.46	27.55	27.62	0.20
4	32.52	31.92	32.68	32.38	0.39	33.81	33.79	33.21	33.60	0.34
5	38.26	37.66	38.72	38.21	0.53	39.16	39.07	38.33	38.86	0.45
6	44.18	42.67	43.82	43.56	0.78	44.29	44.27	42.78	43.78	0.86
7	49.52	47.43	48.22	48.39	1.05	49.23	48.84	46.96	48.34	1.21
8	54.53	51.68	53.03	53.08	1.42	53.85	53.27	51.92	53.01	0.98
10	66.53	61.20	64.82	64.18	2.71	62.79	61.65	60.10	61.51	2.19
12	79.95	71.58	76.92	76.15	4.23	73.51	71.04	67.06	70.54	3.25
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.07	5.92	6.88	6.29	0.51	7.64	7.83	7.15	7.54	0.35
0.50	8.74	8.83	9.65	9.07	0.50	10.48	10.58	10.01	10.36	0.30
0.75	11.66	11.77	12.64	12.03	0.53	13.15	13.31	12.52	12.99	0.41
1	14.05	14.20	15.06	14.43	0.54	15.39	15.70	15.14	15.41	0.28
2	21.96	21.89	23.13	22.33	0.68	23.01	23.56	23.37	22.98	0.59
3	29.06	28.15	30.09	29.10	0.96	29.86	30.34	28.74	29.65	0.81
4	35.25	33.81	35.84	34.97	1.04	35.15	36.10	33.79	35.02	1.16
5	40.15	38.55	40.90	39.87	1.20	40.34	41.00	38.19	39.84	1.46
6	45.44	43.70	45.70	44.95	1.08	45.79	46.42	43.15	45.12	1.73
7	50.44	48.12	50.15	49.57	1.26	48.99	50.01	46.52	48.50	1.79
8	53.43	51.83	52.75	52.67	0.79	52.99	54.03	50.50	52.50	1.81
10	63.78	61.42	60.65	61.95	1.63	59.75	60.22	56.84	58.94	1.82
12	77.64	75.07	72.21	74.97	2.71	70.27	68.80	64.61	67.89	2.93

Table 44 Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and dibasic calcium phosphate (Formulation F20) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.1 N HCl					PBS pH 3				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	7.90	7.95	7.32	7.73	0.35	4.31	4.33	4.42	4.35	0.06
0.50	10.50	10.52	9.80	10.27	0.41	6.24	6.26	6.32	6.27	0.04
0.75	13.17	13.26	12.50	12.97	0.41	7.99	8.01	8.09	8.03	0.05
1	15.34	15.34	14.53	15.07	0.46	9.75	9.82	9.89	9.82	0.07
2	21.16	21.58	20.72	21.15	0.42	15.67	15.75	15.76	15.73	0.04
3	27.18	27.11	26.07	26.79	0.61	21.57	21.57	21.96	21.70	0.22
4	31.94	31.86	30.49	31.43	0.81	26.98	27.45	27.22	27.22	0.23
5	36.25	36.34	34.95	35.85	0.77	31.74	31.51	31.67	31.64	0.11
6	40.69	40.61	39.29	40.20	0.78	35.06	35.45	35.85	35.46	0.39
7	44.93	44.68	43.68	44.43	0.66	40.72	39.56	39.77	40.02	0.62
8	49.14	48.93	47.59	48.55	0.84	44.10	43.90	44.11	44.03	0.11
10	57.51	56.48	54.91	56.30	1.30	52.60	53.18	52.81	52.86	0.29
12	64.73	63.89	62.31	63.64	1.22	60.41	61.39	60.22	60.67	0.62
Time(hr)	PBS pH 6.8					PBS pH 7.4				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.60	5.54	5.56	5.57	0.03	4.95	4.89	4.89	4.91	0.03
0.50	7.74	7.71	7.86	7.77	0.07	7.27	7.31	7.29	7.29	0.02
0.75	9.91	9.89	10.01	9.94	0.06	9.60	9.44	9.36	9.47	0.12
1	11.79	11.81	11.93	11.84	0.07	11.41	11.29	11.23	11.31	0.09
2	18.35	18.59	18.68	18.54	0.17	18.02	17.77	17.53	17.77	0.24
3	24.55	24.56	25.13	24.75	0.33	23.99	23.58	23.42	23.66	0.29
4	30.10	29.94	30.11	30.05	0.09	29.55	29.06	28.73	29.11	0.41
5	35.54	35.21	35.55	35.43	0.19	34.64	34.22	34.01	34.29	0.31
6	39.82	39.73	40.16	39.90	0.22	39.43	38.81	38.99	39.08	0.32
7	44.71	44.78	45.13	44.87	0.22	44.06	43.23	43.42	43.57	0.43
8	48.79	48.59	50.23	49.20	0.89	48.74	47.30	47.50	47.85	0.78
10	58.44	56.61	60.10	58.38	1.74	58.09	56.23	56.02	56.78	1.13
12	67.78	65.32	70.68	67.93	2.68	67.73	65.25	63.64	63.54	2.06

Table 44 (Continued) Percentage amounts of theophylline from matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and dibasic calcium phosphate (Formulation F20) in various dissolution media

Time (hr)	Percentage amount of drug release									
	0.01 M NaCl					0.05 M NaCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.33	3.36	3.26	3.32	0.05	4.24	4.23	4.35	4.27	0.07
0.50	5.24	5.28	5.22	5.25	0.03	6.49	6.52	6.70	6.57	0.11
0.75	7.06	7.12	7.06	7.08	0.03	8.52	8.59	8.81	8.64	0.15
1	8.61	8.71	8.63	8.65	0.05	10.27	10.33	10.45	10.35	0.09
2	14.82	14.83	14.59	14.75	0.17	16.13	16.17	16.14	16.15	0.02
3	21.42	21.11	21.02	21.18	0.21	22.09	22.33	22.02	22.15	0.16
4	27.14	26.90	26.90	26.98	0.14	27.25	27.48	27.41	27.38	0.12
5	33.47	33.08	32.83	33.13	0.32	32.53	32.39	32.39	32.44	0.09
6	39.88	39.48	39.47	39.61	0.23	36.84	37.04	37.04	36.97	0.11
7	47.75	46.17	47.54	47.16	0.85	41.33	41.14	41.73	41.40	0.30
8	56.70	53.33	55.50	55.18	1.70	46.45	45.68	47.05	46.39	0.68
10	76.71	70.76	73.14	73.54	2.99	57.28	55.72	59.06	57.35	1.67
12	91.06	87.40	88.83	89.09	1.84	63.35	63.13	67.48	64.65	2.45
Time(hr)	0.1 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.14	5.22	5.26	5.21	0.06	6.50	6.24	5.95	6.23	0.27
0.50	7.33	7.45	7.67	7.48	0.17	8.71	8.71	8.48	8.63	0.13
0.75	9.60	9.66	10.01	9.75	0.21	10.81	10.88	10.80	10.83	0.05
1	11.34	11.42	11.91	11.56	0.30	12.96	12.71	12.54	12.74	0.21
2	17.07	17.23	17.56	17.29	0.25	18.88	18.71	18.37	18.65	0.25
3	22.86	22.87	23.44	23.06	0.32	24.37	24.12	23.86	24.12	0.25
4	27.77	28.17	28.43	28.12	0.33	28.78	28.86	28.35	28.66	0.27
5	32.57	33.29	33.08	32.98	0.37	33.24	33.40	32.97	33.20	0.21
6	37.29	38.10	37.53	37.64	0.41	37.85	37.85	37.21	37.63	0.37
7	42.04	42.65	43.06	42.58	0.52	41.50	41.50	41.26	41.42	0.14
8	44.85	45.67	46.48	45.67	0.81	45.60	45.80	45.15	45.51	0.33
10	52.43	54.45	55.66	54.18	1.63	52.58	52.38	52.74	52.56	0.18
12	60.48	63.11	66.31	63.30	2.91	59.84	59.63	61.01	60.16	0.74

Table 45 Percentage amounts of theophylline from matrices prepared with various compression forces in DI water

Time (hr)	Percentage amount of drug release									
	7:3: Supertab® / 1000 lbs					7:3: Supertab® / 2000 lbs				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.64	4.72	4.53	4.63	0.09	3.87	3.69	3.65	3.74	0.12
0.50	7.08	7.27	6.91	7.09	0.17	6.20	5.99	5.94	6.04	0.14
0.75	9.64	9.79	9.47	9.63	0.16	8.54	8.34	8.36	8.41	0.11
1	11.88	12.04	11.66	11.86	0.19	10.99	10.81	10.79	10.87	0.11
2	19.77	20.23	19.19	19.97	0.23	19.06	18.60	18.67	18.78	0.24
3	27.30	27.91	27.37	27.53	0.33	26.46	26.44	26.29	26.40	0.09
4	33.34	34.33	33.56	33.74	0.51	32.66	33.02	33.17	32.95	0.26
5	41.01	42.31	451.61	41.64	0.64	39.16	39.30	39.37	39.27	0.11
6	48.34	49.32	48.72	48.79	0.49	45.44	45.62	45.44	45.50	0.10
7	55.20	56.19	56.33	55.91	0.61	51.17	51.17	51.17	51.17	0.00
8	61.57	62.75	62.34	62.22	0.59	56.59	56.77	56.20	56.52	0.28
10	73.23	74.24	73.45	73.64	0.53	67.67	68.98	68.78	68.48	0.70
12	81.09	81.74	80.94	81.26	0.42	78.68	79.82	79.62	79.38	0.60
Time(hr)	7:3: Supertab® / 4000 lbs					3:7: Supertab® / 1000 lbs				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.18	3.20	3.07	3.15	0.07	2.71	2.70	2.82	2.74	0.06
0.50	5.31	5.44	5.27	5.34	0.08	4.83	4.78	4.98	4.86	0.11
0.75	7.64	7.77	7.54	7.65	0.11	6.82	6.80	6.95	6.85	0.08
1	10.03	10.21	9.93	10.05	0.13	8.76	8.95	9.01	8.91	0.13
2	18.12	18.13	18.12	18.12	0.00	16.14	16.66	16.97	16.59	0.41
3	25.66	25.59	25.28	25.51	0.20	25.07	25.45	27.02	25.85	1.03
4	32.08	32.16	31.41	31.88	0.41	37.52	38.19	39.93	38.55	1.24
5	38.42	38.05	37.43	37.96	0.50	52.10	52.26	53.42	52.59	0.72
6	44.06	44.25	43.47	43.92	0.40	63.85	64.80	65.04	64.56	0.62
7	48.27	49.40	47.87	48.51	0.79	74.74	74.78	74.65	74.72	0.06
8	53.28	55.36	51.75	53.46	1.81	83.15	83.18	81.39	82.58	1.02
10	65.08	67.93	62.97	65.32	2.48	92.39	92.79	89.49	91.56	1.80
12	77.38	80.25	74.30	77.31	2.97	98.01	97.86	96.19	97.35	1.01

Table 45 (Continued) Percentage amounts of theophylline from matrices prepared with various compression forces in DI water

Time (hr)	Percentage amount of drug release									
	3:7: Supertab® / 2000 lbs					3:7: Supertab® / 4000 lbs				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	2.61	2.262	2.66	2.63	0.02	2.24	2.24	2.31	2.26	0.04
0.50	4.68	4.71	4.68	4.69	0.02	3.94	3.90	3.99	3.94	0.04
0.75	6.64	6.70	6.61	6.65	0.04	5.73	5.71	5.88	5.77	0.09
1	8.65	8.71	8.54	8.63	0.08	7.73	7.73	8.01	7.82	0.16
2	16.54	16.62	16.32	16.49	0.15	13.46	13.66	13.87	13.67	0.21
3	24.75	24.68	24.31	24.58	0.24	21.98	22.28	22.89	22.38	0.46
4	37.30	37.37	33.64	36.10	2.13	29.75	29.97	30.96	30.23	0.64
5	48.48	49.45	46.35	48.10	1.58	41.10	41.85	42.47	41.81	0.68
6	62.45	63.58	60.52	62.19	1.54	51.14	53.02	54.91	53.03	1.88
7	72.43	73.57	71.59	72.53	0.99	62.12	64.95	67.06	64.71	2.47
8	80.45	81.79	81.65	81.30	0.73	74.34	75.90	77.09	75.78	1.37
10	90.80	91.59	92.57	91.65	0.88	88.74	90.68	91.70	90.37	1.50
12	97.90	98.33	99.32	98.51	0.72	97.32	98.17	97.90	97.80	0.43
Time(hr)	7:3:Emcompress® / 1000 lbs					7:3:Emcompress® / 2000 lbs				
0	0	0	0	0	0	0	0	0	0	0
0.25	4.98	4.65	4.65	4.60	0.09	4.25	4.57	4.72	4.52	0.24
0.50	7.46	7.49	7.35	7.43	0.07	7.52	7.86	7.82	7.73	0.18
0.75	10.12	10.30	10.16	10.19	0.09	10.00	10.26	10.48	10.24	0.24
1	12.81	12.81	12.89	12.84	0.04	12.62	12.96	12.85	12.81	0.18
2	21.35	21.04	21.19	21.19	0.15	21.34	21.67	21.36	21.46	0.18
3	29.90	28.72	29.51	29.37	0.60	28.95	29.36	28.73	29.02	0.32
4	36.11	35.00	35.79	35.63	0.57	35.23	35.72	34.46	35.14	0.63
5	42.93	41.42	42.61	42.32	0.79	41.02	41.44	40.24	40.91	0.60
6	48.13	46.71	47.33	47.39	0.71	45.92	46.74	45.53	46.06	0.61
7	53.35	52.12	52.55	52.67	0.62	51.52	51.95	50.33	51.26	0.83
8	57.65	56.79	57.03	57.16	0.44	55.40	55.83	54.59	55.27	0.63
10	60.22	66.61	67.83	64.89	4.09	63.05	63.49	62.23	62.92	0.63
12	77.91	76.34	78.16	77.47	0.98	71.16	71.41	70.14	70.91	0.67

Table 45 (Continued) Percentage amounts of theophylline from matrices prepared with various compression forces in DI water

Time (hr)	Percentage amount of drug release									
	7:3:Emcompress® / 4000 lbs					3:7:Emcompress® / 1000 lbs				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.76	3.98	3.67	3.81	0.16	3.13	3.02	2.98	3.05	0.08
0.50	6.81	7.11	6.65	6.86	0.23	5.49	5.44	5.30	5.41	0.09
0.75	9.24	9.58	9.10	9.30	0.24	7.84	7.69	7.63	7.72	0.11
1	11.64	12.11	11.53	11.75	0.30	10.27	10.03	9.95	10.08	0.17
2	19.66	20.30	19.50	19.82	0.42	19.21	18.91	18.75	18.96	0.23
3	27.02	27.35	26.46	26.94	0.45	27.45	27.22	26.99	27.22	0.23
4	33.04	33.30	32.24	32.86	0.55	35.03	35.09	33.81	34.65	0.72
5	38.73	38.76	37.77	38.42	0.56	41.87	41.93	40.93	41.58	0.55
6	44.23	44.07	42.83	43.71	0.76	48.76	49.31	48.34	48.80	0.48
7	49.02	48.85	47.60	48.49	0.77	56.22	55.84	55.80	55.95	0.23
8	53.86	52.90	52.03	52.93	0.91	63.95	63.01	63.71	63.55	0.49
10	61.69	60.92	59.65	60.75	1.03	76.26	75.87	77.33	76.49	0.75
12	69.80	68.03	67.14	68.32	1.35	87.01	87.55	88.47	87.68	0.73
Time(hr)	3:7:Emcompress® / 2000 lbs					3:7:Emcompress® / 4000 lbs				
0	0	0	0	0	0	0	0	0	0	0
0.25	2.91	3.02	2.92	2.95	0.06	2.68	2.83	2.85	2.78	0.09
0.50	5.17	5.38	5.10	5.22	0.14	4.77	4.95	4.93	4.88	0.09
0.75	7.47	7.73	7.37	7.51	0.19	7.10	7.31	7.33	7.24	0.12
1	9.73	10.08	9.59	9.80	0.25	9.22	9.39	9.41	9.34	0.10
2	18.52	18.76	17.69	18.32	0.55	17.31	17.69	17.69	17.56	0.22
3	26.98	27.29	25.54	26.61	0.93	25.37	25.39	25.39	25.38	0.01
4	34.48	34.12	32.80	33.80	0.88	32.10	31.82	32.04	31.99	0.15
5	40.93	40.79	38.71	40.14	1.24	38.98	39.06	38.69	38.91	0.19
6	47.02	46.66	44.51	46.07	1.35	45.05	44.31	44.31	44.56	0.42
7	52.59	52.22	50.62	51.81	1.05	51.35	50.04	50.04	50.48	0.75
8	59.34	58.41	56.41	58.05	1.49	58.65	55.26	55.26	56.39	1.95
10	72.54	71.60	69.77	71.30	1.41	66.97	65.61	65.42	66.00	0.84
12	85.51	84.17	82.51	84.06	1.50	80.25	76.99	76.61	77.95	1.99

Appendix E

Percentage Swelling and Erosion of Matrices

Table 46 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and spray dried lactose (Formulation F11) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	17.04	17.88	18.07	17.67	0.54	15.97	17.17	17.23	16.79	0.71
0.50	27.02	26.85	26.61	26.83	0.20	27.99	29.30	27.16	28.15	1.07
0.75	27.96	27.24	28.20	27.80	0.49	38.68	35.94	36.42	37.01	1.46
1	34.42	35.97	38.36	36.25	1.98	36.49	39.15	37.81	37.82	1.33
2	48.63	50.38	52.28	50.43	1.82	54.25	55.20	58.48	55.98	2.21
4	65.17	60.65	61.63	62.48	2.38	71.95	70.59	69.39	70.64	1.28
6	69.40	74.16	72.33	71.96	2.39	82.01	82.98	84.39	83.13	1.19
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	22.91	25.52	20.64	23.02	2.44	22.51	23.96	20.14	22.20	1.92
0.50	26.31	27.01	29.16	27.49	1.48	29.39	31.19	27.05	29.21	2.07
0.75	32.09	34.47	34.24	33.60	1.31	38.99	38.64	35.06	37.56	2.17
1	36.09	37.20	37.03	36.77	0.59	45.88	42.00	44.52	44.13	1.97
2	55.45	63.93	61.14	60.17	4.32	59.38	58.73	64.18	60.76	2.97
4	67.76	68.25	69.47	68.49	0.87	68.31	73.35	69.79	70.48	2.59
6	76.51	77.82	73.69	76.01	2.11	74.85	72.18	72.44	73.15	1.47
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	16.73	18.45	17.09	17.42	0.91	25.24	24.28	24.54	24.69	0.50
0.50	26.92	26.82	26.30	26.68	0.33	34.09	32.09	31.84	32.67	1.22
0.75	31.79	31.86	30.27	31.31	0.89	36.04	38.05	38.12	37.40	1.18
1	33.57	34.78	32.04	33.47	1.37	42.74	43.60	45.16	43.83	1.22
2	47.51	44.09	43.83	45.15	2.05	57.78	55.75	55.78	56.44	1.16
4	66.07	66.31	65.94	66.11	0.18	72.95	71.82	69.02	71.27	2.02
6	76.62	76.85	77.22	76.90	0.30	77.92	77.87	77.45	77.74	0.25

Table 47 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and spray dried lactose (Formulation F12) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	41.92	42.03	43.69	42.54	0.99	26.68	25.14	28.92	26.92	1.90
0.50	49.62	50.59	48.38	49.53	1.10	20.93	20.88	21.81	21.21	0.52
0.75	53.89	56.02	56.08	55.33	1.24	19.66	16.56	17.97	18.06	1.55
1	56.25	56.37	59.51	57.38	1.84	19.27	18.91	19.08	19.09	0.18
2	72.83	75.24	77.03	74.37	1.33	13.09	12.96	14.22	13.42	0.69
4	71.41	72.20	71.77	71.79	0.40	8.91	8.69	9.63	9.08	0.49
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	19.16	21.53	20.94	20.54	1.23	21.81	22.88	21.35	22.01	0.78
0.50	20.92	23.47	23.81	22.73	1.58	20.54	20.33	23.60	21.49	1.83
0.75	26.24	24.37	23.76	24.79	1.29	21.30	19.21	21.47	20.66	1.26
1	22.22	23.76	22.12	22.70	0.91	24.53	23.96	26.50	25.00	1.33
2	29.85	28.85	29.85	29.52	0.57	26.76	26.81	29.74	27.77	1.70
4	34.47	30.90	33.56	32.98	1.85	36.01	34.02	36.60	35.54	1.35
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	30.75	31.22	32.34	31.43	0.81	19.68	19.02	16.76	18.48	1.52
0.50	40.65	39.51	40.98	40.38	0.77	15.81	15.61	17.71	16.38	1.15
0.75	41.15	42.47	42.03	41.88	0.67	18.16	19.52	18.67	18.78	0.68
1	43.63	44.63	48.27	45.51	2.44	17.51	14.23	15.07	15.60	1.70
2	56.14	53.61	55.79	55.18	1.37	16.86	19.32	19.83	18.67	1.58
4	69.47	67.01	65.10	67.20	2.18	33.79	33.96	30.43	32.73	1.99

Table 48 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and spray dried lactose (Formulation F12) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	7.65	6.48	7.05	7.06	0.58	15.51	16.97	17.93	16.80	1.21
0.50	9.18	9.50	9.64	9.44	0.24	22.62	21.60	22.45	22.22	0.54
0.75	12.07	12.53	12.77	12.46	0.35	28.27	39.51	39.84	29.21	0.82
1	14.46	14.62	14.79	14.63	0.16	28.32	31.07	32.11	30.50	1.95
2	24.18	23.31	23.45	23.64	0.46	45.50	47.22	46.65	46.46	0.87
4	40.64	41.11	41.05	40.93	0.25	63.06	62.04	61.11	62.07	0.97
6	54.62	53.60	54.63	54.28	0.59	79.52	76.68	76.78	77.66	1.61
Time (hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	15.73	13.77	14.43	14.64	0.99	14.14	14.36	15.67	14.72	0.82
0.50	18.38	18.18	17.10	17.88	0.70	17.84	19.29	19.34	18.82	0.85
0.75	22.38	23.69	23.27	23.11	0.66	23.70	23.18	24.55	23.81	0.69
1	27.20	28.24	30.02	28.49	1.42	25.27	26.53	24.88	25.56	0.85
2	36.02	36.06	36.62	36.23	0.33	36.80	36.75	37.07	36.87	0.17
4	49.38	50.50	47.18	49.02	1.68	53.18	53.31	52.22	52.91	0.59
6	51.23	52.33	53.15	52.23	0.95	58.67	60.18	60.47	59.77	0.96
Time (hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	8.01	8.88	8.79	8.56	0.48	19.79	20.86	20.36	20.34	0.53
0.50	12.80	13.47	13.61	13.29	0.43	21.96	22.86	21.44	22.09	0.71
0.75	15.79	15.35	16.48	15.87	0.56	27.78	26.11	26.87	26.92	0.83
1	17.81	18.93	17.58	18.11	0.71	32.16	34.15	34.05	33.46	1.12
2	26.72	28.24	27.38	27.45	0.76	41.61	43.37	41.34	41.11	1.10
4	42.34	43.66	42.95	42.98	0.66	55.17	55.49	56.83	55.83	0.88
6	56.61	58.30	57.22	57.38	0.85	69.54	69.03	70.60	69.72	0.80

Table 49 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and spray dried lactose (Formulation F13) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	48.49	51.32	53.55	51.12	2.53	23.71	23.14	22.83	23.23	0.44
0.50	59.99	61.68	62.27	61.31	1.18	23.14	23.45	23.14	23.24	0.17
0.75	72.13	75.05	70.43	72.54	2.33	21.08	22.58	23.01	22.22	1.01
1	79.61	76.53	79.91	78.68	1.87	23.60	24.07	23.45	23.74	0.32
2	107.78	109.65	106.45	107.96	1.60	27.13	29.49	30.14	28.92	1.57
4	91.19	91.37	89.73	90.77	0.90	26.81	24.40	27.80	26.34	1.74
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	23.91	24.22	27.49	25.21	1.98	26.45	25.46	27.17	26.36	0.86
0.50	27.91	27.80	30.11	28.61	1.30	28.59	29.53	29.32	29.15	0.49
0.75	31.65	32.44	32.50	32.20	0.47	30.53	30.22	31.22	30.66	0.51
1	32.82	35.82	35.82	34.82	1.73	33.24	33.19	33.24	33.22	0.03
2	47.99	48.61	48.55	48.38	0.34	44.41	41.81	44.41	43.54	1.50
4	60.15	63.68	62.68	62.17	1.81	63.11	59.36	61.91	61.46	1.91
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	36.90	38.47	38.20	37.85	0.84	19.52	19.32	21.30	20.05	1.08
0.50	46.25	47.42	46.81	46.83	0.58	18.67	20.74	20.54	19.98	1.14
0.75	55.16	52.69	53.38	53.74	1.27	22.01	23.50	23.65	23.06	0.90
1	62.21	65.88	64.45	64.18	1.85	26.29	24.07	24.27	24.88	1.22
2	80.11	79.11	82.78	80.67	1.89	31.54	35.55	36.63	34.57	2.68
4	97.18	98.47	94.41	96.69	2.07	49.68	48.94	47.37	48.66	1.18

Table 50 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and spray dried lactose (Formulation F13) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.71	5.10	5.28	5.03	0.29	14.91	15.79	14.33	15.01	0.74
0.50	7.51	8.57	7.30	7.79	0.67	20.17	20.38	19.03	19.86	0.72
0.75	9.32	9.27	11.00	9.87	0.98	26.90	25.60	24.95	25.81	0.99
1	12.44	13.30	12.84	12.86	0.43	28.28	29.28	30.43	29.33	1.07
2	20.98	20.60	21.16	20.91	0.28	36.85	37.16	37.32	37.11	0.24
4	42.09	41.60	42.14	41.94	0.31	56.50	57.73	55.95	56.73	0.91
6	59.44	59.61	59.92	59.65	0.24	75.00	76.14	76.73	75.95	0.88
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	8.66	8.85	9.67	9.06	0.53	10.46	11.24	11.04	10.91	0.40
0.50	12.54	13.33	12.89	12.92	0.39	14.94	14.23	14.68	14.62	0.36
0.75	16.37	16.38	16.40	16.39	0.01	18.67	17.85	18.63	18.39	0.46
1	18.74	19.10	19.49	19.11	0.37	21.46	21.63	22.68	21.92	0.66
2	28.33	28.48	28.35	28.39	0.07	29.61	31.68	29.55	30.28	1.21
4	40.83	41.45	40.57	40.95	0.45	43.98	44.31	43.89	44.06	0.22
6	49.30	48.08	47.64	48.34	0.86	51.68	51.46	53.28	52.14	0.99
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.55	6.81	7.07	6.81	0.26	13.93	13.98	13.71	13.87	0.14
0.50	9.64	10.09	10.53	10.09	0.44	20.09	19.13	20.09	19.77	0.55
0.75	13.04	12.60	12.69	12.78	0.23	21.46	21.02	23.21	21.90	1.16
1	15.36	15.26	15.85	15.49	0.31	25.45	25.66	27.86	26.32	1.33
2	24.28	24.30	24.60	24.39	0.18	35.21	32.20	34.13	33.84	1.52
4	38.79	39.33	39.47	39.20	0.35	49.40	50.67	48.36	49.48	1.16
6	63.11	62.80	63.79	63.24	0.50	62.27	65.49	64.03	63.93	1.61

Table 51 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and spray dried lactose (Formulation F14) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	63.27	65.58	66.53	65.13	1.67	23.35	28.01	24.12	25.16	2.50
0.50	80.73	83.22	83.28	82.41	1.45	23.55	23.04	24.22	23.60	0.59
0.75	89.53	87.31	91.45	89.43	2.07	31.86	29.27	27.24	29.46	2.31
1	98.81	103.67	102.61	101.71	2.55	29.32	29.22	29.37	29.30	0.08
2	146.02	148.11	151.68	148.61	2.86	37.11	36.90	38.69	37.57	0.97
4	123.32	124.61	120.33	122.75	2.19	41.31	44.80	45.19	43.77	2.13
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	28.64	28.95	29.37	28.99	0.36	28.69	27.91	29.11	28.57	0.61
0.50	30.85	31.81	33.35	32.01	1.26	33.99	34.63	33.46	34.03	0.58
0.75	39.67	39.12	42.36	40.38	1.73	37.65	37.3	39.72	38.24	1.29
1	43.24	43.47	44.52	43.74	0.68	44.80	42.14	44.74	43.89	1.51
2	57.18	54.81	57.59	56.53	1.49	56.49	59.45	57.01	57.65	1.58
4	82.07	81.72	84.83	82.87	1.70	79.61	81.91	81.72	81.08	1.27
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	44.46	46.02	48.44	46.31	2.00	23.09	23.45	23.50	23.35	0.22
0.50	55.22	57.16	58.62	57.00	1.70	26.50	28.22	25.82	26.85	1.23
0.75	65.40	70.01	67.61	67.67	2.30	32.07	31.17	30.16	31.14	0.95
1	78.13	74.93	78.56	77.21	1.98	33.46	35.07	36.90	35.14	1.72
2	107.78	105.46	108.51	107.25	1.59	47.54	45.52	46.71	46.58	1.01
4	148.60	150.84	147.91	149.12	1.53	62.56	65.97	63.03	63.85	1.84

Table 52 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and spray dried lactose (Formulation F14) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.43	4.48	4.57	4.49	0.06	9.68	10.97	11.23	10.63	0.83
0.50	6.63	6.96	7.10	6.90	0.24	16.72	16.04	17.77	16.84	0.86
0.75	8.66	8.97	9.00	8.87	0.19	21.24	20.97	21.73	21.31	0.38
1	9.99	10.28	10.50	10.26	0.26	22.10	22.85	22.81	22.58	0.42
2	19.84	19.79	19.67	19.77	0.09	34.76	34.20	34.33	34.43	0.29
4	41.37	43.12	43.88	42.79	1.28	47.69	46.96	46.92	47.19	0.43
6	66.01	66.31	65.36	65.89	0.48	60.82	60.58	61.81	61.07	0.65
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.90	8.12	7.78	7.93	0.17	6.46	7.73	7.26	7.15	0.63
0.50	11.31	10.74	11.61	11.22	0.44	9.69	9.26	9.91	9.62	0.32
0.75	14.28	14.59	14.26	14.38	0.18	12.95	13.29	12.50	12.91	0.39
1	16.32	16.98	17.59	16.96	0.63	14.84	13.90	15.55	14.76	0.83
2	25.20	25.85	25.52	25.52	0.32	21.86	21.75	22.16	21.92	0.21
4	38.04	36.81	37.05	37.30	0.64	40.73	40.61	39.86	40.40	0.46
6	49.86	48.70	47.89	48.81	0.99	50.29	48.43	48.84	49.18	0.97
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.20	6.66	6.49	6.45	0.23	10.66	11.18	11.60	11.15	0.46
0.50	9.19	9.49	9.50	9.40	0.17	15.14	14.52	15.32	14.99	0.41
0.75	11.21	11.40	11.65	11.42	0.22	19.19	17.99	18.23	18.47	0.63
1	13.57	13.83	14.08	13.83	0.25	20.73	20.41	21.35	20.83	0.48
2	22.54	23.09	22.63	22.75	0.29	29.89	30.19	29.89	29.99	0.17
4	36.28	37.01	36.81	36.70	0.37	45.05	43.04	44.15	44.08	1.01
6	55.00	57.34	58.08	56.47	1.61	66.01	65.35	67.19	66.18	0.93

Table 53 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and spray dried lactose (Formulation F15) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	69.43	70.43	72.61	70.83	1.63	28.80	27.70	27.59	28.03	0.66
0.50	97.79	95.70	95.05	96.18	1.43	28.53	30.48	29.22	29.41	0.98
0.75	113.08	112.74	114.70	113.50	1.04	33.46	34.04	34.47	33.99	0.51
1	116.83	116.99	120.04	117.96	1.81	37.96	38.31	35.76	37.34	1.38
2	157.05	155.71	157.85	156.86	1.09	43.52	45.47	47.71	45.56	2.09
4	138.42	140.14	140.14	139.57	0.99	64.33	64.25	60.86	63.15	1.98
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	29.32	31.17	33.51	31.33	2.09	30.85	32.34	33.83	32.34	1.49
0.50	38.74	40.93	40.16	39.94	1.10	39.40	41.04	41.64	40.69	1.16
0.75	48.72	44.91	47.42	47.02	1.93	48.16	50.53	52.30	50.33	2.07
1	52.01	54.30	53.78	53.36	1.20	56.20	57.70	57.36	57.09	0.78
2	76.40	77.20	78.13	77.24	0.86	77.63	79.30	79.49	78.81	1.02
4	109.58	106.38	106.12	107.03	2.29	110.99	115.11	115.45	113.85	2.48
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	50.93	50.55	55.70	52.39	2.87	28.01	29.37	31.59	29.66	1.80
0.50	63.38	67.79	66.87	66.01	2.32	33.35	34.63	33.72	33.90	0.66
0.75	82.16	82.35	81.85	82.12	0.25	39.34	40.27	40.44	40.02	0.58
1	97.27	94.41	95.44	95.71	1.44	45.75	45.08	45.86	45.56	0.42
2	127.12	127.71	130.65	128.49	1.89	64.63	65.05	66.06	65.24	0.73
4	194.05	191.65	188.86	191.52	2.59	99.79	97.44	99.92	99.05	1.39

Table 54 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and spray dried lactose (Formulation F15) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.03	4.11	4.18	4.11	0.08	10.13	10.58	11.19	10.63	0.52
0.50	5.75	5.81	6.12	5.89	0.20	14.54	14.35	14.09	14.33	0.22
0.75	8.09	8.09	8.09	8.09	0.00	15.68	15.89	16.29	15.95	0.31
1	9.35	10.06	9.89	9.77	0.37	18.54	18.45	17.62	18.20	0.50
2	19.06	19.57	19.64	19.42	0.31	25.90	26.33	26.70	26.31	0.39
4	45.12	45.45	46.01	45.53	0.45	36.42	37.36	37.27	37.02	0.51
6	79.88	77.82	78.01	78.57	1.13	44.35	44.88	45.91	45.05	0.79
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	6.11	5.69	6.04	5.95	0.22	5.62	5.97	5.91	5.83	0.18
0.50	8.87	9.03	9.24	9.05	0.18	8.01	8.33	8.29	8.19	0.16
0.75	11.12	11.31	11.49	11.31	0.18	11.56	11.55	11.59	11.57	0.02
1	13.32	14.30	14.39	14.01	0.59	13.47	13.01	13.66	13.38	0.33
2	20.65	20.63	20.67	20.65	0.02	14.96	14.40	13.23	14.19	0.88
4	30.70	29.58	30.21	30.16	0.56	30.51	30.78	31.26	30.85	0.37
6	36.39	37.93	37.97	37.43	0.89	35.21	34.76	35.28	35.08	0.28
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.45	5.75	5.93	5.71	0.24	7.87	7.94	7.61	7.81	0.17
0.50	7.89	7.83	8.05	7.92	0.11	11.65	10.79	10.37	10.94	0.65
0.75	9.42	9.73	9.83	9.66	0.21	12.86	12.45	13.24	12.85	0.39
1	11.55	11.67	11.92	11.71	0.19	14.44	15.10	15.11	14.89	0.38
2	16.99	17.48	17.91	17.46	0.45	21.83	22.01	21.59	21.81	0.21
4	29.22	31.05	31.27	30.51	1.12	32.73	33.41	33.34	33.16	0.37
6	60.67	61.10	60.95	60.90	0.21	47.06	45.16	43.79	45.34	1.64

Table 55 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 10:0 and dibasic calcium phosphate (Formulation F16) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	6.59	6.85	6.37	6.61	0.23	9.85	10.64	10.11	10.20	0.40
0.50	9.10	9.96	9.13	9.40	0.48	15.92	18.61	18.42	17.65	1.50
0.75	12.75	12.34	12.28	12.46	0.25	22.10	24.30	22.80	23.06	1.12
1	14.79	14.88	15.23	14.96	0.23	24.68	28.32	27.15	26.72	1.85
2	24.22	24.95	23.81	24.33	0.57	40.02	38.22	36.55	38.27	1.73
4	37.01	38.36	38.63	38.00	0.87	56.29	55.81	55.10	55.73	0.59
6	46.72	45.65	46.48	46.28	0.56	72.75	69.78	69.60	70.71	1.76
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.14	8.45	6.97	7.52	0.81	7.76	6.50	7.45	7.24	0.65
0.50	11.54	11.21	10.82	11.19	0.36	11.20	12.10	13.01	12.11	0.90
0.75	14.25	16.56	14.55	15.12	1.25	16.16	14.43	14.79	15.13	0.91
1	16.68	17.21	17.67	17.18	0.49	17.98	16.98	18.04	17.66	0.59
2	25.92	23.64	25.42	24.99	1.19	24.99	26.64	26.29	25.97	0.86
4	37.61	37.01	37.45	37.35	0.31	34.23	36.23	36.94	35.80	1.40
6	45.76	49.13	49.91	48.27	2.20	40.83	42.94	40.10	41.29	1.47
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.34	5.03	5.07	5.15	0.16	7.12	8.24	8.05	7.80	0.60
0.50	6.94	7.81	8.05	7.60	0.58	11.29	11.04	10.80	11.05	0.24
0.75	10.86	10.14	11.48	10.82	0.66	13.41	15.22	14.63	14.42	0.92
1	13.85	12.94	13.10	13.30	0.48	14.41	14.34	13.97	14.24	0.23
2	22.43	21.55	24.29	22.76	1.39	22.99	22.81	22.24	22.68	0.39
4	38.49	37.85	38.03	38.12	0.32	30.75	30.03	31.20	30.66	0.58
6	49.29	46.81	45.46	47.19	1.94	37.55	37.72	35.89	37.06	1.01

Table 56 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and dibasic calcium phosphate (Formulation F17) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	29.58	30.59	31.01	30.39	0.73	19.73	21.30	22.58	21.20	1.42
0.50	32.55	33.56	32.76	32.96	0.53	20.83	19.66	17.01	19.17	1.95
0.75	39.94	39.34	39.61	39.63	0.31	20.79	19.07	22.01	20.62	1.47
1	38.69	42.64	42.75	41.36	2.31	19.69	17.61	17.46	18.25	1.24
2	43.96	45.52	45.58	45.02	0.91	19.01	15.46	18.57	17.68	1.93
4	49.40	51.38	47.20	49.33	2.09	19.88	17.81	17.71	18.47	1.22
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	18.61	20.39	20.86	19.95	1.18	20.94	23.50	22.42	22.29	1.28
0.50	22.27	20.33	19.98	20.86	1.23	24.84	26.08	26.45	25.79	0.84
0.75	21.91	22.58	21.66	22.05	0.47	25.68	26.85	24.01	25.52	1.42
1	25.98	26.65	24.32	25.65	1.19	28.22	26.65	28.74	27.87	1.08
2	30.59	28.32	30.27	29.73	1.22	34.20	36.79	35.76	35.59	1.30
4	37.33	38.31	37.93	37.85	0.49	48.01	46.98	45.35	46.78	1.33
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	23.50	25.82	27.44	25.59	1.97	20.59	18.62	18.62	19.27	1.13
0.50	29.48	28.74	28.90	29.01	0.38	21.66	19.83	20.74	20.74	0.91
0.75	30.75	33.14	31.33	31.74	1.24	23.14	20.54	22.32	22.00	1.33
1	34.85	34.96	35.44	35.08	0.31	22.78	19.88	22.94	21.86	1.72
2	38.31	42.09	40.76	40.39	1.91	28.17	26.34	27.96	27.49	0.99
4	42.64	45.08	41.37	43.03	1.88	41.09	41.31	39.01	40.47	1.26

Table 57 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 7:3 and dibasic calcium phosphate (Formulation F17) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	4.40	4.03	4.22	4.22	0.18	13.81	14.89	14.31	14.34	0.53
0.50	5.96	5.61	6.14	5.90	0.27	17.34	18.13	19.19	18.22	0.93
0.75	8.56	8.06	8.89	8.50	0.42	23.14	24.15	22.92	23.40	0.65
1	10.61	9.59	9.72	9.97	0.55	27.57	28.68	26.40	27.55	1.13
2	16.48	16.51	16.37	16.46	0.07	38.79	40.34	39.52	39.55	0.77
4	26.93	28.29	27.88	27.70	0.69	54.86	56.60	55.56	55.67	0.87
6	44.03	41.06	40.96	42.02	1.74	67.99	65.46	66.21	66.55	1.30
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	7.42	7.67	6.32	7.14	0.71	6.19	6.83	6.57	6.53	0.32
0.50	9.45	9.94	9.07	9.49	0.44	8.44	9.00	9.02	8.82	0.32
0.75	11.75	13.43	11.90	12.36	0.93	11.29	12.04	12.91	12.08	0.80
1	13.18	14.27	15.02	14.15	0.92	12.76	14.54	13.25	13.51	0.91
2	22.03	22.37	22.99	22.46	0.48	20.02	19.91	18.45	19.46	0.87
4	32.84	32.22	30.74	31.93	1.07	30.02	32.37	32.62	31.67	1.42
6	43.20	43.47	40.58	42.42	1.59	38.81	38.96	37.80	38.52	0.62
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.55	5.41	5.12	5.36	0.22	6.88	5.91	5.47	6.09	0.72
0.50	7.53	8.23	7.20	7.65	0.52	8.78	9.85	10.12	9.58	0.71
0.75	10.22	10.14	11.15	10.50	0.55	14.23	14.10	12.30	13.55	1.07
1	12.65	13.02	12.70	12.79	0.20	16.16	15.21	15.30	15.56	0.52
2	17.46	17.93	17.42	17.60	0.28	21.49	21.99	23.18	22.22	0.86
4	31.67	31.98	32.26	31.97	0.29	28.02	29.12	28.57	28.57	0.55
6	40.58	40.69	40.26	40.51	0.22	37.61	39.93	38.03	38.52	1.23

Table 58 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and dibasic calcium phosphate (Formulation F18) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	37.44	37.17	39.83	38.15	1.46	23.19	22.17	23.32	22.56	0.55
0.50	45.19	42.86	45.69	44.58	1.51	21.76	21.66	24.37	22.60	1.54
0.75	50.42	51.04	52.92	51.46	1.30	23.35	21.81	21.61	22.25	0.95
1	58.98	59.22	57.41	58.54	0.98	24.84	21.61	22.17	22.87	1.72
2	71.86	69.57	70.13	70.52	1.19	25.46	28.38	27.49	27.11	1.49
4	72.86	71.95	71.46	72.09	0.71	35.33	35.17	32.44	34.32	1.62
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	23.60	24.94	24.58	24.38	0.69	26.29	24.58	27.17	26.02	1.31
0.50	25.71	24.12	24.76	24.86	0.79	29.95	29.53	28.90	29.46	0.52
0.75	29.22	28.27	28.74	28.74	0.47	33.83	31.49	33.88	33.07	1.36
1	29.27	29.81	29.22	29.43	0.32	36.52	35.44	35.39	35.78	0.63
2	38.63	38.31	40.16	39.03	0.99	45.24	43.35	46.47	45.02	1.57
4	50.96	50.74	51.95	51.22	0.64	60.56	61.27	63.39	61.74	1.47
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	32.18	31.70	31.70	31.86	0.27	19.17	20.18	19.42	19.59	0.52
0.50	35.28	36.30	37.06	36.21	0.89	20.69	21.81	22.68	21.73	0.99
0.75	41.75	43.85	41.59	42.40	1.26	25.46	25.72	25.77	25.65	0.16
1	47.37	44.74	46.42	46.18	1.32	27.28	29.27	27.65	28.07	1.05
2	55.33	56.16	58.22	56.57	1.48	34.39	31.69	34.58	33.55	1.61
4	72.01	73.65	70.31	71.99	1.66	47.65	48.27	48.61	48.17	0.48

Table 59 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 5:5 and dibasic calcium phosphate (Formulation F18) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	3.06	2.80	2.91	2.92	0.13	14.29	13.92	14.02	14.08	0.19
0.50	5.11	4.99	5.29	5.13	0.15	16.68	16.52	16.48	16.56	0.10
0.75	6.88	7.20	7.30	7.13	0.21	22.17	20.55	20.50	21.07	0.95
1	8.29	8.48	8.42	8.40	0.10	24.87	26.62	25.95	25.81	0.88
2	14.46	14.50	15.01	14.65	0.30	35.34	35.52	35.73	35.53	0.19
4	28.09	27.28	28.24	27.87	0.51	50.66	49.43	51.66	50.58	1.11
6	37.71	37.68	37.32	37.57	0.22	61.75	60.94	62.66	61.79	0.86
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.32	5.40	5.75	5.49	0.22	5.10	5.98	5.11	5.40	0.50
0.50	7.53	7.93	7.52	7.66	0.23	7.47	7.68	7.93	7.69	0.23
0.75	10.57	10.55	10.83	10.65	0.15	9.43	9.68	10.15	9.75	0.36
1	12.04	11.32	12.34	11.90	0.52	12.36	11.58	12.14	12.03	0.40
2	18.52	19.01	18.45	18.66	0.31	17.56	17.69	17.94	17.73	0.19
4	28.64	29.40	29.44	29.16	0.45	28.82	29.56	28.28	28.88	0.64
6	35.23	37.88	37.53	36.88	1.43	36.80	36.65	37.33	36.93	0.35
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.90	4.03	4.20	4.05	0.15	5.50	5.50	5.83	5.61	0.19
0.50	6.63	6.40	6.62	6.55	0.13	8.49	8.38	8.69	8.52	0.16
0.75	9.30	9.17	9.47	9.31	0.14	10.91	11.30	11.02	11.07	0.20
1	10.89	11.01	11.41	11.11	0.27	14.32	13.17	14.15	13.88	0.62
2	15.46	16.40	15.93	15.93	0.46	19.51	20.40	20.68	20.20	0.61
4	27.78	27.05	28.64	27.82	0.79	29.58	28.19	28.70	28.82	0.70
6	39.70	39.47	38.35	39.17	0.72	36.81	36.01	36.10	36.30	0.44

Table 60 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and dibasic calcium phosphate (Formulation F19) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	43.02	42.64	45.86	43.84	1.75	24.89	24.58	24.01	24.50	0.44
0.50	56.49	57.94	55.74	56.72	1.11	25.13	24.78	26.85	25.59	1.11
0.75	62.62	63.45	64.94	63.67	1.17	28.53	27.75	27.70	27.99	0.46
1	76.42	75.99	77.17	76.52	0.59	30.38	28.01	31.01	29.80	1.58
2	91.83	93.15	95.14	93.37	1.66	33.56	36.09	36.19	35.28	1.48
4	110.45	111.06	112.94	111.48	1.29	46.36	45.63	48.68	46.89	1.59
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	25.82	26.50	24.37	25.57	1.08	29.53	28.06	28.53	28.71	0.75
0.50	30.53	32.44	30.64	31.21	1.07	36.14	34.74	34.69	35.19	0.82
0.75	33.62	35.82	34.74	34.72	1.10	37.93	39.56	39.12	38.87	0.84
1	37.65	37.55	37.33	37.51	0.16	43.52	41.00	43.35	42.62	1.41
2	50.13	52.46	51.04	51.21	1.17	57.34	57.05	57.50	57.30	0.23
4	69.53	71.74	70.53	70.60	1.10	75.04	76.06	72.55	74.55	1.80
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	39.38	37.09	38.36	38.28	1.14	22.47	23.55	23.40	23.14	0.58
0.50	46.30	47.82	48.10	47.41	0.96	26.71	27.38	26.76	26.95	0.37
0.75	54.16	51.98	53.49	53.21	1.11	29.43	29.48	29.53	29.48	0.05
1	61.79	64.39	61.56	62.58	1.57	32.02	31.96	33.47	32.48	0.85
2	73.89	75.79	75.36	75.01	0.99	44.85	43.30	42.03	43.39	1.41
4	93.60	96.23	95.21	95.01	1.32	62.81	61.74	61.45	62.00	0.71

Table 61 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 3:7 and dibasic calcium phosphate (Formulation F19) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	2.82	2.96	3.07	2.95	0.12	11.57	11.70	11.97	11.74	0.20
0.50	4.69	4.81	4.82	4.77	0.07	16.05	17.65	16.86	16.86	0.80
0.75	5.56	6.10	6.12	5.93	0.31	19.33	18.81	19.92	19.36	0.55
1	7.59	8.32	8.19	8.03	0.39	22.02	20.94	21.28	21.41	0.55
2	13.63	12.26	12.18	12.69	0.81	33.24	31.96	30.95	32.05	1.14
4	25.88	25.39	25.63	25.63	0.24	42.05	43.61	43.26	42.97	0.81
6	39.16	39.17	39.24	39.19	0.05	56.08	57.33	59.44	57.62	1.69
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	5.16	4.46	5.04	4.88	0.37	4.18	4.39	4.70	4.42	0.26
0.50	7.50	7.09	7.56	7.38	0.26	6.31	6.40	6.50	6.40	0.10
0.75	9.34	9.06	9.13	9.18	0.14	8.45	8.51	8.69	8.55	0.12
1	11.16	10.89	11.19	11.08	0.16	9.56	10.22	10.39	10.06	0.44
2	15.95	16.11	16.35	16.14	0.20	16.44	16.58	16.87	16.63	0.22
4	25.62	25.19	25.28	25.36	0.22	26.83	26.34	26.32	26.50	0.29
6	34.41	34.76	34.42	34.53	0.19	35.94	36.43	35.57	35.98	0.43
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.75	3.66	3.80	3.74	0.07	5.19	5.11	5.38	5.23	0.14
0.50	6.06	6.01	6.08	6.05	0.04	7.54	8.16	7.59	7.76	0.34
0.75	7.70	7.74	7.59	7.67	0.08	9.17	8.55	9.97	9.23	0.71
1	9.17	9.40	9.20	9.26	0.12	10.95	11.85	11.41	11.41	0.45
2	14.02	14.22	14.67	14.30	0.33	15.86	15.86	15.85	15.86	0.01
4	25.38	24.50	25.50	25.13	0.54	24.97	26.48	25.66	25.71	0.75
6	37.40	37.17	38.25	37.61	0.57	33.34	34.67	34.26	34.09	0.68

Table 62 Percentage swelling of matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and dibasic calcium phosphate (Formulation F20) in various media

Time (hr)	Percentage swelling of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	58.17	60.98	61.27	60.14	1.71	30.54	30.48	28.38	29.80	1.22
0.50	78.34	81.54	80.47	80.12	1.62	32.18	30.64	31.22	31.35	0.77
0.75	91.26	91.70	94.02	92.33	1.48	33.03	32.76	34.96	33.58	1.19
1	98.10	101.76	102.68	100.84	2.42	36.93	36.84	35.04	36.27	1.06
2	125.54	127.90	124.91	126.12	1.57	44.85	43.91	44.24	44.34	0.47
4	167.61	170.84	166.82	168.42	2.13	54.57	56.24	55.22	55.34	0.84
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	29.06	30.22	28.64	29.31	0.81	33.88	34.96	34.20	34.35	0.55
0.50	38.03	37.17	37.55	37.58	0.43	40.44	42.80	42.14	41.79	1.22
0.75	43.30	43.03	44.52	43.62	0.79	49.11	50.25	48.49	49.28	0.88
1	48.10	47.87	47.20	47.72	0.46	57.88	55.39	56.14	56.47	1.27
2	63.03	62.56	64.16	63.25	0.82	77.91	77.20	78.17	77.76	0.51
4	91.41	89.92	89.90	90.41	0.86	109.25	109.78	109.98	109.67	0.38
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	48.55	47.87	47.82	48.08	0.40	27.64	27.70	26.29	27.21	0.79
0.50	59.27	59.18	60.15	59.53	0.53	33.88	34.47	34.53	34.29	0.35
0.75	68.09	68.09	69.29	68.49	0.69	37.52	38.52	39.98	38.68	1.23
1	81.72	81.35	80.91	81.33	0.40	44.30	44.41	43.85	44.19	0.29
2	110.21	112.50	111.05	111.25	1.15	59.57	60.22	60.62	60.13	0.53
4	146.92	144.31	146.27	145.84	1.35	77.36	79.79	80.11	79.08	1.50

Table 63 Percentage erosion of matrices containing 15% polymer in the HPMC:XG ratio of 0:10 and dibasic calcium phosphate (Formulation F20) in various media

Time (hr)	Percentage erosion of matrices									
	DI water					0.1 N HCl				
	1	2	3	Mean	SD	1	2	3	Mean	SD
0	0	0	0	0	0	0	0	0	0	0
0.25	2.36	2.49	2.27	2.37	0.11	10.68	10.66	10.96	10.77	0.17
0.50	3.43	3.37	3.40	3.40	0.03	14.50	14.99	15.18	14.89	0.34
0.75	4.48	4.76	4.64	4.63	0.13	17.36	16.66	17.66	17.23	0.51
1	6.48	6.41	6.62	6.50	0.10	18.84	18.60	18.05	18.50	0.40
2	15.24	14.72	14.84	14.94	0.27	25.99	27.13	26.48	26.53	0.57
4	24.61	23.05	23.68	23.78	0.78	33.02	34.53	34.02	33.86	0.76
6	48.35	49.94	49.57	49.29	0.82	44.01	43.73	43.95	43.90	0.14
Time(hr)	PBS pH 3					PBS pH 6.8				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.30	3.12	3.23	3.21	0.09	3.21	3.35	3.10	3.22	0.12
0.50	4.42	4.24	4.59	4.42	0.17	4.71	4.32	4.76	4.60	0.24
0.75	6.61	6.98	7.01	6.86	0.22	6.42	6.56	6.71	6.56	0.14
1	7.74	7.77	7.85	7.78	0.05	6.08	6.35	6.76	6.40	0.34
2	11.88	11.66	11.37	11.64	0.25	11.14	11.53	11.34	11.34	0.20
4	19.37	19.75	19.92	19.68	0.28	19.83	19.66	20.21	19.90	0.28
6	26.65	26.73	27.17	26.85	0.28	26.61	26.23	25.99	26.28	0.31
Time(hr)	0.01 M NaCl					0.2 M NaCl				
0	0	0	0	0	0	0	0	0	0	0
0.25	3.34	3.29	3.53	3.39	0.12	3.75	3.53	3.15	3.48	0.30
0.50	4.96	4.99	4.86	4.94	0.07	5.70	5.66	4.81	5.39	0.50
0.75	6.05	6.14	6.27	6.15	0.11	6.95	6.29	6.37	6.53	0.36
1	7.28	7.18	7.12	7.19	0.07	7.84	8.25	8.04	8.05	0.20
2	10.60	10.28	10.58	10.48	0.18	10.27	10.42	10.54	10.41	0.13
4	19.53	19.98	19.89	19.80	0.23	17.57	17.85	18.05	17.82	0.24
6	34.18	34.68	31.59	33.48	1.65	23.52	23.19	22.66	23.12	0.43

VITA

Miss Parinda Srinarong was born on December 3, 1972. She got her Bachelor Degree in Pharmacy in 1995 from the Faculty of Pharmacy, Chiangmai University, Chiangmai, Thailand. She works at the Research and Development Institute, Government Pharmaceutical Organization.