PREPARATION OF SUSTAINED RELEASE INDOMETHACIN TABLET USING MOLD TECHNIQUE

By

Anongnart Mesnukul

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree

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การเตรียมยาเม็ดอินโดเมทาซินออกฤทธิ์นานโดยเทคนิคหล่อขึ้นรูป

โดย

นางสาวอนงนารถ เมสนุกูล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

สาขาวิชาเทคโนโลยีเภสัชกรรม

บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร

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The graduate school, Silpakorn University was approved and accordite the thesis title of “Preparation of Sustained Release Indomethacin Tablet Using Mold Technique” by Miss Anongnart Mesnukul as a partial fulfillment of the requirements for the degree of master of pharmacy, program of pharmaceutical technology.

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Aqueous dissolution of indomethacin was improved using different molecular weights and ratio of polyethylene glycols (PEGs) as carriers for the solid dispersion systems prepared by melting method**.** Then the systems was fabricated into tablets with mold technique. Effects of ratio, type and amount of carrier on physical properties were investigated. An addition of xanthan gum or hydroxypropyl methylcellulose (HPMC) as hydrophilic polymer was performed to sustain the drug release. Drug releases from systems containing higher amount of HPMC or xanthan gum were slower than those of systems containing less amount of both polymers. Incorporation of higher amount of talcum, lactose or drug into PEG matrix containing 5% w/w xanthan gum minimized the drug dissolution and retarded the drug release in phosphate buffer pH 6.2 since the amounts of PEG4000 and PEG400 which were the drug carriers were decreased as the amounts of these substances were increased. Rotational speed of basket affected the drug release of tablet containing 75-mg indomethacin and 5% xanthan gum. Tablet coated with Eudragit L100 could prolong drug release in pH change system. The drug release from this coated tablet followed Higuchi's model.

Program of Pharmaceutical Technology Graduate School, Silpakorn University Academic Year 2008
Student's signature .....
Thesis Advisor's signature .....

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การละลายในตัวกลางที่เป็นน้ำของอินโดเมทาซินถูกทำให้เพิ่มขึ้นโดยการใช้สารตัวพาที่เป็นโพลีเอทิลลีนไกลคอลที่มีน้ำหนักโมเลกุลและอัตราส่วนต่างกัน โดยการเตรียมเป็นยาเม็ดโซลิดดิสเพอร์ชั่นด้วยวิธีการหลอมผสมสารและหล่อขึ้นรูปเป็นยาเม็ดโดยใช้แบบพิมพ์ ทั้งนี้ทำการศึกษาผลของอัตราส่วน ชนิด และปริมาณสารตัวพาต่อคุณสมบัติทางกายภาพของยาเม็ด การเติมแซนแทนกัมและไฮดรอกซีโพรพิลเมทิลเซลลูโลสเป็นพอลิเมอร์ก่อเมทริกซ์ได้ถูกนำมาใช้เพื่อยืดระยะเวลาในการปลดปล่อยยา พบว่าระบบที่มีไฮดรอกซีโพรพิลเมทิลเซลลูโลสหรือแซนแทนกัมในปริมาณสูงกว่ามีการปลดปล่อยยาช้ากว่ายาเม็ดที่มีปริมาณพอลิเมอร์ทั้งสองชนิดนี้ในปริมาณน้อยกว่า โดยการเติมทัลคัม แลคโตสหรือยาลงไปในปริมาณที่มากขึ้น มีผลทำให้การปลดปล่อยยาอินโดเมทาซินจากยาเม็ดเมทริกซ์ช้าลงเมื่อทดสอบในสารละลายฟอสเฟตบัฟเฟอร์พีเอช 6.2 ทั้งนี้เนื่องจากปริมาณโพลีเอทิลลีนไกลคอล 4000 และ โพลีเอทิลลีนไกลคอล 400 ซึ่งเป็นสารตัวพาลดลงเมื่อปริมาณของสารต่างๆดังกล่าวเพิ่มขึ้น ความเร็วในการหมุนของตะกร้ามีผลต่อการปลดปล่อยยาจากยาเม็ดที่มีอินโดเมทาซิน 75 มิลลิกรัมและแซนแทนกัม 5% โดยน้ำหนัก ยาเม็ดนี้ที่เคลือบด้วยยูดราจิดแอล 100 สามารถยืดระยะเวลาการปลดปล่อยยาได้ในสารละลายตัวกลางที่มีการเปลี่ยนแปลงพีเอช โดยมีรูปแบบการปลดปล่อยยาจากยาเม็ดเคลือบเป็นไปตามสมการของฮิกูชิ

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ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์……..

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LIST OF ABBREVIATIONS

^{o}C	degree Celsius
cd	coefficient of determination
cm	centimeter
Da	dalton
et al.	and others
g	gram
HPMC	hydroxypropyl methylcellulose
HCl	hydrochloric acid
mg	milligram
mJ	milijoule
mm	millimeter
ml	mililiter
msc	model selection criterion
N	newton
nm	nanometer
PEG	polyethylene glycol
PVP	polyvinyl pyrrolidone
rpm	round per minute
S.D.	standard deviation
%w/w	percent of weight by weight
μm	micrometer
μg	microgram

CHAPTER I

INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility are often needed. Many methods are available to improve this characteristic, including salt formation, micronization, and addition of solvent or surface-active agent (Fujii *et al*., 2005). Formulation of solid dispersions is another strategy that can increase the solubility and dissolution rate of drugs (Chiou and Riegelman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000; Wang *et al*., 2007 a). Although the use of solid dispersions has been reported frequently in the field of pharmaceuticals, only a few solid dispersion systems are used commercially. Typically, the term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is homogeneously dispersed in a inert matrix, usually with a view for enhancing oral bioavailability. More specifically, in the classic review, defined this system as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method, suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state'. Practically, the carrier has been a water-soluble or water miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. In particular, polymers such as polyethylene glycols and polyvinylpyrrolidone have been extensively used as carriers for dispersions due to their low melting point and hydrophilic nature (Trapani *et al*., 1999). These carriers are employed in the case of enhancing the aqueous solubility of insoluble drugs. Furthermore, solid polyethylene glycols such as PEG 4000 could be used easily to prepare tablet by melting method.

The use of hydrophilic matrices has become extremely popular in controlling the release rate of drugs from solid dosage forms. These systems are attractive approaches from an economic consideration as well as process development view point (Juarez *et al*., 2001; Vazquez *et al*., 1992). A sustained release matrix tablet consists of a compressed compact containing a mixture of one or more active ingredient(s) with one or more gel forming agent(s), which retards the release of the drug (Rao *et al*., 1988). For many reasons, oral drug delivery continues to be the preferred

route of drug substances administration (Bae *et al*., 1991; Deshapande *et al*., 1996). Although various types of polymers, used as rate controlling agents in hydrophilic matrices, have been extensively reviewed (Neau *et al*., 1999; Rao *et al*., 2001; Zhang and Schwarts, 2003). Water soluble polymers, such as cellulose ethers, are probably the most frequently encountered in pharmaceutical literature and have gained popularity in the formulation of oral hydrophilic matrices, due to their swelling properties. Additionally, cellulose ethers have good compression characteristics such that they can be directly compressed to form sustained release swellable matrices (Vueba *et al*., 2004; Hayashi *et al*., 2005).

Indomethacin is a widely used non-steroidal anti-inflammatory drug. It is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. Prostaglandins are hormone-like molecules normally found in the body, where they have a wide variety of effects, some of which lead to pain, fever, and inflammation. Because of its low water solubility (5 μg/ml) (Hancock and Parks, 2000), therefore indomethacin is used as a model drug in the study.

Xanthan gum is a useful pharmaceutical excipient, since it is of natural origin, biocompatible and safe. It is used as a tablet excipient to increase or decrease the drug release rate. Xanthan gum has been evaluated as a hydrophilic matrix for controlled release preparation, using different model drugs including theophylline, cephalexin, prednisolone, and indomethacin (Yeole *et al*., 2006). Therefore, this is interesting to investigate its effect on drug release from PEG matrix tablet prepared by mold technique.

As reported by Ozeki *et al*. (1994, 1995), behavior of water-soluble polymers during dissolution has a key factor in mechanism of drug release from solid dispersions prepared with water-insoluble and water-soluble polymers. The dissolution of a drug with poor water solubility might be improved by using a solid dispersion technique. The melting was a suitable method for drug which was stable at elevated temperatures. Xanthan gum is a hydrophilic polymer and upon contact with dissolution medium it can form a quite viscous gel to retard the drug release rate for developing controlled-release oral drug delivery systems.

In this study, indomethacin solid dispersion tablets were prepared with melting and mold method using PEG4000 combined with PEG 400 (7:3) as inert carriers. Xanthan gum used as hydrophilic polymer was also added in the developed system to prepare the model formulation

having functions of both the drug solubility enhancement and the extended release properties. Effects of type and amount of hydrophilic polymer, type and amount of diluents, drug loading, pH of dissolution medium, tablet size, rotational speed of basket and tablet coating with Eudragit L 100 on the physical properties and *in vitro* drug-release behavior of the systems were investigated.

The objectives of this study were:

1. To investigate the physical properties of indomethacin tablet prepared by mold technique using PEG as a drug carrier.
2. To investigate the effects of hydroxypropyl methylcellulose (HPMC) and xanthan gum on the physical properties and the drug release from tablet prepared by mold technique using PEG as a drug carrier.
3. To investigate the effects of amount of indomethacin, lactose and talcum on the physical properties and the drug release.
4. To investigate the effects of tablet size, hydrodynamic force and film coating on the drug release.
5. To improve the solubility of indomethacin by using solid dispersion technique and to develop the sustained-release dosage form with an addition of hydrophilic polymers.

CHAPTER II

REVIEW OF RELATED LITERATURE

1. Solid dispersion

First generation solid dispersions

The first description of solid dispersions was from Sekiguchi and Obi (1961). They noted that the formulation of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water soluble drugs. In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole and chloramphenicol using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability. The classification of solid dispersions is shown in Figure 1.

Margarit *et al*. (2001) analyzed the physicochemical characteristics of solid dispersions of pizotifen malate and povidone at different proportions; they used X-ray diffraction, infrared spectrometry, and differential scanning calorimetry (DSC) and tested the solubility of the solid dispersions in equilibrium. The results were compared with findings for physical mixtures with the same proportions. A solid dispersion with a drug proportion of 16%–17% formed a eutectic mixture. Solubility of pizotifen malate increased with the proportion of drug in the solid dispersion up to a drug:polymer ratio of 40:60. The hydrotropic effect of the polymer also favored solubility. In physical mixtures, this effect was greatest at a drug:polymer ratio of 10:90; solubility at this proportion was equal to that of the solid dispersion at the same proportion.

Second generation solid dispersions

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. They are divided into fully synthetic

polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins.

Fujii *et al*. (2005) prepared a solid dispersion of indomethacin, using a new method that avoided solvents and their associated problems. Furthermore, a typical dosage form, tablets, could be prepared from solid dispersion powders by direct compression. Drug solubility and dissolution rate were improved in both solid dispersion powders and tablets.

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying property, therefore third generation solid dispersions appeared. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailability.

Im *et al*. (2008) improved the solubility and *in vitro* dissolution of Coenzyme Q10 from binary solid dispersions using poloxamer 407. Solubility increased rapidly with increasing concentrations of poloxamer 407 in water. Gibbs free energy (ΔG°_{tr}) values were all negative and decreased with increasing concentration of poloxamer 407.

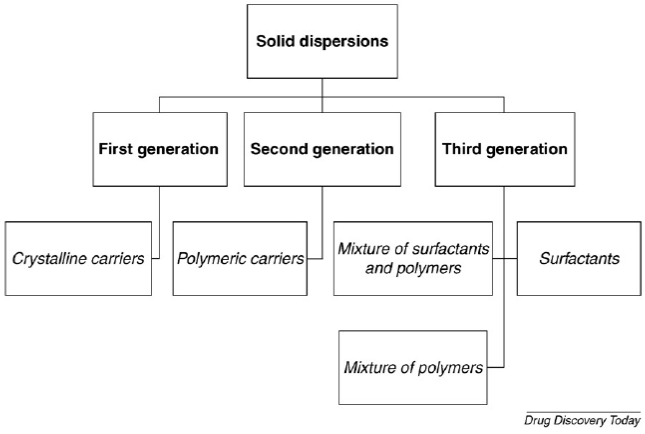


Figure 1 The classification of solid dispersions (Vasconcelos *et al*., 2007).

Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs (Vasconcelos *et al*., 2007).

- Solid dispersions appear to be a better approach to improve drug solubility than other techniques, because they are easier to produce and more applicable.
- Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do.
- Solid dispersions are more efficient than the particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 μm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability.
- Solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle.

The advantageous properties of solid dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Solid dispersions disadvantages

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full

potential of amorphous solids requires their stabilization in solid state, as well as during *in vivo* performance. Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing (Vasconcelos *et al*., 2007).

Manufacturing processes

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions (Figure 2).

Melting method

Sekiguchi *et al*. (1961) were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, reducing, therefore, the process temperature.

Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature. A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled. The use of the carriers partially suspended, instead of dissolved, was also reported in the preparation of a solid dispersion of indometacin, in which the drug and ethylcellulose were dissolved in ethanol and HPMC was suspended(Vasconcelos *et al*., 2007).

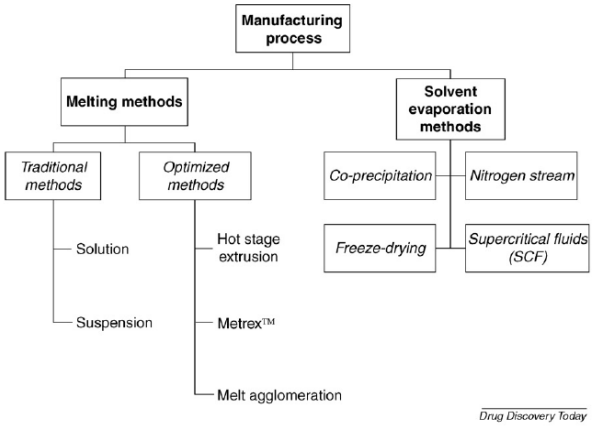


Figure 2 Manufacturing processes used to produce solid dispersions. (Vasconcelos *et al*., 2007).

2. Polyethylene Glycol

Polyethylene glycol (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. Polyethylene glycols are stable, hydrophilic substance that are essentially nonirritant to the skin. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment base. Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol (Handbook of Pharmaceutical Excipients, 2003).

Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant concentration holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tent to be more irritating to mucous membranes than fats (Handbook of Pharmaceutical Excipients, 2003).

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential

absorption of moisture from gelatin in the shell. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersion with an appropriate polyethylene glycol.

2.1 Chemical names: α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

2.2 Chemical structure:

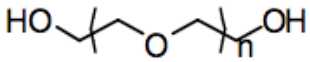


Figure 3 Chemical structure of polyethylene glycol (PEG)

2.3 Physical properties

2.3.1 Appearance

Polyethylene glycol grades 200-600 are liquids; grades 1000 are above are solid at ambient temperatures. Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

2.3.2 Melting point

37-40 ^{o}C for PEG 1000

44-48 ^{o}C for PEG 1500

40-48 ^{o}C for PEG 1540

45-50 ^{o}C for PEG 2000

48-54 ^{o}C for PEG 3000

50-58 ^{o}C for PEG 4000

55-63 ^{o}C for PEG 6000

60-63 ^{o}C for PEG 8000

60-63 ^{o}C for PEG 20000

2.3.3 Solubility

All grade of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycol (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol and methanol they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil (Handbook of Pharmaceutical Excipients, 2003).

2.4 Stability

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solution can be sterilized by autoclaving, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

Polyethylene glycols should be stored in well- closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for storage of liquid grades (Handbook of Pharmaceutical Excipients, 2003).

3. Extended release matrix systems

Extended release dosage forms are formulated in such manner as to make the contained drug available over an extended period of time following administration. Expressions such as controlled-release, prolonged-action, repeat action and sustained release have also been used to describe such dosage forms. A typical controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced fluctuations via slow release over an extended period of time. In practical terms, an oral controlled release should allow a reduction in dosing

frequency as compared to when the same drug is presented as a conventional dosage form. A matrix device consists of drug dispersed homogenously throughout a polymer matrix. Two major types of materials are used in the preparation of matrix devices. The first type is hydrophobic carrier such as glycerides-glyceryltristearate, polyethylene, ethyl cellulose. Another type is hydrophilic polymer such as methylcellulose, xanthan gum, hydroxypropyl methylcellulose and Carbopol®. (Abdelbary *et al*., 2008).

Advantages of the matrix systems

- Easy to manufacture
- Versatile, effective, low cost
- Can be made to release high molecular weight compounds
- Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release

Disadvantages of the matrix systems

- The remaining matrix must be removed after the drug has been released
- The drug release rates vary with the square root of time. Release rate continously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Mechanisms of drug release from matrix systems

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

3.1 Dissolution controlled release

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to

prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by :

- Preparing an appropriate salt or derivative

- Coating the drug with a slowly dissolving material-encapsulation dissolution control

- Incorporating the drug into a tablet with a slowly dissolving carrier-matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equations:

$$\frac{dC}{dt} = k_d.A.(C_s - C) = \frac{D}{h}.A.(C_s - C) \qquad [1]$$

where $\frac{dC}{dt}$ = dissolution rate

k_d = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)

D = diffusion coefficient

C_s = saturation solubility of the solid

C = concentration of solute in the bulk solution

Equation 1. predicts that the rate of release can be constant only if the following parameters are held constant : surface area, diffusion coefficient, diffusion layer thickness and concentration difference. However, under normal conditions, it is unlikely that these parameters will remain constant, especially surface area, and that is the case for combination diffusion and dissolution systems.

3.1.1 Encapsulated dissolution control

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in spacetabs or placed in capsules as in the spansule products. Once the polymeric membrane has dissolved, all drugs inside the membrane are immediately available for dissolution and absorption. Since the time required for dissolution of the coat is a function of its thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide

spectrum of coated particles of varying thicknesses, respectively. It is a common practice to employed 1/4 or 1/3 of the particles in non sustained release of drug. Alternatively, a portion of drug can be placed in a rapidly dissolving coating membrane to quickly establish therapeutic levels.

There are several ways to prepare drug-coated beads or granules. A common procedure is to coat nonpareil seeds with the drug followed by a coat of slowly dissolving material such as carbohydrate sugars and cellulose, polyethylene glycol, polymeric materials and wax. One of the principle methods of coating drug is microencapsulation wherein the drug solution or crystal is encapsulated with a coating substance. The most common approach for microencapsulation is coacervation, which involves the addition of hydrophilic substance to a solution of colloid. Whether a drug is water sensitive or not, it can be microencapsulated if drug is protected from the aqueous environment by coating with polymer.

3.1.2 Matrix dissolution control

Two general methods of preparing drug-polymer particles exist are aqueous dispersion and congealing methods. The aqueous dispersion method, drug-polymer mixture is simly sprayed or placed in water and then collected. In the congealing method, drug is mixed with polymeric substances or waxes. The wax or polymer drug material can be cooled and put through a screen to obtain the correct particle size or it can be spray congealed. Usually the aqueous dispersion method shows a higher release rate than wax congealing or spraying, probably due to the increased area and entrapment of water.

It was noted earlier that reducted drug solubility plus larger particle size could be used to modify availability rates. However, these approaches, alone or in combination, are limited in their usefulness. There is an upper restriction on the size of particle, one can employ for the oral route while the low solubility approach will produce a changing dissolution rate as the area for dissolution decreases.

An alternate approach is to compress the drug with a slowly dissolving carrier of some sort into a tablet form. The rate of drug availability is controlled by the rate penetration of the dissolution fluid into the matrix, porosity of the tablet matrix, the presence of hydrophobic additives.

3.2 Diffusion controlled release

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer. In general, two types or subclasses of diffusional systems are recognized.

3.2.1 Reservior devices

Film coating are the constitutes as the main factor in controlling drug release. Examples of materials used to control drug release include hardness gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used commonly used systems in the pharmaceutical industry.

3.2.2 Matrix devices

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions :

a) A pseudo-steady state is maintained during drug release.

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

c) The diffusion coefficient of drug in the matrix remain constant (no change occurs in the characteristics of the polymer matrix).

d) The bathing solution provides sink conditions at all times.

e) No interaction occurs between the drug and the matrix.

f) The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (excess solute is present).

g) Only the diffusion process occurs.

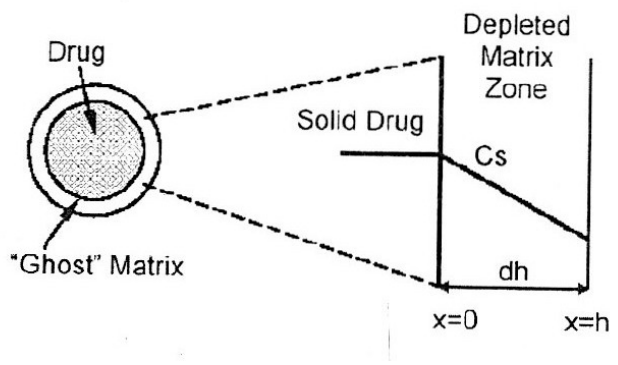


Figure 4 Release from a monolithic matrix system can be graphically depicted (Abdelbary *et al*., 2008).

3.3 Diffusion and dissolution systems (Bimodal release)

In certain systems, there is a bimodal or anomalous release or the active ingredient. In these systems there is diffusion as described previously; additionally, the extended release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution.

A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodable matrix :

a) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix. A description of this process requires the concentration of device geometry, axial and radial direction of mass transport, and the significant dependence of the water diffusion, coefficient on the matrix swelling ratio.

b) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

c) Upon contact with water the drug dissolves and diffuses out of the device.

d) With increasing water content, the diffusion coefficient of the drug increase substantially.

e) In the case of a poorly water soluble drug, dissolved and non-dissolved drug coexist within the polymer-matrix.

f) In the case of high initial drug loading, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive to diffusion.

g) Finally, the polymer itself dissolves.

These systems are described in terms of fronts. The following fronts have been defined, with regard to anomalous release systems : the swelling front, the erosion front, and the diffusion front (Figure 4).

- The “swelling front” separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the Tg of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environment temperature).

- The “erosion front” separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer concentration gradient and the well stirred medium.

- The “diffusion front” is between the swelling and erosion front and separated the areas of non dissolved drug from the area of dissolved drug.

With regard to swelling matrix systems, alternate models have been proposed to describe the diffusion, swelling, and dissolution processes occurring with into the system and these phenomena lead to drug relase.

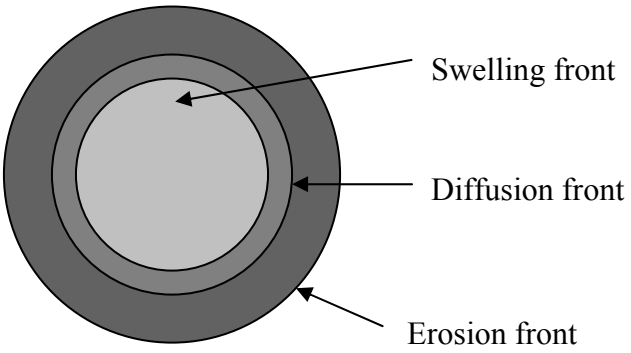


Figure 5 Fronts in bimodal release system.

Matrix system

In matrix devices, the drug is dispersed throughout the three dimension structures of the hydrogel. Release occurs due to diffusion of the drug throughout the macromolecular mesh or

water-filled pores. In these systems, the release rate is proportional to time to the one-half power. This is significant that it is impossible to obtain time independent or zero-order release in this type of system with simple geometries.

Drug can be incorporated into the gels by where the gels by equilibrium partitioning, where the gel is swollen to equilibrium in concentrated drug solution, or during the polymerization reaction. Equilibrium partitioning is the favorable loading method for drug-polymer systems with large partition coefficients or for sensitive macromolecular drugs such as peptides or proteins that could be degraded during the polymerization.

There are two principle categories of matrix device. If the active material dissolved in the polymer medium, the device is called a matrix solution. A device of this kind is often used when the active material is a liquid; some polymers can easily dissolve up to 20% or more of these liquids. If the active agent has more limited solubility in the polymer medium, then only a portion of agent is dissolved in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called a matrix dispersion.

1. Matrix solution

In this section, devices which contain drug dissolved at or below the saturation solubility of drug in the polymer matrix are considered. For slabs and/or cylinder, drug is released by diffusion from both the planar ends and the cylindrical portion of the devices.

2. Matrix dispersion

Matrix dispersions differ from those described in the previous section in matrix solution, it is assumed that drug is present as finely divided particle uniformly dispersed in the polymer matrix.

In such device, drug is release by diffusion within the polymer matrix. With time, two zones can be defined. One zone is composed of polymer containing dispersed drug. The second zone, termed the zone of depletion, is assumed to be constant and equal to the initial drug load. However, within the zone of depletion a concentration gradient exists. As noted earlier, the nature of this gradient is dependent upon the geometry of the device.

3. Matrix tablets

The matrix system also appears to be a very attractive approach from process development and scale-up point of view. Various materials like waxes, hydrophilic polymer and gums have been employed in the formulation of matrix type tablets.

Matrix tablets can be classified to:

3.1 Hydrophilic matrix tablets

There are many hydrophilic polymers which used as matrix materials; i.e., sodium carboxymethylcellulose, methylcellulose, hydroxypropyl cellulose and hydroxyl cellulose ether polymer such as hydroxypropyl methylcellulose (HPMC). In particular, high-viscosity grade HPMC (1,000-1,500 cps) is used to prepare matrix tablets by a dry-granulation method. The combination of high- and low-viscosity grades of HPMC was shown to be applicable as the matrix base to prepare diclofenac sodium and Zileuton sustained-release tablets.

A new ternary polymeric matrix system composed of pectin, HPMC and highly water-soluble drugs such as diltiazem HCl was developed by direct tablet compression. Two external layers can accomplish with further adjustments in the drug release rate. This system, the geometric trilayer tablets, was applied to develop a once a day formulation of diltiazem HCl.

3.2 Hydrophobic matrix tablets

To prepare a sustained-release tablet of water-soluble drugs, the drugs are mixed with hydrophobic matrices. With hydrophobic materials like fatty alcohols, acids, and esters, slow release drug particle are prepared and compressed into tablets. Voltaren SR® is commercial product of diclofenac sodium and is a hydrophobic matrix tablets consisting of a cetyl alcohol matrix. Ethylcellulose (EC), an inert and hydrophobic polymer that has been widely used in a number of dosage forms, was used as a matrix substance to prepare a sustained-release tablet of a water-soluble drug, pseudoephedrine HCl, by direct-compression technology. The lower-viscosity grades of EC are more compressible than the higher-viscosity grades, resulting in harder tablets and slower release rate. To prepare sustained-release tablets of a highly water-soluble drug, a cholinergic channel modulator for treatment of cognitive disorder, a hydrophobic matrix composed of carnauba wax and partially hydrogenated cottonseed oil were used as the rate-controlling material.

3.3 Plastic matrix tablets

Sustained-release tablets can also be prepared by formulations using an inert pharmaceutical polymers such as polyvinyl chloride, polyvinyl acetate, and methyl methacrylate. These polymers protect the tablet from disintegration due to the effect to peristalsis and turbulence and also reduce the dissolution rate of the drug inside the tablet. This technology was applied to theophylline (Theograd®), sodium valproate, and iron. Theograd® tablets consist of a matrix of a methylacrylate/methylmethacrylate copolymer that is mixed with theophylline and compresses into 250-350 mg tablets.

4. Evaluation of matrix system

The polymers swelling process has been studied by a variety of experimental techniques such as erosion and water uptake, observing polymer during (morphological study), radial dimension change, textural analysis for studying swelling behavior and scanning electron microscopy (SEM) analysis.

4.1 Erosion and water uptake

The *in vitro* swelling behavior was estimated by water uptake amount of the tablets. Water uptake and mass loss were determined gravimetrically according to the following equations: (Varshosaz *et al*., 2006).

$$\% \text{ Water uptake} = \frac{100\ (\text{wet weight} - \text{remaining dry weight})}{\text{remaining dry weight}} \qquad [2]$$

$$\% \text{ Erosion} = \frac{100\ (\text{remaining dry weight-original dry weight})}{\text{original dry weight}} \qquad [3]$$

Vueba *et al*. (2004) prepared different ketoprofen:excipient formulations to determine the effect of the polymer substitution and type of diluent on the drug-release mechanism. Substituted cellulose—methylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose were used as polymers, while lactose monohydrate and β-cyclodextrin were tested as diluents. The

swelling experiments, in turn, showed that the water uptake increased with the polymer viscosity, which was a rather important factor to consider when preparing hydrophilic matrix tablets.

In hydrophilic polymeric matrix systems, the carrier on the surface of the matrix initially hydrates during dissolution to generate an outer viscous gel layer. This phase is then sequentially followed by matrix bulk hydration, swelling and erosion. The overall dissolution rate and, ultimately, drug availability are controlled by the rate of matrix swelling, drug diffusion through the gel layer and/or matrix erosion. Roy *et al*. (2002) investigation was to comparatively evaluate two cellulose ethers, i.e., hydroxyethylcellulose and hydroxypropylcellulose, with a view to understand their drug release behavior from matrix tablets. Since the rate of polymer swelling and matrix erosion dictate the kinetics and mechanism of drug release from the matrices, the investigations were designed to study the rate of hydration of these polymers, rate of matrix erosion in the dissolution medium and the kinetics and mechanism of drug release from their matrices. Swelling and erosion of HEC are occurring simultaneously resulting in moving boundary conditions which continuously modify the effective diffusivity of the drug. Erosion increases the drug dissolution rate thus compensating for the high swelling index and the consequent slowing of drug diffusion by the increasing diffusional path length.

4.2 Morphological studies

The morphological changes, which occurred in the structure of the matrix when it came into contact with the dissolution fluids, are studied with a visual observation. To analyze the morphological behaviour of the systems during the release process, tablets were withdrawn from the dissolution vessels at different time intervals, were sectioned and their photographs were recorded using a digital microscope camera.

Conti *et al*. (2007 b) investigated of the swelling behaviour of matrix systems containing a mixture of hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) with a model soluble drug to find the correlation between the morphological behaviour and the drug release performance. The swelling study was conducted on tablets containing only the drug and the two polymers mixture (MB) and on reference tablets containing each polymer and the same drug, at three different pHs. MB matrices show a similar swelling trend at pH 4.5 and 6.8, while they have different behaviour in acidic fluid. At pH 1 the gel layer formed by

NaCMC is characterized by a rigid structure of a partially chemically crosslinked hydrogel while HPMC and MB matrices form a physical not crosslinked gel. At pH 4.5 and 6.8, all the systems show the typical morphological behaviour of a swellable matrix in which the macromolecular chains in the gel network are held together by weak bondings (physical gel). In these buffers, MB systems maintain a constant drug release rate coupling diffusion and erosion mechanism: the gel and infiltrated layers thicknesses are maintained constant and a zero-order release kinetics can be achieved.

4.3 Radial dimensional change

Billa *et al*. (2000) investigated the processing variables at the laboratory and pilot scales that could affect hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. Measurement of hydration rates of XG-containing matrices were carried out to relate the observed phenomena of drug release with the rates of polymer hydration. Therefore, a larger tablet diameter was used to distinguish and clearly measure the hydrated boundary. The radial dimension change expressed as a percentage (D_w%) was calculated using the expression

$$\text{Percent diameter change } (D_W) = (D_1\text{-}D_0)/D_0 \times 100 \qquad [4]$$

where D_1 and D_0 are the diameter of swollen and dried tablets, respectively. The percentage swelling of the original tablet was calculated and plotted vs. time to reflect the rate of hydration.

4.4 Textural analysis

Texture analyzer is a versatile research and development instrument that has been widely used in the food industry. By using different probes and assessment criteria, it is possible for food scientists to monitor or demonstrate the texture quality and palpability of different foods. The pharmaceutical applications of a texture analyzer for quality control purposes have significantly increased for the past several years. It has been used to optimize adhesiveness and cohesiveness of water-in oil emulsions (Lemaitre-Aghazarian *et al*., 2004), test tablet disintegration from fast-dissolving preparations (El-Arini and Clas, 2002), and evaluate mucoadhesive properties of various polymers (Cilurzo *et al*., 2005). The operation of a texture analyzer, on the other hand, is

relatively simple, versatile and cost-effective; it is possible to use the same instrument for multiple measurements by changing either testing probes or measurement parameters.

Compression analysis and relaxation experiments were carried out on the gels at room temperature. From a typical compression experiment, the following parameters can be acquired: (1) system hardness, i.e., the maximum positive force required to attain a given deformation, Fmax; (2) work of cohesion, given by the positive dashed area under the force–time curve, between a and b. It represents the work needed to overcome the internal bonds of the material; (3) work of adhesion, given by the negative area under the force–time curve, between c and d. It represents the work needed to pull the probe away from the sample. Increasing polymer concentration (c_p) value from 2% to 4% of carboxylated polymer (Sclerox) enhanced the work of cohesion and the hardness parameter. The work of adhesion was also estimated and obtained results indicated that, while for the sample at c_p=2% and 3%, the adhesion was relatively high, in the case of c_p=4%, the adhesion became almost negligible (Coviello *et al*., 2005).

4.4.1 Evaluation of the formation of hydrogel layer

Texture analyzer was used to evaluate the formation of hydrogel layer from a series of modified release matrix tablets of pseudoephedrine (Li *et al*., 2007). The correlation among drug release rate, polymer content in tablet and gel layer formation of both hydrophilic matrix polymer and water-insoluble lipidbased excipient was attempted. The primary objectives of the study were to explore the applicability of texture analysis and to devise simplified mathematical interpretation in formulation evaluation and optimization.

4.4.2 Evaluation of swelling rate and/or change in the thickness of the matrix tablet

Polymer hydration and swelling play an important role in controlling the rate of drug release from hydrophilic matrices. Therefore, swelling rate and/or change in the thickness of the matrix (tablet) when exposed to the dissolution medium has been frequently reported and cited in the literature. Two methods are commonly used to generate these data. In the first method a tablet is sandwiched between two Plexiglas plates and placed in a dissolution medium. Radial expansion of the constrained plates is then used as an indirect measure of polymer swelling rate. In the second method a tablet is placed in the dissolution medium. At a given time interval the swollen tablet is removed from the vessel. The thickness of the swollen layer is then measured by

a penetration probe fitted to a texture analyzer (Jamazad *et al*., 2005). The first method is useful as a qualitative and/or indirect method for estimating the swelling tendency of the polymer; however, it fails to provide useful information on the influence of fluid dynamics or the erosion-rate of the glassy core. While the second method provides more precise swelling and erosion data of the outer layer, it does not provide information on the erosion of the glassy core. Furthermore, the destructive nature of the method necessitates the use of a fresh sample at each time point in order to provide much desired time-dependent swelling kinetics, which renders the method both time and labor intensive (Nazzal *et al*., 2007).

Furthermore, different techniques based on measuring the penetration of a probe in the gel layer of a swollen tablet have been applied to investigate gel layer thickness by determination of the position of swelling and erosion fronts. Some of these represent methods of gel structure analysis, which provide information not only on gel layer thickness but also on the texture (strength) of the gel. Gel layer thickness was obtained calculating the difference between the maximum penetration distance of the swollen and the dry tablets. Furthermore axial expansion of the tablet may be analyzed, as the apparatus gauges tablet height. In contrast to alternative penetration methods like TMA, penetrometer and consistometer measurements, which simply base on the determination of the penetration distance at a distinct force, the texture analyser also provides information on gel structure, as complete force-distance-diagrams are recorded during the penetration process (Zuleger *et al*., 2002).

4.5 Scanning electron microscopy (SEM) analysis

Traditionally, scanning electron microscopy (SEM) and mercury porosimetry have been used to characterize microparticle porosities and morphologies. However, these methods have their specific disadvantages. SEM gives only information on pore sizes above a certain pore diameter. Mercury porosimetry often provides incomplete information because mercury is a non-wetting liquid that is difficult to imbibe into small pores. The high pressure that has to be applied can deform the porous network and close small pores.

Wang *et al*. (2007 b) developed a novel smart hydrogel of IPN PAA/triazole modified PVA (TMIPN) with PAA as an essential material of gel forming, followed by interpenetration with triazole modified PVA, which was characterized by FTIR, DSC and SEM. The

swelling/deswelling and controlled release behavior of TMIPN hydrogels were studied in detail. The mechanism of the swelling and the deswelling was discussed and the results were confirmed further by scanning electron microscope (SEM). The swelling/deswelling behavior of TMIPNs and the controlled release properties were also investigated by contrast method. The results showed that: (1) TMIPNs had the strong swelling capability in distilled water at room temperature; (2) TMIPNs had remarkable pH-sensitivity and saltsensitivity; (3) the controlled release behavior of TMIPNs possessed apparent pH, salt and other physical stimulus responsibility and was concerned with the swelling/deswelling of TMIPNs.

5. Hydroxypropyl methylcellulose

Hydroxypropylmethylcellulose (HPMC) has been extensively used since the early 1960s as a rate controlling polymer in oral extended-release dosage forms. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion. Then, the incorporated drug diffuses out of the system (Siepmann and Peppas, 2000). This popularity can be attributed to the polymer's non-toxic nature, its availability in different chemical substitution and hydration rates (for example, USP Type 2208 (Methocel K), 2910 (Methocel E), 2906 (Methocel F), good compressibility

5.1 Physicochemical characterization of HPMC

Where R is H, CH_3 or $CH_3CH(OH)CH_2$

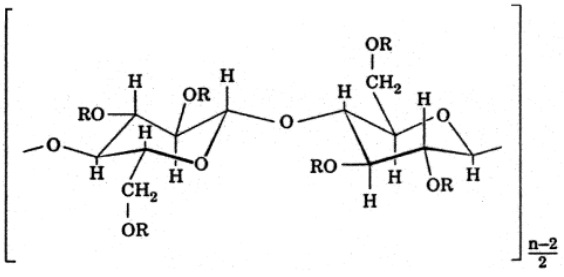


Figure 6 Chemical structure of HPMC (Siepmann *et al*., 2001).

HPMC is a propylene glycol ether of methylcellulose; its chemical structure is illustrated in Figure 6. The substituent R represents either a $–CH_3$ or a $– CH_2CH(CH_3)OH$ group, or a hydrogen atom. The physicochemical properties of this polymer are strongly effected by: (i) the methoxy group content; (ii) the hydroxypropoxy group content; and (iii) the molecular weight. The USP distinguishes three different types of HPMC, classified according to their relative $–OCH_3$ and $–OCH_2CH(CH_3)OH$ content: HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy-groups, the last two numbers the percentage of hydroxypropoxy-groups, determined after drying at 105 ^oC for 2 hours. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 1 In addition, the USP describes a method to determine the apparent viscosity of an aqueous 2% solution of the polymerusing a suitable viscosimeter of the Ubbelohde type. This apparent viscosity serves as a measure for the average chain length of the polymer. The measured value must lie within the 80.0 to 120.0% range of the viscosity stated on the label for HPMC types of 100 mPa s or less, and within the 75.0 to 140.0% range for HPMC types of higher viscosity (Siepmann and Peppas, 2001).

Table1 USP specifications for different types of HPMC, classified according to their degree of methoxy- and hydroxypropoxy- substitution (Siepmann *et al*., 2001).

Substitution type	**Methoxy (%)**		**Hydroxypropyl (%)**	
	Min.	**Max.**	**Min.**	**Max.**
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

Interestingly, Dahl *et al*. (1990) reported broad variations concerning important characteristics of seven batches HPMC 2208 with a labled viscosity of 15,000 mPa s, provided by two different manufactures. All samples had similar viscosities, except one batch which was outside the USP specifications. The methoxy-group content was uniformly high and three batches fell outside the USP limits of 19.0 to 24.0%. The hydroxypropoxy-group content (although within

the USP specifications of 4.0 to 12.0%), varied relatively more than the methoxy group content. These variations lead to significant differences concerning the resulting release rate of naprox- en from compressed matrix tablets in vitro. The authors concluded that each batch (even from the same manufacturer) should be carefully controlled and that the specifications of the USP and other pharmacopoeas might have to be reinforced.

5.2 Physicochemical properties of HPMC

5.2.1 Melting point: browns at 190-220 ^{o}C; chars at 225-230 ^{o}C. Glass transition temperature is 170-180 ^{o}C.

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

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

HPMC is oderless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a various colloidal solution, insoluble in alcohol, ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixture of methylene chloride and isopropyl alcohol and other organic solvents. HPMC is vary stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is compatible in the extreme pH conditions and with oxidizing materials. HPMC can be used as a film-former, thickening agent, protective colloid, emulsifier, suspending agent and stabilizer. High viscosity grades are used to retard the release of water soluble drugs (Ford *et al*., 1985).

Dissolution studies of indomthacin controlled release tablets showed that for a poorly water soluble drug, not only was the polymer to drug ratio important in controlling the

release, but both viscosity grade of HPMC and particle size of the drug were to be the only mechanism by which poorly soluble drugs release from matrix tablet (Ford *et al*., 1985).

5.3 Factors influencing the release drug from HPMC matrix system

5.3.1 Type and amount of HPMC

The releases of ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, ribavirin, theophyline, tinidazole, propylthiouracil, and sulfamethoxazole from HPMC matrices having different HPMC concentration (w/w, 16.5–55%) follow the power law. These drugs have very different physicochemical properties (solubilities of 1.126–125.5 g/100 ml in water and molecular volumes of 0.1569–0.4996 nm^3). There is good correlation between the fractional drug release and release time, HPMC concentration, solubility and molecular volume of drug. HPMC concentration has little effect on the diffusional exponent, but it has great effect on the kinetic constant in Peppas' equation. Increasing HPMC concentration will decrease kinetic constant, so decrease release rate of a drug from HPMC matrices. The effect of HPMC concentration is also related with the solubility and molecular volume of a drug. Both solubility and molecular volume of a drug affect the diffusional exponent. Less solubility and greater molecular volume result in greater diffusional exponent. The equation derived using a training set of HPMC matrices having different HPMC concentration and different drugs displays good prediction ability when it is used to predict tinidazole release from HPMC matrices. It is possible to predict M_t/M_∞ values of a drug from formulation and its physicochemical properties (Fu *et al*., 2004).

Mahaguna *et al*. (2003) investigated the influence of HPMC molecular weight on pharmacokinetic and pharmacodynamic parameters of controlled release formulations containing alprazolam, excipients, and either HPMC K4MP or HPMC K100LVP. The tablats containing either HPMC K4MP or HPMC K100LVP had similar dissolution profile and the dissolution profile did not change through 6 months at 40 C/75%RH or 12 months at 25 C/65%RH. The pharmacokinetic and pharmacodynamic results irrespevtive of formulation or diet used in the controlled released tablet.

5.3.2 Type and amount of various fillers

Three controlled-release acetaminophen tablets containing hydroxypropyl methylcellulose (HPMC) with or without highly water soluble fillers, lactose or polyethylene

glycol 6000 (PEG6000), were prepared. Water penetration into the matrix as enhanced by addition of fillers in the matrices, but the three tablets showed similar *in vitro* dissolution profiles, indicating that fillers in the HPMC matrices little affected the *in vitro* drug release. In contrast, the fillers in HPMC matrices did affect the *in vivo* performance in dogs. The absorption profile of HPMC matrix with PEG6000 was the fastest, followed by that with lactose and without water soluble filler, in that order. As the matrix with PEG6000 had a large amount of water and gelated a large portion of the matrix when in contact with water, the gel layer would be disintegrated by the gastrointestinal motility. It was found that dissolution of gel-forming HPMC matrices under mechanical stress by glass beads well correlated with the in vivo performance of the matrix, with little correlation by the conventional paddle method (Sako *et al*., 2002).

5.3.3 Type of drug

Different liquisolid formulations of carbamazepine were accomplished by dissolving the drug in the non-toxic hydrophilic liquids, and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and Aerosil® in liquisolid formulations, some additives namely polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of the carrier on dissolution rate of liquisolid compacts were studied. X-ray crystallography and differential scanning calorimetery (DSC) were used for evaluation of physicochemical properties of carbamazepine in liquisolid formulations. The results showed that the drug loading factor was increased significantly in the presence of additives. Liquisolid formulations containing PVP as additive, exhibited significantly higher drug dissolution rates compared to the compacts prepared by the direct compression technique. It was shown that microcrystalline cellulose had more liquid retention potential in comparison with lactose, and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. By decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed. Further decrease in the ratio of microcrystalline cellulose:silica from 10 to 5 resulted in a significant reduction in dissolution rate. Increasing of PVP concentration in liquid medication caused a dramatic increase in dissolution rate at first 30 min. The results showed that the dissolution rate of liquisolid tablets was not significantly affected by storing the tablets at 25 ˚C/75% relative

humidity for a period of 6 months. The results of DSC and X-ray crystallography did not show any changes in crystallinity of the drug and interaction between carbamazepine and excipient during the process (Siepmann *et al*., 2001).

5.3.4 Effect of pH of dissolution medium

Hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) were used as polymeric carriers to improve controlled release performances of matrix tablets containing a soluble drug. The drug release behaviour of the systems containing these two polymers mixture and each material separately was investigated (Siepmann *et al*., 2001). To evaluate the effect of the dissolution medium pH, on the drug release performance, release tests were conducted at pH 1, 4.5 and 6.8. *In vitro* release studies demonstrated that the mixture of the two cellulose derivatives enables a better control of the drug release profiles at pH 4.5 and at 6.8 both in term of rate and mechanism (Suh *et al*., 1996). Texture analysis on the swollen tablets helps to understand drug release kinetics and mechanism. In fact, the results obtained confirm that a gel, which is characterized by high strength and consistence is less susceptible to erosion and chains disentanglement and the drug release mechanism is mainly governed by diffusion. On the contrary, gels, which show a low strength and texture, have low resistance to the fluid erosion action and the release of the active molecule is manly due to polymer relaxation and chains disentanglement moving the drug delivery kinetic towards an erosion/relaxation mechanism (Conti *et al*., 2007 a).

5.3.5 The agitation rate of the release medium

The effect of dissolution medium variables, such as medium composition, ionic strength and agitation rate, on the swelling and erosion of hypromellose (hydroxypropyl methylcellulose, HPMC) matrices of different molecular weights was examined. Swelling and erosion of HPMC polymers was determined by measuring the wet and subsequent dry weights of matrices. It was possible to describe the rate of dissolution medium uptake in terms of a square root relationship and the erosion of the polymer in terms of the cube root law. The extent of swelling increased with increasing molecular weight, and decreased with increasing agitation rate. The erosion rate was seen to increase with decrease in polymer molecular weight, with a decrease in ionic strength and with increasing agitation rate. The sensitivity of polymer erosion to the

degree of agitation may influence the ability of these polymers to give reproducible, agitation-independent release, compared to more rigid non-eroding matrix materials, in the complex hydrodynamic environment of the gastrointestinal tract (Siepmann *et al*., 2001).

6. Xanthan gum

Xanthan gum is a natural polysaccharide and an important industrial biopolymer. It was discovered in the 1950s at the Northern Regional Research Laboratories (NRRL) of the United States Department of Agriculture (Margaritis and Zajic, 1978). The polysaccharide B-1459, or xanthan gum, produced by the bacterium *Xanthomonas campestris* NRRL B-1459 was extensively studied because of its properties that would allow it to supplement other known natural and synthetic water-soluble gums. Extensive research was carried out in several industrial laboratories during the 1960s, culminating in semicommercial production as Kelzan by Kelco. Substantial commercial production began in early 1964. Today, the major producers of xanthan are produced by Merck and Pfizer the United States, Rhone Poulenc and Sanofi-Elf in France, and Jungbunzlauer in Austria (Ochoa *et al*., 2000).

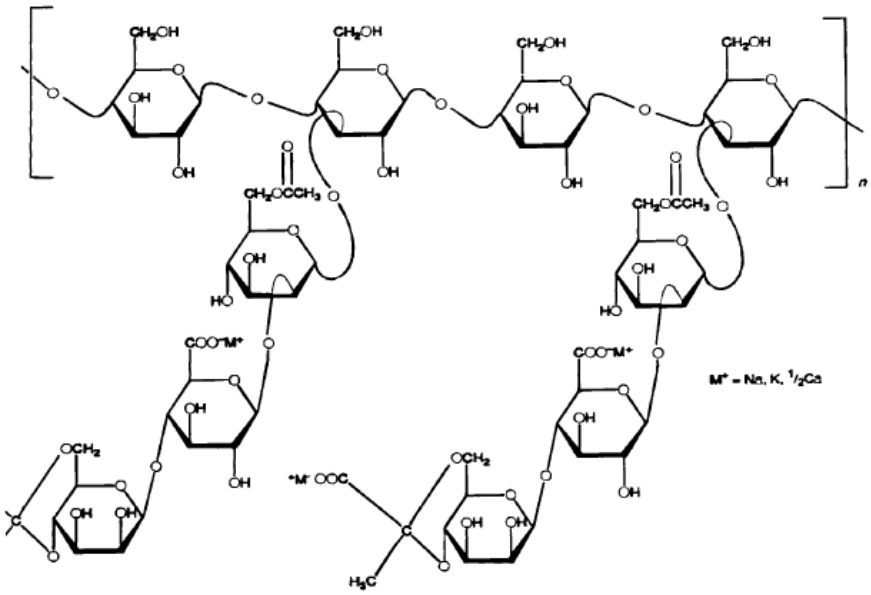


Figure 7 Structure of extracellular polysaccharide of *X. campestris* (Ochoa *et al*., 2000).

Xanthan gum is a heteropolysaccharide with a primary structure consisting of repeated pentasaccharide units formed by two glucose units, two mannose units, and one glucuronic acid unit, in the molar ratio 2.8:2.0:2.0 (Fig. 7). Its main chain consists of β-D-glucose units linked at the 1 and 4 positions. The chemical structure of the main chain is identical to that of cellulose. Trisaccharide side chains contain a D-glucuronic acid unit between two D-mannose units linked at the O-3 position of every other glucose residue in the main chain. Approximately one-half of the terminal D-mannose contains a pyruvic acid residue linked via keto group to the 4 and 6 positions, with an unknown distribution. D-Mannose unit linked to the main chain contains an acetyl group at position O-6. The presence of acetic and pyruvic acids produces an anionic polysaccharide type. Average composition of the various polysaccharides produced by some bacteria of the genus *Xanthomonas* is shown in Table 2 (Kennedy and Bradshaw, 1984).

The trisaccharide branches appear to be closely aligned with the polymer backbone. The resulting stiff chain may exist as a single, double, or triple helix, which interacts with other polymer molecules to form a complex. The molecular weight distribution ranges from 2×10^6 to 20×10^6 Da. This molecular weight distribution depends on the association between chains, forming aggregates of several individual chains. The variations of the fermentation conditions used in production are factors that can influence the molecular weight of xanthan.

Table 2 Average percent composition of polysaccharides produced by *Xanthomonas* bacteria (adapted from Kennedy and Bradshaw, 1984)

Bacteria	D-Glucose	D-Mannose	D-Glucoronic acid	Pyruvate	Acetate
X. campestris	30.1	27.3	14.9	7.1	6.5
X. fragaria 1822	24.6	26.1	14.0	4.9	5.5
X. gummisudans 2182	34.8	30.7	16.5	4.7	10.0
X. juglandis 411	33.2	30.2	16.8	6.9	6.4
X. phaseoli 1128	30.9	28.6	15.3	1.8	6.4
X. vasculorum 702	34.9	30.2	17.9	6.6	6.3

Solutions of xanthan obtained by dissolution at moderate temperatures tend to be highly viscous. The dissolution temperature greatly affects viscosity by controlling the molecular conformation and appearance of ordered structures. The xanthan molecule seems to have two conformations, helix and random coil, depending on the dissolution temperature (Morris, 1977; Horton *et al*., 1985; Garcia-Ochoa and Casas, 1994). An important property of xanthan solutions is the interactions with plant galactomannans such as locust bean gum and guar gum. The addition of any of these galactomannans to a solution of xanthan at room temperature causes a synergistic increase in viscosity. The toxicological and safety properties of xanthan gum for food and pharmaceutical applications have been extensively researched. Xanthan is non-toxic and does not inhibit growth. It is non-sensitizing and does not cause skin or eye irritation. On this basis, xanthan has been approved by the United States Food and Drug Administration (FDA) for use a food additive without any specific quantity limitations. In 1980, the European Economic Community xanthan gum to the food emulsifier/stabilizer list, as item E-415.

Xanthan gum has been used in a wide variety of foods for a number of important reasons, including emulsion stabilization, temperature stability, compatibility with food ingredients, and its pseudoplastic rheological properties. Table 2 lists some current uses of xanthan gum in food and other applications. Because of its properties in thickening aqueous solutions, as a dispersing agent, and stabilizer of emulsions and suspensions, xanthan gum is used in pharmaceutical formulations, cosmetics, and agricultural products. It is used in textile printing pastes, ceramic glazes, slurry explosive formulations, and rust removers. High viscosity of solutions and water solubility of the polymer have created important applications for xanthan in the petroleum industry where it is commonly used in drilling fluids and in enhanced oil recovery processes.

Table 3 Main industrial applications of xanthan gum (Ochoa *et al*., 2000)

Application	Concentration (% w/w)	Functionality
Salad dressings	0.1±0.5	Emulsion stabilizer; suspending agent, dispersant
Dry mixes	0.05±0.2	Eases dispersion in hot or cold water
Syrups, toppings, relishes, sauces	0.05±0.2	Thickener; heat stability and uniform viscosity
Beverages (fruit and non-fat dry milk)	0.05±0.2	Stabilizer
Dairy products	0.5±0.2	Stabilizer; viscosity control of mix
Baked goods	0.1±0.4	Stabilizer; facilitates pumping
Frozen foods	0.05±0.2	Improvesfreeze±thaw stability
Pharmaceuticals (creams and suspensions)	0.1±1	Emulsion stabilizer; uniformity in dosage formulations
Cosmetic (denture cleaners, shampoos, lotions)	0.2±1	Thickener and stabilizer Agriculture (additive in animal feed and pesticide formulations)
Suspension stabilizer	0.03±0.4	improved sprayability, reduced drift, increased cling and permanence
Textile printing and dyeing	0.2±0.5	Control of rheological properties of paste; preventing dye migration
Ceramic glazes	0.3±0.5	Prevents agglomeration during grinding
Slurry explosives	0.3±1.0	Thickens formulations; improves heat stability (in combination with guar gum)
Petroleum production	0.1±0.4	Lubricant or friction reduction in drill-hole
Enhanced oil recovery	0.05±0.2	Reduces water mobility by increasing viscosity and decreasing permeability

6.1 Properties of xanthan gum

Xanthan gum is highly soluble in both cold and hot water, and this behavior is related with the polyelectrolyte nature of the xanthan molecule. Xanthan solutions are highly viscous even at low polymer concentrations. These properties are useful in many industrial applications, especially in the food industry where xanthan is used as a thickener, and to stabilize suspensions and emulsions (Table 3). The thickening ability of xanthan solutions is related with viscosity; a high viscosity resists flow. Xanthan solutions are pseudoplastic, or shear thinning, and the viscosity decreases with increasing shear rate. The viscosity also depends on temperature (both dissolution and measurement temperatures), the biopolymer concentration, concentration of salts, and pH. Other typical properties of xanthan gum are given in Table 4 (Ochoa *et al*., 2000).

Table 4 Typical physical properties of commercial xanthan gum (Ochoa *et al*., 2000)

Property	Value
Physical state	Dry, cream-colored powder
Moisture (%)	8-15
Ash (%)	7-12
Nitrogen (%)	0.3-1.0
Acetate content (%)	1.9-6.0
Pyruvate content (%)	1.0-5.7
Monovalent salts (g L^{-1})	3.6-14.3
Divalent salts (g L^{-1})	0.085-0.17
Viscosity (cP)	13-35

(15.8 s^{-1}, CP=1 g L^{-1}, TD=25°C, TM=25°C)

6.1.1 Influence of temperature

Xanthan solution viscosity depends on both the temperature at which the viscosity is measured (measurement temperature, TM) and the temperature at which the xanthan is dissolved (dissolution temperature, TD). The viscosity decreases with increasing temperature . This behavior is fully reversible between 10 and 80°C. The solution viscosity also depends on the

polymer dissolution temperature the viscosity declines as the dissolution temperature is increased up to 40°C. Between 40 and 60°C, the viscosity increases with increasing temperature. For temperatures >60°C, the viscosity declines as the temperature is raised. This behavior is associated with conformational changes of the xanthan molecule. The conformation shifts from an ordered (low-dissolution temperature) to a disordered (high dissolution temperature) state. Conformational transition observed corresponds to a helix-coil transition of the backbone with simultaneous release of the lateral chains followed by progressive decrease of the rigidity of the (1-4)-β-D glucan chain as the temperature rises between 40 and 60°C. The transition temperature can vary depending on the salt concentration, independently of the polymer concentration (Kang and Pettit, 1993).

6.1.2 Influence of polymer and salt concentration

The viscosity of xanthan solutions increases strongly with increasing concentration of the polymer. The behavior is attributed to the intermolecular interaction or entanglement, increasing the effective macromolecule dimensions and molecular weight. The presence of salts in solution influences the xanthan viscosity. At low polymer concentration the viscosity declines slightly when a small amount of salt is added to solution. This effect has been attributed to the reduction in molecular dimensions resulting from diminished intermolecular electrostatic forces (Smith and Pace, 1982). Viscosity increases at higher xanthan concentration or when a large amount of salt is added. This effect is probably due to increased interaction between the polymer molecules. The viscosity of a xanthan solution is independent of the salt concentration when the salt content exceed 0.1% w/v (Kang and Pettit, 1993).

6.1.3 Influence of pH

Viscosity of xanthan solutions is unaffected by pH changes between pH 1 and 13. At pH 9 or higher, xanthan is gradually deacetylated (Tako and Nakamura, 1984), while at pH lower than 3 xanthan loses the pyruvic acid acetyl groups (Bradshaw *et al*., 1983). Either deacetylation or depyruvylation has scarcely any effect on xanthan solution viscosity. Both deacetylated or depyruvylated xanthan shows similar rheological properties as native xanthan. The viscosities of the various solutions converge at high shear rates because molecular interactions decrease with increasing shear rate (Ochoa *et al*., 2000).

6.1.4 Pseudoplastic behavior

Xanthan solutions have a non-Newtonian rheology. Apparent viscosity decreases as shear rate increases. No hysteresis is evident and shear-thinning and recovery are instantaneous (Kang and Pettit, 1993). However, xanthan solutions exhibit an initial yield stress that must be overcome for the solution to flow. Yield stress imparts stability to emulsions in low stress situations during storage or transportation when the prevailing stress is less than the yield stress.

6.1.5 Influence of fermentation conditions on xanthan properties

The molecular weight and the extent of pyruvic acid and acetal substitutions of xanthan depend on the Xanthomonas strain, the medium composition, and the operational conditions used. The nature of the polymer can modify the rheological properties of xanthan solutions (Milas *et al*., 1985). The pyruvate and acetate contents in xanthan affect the interaction between molecules of xanthan, and between xanthan and other polymers (e.g. galactomannans).

There is no general agreement on the influence of the specific fermentation conditions on the properties (molecular weight and structure). Optimal pyruvylation is obtained by culturing Xanthomonas at 27°C. Kennedy *et al*. (1982) found enhanced pyruvylation when the nitrogen concentration increased, but has been reported more pyruvic acid substitution and less acetate content when nitrogen source was the limiting nutrient. Trilsbach *et al*. (1984) did not find any relationship between the extent of pyruvylation and the medium composition. The molecular weight of the polymer increases in the absence of oxygen limitation, but the acetate and pyruvate contents are barely affected by dissolved oxygen (Cadmus *et al*., 1978). The acetate/pyruvate content and the xanthan molecular weight increase with time in batch culture. The culture temperature at which xanthan is produced has a significant impact on both the amount produced and the molecular structure of xanthan. A relatively high molecular weight was obtained at 25°C compared to culture at higher temperatures. The acetate and pyruvate content decreased slightly when culture temperature was increased. These results agreed with those of Cadmus *et al*.(1978) and Shu and Yang (1990). The initial nitrogen concentration also affects xanthan production. Biomass growth increases when nitrogen concentration increases, reaching a maximum at 1.1 g L^{1} of NH_4NO_3, with a negligible effect on xanthan production. This variable has no effect on molecular weight and acetate content of the xanthan produced; however, an increase in the initial

nitrogen concentration decreases the pyruvate content. These results are consistent with those of Davidson (1978).

6.1.6 Interaction of xanthan with galactomannan

Xanthan interacts with galactomannans (e.g. locust bean gum, guar gum), so that the viscosity of a mixture of these polymer is increased synergistically. The viscosity of these mixtures depends on xanthan and galactomannans structures (Dea *et al*., 1986; Casas and Garcia-Ochoa, 1999). As noted above, xanthan changes its conformation on solution depending on the dissolution temperature. When xanthan is dissolved at low temperature (< 40°C), it has an ordered conformation that allows a better interaction between xanthan and galactomannan molecules (Dea *et al*., 1977; Tako and Nakamura, 1984; Casas and Garcia-Ochoa, 1999). Dissolution temperature also influences the nature of the dissolved galactomannan. Locust bean and guar gums are the galactomannans most commonly employed in the industry (Maier *et al*., 1993). They are formed by a backbone chain of mannose units linked to a monomolecular unit of galactose. The relation between galactose and mannose and its distribution in the backbone is typical of every galactomannan. Galactose residues are not uniformly distributed; there are regions without galactose (smooth regions) and others with many galactose residues (hairy regions). Smooth regions are the ones that favor interaction with the xanthan molecule, but this region is soluble only at ~80°C. Thus, interaction between xanthan and galactomannan is favored when xanthan is dissolved at a low temperature (40°C) and galactomannan at a high temperature (80°C).

7. Indomethacin

Indomethacin is non-steroidal anti-inflammatory agent with anti-pyretic and analgesic properties. It has been used in the symptomatic management of painful and inflammatory conditions. Indomethacin sodium is given to infant to close a patent ductus arteriosus.

7.1 Chemical names : Indomethacin is 1-(4 Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. It's proprietary names include Amuno, Artracin, Confortid, Imbrilon, Indocid, Indocin, Indoflex, Indolan, Mobilan, and Rheumacin.

7.2 Formula : $C_{19}H_{16}ClNO_4$

7.3 Molecular weight : 357.81

7.4 Chemical structure :

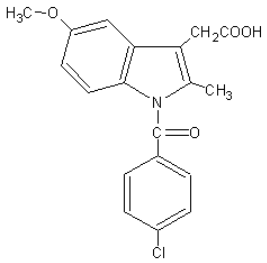


Figure 8 Chemical structure of Indomethacin

7.5 Physical properties

7.5.1 Appearance

A white to yellow-tan, odorless or almost oderless, crystalline powder. Melting point is about 158 ^{o}C to 162 ^{o}C.

7.5.2 Crystal properties

Indomethacin is known to exist in several polymorphic forms which are different is melting point and solubility. Most authors refer to these polymorphs as Form I (γ-type) and Form II (α-type). However there are some other less common forms. Form I is the highest melting and lowest solubility polymorph and is, therefore the thermodynamically stable crystalline modification of indomethacin. However, both Form I and Form II are equally biologically available and active.

Table 5 Melting points of indomethacin polymorphs (Otsuka *et al*., 2003).

Form	Melting point (^{o}C)
Form I (type γ)	160-161.5
Form II (type α)	154-155.5
Form III	148
Form IV	134
Type β	158-160.5

7.5.3 Solubility

Indomethacin is practically insoluble in water, soluble 1 in 50 of ethanol, 1 in 30 of chloroform, and 1 in 40 to 45 of ether, and soluble in acetone. Its solubility data have been reported in table 6.

Table 6 Solubility data of indomethacin (Bandi *et al*., 2004).

Solvent	Temp (^{o}C)	Solubility
Water	25	0.4 mg/100 mL[a] 0.42 mg/100 mL[b] 0.88 mg/100 mL[c]
Water	RT	practically insoluble
Phosphate buffer pH 5.6	25	3 mg/100 mL[a] 5 mg/100 mL[b]
Phosphate buffer pH 6.2	25	11 mg/100 mL[a] 16 mg/100 mL
Phosphate buffer pH 7.0	25	54 mg/100 mL[a] 80 mg/100 mL[b]
Ethyl alcohol (95%)	RT	1:50
Chloroform	RT	1:30
Ether	RT	1:45
Methanol	25	32 mg/gm
Benzene	25	5 mg/gm
n-butanol	25	19 mg/gm
sec-butanol	25	27 mg/gm

[a]Form I, [b]Form II, [c]Form III

7.5.4 Dissociation constant

pKa equals 4.5 for the carboxyl group of indomethacin.

7.6 Stability

In general, the integrity of indomethacin powder and formulated products exists for at least five years at room temperature. Exposure to strong direct sunlight induces an increase in the color of indomethacin, however, degradation is slight. Indomethacin is stable in neutral or slightly acidic media but undergoes alkaline hydrolysis to p-chlorobenzoate and 2-methyl-5-methoxy-indole-3-acetate which are primary metabolic products.

The half-life at room temperature is about 200 hours in pH 8.0 buffer and about 90 minutes in pH 10.0 solutions. Some injectable formulations were stable after 4 months storage at 50 ^{o}C.

7.7 Dosage and administration

Indomethacin has analgesic, anti-inflammatory and antipyretic properties. It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gout arthritis. It may also be used in mild to moderate pain in conditions such as dysmenorrhea.

In usual initial dose by mouth in musculoskeletal and joint disorder is 25 mg two or three times daily with food, increase, if required, by 25 to 50 mg daily at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffness, 100 mg may be administered by mounth, or rectally as a suppository. In acute gout arthritis a suggested dose is 50 mg three times daily and in dysmenorrheal up to 75 mg daily has been suggested.

Indomethacin is used as the sodium salt to close a patent ductus arteriosus in premature infants. It is given as a short occurs of therapy of three intravenous injections given at 12-24 hour intervals. The dose of indomethacin sodium depends upon the age of the neonate and the following dose has been suggested based upon the age at first dose.

8. The release pattern of matrix system

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

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

3. First order release model

8.1 Zero-order release model

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

$$\frac{dM_t}{dt} = k \qquad [5]$$

Where k is a constant, t is a time and M_t is the mass of active agent released. This model of release is called zero-order release model.

8.2 Square-root-time release model (Higuchi's model)

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

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad [6]$$

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

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

$$Q = [D\varepsilon/\ \tau\ (2A - \varepsilon C_s)\ C_s t]^{1/2} \qquad [7]$$

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

The assumptions made deriving equation are as follows:

1. A pseudo-steady state is maintained during release
2. A>>>Cs, i.e. excess solute is present
3. The system is in perfectly sink condition in which Cs is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix
5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs

In general Higuchi's equation is usually desired and used as:

$$Q = k_h t^{1/2} \quad [8]$$

Where k_h = higuchi's constant

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

In order to further verify that the relase follows Higuchi's model, Higuchi's equation is converted into logarithmic from as:

$$\log Q = \log k_h + ½ \log t \quad [9]$$

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

8.3 First-order release model

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

$$\frac{dM_t}{dt} = k(M_0 - M_t) \quad [10]$$

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

$$\frac{dM_t}{dt} = kM_0 \exp^{-kt} \quad [11]$$

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

On the assumption that the exposed surface area of matrix decreases exponential of time, Wagner (1969) suggested that drug release from most controlled-relase matrices could be described by apperent first order kinetics, thus:

$$A^t = A_0 e^{-k_1 t} \quad [12]$$

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

Simplifying and taking the logarithm of equation 12 yields

$$\log A^t = \log A_0 - \frac{k_1 t}{2.303} \quad [13]$$

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

For Higuchi's model, the rate will be inversely proportional to the total amount of drug release in accordance with equation (Higuchi, 1963 and Sa *et al*., 1990).

$$\frac{dQ}{dt} = \frac{k_H^2 S^2}{2Q'} \quad [14]$$

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

$$\frac{dQ}{dt} = kA_0 - kQ \quad [15]$$

Where A= A_0- Q'. This indicated rate will be proportional to Q'. The rates of release are determined by measuring the slope at different points on the percentage of drug release versus times curves.

The plots of rates of release versus 1/ Q' are linear, indicating that the release is fitted with Higuchi model. If the plots of rates of release versus Q' are linear, indicating that first order model is operative.

The release model for each classes of device is illustrated in Figure 6 (Baker, 1987). The release models of zero-order, square-root time and first-order are depicted, respectively (equation 1, 2 and 6).

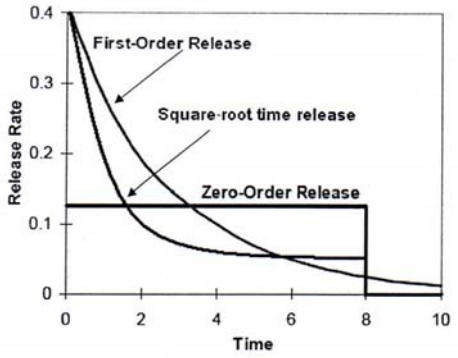


Figure 9 Zero-order, first-order and square-root time release patterns from devices containing the same initial active agent content.

9. Release mechanism of controlled release system

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

$$\frac{M_t}{M_\alpha} = kt^n \qquad [16]$$

Where $\frac{M_t}{M_\alpha}$ = the fractional of release of drug up to time t

t = the release time

k = a constant incorporating structure and geometric characteristics of the controlled relase device

n = the release exponent, indicative of the mechanism of drug release

Clearly, at desirable mechanism for many applications that which leads to be equals 1, this characterizes zero-order release behavior. Table 7 summarizes the general dependence of n on the diffusional mechanism (Peppas, 1985).

Table 7 Interpretation of diffusional release mechanism from drug release data from thin polymer film (Peppas, 1985).

Release exponent (n)	Drug transport mechanism	Rate as a function
0.5	Fickian diffusion	$t^{1/2}$
0.5<n<1.0	Anomalous (non-Fickian) Transport	t^{n-1}
1.0	Case-II transport	Zero-order (time-inpendent)
n>1.0	Super case-II transport	t^{n-1}

The empirical equation 16 could be modified for application to non planar geometric. The relationship between the diffusional exponent n and corresponding release mechanism is clearly depend on the geometry employed as shown in Table 7, 8 and 9 (Rigger and Peppas, 1987).

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

Table 8 Diffusional exponent and mechanisms of diffusional release from various non-swellable controlled release systems.

Release exponent			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.0	0.45<n<1.0	0.43<n<1.0	Anomalous (non-Fickian) transport
1.0	1.0	1.0	Zero-order (time-independent)

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

In swellable matrices, when the system does not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and case-II transport, respectively. When the value of n is > 0.45 and < 0.89, the release was said to be non-Fickian (Rittger and peppas, 1987). When the value of n was greater than that of the case-II transport, the release is said to be super case-II transport. Table 9 summarizes the range of values of diffusional exponent, n, and the released transport mechanism for each a geometry (Rittger and Peppas, 1987). A value of n =1, mean that the drug release can exist for any geometry; only slabs do this release coincide with case-II transport.

Table 9 Diffusional exponent and mechanisms of drug from various swellable controlled release systems.

Diffusion exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.89	Anomalous (non-Fickian) transport
1.0	0.89	0.89	Zero-order (time-independent)

10. MicroMath® Scientist™ for Windows™

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

Least square fitting the experimental dissolution data (cumulative drug release > 10% and up to 80%) to the mathematical equations (power law, first order, Higuchi's and zero order) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Sofware, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (msc) (MicroMath Scientist Handbook, 1995), given below.

$$msc = \ln\left\{\frac{\sum_{i=1}^{n} w_i (Y_{obs_i} - \overline{Y}_{obs})^2}{\sum_{i=1}^{n} w_i (Y_{obs_i} - Y_{cal_i})^2}\right\} - \frac{2p}{n} \quad [17]$$

When Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is weight that applies to the i-th point, n is number of points and p is number of parameters.

CHAPTER III

METHOD OF STUDY

1. Materials

1.1 Model drug

Indomethacin (Batch No. 050814, China National Chemical Imp. Exp., China)

1.2 Additives

Di-sodium hydrogen orthophosphate (lot no. 405300, Ajax Finechem, Australia)

Ethyl alcohol absolute (lot no. V5C933235C, Rohm GmbH Chemische Fabrick, Germany)

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

Hydrochloric acid (lot no. E23W60, J.T. Baker, USA)

Hydroxypropyl methylcellulose K 15M (Methocel® K15M) (lot no. NH 16012N11, Colorcon Asia Pracific, Ltd.)

Polyethylene glycol 4000 (lot no. 504907, P.C. Drug Center Co., Ltd., Thailand)

Polyethylene glycol 400 (lot no. PO76049, P.C. Drug Center Co., Ltd., Thailand)

Potassium dihydrogen orthophosphate (lot no. E23W60, Ajax Finechem, Australia)

Lactose (lot no. 080200 A 9249, Auckland, New Zealand)

Sodium chloride (lot no. AF 407256, Ajax Finechem, Australia)

Sodium hydroxide (lot no. AF 310204, Ajax Finechem, Australia)

Talcum (lot no. M 512312, Ajax Finechem, Australia)

Triethyl citrate (lot no. 0000078425, Vertellus, USA)

Xanthan gum (Xantural 75®) (lot no. 01-100, CP Kelco U.S., Inc. USA.

1.3 Equipments

Analytical balance (Sartorius model BP2100S and Sartorius model CP224S, Germany)

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

Digital camera (Samsung Digimax i5, Korea)

Dissolution apparatus (Erweka DT 70, Germany)

Film coating unit (Rama Cota, Thailand)

Freeze dryer (Triad™ Labconco, Missouri, USA)

Hardness tester (Pharma test PTB 311, Germany)

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

Texture analyzer (Charpa Techcenter, Godalming, Stable micro Systems Ltd., UK)

UV-vis spectrophotometer (Perkin-Elmer, Germany)

2. Methods

2.1 Preparation of tablet by mold technique

Indomethacin was used as a model drug for tablets prepared by a mold technique. The amount of indomethacin per tablet was 75 mg. The effect of polymers and excipients filled in tablets on physical properties and drug release of prepared tablets were determined. The tablet was prepared by melting PEG 4000 on the water bath and mixed with PEG 400 and then the mixtures were poured into the stainless steel mold with diameter of 12 mm. The 48 tablets could be prepared for each time with the stainless steel mold, therefore the formula weight of about 42 g was used for each preparation.

2.1.1 Effect of ratio of PEG4000:PEG400

Tablet of about 0.87 g containing various ratio of PEG 4000 and PEG 400 were prepared with the melting and mold technique. The different ratio of PEG4000:PEG400 such as 9.5:0.5, 9:1, 8.5:1.5, 8:2, 7.5:2.5, 7:3, 6.5:3.5, 6:4 and 5.5:4.5 (F1-F9) were utilized as drug carrier to investigate the effect of them on the physical properties of tablets. Tablet

preparation was performed by melting PEG4000 on the water bath and mixed with PEG400 and then the mixture was poured into the stainless steel mold.

Table 10 Composition of tablet containing different ratio of PEG4000:PEG400

Formula	Ratio of PEG4000:PEG400	PEG4000 (g)	PEG400 (g)
F1	9.5:0.5	39.672	2.080
F2	9:1	37.584	4.176
F3	8.5:1.5	35.496	6.264
F4	8:2	33.408	8.352
F5	7.5:2.5	31.320	10.44
F6	7:3	29.232	12.528
F7	6.5:3.5	27.144	14.616
F8	6:4	25.056	16.704
F9	5.5:4.5	22.968	18.792

2.1.2 Effect of hydrophilic polymer

The effect of different types and amounts of hydrophilic polymers (hydroxypropyl methylcellulose (HPMC) and xanthan gum) on the physical properties and drug release from matrix tablet were investigated. Tablets of about 0.87 g containing 75-mg of indomethacin, PEG4000: PEG400 (7:3) and different amount of HPMC or xanthan gum were prepared with the melting and mold technique. The 48 tablets could be prepared for each time with the stainless steel mold, therefore the formula weight of about 42 g was used for each preparation. PEG 4000 was melted on the water bath and mixed with PEG 400 and HPMC or xanthan gum, drug was then added to obtain a homogenous mixture and then they was poured into the stainless steel mold. The formula (F10-F19) containing different amount of HPMC or xanthan gum are shown in Table 11. Drug release from these tablets was compared to capsule containing 75-mg indomethacin powder.

Table 11 Composition formula of indomethacin tablet containing different hydrophilic polymers

Formula	Indomethacin (mg)	PEG 4000:PEG400 (Ratio)	Hydrophilic polymer	
			HPMC (%w/w)	Xanthan gum (%w/w)
F10	75	7:3	5	-
F11	75	7:3	10	-
F12	75	7:3	15	-
F13	75	7:3	20	-
F14	75	7:3	25	-
F15	75	7:3	-	5
F16	75	7:3	-	10
F17	75	7:3	-	15
F18	75	7:3	-	20
F19	75	7:3	-	25

2.1.3 Effect of diluents

The effect of different types and amounts of diluents (lactose and talcum) on the physical properties and drug release from matrix tablet were investigated. Tablets of about 0.87 g containing 75-mg of indomethacin, PEG4000: PEG400 (7:3), 5% xanthan gum and different amount of talcum or lactose were prepared with the melting and mold technique as described above in 2.1.2. The 48 tablets could be prepared for each time with the stainless steel mold, therefore the formula weight of about 42 g was used for each preparation. The formula (F20-F29) containing talcum or lactose are shown in Table 12.

Table 12 Composition formula of indomethacin tablets containing different diluents

Formula	Indomethacin (mg)	PEG 4000:PEG400 (Ratio)	Xanthan gum (%w/w)	Diluents	
				Lactose (%w/w)	Talcum (%w/w)
F20	75	7:3	5	15	-
F21	75	7:3	5	25	-
F22	75	7:3	5	35	-
F23	75	7:3	5	45	-
F24	75	7:3	5	55	-
F25	75	7:3	5	-	15
F26	75	7:3	5	-	25
F27	75	7:3	5	-	35
F28	75	7:3	5	-	45
F29	75	7:3	5	-	55

2.1.4 Effect of amounts of indomethacin

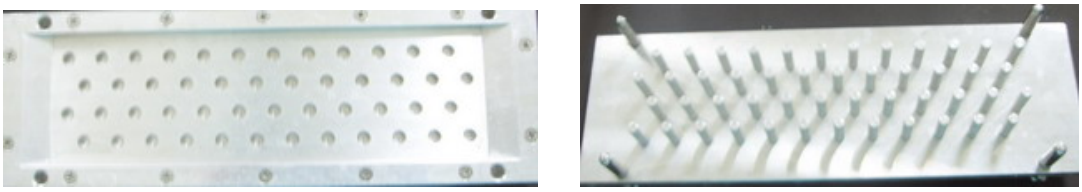
The effect of amounts of indomethacin on the physical properties and drug release from matrix tablet was investigated. Tablets of about 0.87 g containing 75-mg of indomethacin, PEG4000: PEG400 (7:3), 5% xanthan gum and different amounts of indomethacin were prepared with the melting and mold technique as described above in 2.1.2. The 48 tablets could be prepared for each time with the stainless steel mold, therefore the formula weight of about 42 g was used for each preparation. The formula (F30-F35) containing different amount of indomethacin are shown in Table 13.

Table 13 Composition formula of indomethacin tablet containing different amounts of indomethacin

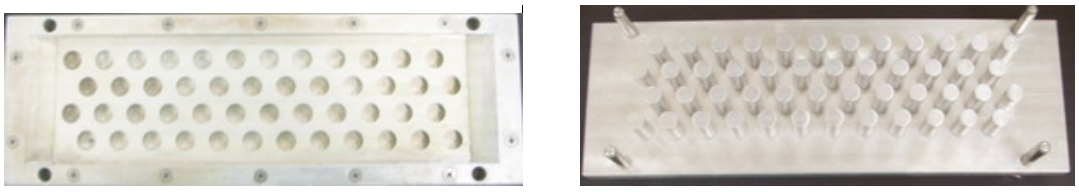
Formula	Indomethacin (mg)	PEG 4000:PEG400 (Ratio)	Xanthan gum (%w/w)
F30	25	7:3	5
F31	50	7:3	5
F32	75	7:3	5
F33	100	7:3	5
F34	150	7:3	5
F35	300	7:3	5

2.1.5 Effect of tablet size

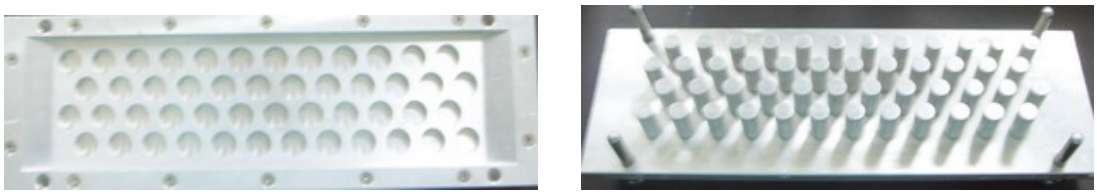
The photographs of stainless steel molds with different diameter (8, 12 and 16 mm) are shown in Figure 10. The tablets prepared from molds with different sizes are shown in Figure 11. The effect of amount of xanthan gum on the physical properties and drug release from matrix tablets was investigated. Tablets of about 0.4, 0.87 and 1.3 g containing 75-mg of indomethacin, PEG4000: PEG400 (7:3) 5% xanthan gum and different amounts of indomethacin were prepared with the melting and mold technique as described above in 2.1.2. The 48 tablets could be prepared for each time with the stainless steel mold of three sizes. Formula weight of about 19.2, 42 and 62.4 g were used for each preparation. The formula (F36-41) of tablets containing different amount of xanthan gum with different size are shown in Table 14.



Stainless steel mold with diameter of 8 mm.



Stainless steel mold with diameter of 12 mm.



Stainless steel mold with diameter of 16 mm.

Figure 10 Stainless steel mold with different diameter.

Figure 11 Large, medium and small tablets (arrange from top to down)

Table 14 Composition formula of indomethacin tablet containing different amount of xanthan gum prepared using stainless steel mold with different diameter

Formula	Mold Size (mm)	Indomethacin (mg)	PEG 4000:PEG400 (Ratio)	Xanthan gum (%w/w)
F36	8	75	7:3	-
F37	8	75	7:3	5
F38	12	75	7:3	-
F39	12	75	7:3	5
F40	16	75	7:3	-
F41	16	75	7:3	5

2.2 Evaluation of tablet

2.2.1 Weight variation

Weight variation of tablet was determined by analytical balance. Twenty tablets were individually weighted. The average and standard deviation were then calculated (n=20).

2.2.2 Hardness, Thickness and Diameter

Ten tablets of each formulation were individually measured using hardness tester that could measure the thickness and diameter at the same time. The average and their standard deviation were then calculated (n=10).

2.2.3 Content uniformity

The content of indomethacin was determined using UV-spectrophotometer. Solvent comprising methanol and phosphate buffer pH 7.5 (1:1) was used to dissolve indomethacin for drug content assay. The single tablet was transferred to a 250 mL volumetric flask. The 100 mL of solvent was added and the mixture was sonicated for about 30 minutes and this mixture was diluted with the methanol and phosphate buffer pH 7.5 (1:1) mixtures to volume, and then was mixed and sonicated. The 2 mL stock solution was pipetted and

adjusted to volume in 25 mL volumetric flask. The amount of drug was determined using UV-spectrophotometer at 323 nm (n=10).

2.2.4 Study of drug release

The dissolution of indomethacin tablets was studied by using the basket method, operating at 100 rpm. The 900 mL phosphate buffer pH 6.2 was used as dissolution fluid. The medium temperature was maintained at 37ºC. The samples were withdrawn at predetermined time intervals (5, 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 hours). The amounts of drug released were measured using UV spectrophotometer at 323 nm (Ohara *et al*., 2005). The cumulative percentage of indomethacin released was calculated and plotted against time (Fujii *et al*., 2004).

The dissolution of tablet containing 5% xanthan gum and without xanthan gum was studied by using the 900 mL HCl pH 1.2 as dissolution fluid. The dissolution medium was prepared by dissolved 2 g of sodium chloride and then adding 7 mL of hydrochloric acid in 1000 mL of distilled water.

The dissolution of tablet coated with Eudragit L100 was studies by using pH change system. For the dissolution test with pH change, the drug released in 900 mL HCl buffer of pH 1.2 was conducted for one and half hour. Then the pH was increased to 6.2 by adding 2.585g sodium hydroxide, 3.06g monobasic potassium phosphate and 4.005g dibasic sodium phosphate. The operation was continued until completing 12 hours.

To investigate the effect of rotational speed of basket on the indomethacin release from matrix tablet, the drug dissolution was measured at basket rotational speed of 25, 50, 100 and150 rpm. The dissolution test medium was phosphate buffer pH 6.2 at 37ºC. The dissolution fluids were assayed at different time intervals (5, 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 hours).

Calibration curve of indomethacin in phosphate buffer pH 6.2

Indomethacin of 75-mg was accurately weighed, dissolved in 50 mL methanol and adjusted the volume to 100 mL with methanol. This solution was used as a standard stock solution. The 0.075, 0.15, 0.225, 0.3 and 0.375 mL stock solution was pipetted and adjusted

with phosphate buffer pH 6.2 to volume in 10 mL volumetric flask to make approximately 7.5-37.5 μg/mL of indomethacin. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 323 nm. The calibration curve of indomethacin in phosphate buffer pH 6.2 was exhibited in appendix (Fig 49).

Calibration curve of indomethacin in HCl pH 1.2

Indomethacin of 75-mg was accurately weighed, dissolved in 50 mL methanol and adjusted the volume to 100 mL with methanol. This solution was used as a standard stock solution. The 0.0075, 0.015, 0.0225, 0.03 and 0.0375 mL stock solution was pipetted and adjusted with HCl pH 1.2 to volume in 10 mL volumetric flask to make approximately 0.75-3.75 μg/mL of indomethacin. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 323 nm. The calibration curve of indomethacin in HCl pH 1.2 was exhibited in appendix (Fig 50).

Calibration curve of indomethacin in solvent comprising phosphate buffer pH 7.5 and methanol

Indomethacin of 75-mg was accurately weighed and then dissolved in 100 mL phosphate buffer pH 7.5 and methanol (1:1) and adjusted the volume to 250 mL with phosphate buffer pH 7.5 and methanol (1:1). This solution was used as a standard stock solution. The 0.0075, 0.015, 0.0225, 0.03 and 0.0375 mL stock solution was pipetted and adjusted with phosphate buffer pH 7.5 and methanol (1:1) to volume in 10 mL volumetric flask to make approximately 0.75-3.75 μg/mL of indomethacin. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 323 nm. The calibration curve of indomethacin in solvent containing phosphate buffer pH 7.5 combind with methanol was exhibited in appendix (Fig 52).

2.2.5 Data evaluation

To investigate the mechanism of drug release, the cumulative percentage of drug release profiles were fitted with different mathematical release equations. The release kinetics of indomethacin sustained-release tablets was evaluated by fitting with zero-order, first-order and Higuchi's model (Tanaka *et al*., 2005) and power law equation (Costa and Lobo, 2001). Least square fitting the experimental dissolution data (cumulative drug release > 5%

and up to 80%) to the mathematical equations (power law, zero order, first order and Higuchi's) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (msc) (MicroMath Scientist Handbook, 1995), given below. Model files used in this study are shown in Table 15.

$$msc = \ln\left\{\frac{\sum_{i=1}^{n} w_i (Y_{obs_i} - \overline{Y}_{obs})^2}{\sum_{i=1}^{n} w_i (Y_{obs_i} - Y_{cal_i})^2}\right\} - \frac{2p}{n} \qquad [18]$$

When Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is weight that applies to the i-th point, n is number of points and p is number of parameters.

Table 15 Model files used with Scientist™

// MicroMath Scientist Model File: Power law IndVars: T DepVars: F Params: K,Tl, N F=K*((T-Tl)^N ***
// MicroMath Scientist Model File: Higuchi's model IndVars: T DepVars: F Params: K,Tl, F=K*((T-Tl)^(1/2)) ***
// MicroMath Scientist Model File: First order IndVars: T DepVars: F Params: K,Tl, F=1-EXP(-K*(T-Tl)) ***
// MicroMath Scientist Model File: Zero order IndVars: T DepVars: F Params: K,Tl, F=K*(T-Tl) ***

2.2.6 Study of swelling behavior

Water uptake and Erosion

Erosion and water uptake of the tablet formulations were determined under conditions identical to those described above for dissolution testing. After a predetermined time interval, each basket was withdrawn, blotted to remove excess water and immediately weighed on an analytical balance. Water uptake and mass loss were determined gravimetrically according to the following equations (Varshosaz *et al*., 2006) (n=3).

$$\% \text{ Water uptake} = \frac{100 \text{ (wet weight} - \text{remaining dry weight)}}{\text{remaining dry weight}} \quad [19]$$

$$\% \text{ Erosion} = \frac{100 \text{ (remaining dry weight-original dry weight)}}{\text{original dry weight}} \quad [20]$$

2.2.7 Morphological studies

The morphological change, which occurred in the structure of the matrix when it came into contact with the dissolution fluids, was studied with a visual observation. Tablets were fixed between two acrylic plate (6×6 cm^2) joined by 4 stainless steel screws. Tablets were placed in the dissolution vessels by using the paddle method, operating at 50 rpm. The 900 mL phosphate buffer pH 6.2 was used as dissolution fluid. The distance between the paddle and the vessel bottom was adjusted to 2/3 of the compendial height (5.5 cm). To analyze the morphological behaviour of the systems during the release process, tablets were withdrawn from the dissolution vessels at different time intervals (0.5, 1, 1.5, 2, 4, 6 and 8 hrs) and their photographs were recorded using a digital camera.

2.2.8 Radial dimensional change

Radial dimensional change studies were performed using a modification of a previously described method in 2.2.7. Tablets were fixed between two acrylic plate (6×6 cm^2) joined by 4 stainless steel screws. Briefly, initial diameter of individual matrices (D_0) were measured, taken a photographs and then placed in a dissolution medium (phosphate buffer pH

6.2) at 37±0.5°C. Swollen/hydrated tablets were withdrawn from the medium and individual diameter, (D_1), were measured at time intervals. Percent of the radial (diameter) swelling of tablet was calculated according to the following formula as describe by Ernest *et al*. (2006).

$$\text{Percent diameter change } (D_W) = (D_1\text{-}D_0)/D_0 \times 100 \quad [21]$$

where D_1 and D_0 are the diameter of swollen and dried tablets, respectively. The percentage swelling of the original tablet was calculated and plotted vs. time to indicate the rate of tablet hydration.

2.2.9 Texture analysis

The swelling behavior of the formulations was investigated through textural analysis of swollen tablets. Tablets were placed in the dissolution vessels under conditions identical to those described above for dissolution testing. The hydrated tablets were removed at predetermined intervals, and subjected to textural profiling to determine total work of probe penetration into the entire matrix. All measurements were carried out in triplicate for each time point and tablets were discarded. Textural analysis was performed using a TA.XT2i texture analyzer equipped with a 5 kg load cell and Texture Expert software. The force–displacement–time profiles associated with the penetration of a 3 mm round-tipped steel probe into the swollen matrices were monitored at a data acquisition rate of 200 points per second. Probe approached the sample at pretest speed of 1.0 mm/s. Once a trigger force (when the probe registers a force equal to the trigger force the speed changes to the test speed and the system starts to collect data) of 0.005N was detected (at contact of the probe with tablet) the probe was advanced into the sample at a test speed of 0.5 mm/s until the maximum force of 40N was reached as described by Baumgartner *et al*. (2007).

2.2.10 Differential scanning calorimetry (DSC)

Thermal analysis is the most common approach to study physicochemical interactions of two or more component systems. The DSC thermograms of drug, PEG 4000, PEG 400, HPMC, xanthan, lactose, talcum, tablet containing different ratio of PEG 4000:PEG 400, tablet containing 25% xanthan gum, tablet containing 75-mg or 300-mg indomethacin and tablet containing 35% talcum or 35% lactose were obtained using differential

scanning calorimetry (DSC). In addition, the samples of tablet containing different ratio of PEG 4000: PEG 400, tablet containing 25% HPMC and 25% xanthan gum, tablet containing 75-mg and 300-mg indomethacin and tablet containing 35% talcum and 35% lactose were studies by reverse run. The experiment was done in non-hermetically sealed aluminium pans; the heating rate was 10ºC/min. The heating range was 25-300°C, -30-80°C and -20-170 ºC. Samples of approximately 1.5-2.0 mg were weighed into aluminium pans. DSC study was performed using a differential scanning calorimeter and using nitrogen as purge gas (20 mL/min).

2.2.11 Determination of surface topography of tablets

The surface and cross-sectional topography of the prepared matrix tablet were determined using scanning electron microscope (SEM). Sample was determined after dissolution testing under conditions identical to those described above in 2.2.4. Tablets were withdrawn from the dissolution vessels at different time intervals (5, 30, 240 and 480 minutes). Then they were freeze dried for 24 hrs to dry the samples and to avoid the collapse of porous structures. Samples were fixed on tape and the fine gold sputtering was applied onto the samples before analysis. Micrographs were taken with a scanning electron microscope at an accelerating voltage of 15 kV.

2.3 Tablet coating

The 5% (w/w) Eudragit L100 solution was prepared by dissolving the polymer in absolute ethanol. Triethyl citrate with various amounts (15%, 20%, 25%, 30% and 35% w/w) was added in polymer solution as plasticizer. Tablets were coated by dipping method. Coated tablets were then air-dried about 3 hrs for each time. Drug release from the obtained coated tablets were studied under conditions identical to those described above in 2.2.4. The dissolution data of tablet coated with Eudragit L100 was fitted to the mathematical equations (power law, zero order, first order and Higuchi's) using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The surface and cross-sectional topography of film coated tablet was determined using scanning electron microscope (SEM), under conditions identical to those described above in 2.2.11.

CHAPTER IV

ANALYSIS OF THE DATA

1. Physical properties of tablet

1.1 Physical properties of systems containing different ratio of PEG4000:PEG400

Physical properties of carrier tablet containing different ratio of PEG4000:PEG400 are shown in Table 16. Hardness of carrier tablet was increased as the amount of PEG4000 was increased. Therefore, tablet was very hard and difficult to remove from mold as the high amount PEG 4000 was used, but tablet containing high amount of PEG 400 was too soft. System comprising 70:30 PEG4000:PEG400 was chosen as drug carrier for tablet preparation. The tablet prepared with this system by mold technique could be easily removed from the mold and the desired hardness could be obtained. Other pharmaceutical excipients were included in this system for further investigations. The physical properties of tablet containing different amount of hydrophilic polymer in that system such as HPMC and xanthan gum are shown in Tables 17 and 18, respectively. The hardness of tablet containing HPMC and xanthan gum was exhibited in the range of 14.55 ± 1.98 N to 18.62 ± 1.78 **N** and 14.62 ± 1.75 N to 18.95 ± 1.83 N, respectively. The hardness of prepared tablet was increased as the amount of these two polymers was increased.

Physical properties of indomethacin tablet containing different amount of talcum or lactose are shown in Tables 19 and 20, respectively. The purpose of the incorporation of talcum was the expectation to improve the hardness of tablet and to decrease the moisture adsorption of this system owing to the high amount of hygroscopic PEG in the system. While the incorporation of lactose was expected to enhance the solubility of system as also to decrease the proportion of carriers. The hardness of tablet containing talcum or lactose were increased as the amount of these diluents was increased. Similar effect on the hardness of tablet after incorporation of talcum and lactose was found when the same amount of these diluents were

added. The physical properties of tablets containing different amount of indomethacin are shown in Table 21. The hardness was in the range of 14.33 ± 0.79 N to 40.87 ± 1.15 N. The hardness of in Table 21. The hardness was in rank of 14.33 ± 0.79 N to 40.87 ± 1.15 N. The hardness of prepared tablet was notably increased as the amount of indomethacin was increased. The effect of indomethacin amount on tablet hardness was less than the effect of talcum or lactose amount. The physical properties of 75-mg indomethacin and 5% xanthan gum tablet with different tablet size is shown in Table 22. Hardness of prepared tablet was increased as the tablet size was increased.

Table 16 Physical properties of tablet containing different ratio of PEG4000:PEG400

Ratio of PEG4000:PEG400	Physical Properties				
	Appearance	Weight ± S.D. (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
9.5:0.5	Very hard and difficult to remove from mold	855.4 ± 25.2	6.58± 0.09	11.89± 0.03	55.87± 7.15
9:1	Very hard and difficult to remove from mold	870.7± 19.4	6.58± 0.10	12.01± 0.02	47.46± 7.41
8.5:1.5	Very hard and difficult to remove from mold	883.3± 14.0	6.57± 0.03	12.02± 0.02	34.36± 4.79
8:2	Hard and difficult to remove from mold	894.9± 22.5	6.66± 0.09	11.97± 0.02	28.41± 2.55
7.5:2.5	Hard and difficult to remove from mold	881.9± 10.8	6.55± 0.02	12.02± 0.02	16.45± 1.66
7:3	Hard and easy to remove from mold	891.2± 14.6	6.53± 0.03	12.01± 0.02	14.33±0.79
6.5:3.5	Soft and easy to remove from mold	878.3± 37.5	6.56± 0.08	12.01± 0.02	13.76± 1.48
6:4	Soft and easy to remove from mold	911.2± 27.5	6.65± 0.09	11.99± 0.03	13.76± 1.17
5.5:4.5	Soft and easy to remove from mold	828.5± 19.3	6.60± 0.05	11.97± 0.02	12.25± 2.76

Table 17 Physical properties of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400 and different amount of HPMC

Amount of HPMC (%)	Physical Properties			
	Weight ± S.D. (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
0	891.2 ± 1.46	6.83± 0.21	11.89± 0.03	12.84± 1.55
5	869.9± 8.90	6.92± 0.31	12.01± 0.02	14.59± 1.67
10	877.5± 9.80	6.83± 0.21	12.02± 0.03	15.09± 1.71
15	870.9± 9.80	6.85± 0.20	11.97± 0.02	15.74± 1.80
20	870.0± 2.28	6.72± 0.12	12.02± 0.02	16.44± 1.68
25	852.2± 1.51	6.73± 0.19	12.01± 0.02	17.89± 1.79

Table 18 Physical properties of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400 and different amount of xanthan gum

Amount of xanthan gum (%)	Physical Properties			
	Weight ± SD (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
0	855.1 ± 14.6	6.73± 0.21	11.91± 0.03	14.62± 1.75
5	870.9± 8.90	6.82± 0.22	12.03± 0.02	15.22± 1.65
10	868.5± 9.80	6.73± 0.22	12.02± 0.03	16.68± 1.73
15	873.9± 9.80	6.65± 0.21	12.00± 0.02	17.64± 1.78
20	881.0± 22.8	6.82± 0.19	12.03± 0.02	18.43± 1.78
25	876.2± 15.1	6.72± 0.19	12.02± 0.02	18.95± 1.83

Table 19 Physical properties of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400, 5% xanthan gum and different amount of talcum

Amount of talcum (%)	Physical Properties			
	Weight ± SD (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
15	875.1 ± 31.2	6.75± 0.22	12.01± 0.03	18.8± 5.67
25	880.9± 12.4	6.72± 0.23	12.03± 0.02	24.3± 4.75
35	878.5± 50.1	6.83± 0.25	12.02± 0.03	35.6± 4.27
45	883.9± 63.2	6.75± 0.28	12.05± 0.02	39.7± 3.62
55	886.0± 21.1	6.72± 0.22	12.03± 0.04	47.3± 4.27

Table 20 Physical properties of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400, 5% xanthan gum and different amount of lactose

Amount of lactose (%)	Physical Properties			
	Weight ± S.D. (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
15	883.4 ± 23.4	6.78± 0.19	12.05± 0.02	20.3± 4.67
25	878.9± 31.2	6.82± 0.31	12.08± 0.02	26.4± 5.75
35	870.4± 23.7	6.75± 0.25	12.06± 0.02	34.5± 3.27
45	875.6± 18.7	6.82± 0.26	12.04± 0.02	37.7± 2.92
55	882.1± 25.6	6.79± 0.21	12.05± 0.02	46.7± 3.17

Table 21 Physical properties of tablet containing 70:30 PEG4000:PEG400, 5% xanthan gum and different amount of indomethacin

Amount of indomethacin (mg)	Physical Properties			
	Weight ± S.D. (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
25	891.2± 18.9	6.53± 0.03	12.01± 0.02	14.33± 0.79
50	881.9± 12.3	6.55± 0.02	12.02± 0.02	14.49± 1.67
75	894.9± 24.6	6.66± 0.10	11.97± 0.02	16.46± 1.41
100	883.3± 13.1	6.57± 0.03	12.02± 0.03	18.41± 1.55
150	870.7± 26.7	6.58± 0.10	12.01± 0.02	29.36±1.79
300	895.4 ± 36.3	6.58± 0.09	11.89± 0.03	40.87± 1.15

Table 22 Physical properties of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400, without xanthan gum and 5% w/w xanthan gum prepared using mold with different diameter

Mold diameter (mm)	Amount of xanthan gum (%w/w)	Physical Property			
		Weight ± S.D. (mg)	Thickness ± S.D. (mm)	Diameter ± S.D. (mm)	Hardness ± S.D. (Newton; N)
8	0	891.2± 14.6	6.53± 0.03	8.01± 0.02	14.33± 0.79
8	5	881.9± 10.8	6.55± 0.02	8.02± 0.02	14.49± 1.67
12	0	894.9± 22.5	6.66± 0.09	11.97± 0.02	16.46± 1.41
12	5	883.3± 14.0	6.57± 0.03	12.02± 0.03	18.41± 1.55
16	0	870.7± 19.4	6.58± 0.10	16.01± 0.02	29.36±1.79
16	5	895.4 ± 25.2	6.58± 0.09	16.89± 0.03	40.87± 1.15

2. Factors affecting the drug release from tablet

2.1 Effect of polymer on the drug release

The dissolution profiles of indomethacin from solid dispersion tablets containing different amount HPMC and xanthan gum are shown in Figures 12 and 13, respectively.

2.1.1 The influence of HPMC on the drug release

The dissolution profiles of indomethacin released from matrix system containing different amount of HPMC are shown in Figure 12. The drug released from tablet containing 5% HPMC was faster than those of tablets containing 10%, 15%, 20% and 25% HPMC, respectively. The drug release of tablet containing 10% HPMC was slightly lower than that of tablet containing 5% HPMC and tablet without an addition of HPMC, respectively. Drug release from tablets containing 10%, 15%, 20%, 25% HPMC and capsule were apparently lower than those of tablet containing 5% HPMC and tablet without an addition of HPMC. The result indicated that HPMC could retard the release longer than 8 hrs.

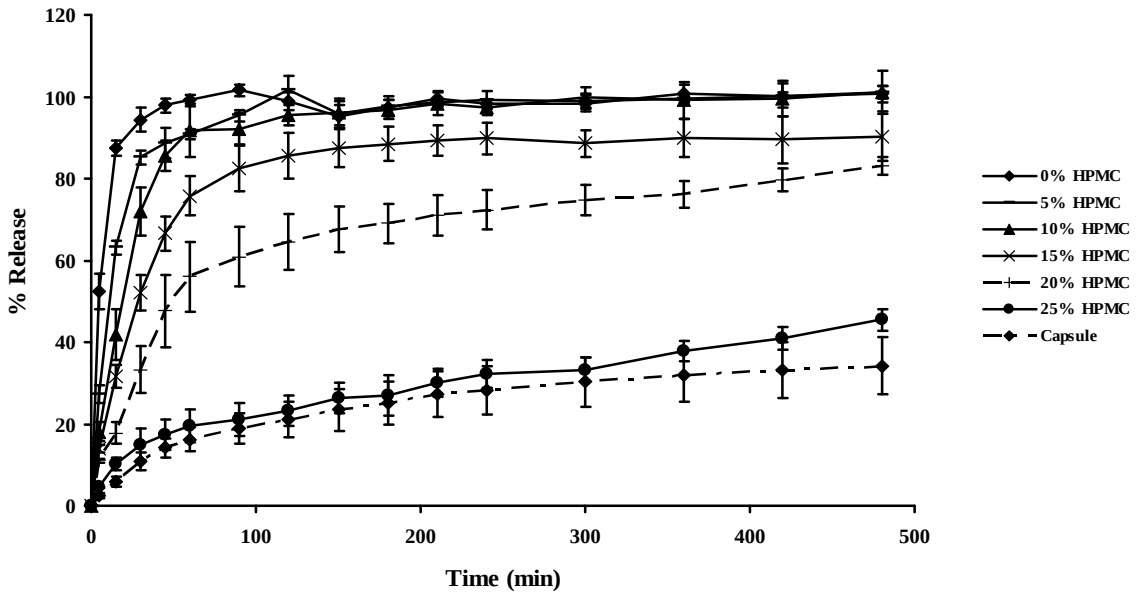


Figure 12 Drug release profiles of tablets containing different amounts of HPMC compared to those of tablet without HPMC and capsule in phosphate buffer pH 6.2 (n=3)

2.1.2 The influence of xanthan gum on the drug release

Dissolution profiles of indomethacin released from matrix systems containing different amounts of xanthan gum are shown in Figure 13. The drug release from tablets containing 5% xanthan gum was faster than those of tablets containing 10%, 15%, 20% and 25% xanthan gum, respectively. The drug release from systems containing 10%, 15%, 20%, 25% xanthan gum and capsule was lower than that of tablet containing 5% xanthan gum and that of tablet without xanthan gum. More increased amount of xanthan gum promoted the greater retardation of the drug release.

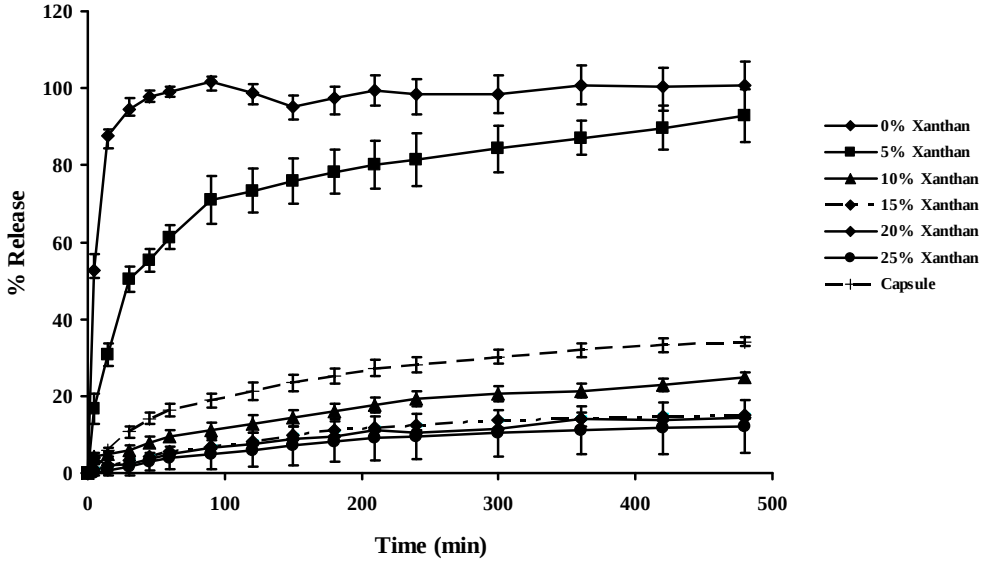


Figure 13 Drug release profiles of tablets containing different amounts of xanthan gum and capsule in phosphate buffer pH 6.2 (n=3)

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

The influence of amount of talcum and lactose on drug release from tablets containing 70:30 PEG4000:PEG400 and 5% xanthan gum was investigated.

2.2.1 The influence of amount of talcum on the drug release

Drug release from system containing 15% talcum was faster than those of tablets containing 25%, 35%, 45% and 55% talcum, respectively (Fig. 14). The drug release profiles form tablets containing 25%, 35%, 45% and 55% talcum were slower than that of tablet

containing 15% talcum but that of tablet without an addition of talcum was faster than tablets containing different amount of talcum. Moreover, the use of talcum in the tablet containing 5% xanthan gum diminished the drug dissolution and retarded the drug release.

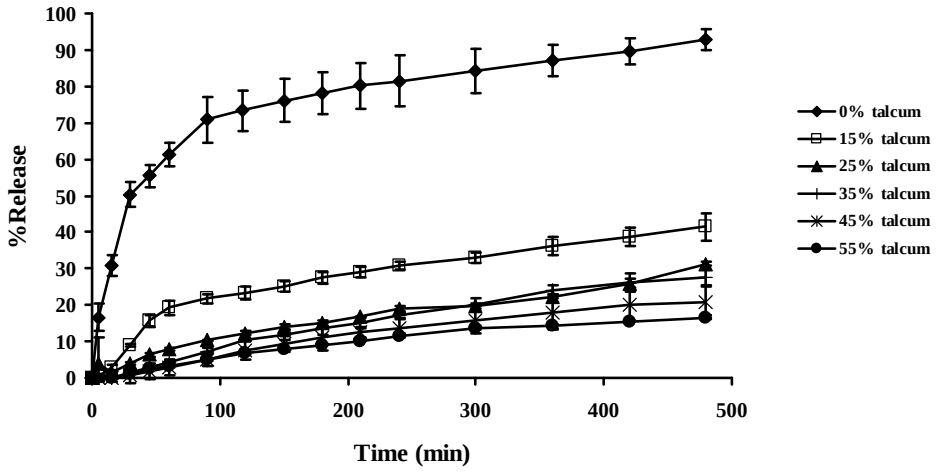


Figure 14 Drug release profiles of tablets containing different amounts of talcum in phosphate buffer pH 6.2 (n=3)

2.2.2 The influence of amount of lactose on the drug release

Dissolution profiles of indomethacin released from matrix tablets containing different amount of lactose are shown in Figure 15. The drug release from tablets containing 15% lactose was faster than that of tablets containing 25%, 35%, 45% and 55% lactose, respectively. However, the drug released from tablet without an addition of lactose was faster than tablets containing different amount of lactose. Moreover, the use of lactose in the tablet containing 5% xanthan gum diminished the drug dissolution and retarded the drug release.

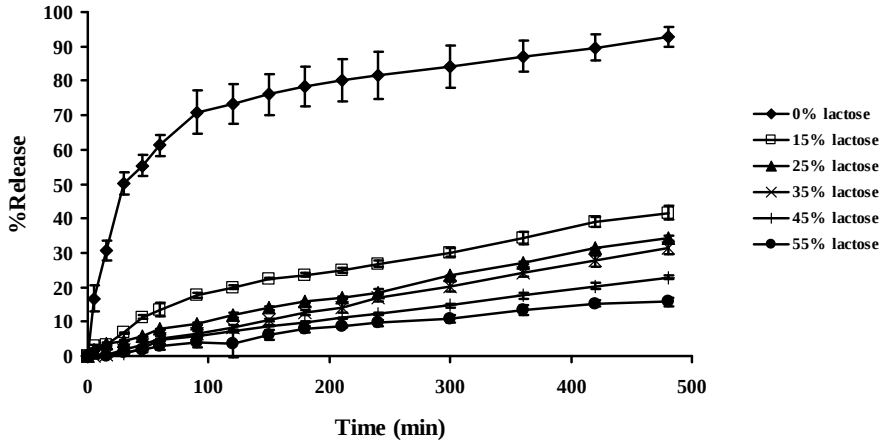


Figure 15 Drug release profiles of tablets containing different amount of lactose in phosphate buffer pH 6.2 (n=3)

2.3 The influence of drug loading on the drug release

Dissolution profiles of indomethacin released from matrix system containing different amount of indomethacin 25, 50, 75, 100, 150 and 300 mg are presented in Figure 16. The drug release from tablets containing 25-mg indomethacin was faster than that of tablets containing 50, 75, 100, 150 and 300-mg indomethacin, respectively. Increased amount of indomehtacin decreased the drug release rate.

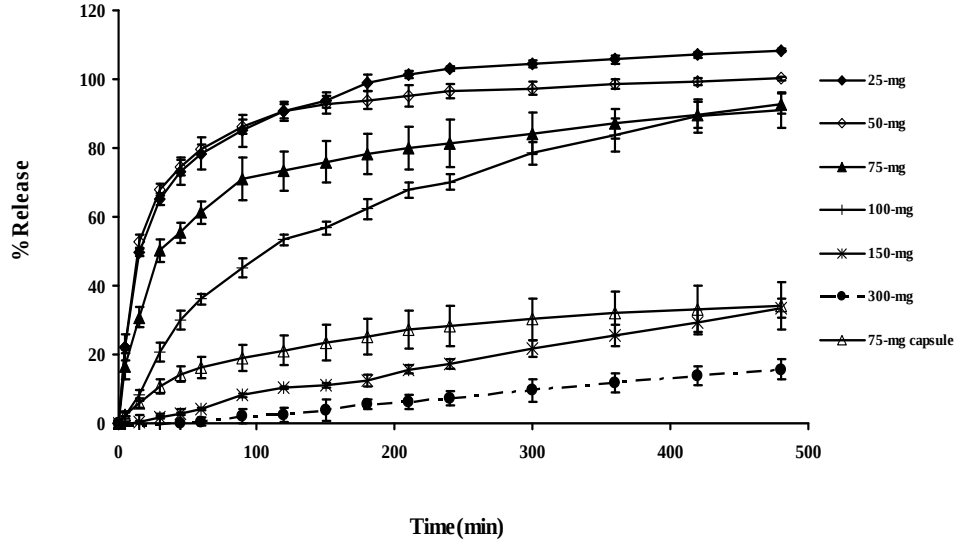


Figure 16 Drug release profiles of tablets containing different amount of indomethacin in phosphate buffer pH 6.2 (n=3)

2.4 The influence of dissolution medium on the drug release

The drug release of selected tablets containing 75-mg indomethacin and 5% xanthan gum in HCl buffer pH 1.2 was compared to tablet containing 75-mg indomethacin without polymer. The drug release from both tablets was similar (Fig. 17). Drug released from tablets containing polymer and without polymer was lower than 10%. The dissolution profiles of indomethacin released from matrix system in pH change systems is presented in Fig. 18. Initial drug release from tablets was very low but the drug release was suddenly increased when pH of medium was enhanced to 6.2 and the drug released was constant after 4 hrs.

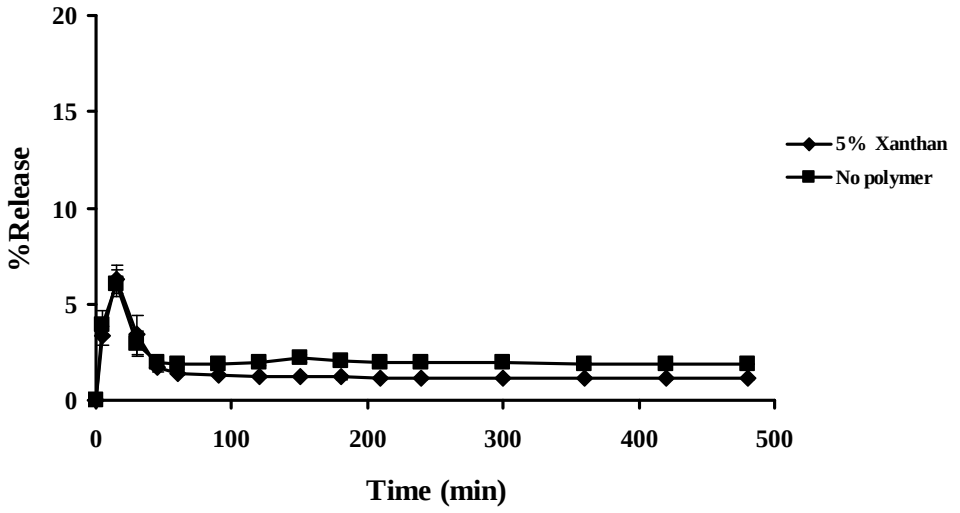


Figure 17 Drug release profiles of tablet containing 75-mg indomethacin and 5% xanthan gum or that of tablet without xanthan gum in HCl buffer pH 1.2 (n=3)

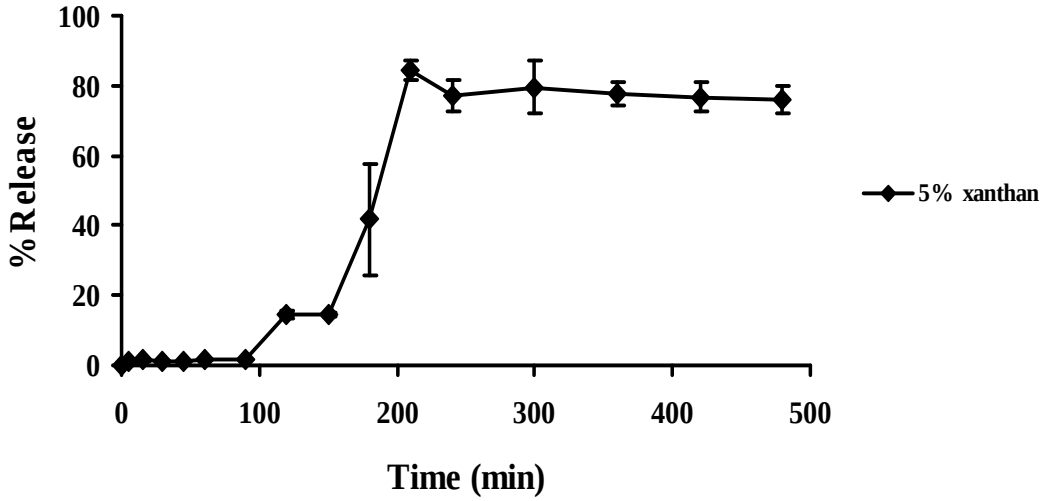


Figure 18 Drug release profiles of tablet containing 5% xanthan gum in pH change system (n=3)

2.5 The influence of tablet size on the drug release

Drug release profiles of tablets prepared by mold technique using mold with different diameter and the same height are shown in Figure 19. Drug release from small tablet containing 5% xanthan gum was slower than that of tablet without xanthan gum. The drug release from small tablets containing 5% xanthan gum and without xanthan gum was slower than that of tablets with medium size and large size, respectively. Percentage of drug release from medium size and large size tablets were near to 100% at 8 hrs.

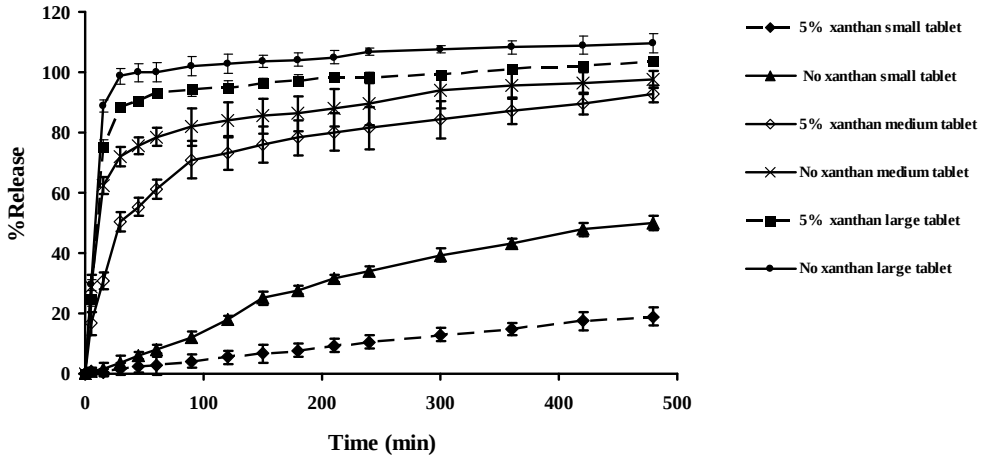


Figure 19 Effect of tablet size on drug release from tablet containing 5% xanthan gum compared with that of tablet without xanthan gum in phosphate buffer pH 6.2 (n=3)

2.6 The influence of hydrodynamic force on the drug release

The formulation containing 5% xanthan gum was chosen for investigate of the influence of hydrodynamic force on the release of indomethacin (Figure 20). The dissolution of indomethacin from tablet was studies using basket method by varying rotational speed of basket. The rate of indomethacin release after using 150 rpm rotational speed was faster than that using 100 rpm, 50 rpm and 25 rpm, respectively.

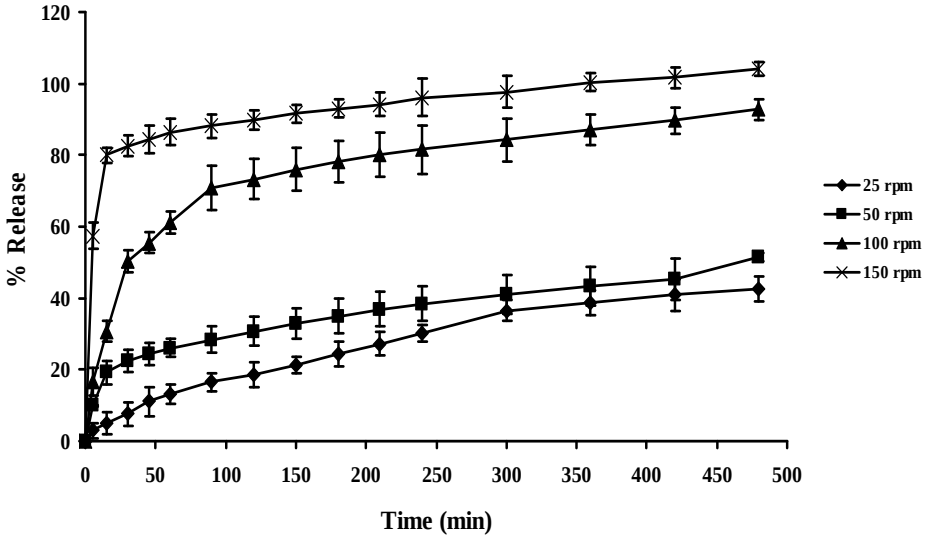


Figure 20 Effect of rotational speed of basket on drug release from tablet containing 75-mg indomethacin and 5% xanthan gum in phosphate buffer pH 6.2 (n=3)

2.7 The influence of tablet coating on the drug release

Enteric-coated systems are designed to provide a protection to tablets in the stomach (Sinha *et al*., 2003). In this study, the prepared matrix tablet was coated with Eudragit L 100 to protect indomethacin to irritate the stomach and to deliver this system to the small intestine. Tablet was coated by dipping method. The selected tablets containing 75-mg indomethacin and 5% xanthan gum was coated with Eudragit L100 and using triethyl citrate at amount of 30% w/w of dry polymer as plasticizer. Drug release profile of coated matrix system in pH change system is shown in Figure 21. Initial drug release from tablets was very low but the drug was gradually released and could be prolonged in phosphate pH 6.2.

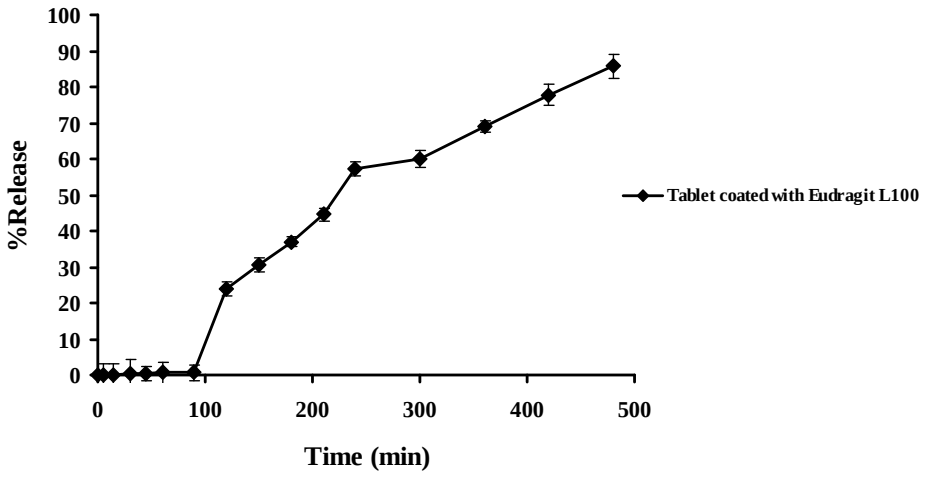


Figure 21 Drug release profile of 75-mg indomethacin tablet containing 5% xanthan gum coated with Eudragit L100 in pH change system (n=3)

The release of indometacin was studied and compared to that of the basis from USP 29 criteria. The percentages of labeled amount of $C_{19}H_{16}ClNO_4$ (indomethacin) dissolved from the developed system at the times specified nearly to conform to acceptance as presented in Table 23.

Table 23 The percentages of labeled amount of indomethacin dissolved at the times specified (USP 29)

Time (hours)	Amount dissolved
1	between 12% and 32%
2	between 27% and 52%
4	between 50% and 80%
12	not less than 80%

3. Water uptake and erosion studies

3.1 The influence of amount of xanthan gum on water uptake of prepared tablet

The swelling behavior of tablets containing different amount of xanthan gum was estimated from water uptake amount of the systems. The percent water uptake was increased as the amount of xanthan gum was increased. The percent water uptake of these matrices was increased with time (Fig. 22).

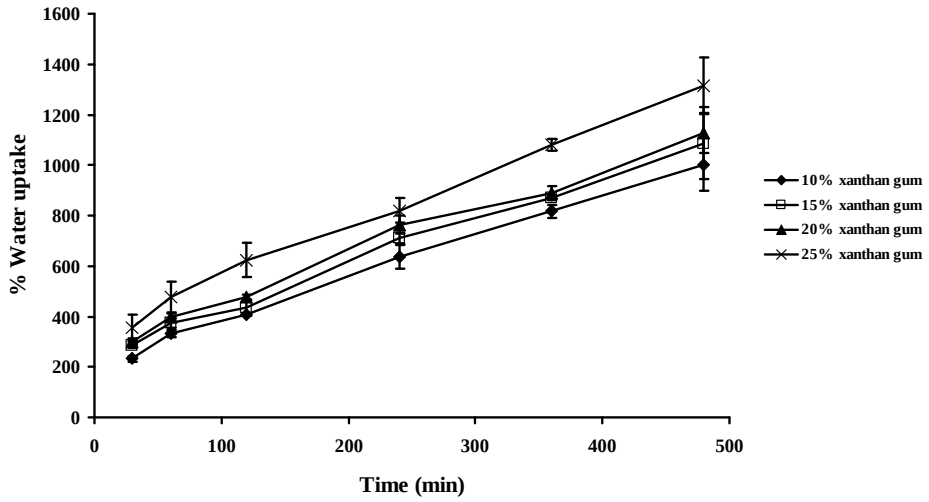


Figure 22 Water uptake of the tablets containing different amounts of xanthan gum in phosphate buffer pH 6.2 (n=3)

3.2 The influence of amount of xanthan gum on tablet erosion

The erosion of tablet containing 25% xanthan gum was lower than that of tablet containing 20%, 15% and 10% xanthan gum, respectively (Fig. 23). The percent erosion was increased with time.

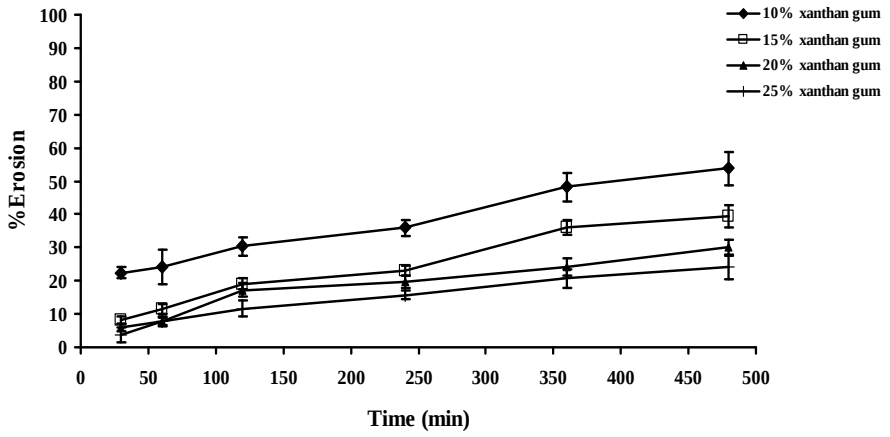


Figure 23 Erosion of tablets containing different amount of xanthan gum in phosphate buffer pH 6.2 (n=3)

4. Morphological studies

4.1 The influence of amount of xanthan gum on tablet morphology

From morphological study, indomethacin tablets containing 5% or 10% xanthan gum in phosphate buffer pH 6.2 exhibited the high hydration at 30 min, 1 hr and 1.5 hrs (Figs. 24-25). Similarly, the outer layer of tablet containing 5% or 10% xanthan gum contained the gel layer and core tablet was completely wetted within 2 hrs, 4 hrs, 6 hrs and 8 hrs. In fact, upon contact with the dissolution fluid, the system hydrated slowly and swelled giving rise to a thick gel layer. The gel thickness increased progressively moving inwards as a function of hydration, the dimensions of the solid core slightly decreased. Photographs of tablets containing 15%, 20% and 25% xanthan gum are shown in Figs. 26, 27 and 28, respectively. The hydration of tablets containing 15%, 20% and 25% xanthan gum was increased with time. Gel thickness increased as a function of hydration whereas the dimension of the solid core gradually decreased.

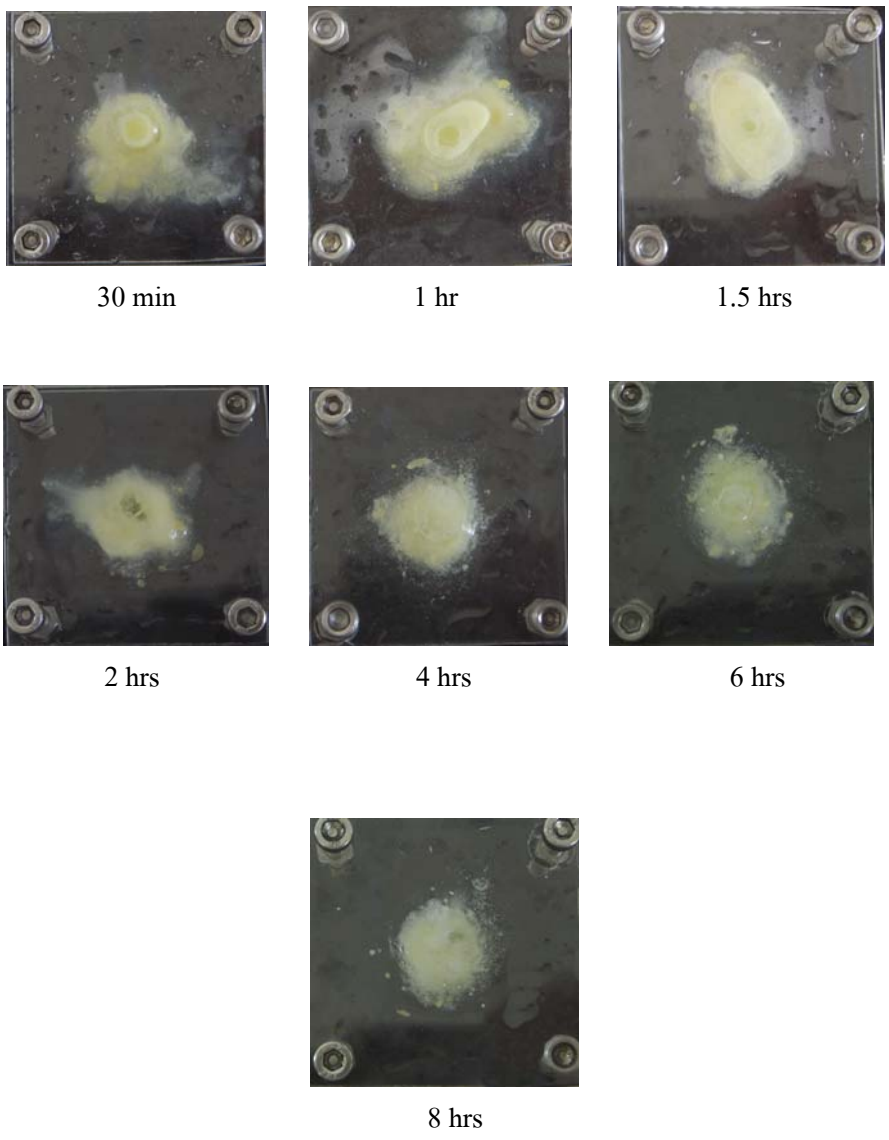
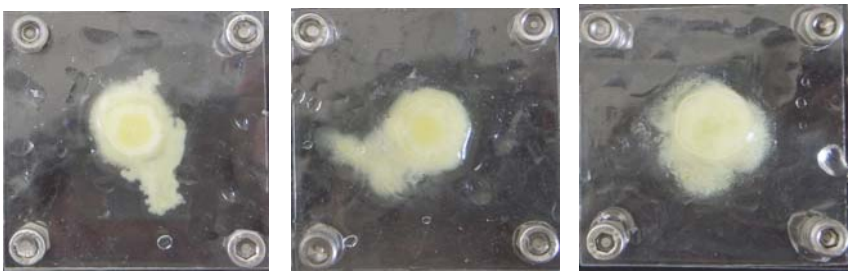
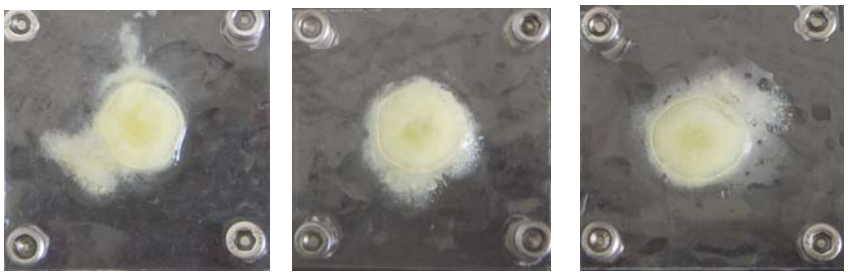


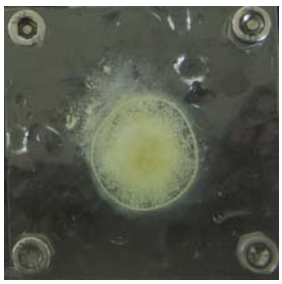
Figure 24 Photographs of 75-mg indomethacin tablet containing 5% xanthan gum after 30 min, 1 hr, 1.5 hrs, 2 hrs, 4 hrs, 6 hrs and 8 hrs of dissolution test in phosphate buffer pH 6.2.



30 min 1 hr 1.5 hrs



2 hrs 4 hrs 6 hrs

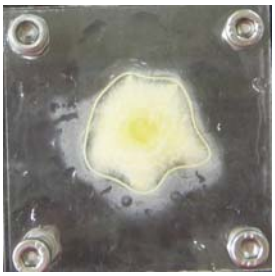


8 hrs

Figure 25 Photographs of 75-mg indomethacin tablet containing 10% xanthan gum after 30 min, 1 hr, 1.5 hrs, 2 hrs, 4 hrs, 6 hrs and 8 hrs of dissolution test in phosphate buffer pH 6.2.

30 min 1 hr 1.5 hrs

2 hrs 4 hrs 6 hrs

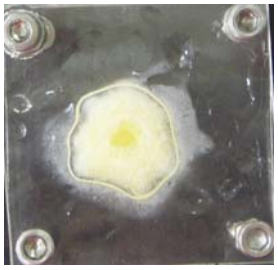


8 hrs

Figure 26 Photographs of 75-mg indomethacin tablet containing 15% xanthan gum after 30 min, 1 hr, 1.5 hrs, 2 hrs, 4 hrs, 6 hrs and 8 hrs of dissolution test in phosphate buffer pH 6.2.

30 min 1 hr 1.5 hrs

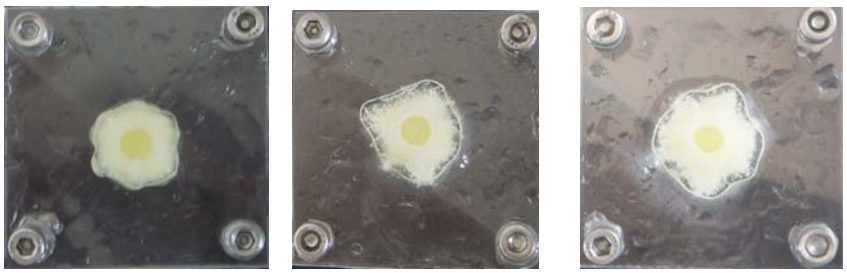
2 hrs 4 hrs 6 hrs



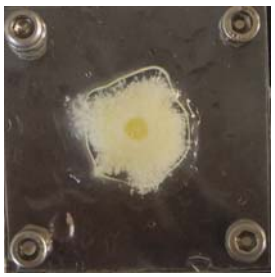
8 hrs

Figure 27 Photographs of 75-mg indomethacin tablet containing 20% xanthan gum after 30 min, 1 hr, 1.5 hrs, 2 hrs, 4 hrs, 6 hrs and 8 hrs of dissolution test in phosphate buffer pH 6.2.

30 min 1 hr 1.5 hrs



2 hrs 4 hrs 6 hrs



8 hrs

Figure 28 Photographs of 75-mg indomethacin tablet containing 25% xanthan gum after 30 min, 1 hr, 1.5 hrs, 2 hrs, 4 hrs, 6 hrs and 8 hrs of dissolution test in phosphate buffer pH 6.2.

5. Radial dimensional change in phosphate buffer pH 6.2

The swelling behavior from radial expansion of tablets as a function of time is shown in Figure 29. Considerable swelling and gel formation were found, especially when the xanthan gum was incorporated at higher amount. Addition of a certain amount hydrophilic polymers increased the surface wettability and, consequently, the water penetration into the matrix was promoted. This value of tablet containing 5% xanthan gum could not be determined because the tablet was gradually eroded and completely dissolved. Therefore, the amount of xanthan gum had a positive effect on percent diameter change since the percent diameter change increased as the amount of xanthan gum was increased.

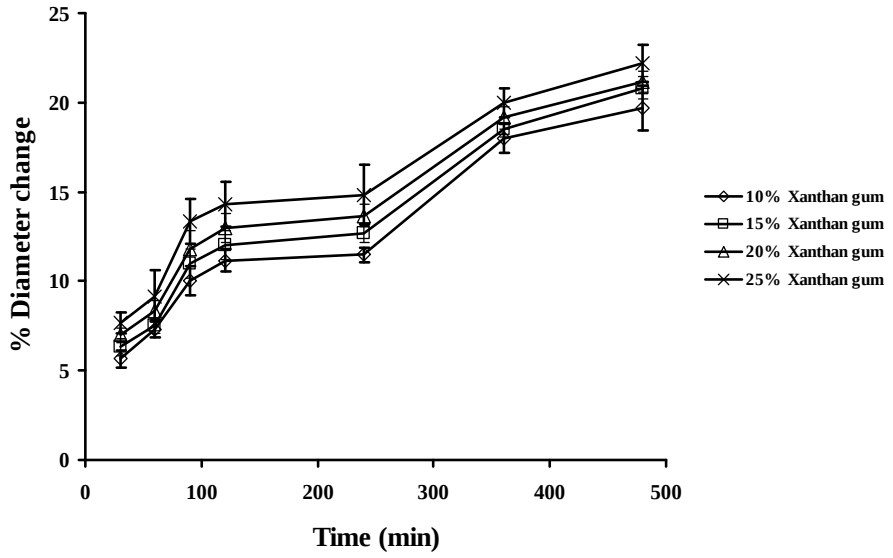
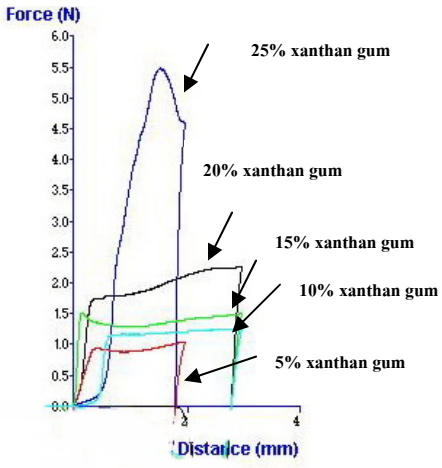


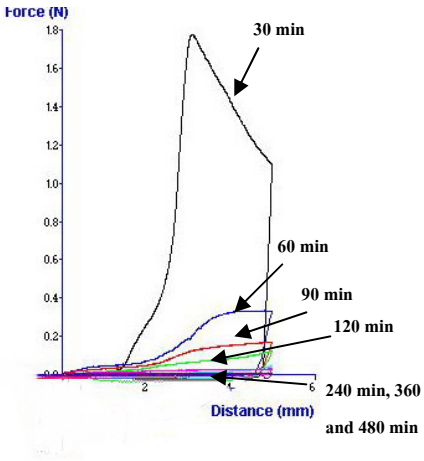
Figure 29 Diameter change of 75-mg indomethacin tablets containing different amount of xanthan gum. (n=3)

6. Texture analysis

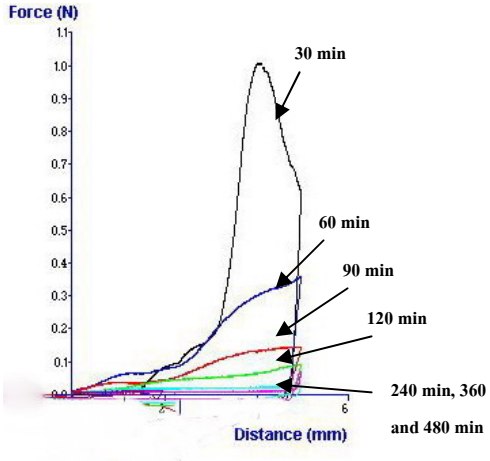
The dynamic structural changes of the gel layer formed during swelling of tablets containing different amount of xanthan gum were followed by force-displacement measurements (Fig. 30). The force required for probe to penetrate the swollen tablet decreased with time as the swelling proceeded and gel strength was reduced. The total work of penetration calculated as the area under the force–displacement curve signified the matrix stiffness or rigidity. Fig. 31 depicts the change in work of penetration versus time of tablets after exposure to swelling medium which they were extended as the hydration increased. A sharp decrease in work of penetration from 0 h (dry tablet) to 1 h could be observed which reflected the initial high rate of hydration of tablets which incidentally coincided with high rate of water uptake and gel formation as shown in Fig. 31. Hydrated tablets demonstrated lower values for work of penetration during 2 to 8 hrs. Total work penetration of tablet containing 25% xanthan gum (after dissolution test) was decreased with time. The hardness of dry tablet containing 25% xanthan gum was apparently higher than dry tablet containing 20%, 15% and 10% xanthan gum, respectively. Dry tablet (before dissolution test) containing 25% HPMC exhibited higher total work penetration than other tablet (after dissolution test). Total work penetration of tablet containing 25% HPMC (after dissolution test) was decreased with time (Figs. 32 and 33). The hardness of dry tablet containing 25% xanthan gum was slightly higher than that of dry tablet containing 25% HPMC. By comparison, total work penetration of tablet containing 25% xanthan gum was slightly higher than that of tablet containing 25% HPMC at 5 minutes and then that value was not significantly different.



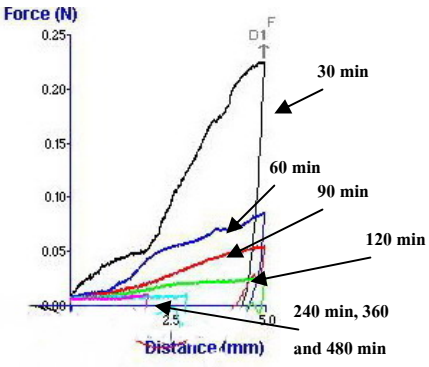
Dry tablet



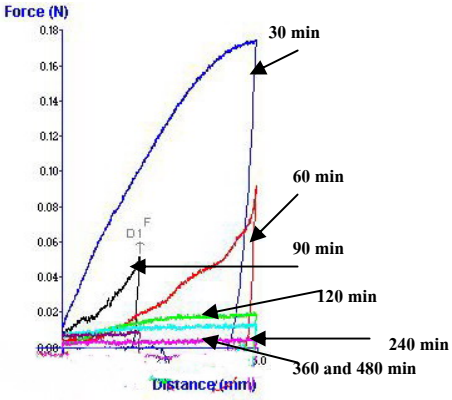
10% xanthan gum



15% xanthan gum



20% xanthan gum



25% xanthan gum

Figure 30 Force–displacement profiles for formulation of dry tablet and tablet containing different amount of xanthan gum at different time points (n=3).

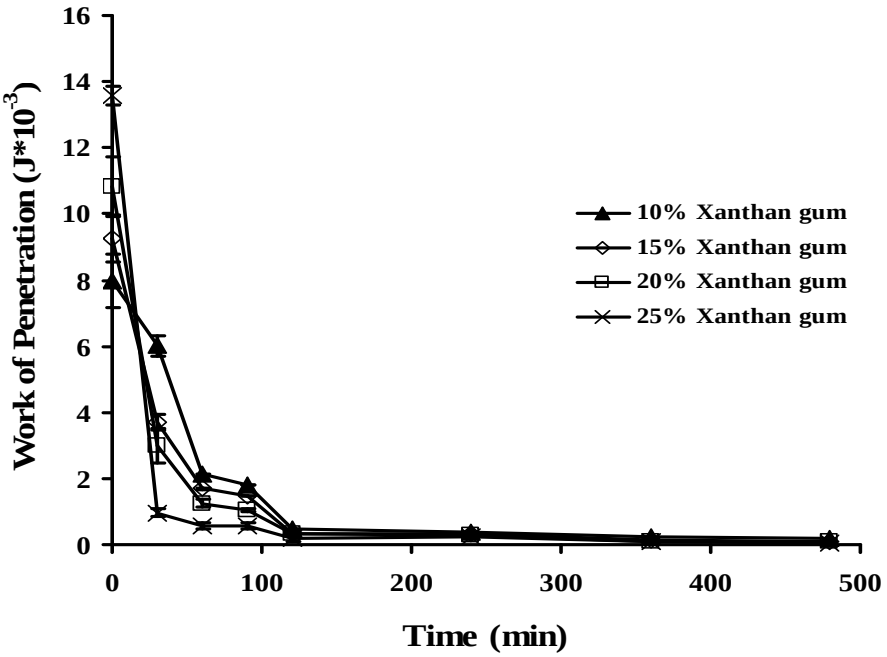


Figure 31 Total work of penetration of tablet containing different amount of xanthan gum at different time points (n=3).

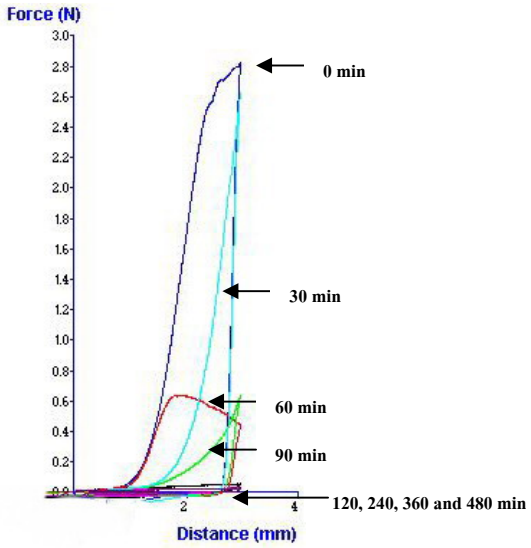


Figure 32 Force–displacement profiles for formulation of tablet containing 25% HPMC at different time points (n=3).

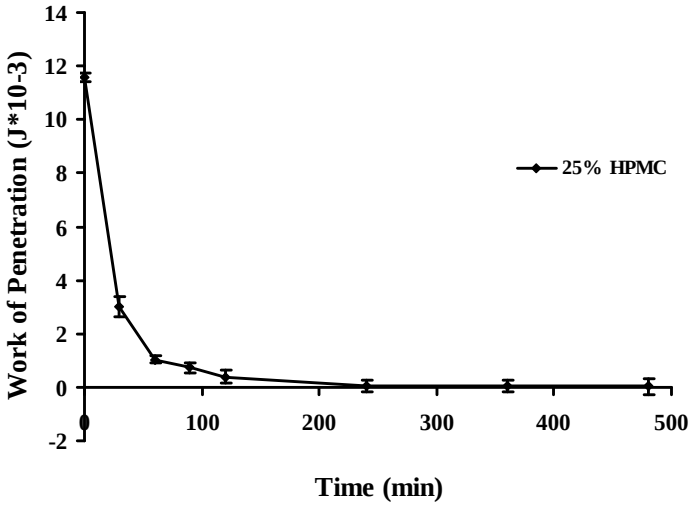


Figure 33 Total work of penetration of tablet containing 25% HPMC at different time points (n=3).

7. The differential scanning calorimetry (DSC)

The endothermic peak and enthalpy from DSC thermograms of indomethacin, PEG4000, PEG400, HPMC, xanthan gum, indomethacin and PEG 4000:PEG 400 (7:3) and systems containing various ratio of PEG4000:PEG400 from DSC study are presented in Table 24. The endothermic peak of pure indomethacin, PEG4000 and PEG400 appeared at 161.4 °C, 58.9 °C and 58.2 °C, respectively. Talcum, HPMC, and xanthan gum showed a broad exothermic peak at 78.2 °C, 56.2 °C and 73.0 °C, respectively. The endothermic peak of systems containing indomethacin and PEG 4000:PEG 400 (7:3) was found at 48.0 °C. The endothermic peak of systems containing various ratio of PEG4000:PEG400 was found in the rank of 46.8 °C to 52.5 °C. The endothermic peak and exothermic peak of thermograms from reverse run for system containing different ratio of PEG4000:PEG400 are shown in Table 25A and 25B, respectively. The endothermic peak and exothermic peak were exhibited in the rank 46.8 °C to 57.1 °C and 21.8 °C to 29.0 °C, respectively. DSC thermograms of HPMC, xanthan gum, indomthacin matrix system containing 25% HPMC, indomthacin matrix system containing 25% xanthan gum, and thermograms from reverse run of indomethacin system containing 25% HPMC and indomethacin matrix system containing 25% xanthan gum exhibited the endothermic peak at 56.2 °C, 73.0 °C, 48.1 °C, 49.7 °C, 50.7 °C and 49.8 °C, respectively (Fig. 34). The 75-mg indomethacin and 300-mg indomethacin tablets exhibited the endothermic peak at 52.2°C and 44.2°C, respectively. There were the exothermic peaks at 25.7 °C and 19.1 °C, respectively, after reverse run to -30 °C. The thermograms of indomethacin tablets containing 75-mg and 300-mg indomethacin heated to 170 °C exhibited the endothermic peak at 51.1°C and 41.8 °C, respectively. There was the exothermic peak of tablets containing 75-mg indomethacin at 24.7 °C after reverse run to -30 °C, but the exothermic peak in system containing 300-mg indomethacin did not appear. The endothermic peak of thermograms from reverse run for system containing 35% talcum and 35% lactose presented at 50.9 °C and 50.2 °C, respectively, and exothermic peak of thermograms from reverse run for systems containing 35% talcum and 35% lactose appeared at 25.8 °C and 24.0 °C, respectively.

Table 24 Endothermic peak and enthalpy from DSC thermograms of different systems from DSC study

No.	Component	Peak		
		Onset (ºC)	**Endothermic Peak (ºC)**	**Enthalpy (mJ/mg)**
1	Indomethacin	158.6	161.4	106
2	PEG 4000	58.9	62.2	172
3	PEG 400	58.2	59.3	123
4	HPMC	54.6	56.2	182
5	Xanthan gum	30.0	58.1	258
6	Indomrthacin and PEG 4000:PEG 400 (7:3)	32.0	48.0	106
7	PEG 4000:PEG 400 (9.5:0.5)	38.5	52.3	108
8	PEG 4000:PEG 400 (9:1)	38.2	51.4	106
9	PEG 4000:PEG 400 (8.5:1.5)	32.7	48.4	98.2
10	PEG 4000:PEG 400 (8:2)	30.5	47.1	88.5
11	PEG 4000:PEG 400 (7.5:2.5)	28.4	46.8	94.2
12	PEG 4000:PEG 400 (7:3)	35.7	52.5	142
13	PEG 4000:PEG 400 (6.5:3.5)	42.8	51.0	105
14	PEG 4000:PEG 400 (6:4)	40.2	50.6	106
15	PEG 4000:PEG 400 (5.5:4.5)	39.1	50.2	108

Table 25 **Data from DSC thermograms of different systems from DSC study with reverse run (A): Endothermic peak and enthalpy and (B): Exothermic peak and enthalpy**

(A)

No.	Component	Peak		
		Onset (°C)	Endothermic Peak (°C)	Enthalpy (mJ/mg)
1	PEG 4000:PEG 400 (9.5:0.5)	36.4	57.1	116
2	PEG 4000:PEG 400 (9:1)	37.3	51.4	108
3	PEG 4000:PEG 400 (8.5:1.5)	33.7	53.3	110
4	PEG 4000:PEG 400 (8:2)	34.4	49.4	143
5	PEG 4000:PEG 400 (7.5:2.5)	30.6	46.8	94.2
6	PEG 4000:PEG 400 (7:3)	37.9	52.2	128
7	PEG 4000:PEG 400 (6.5:3.5)	39.3	50.5	151
8	PEG 4000:PEG 400 (6:4)	38.2	47.0	124
9	PEG 4000:PEG 400 (5.5:4.5)	39.8	50.1	114

Table 25 **Data from DSC thermograms of different systems from DSC study with reverse run (A): Endothermic peak and enthalpy and (B): Exothermic peak and enthalpy (cont.)**

(B)

No.	Component	Peak		
		Onset (°C)	Exothermic Peak (°C)	Enthalpy (mJ/mg)
1	PEG 4000:PEG 400 (9.5:0.5)	13.4	24.9	-124
2	PEG 4000:PEG 400 (9:1)	14.3	25.5	-129
3	PEG 4000:PEG 400 (8.5:1.5)	15.7	29.0	-153
4	PEG 4000:PEG 400 (8:2)	14.4	26.2	-135
5	PEG 4000:PEG 400 (7.5:2.5)	12.6	22.1	-90.1
6	PEG 4000:PEG 400 (7:3)	14.9	25.1	-104
7	PEG 4000:PEG 400 (6.5:3.5)	13.3	23.1	-88.4
8	PEG 4000:PEG 400 (6:4)	14.2	25.0	-88.6
9	PEG 4000:PEG 400 (5.5:4.5)	10.8	21.8	-79.2

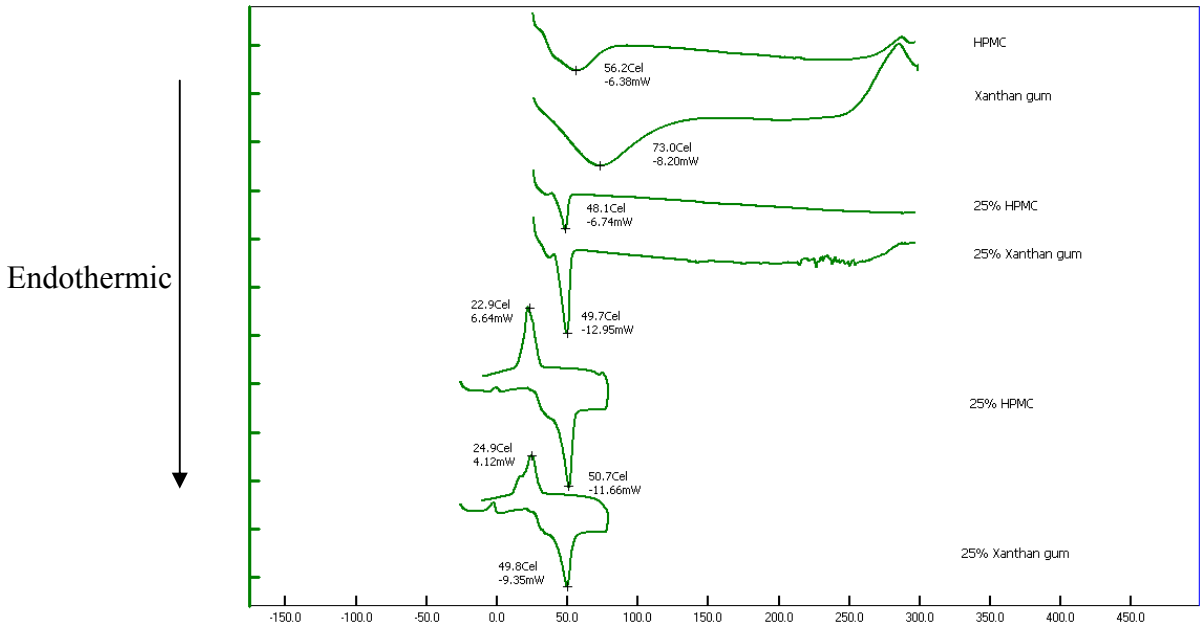


Figure 34 DSC thermograms of HPMC; xanthan gun; indomethacin tablet containing 25% HPMC; indomethacin tablet containing 25% xanthan gum; reverse run of DSC study for indomethacin tablet containing 25% HPMC and reverse run of DSC study for indomethacin tablet containing 25% xanthan gum.

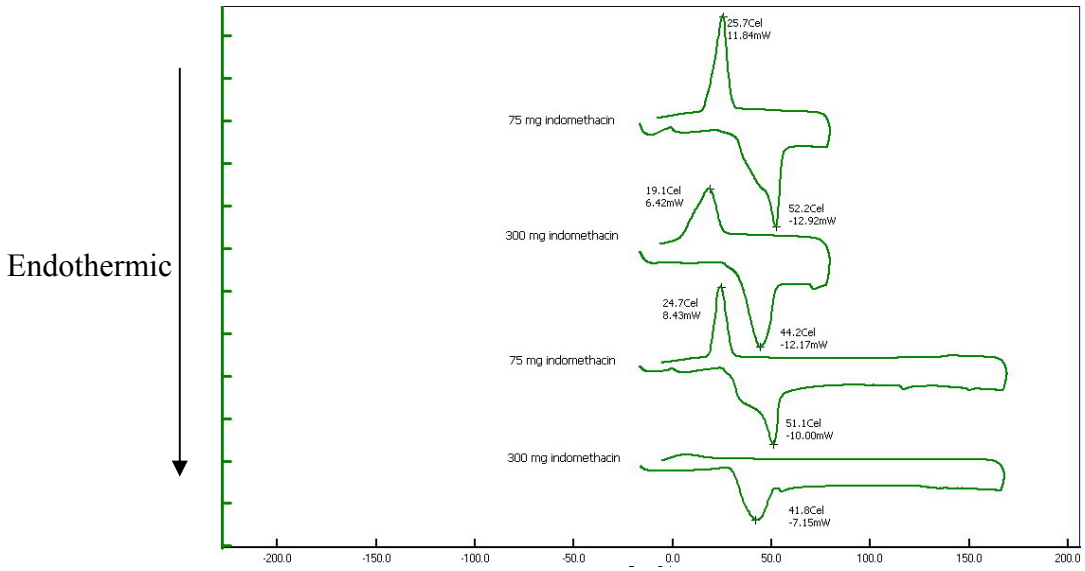


Figure 35 Thermograms from reverse run of DSC study of indomethacin tablet containing 75-mg indomethacin run to 80°C ; indomethacin tablet containing 300-mg indomethacin run up to 80°C; indomethacin tablet containing 75-mg indomethacin run up to 170°C and indomethacin tablet containing 300-mg indomethacin run up to 170°C.

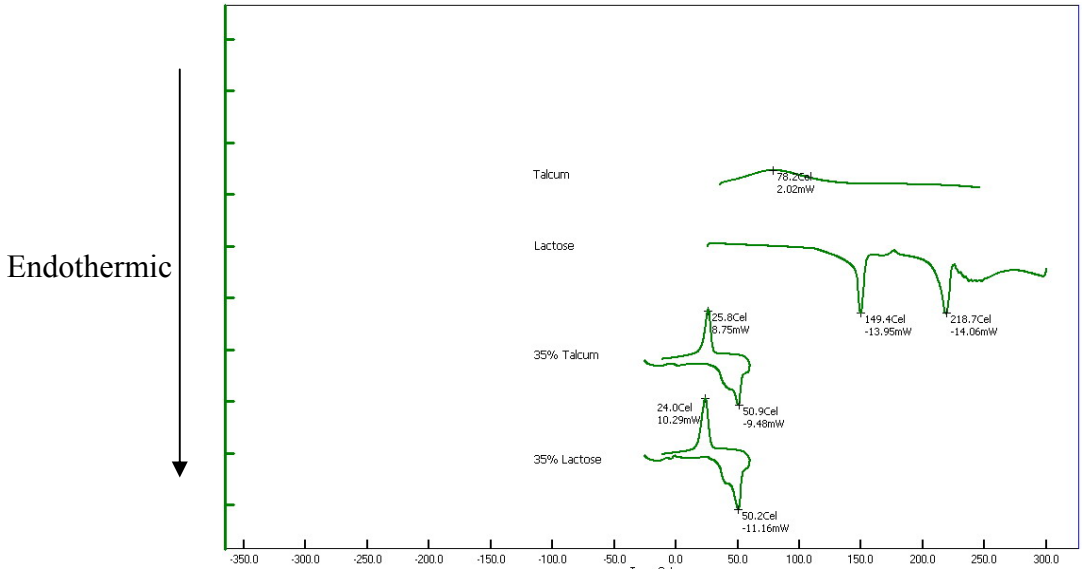
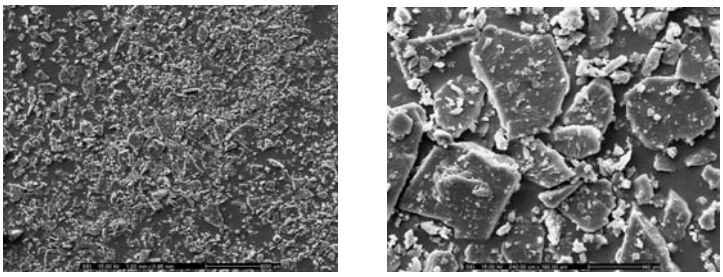


Figure 36 DSC thermograms of talcum and lactose compared with thermograms from reverse run of DSC study of indomethacin tablet containing 35% talcum and indomethacin tablet containing 35% lactose.

8. Cross section and surface topography of tablets

Surface topography and cross section area of the prepared tablet was characterized using scanning electron microscopy (SEM). Micrographs of indomethacin powder are shown in Figure 37. Indomethacin was formed by plate crystals with smooth borders, but irregularly shaped and this morphology was retained also at small size. Scanning electron micrographs of cross-section of indomethacin tablet containing 75-mg indomethacin and 5% xanthan gum before and after dissolution test are presented in Fig 38. Although some particles were observed in the solid dispersion, most drug should be molecular dispersed in the PEG4000:PEG400 matrix. The tablet containing 5% xanthan gum exhibited the less porosity.



100X 500X

Figure 37 SEM micrographs of indomethacin powder at different magnifications

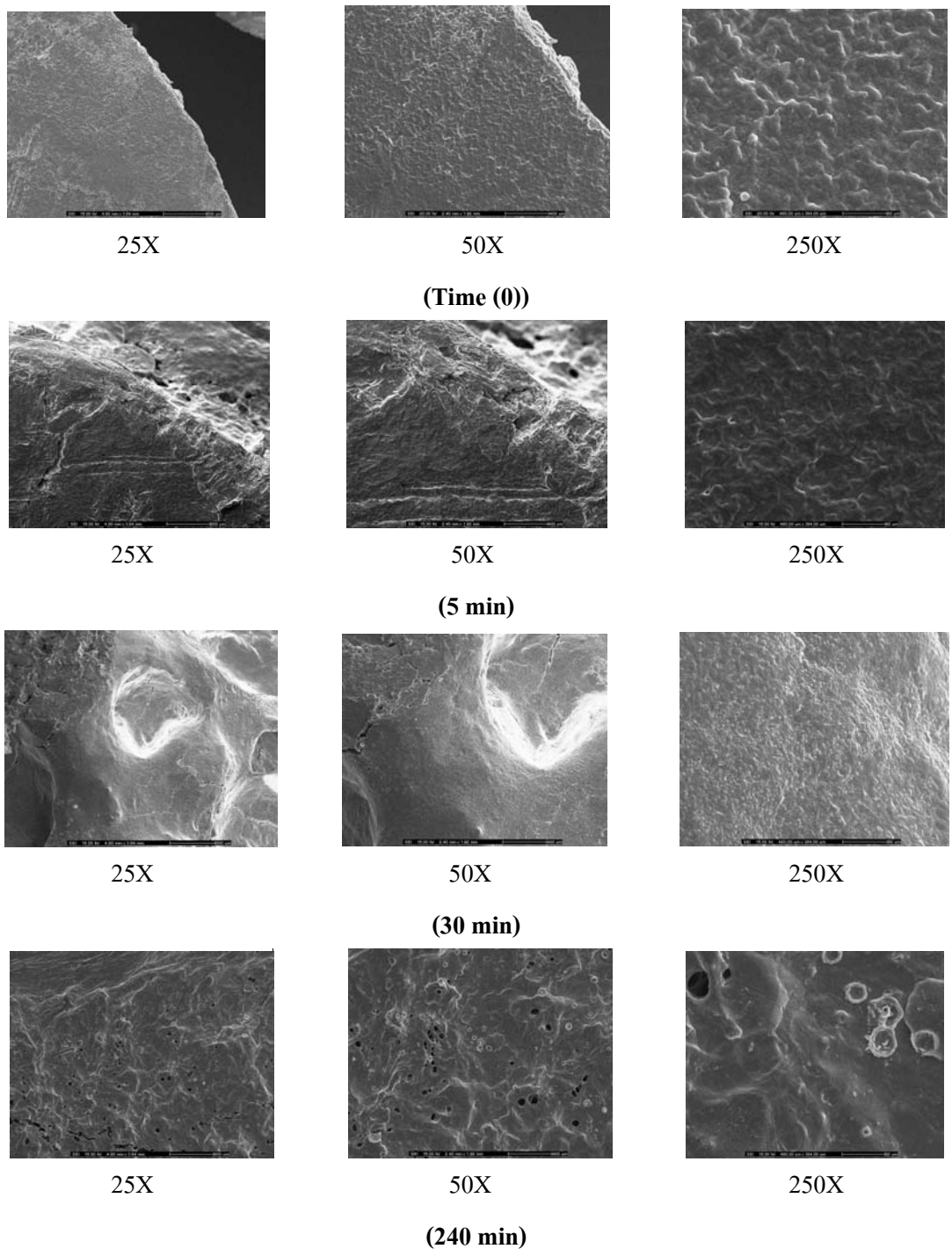


Figure 38 SEM micrographs of tablet containing 75-mg indomethacin and 5% xanthan gum after dissolution test in phosphate buffer pH 6.2 at different time interval with different magnifications

8.1 Effect of polymer on the surface morphology

The SEM images of tablet containing 25% HPMC and 25% xanthan gum after dissolution test in phosphate buffer pH 6.2 at different time intervals are shown in Fig 39. There was no pores or sponge like structure for tablet containing 25% HPMC, the eroded surfaces were formed at 5, 30 and 240 min but exhibited some pores at 480 min. Porosity of the tablet containing 25% xanthan gum was increased with time.

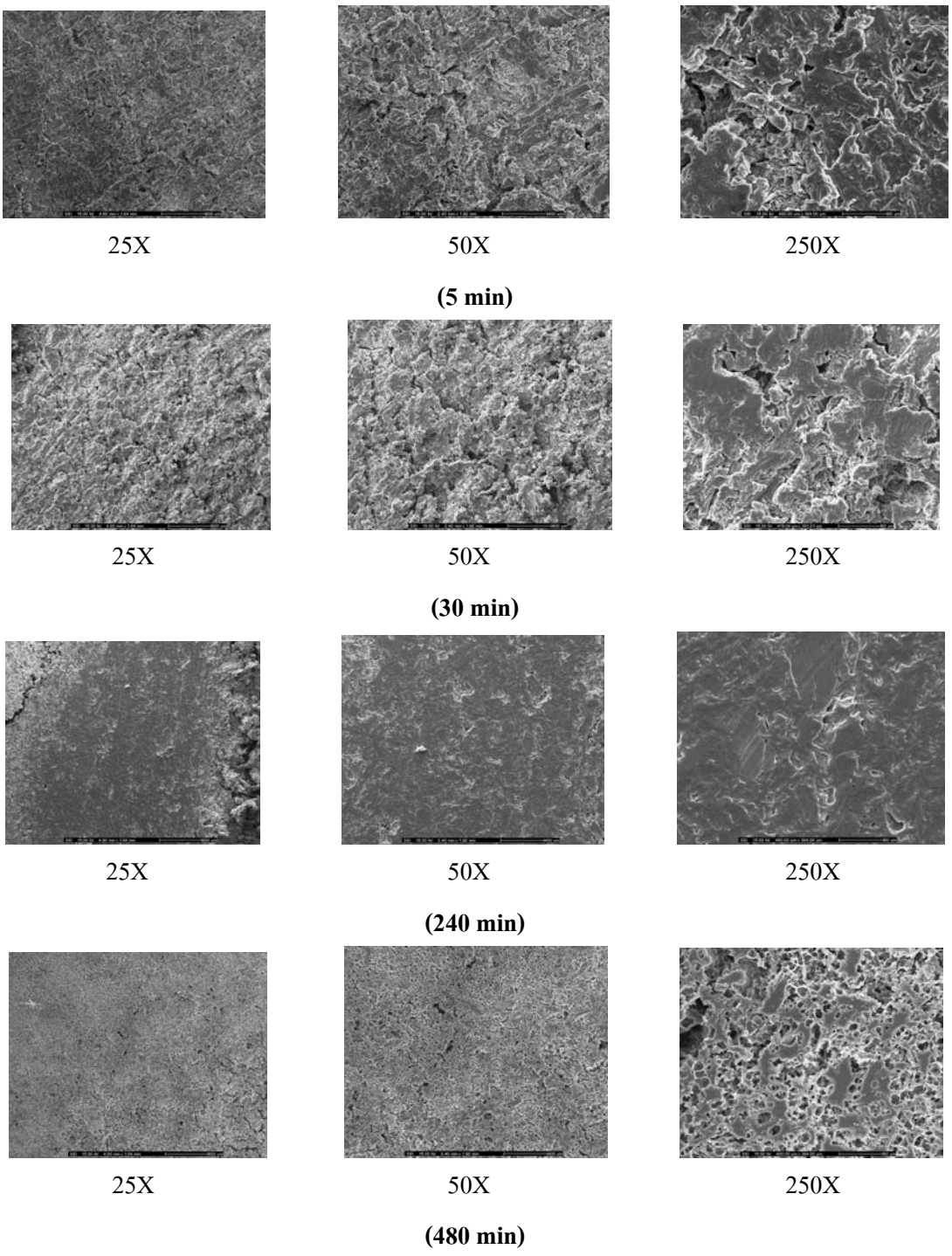
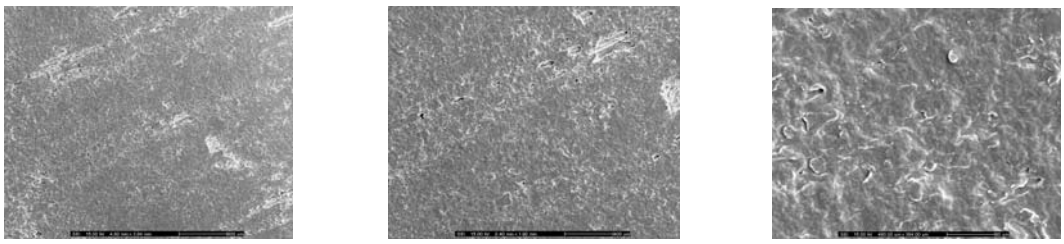
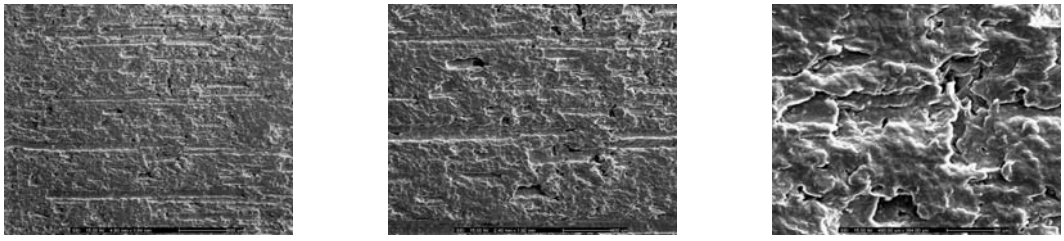


Figure 39 SEM micrographs of tablet containing 75-mg indomethacin and 25% HPMC after dissolution test in phosphate buffer pH 6.2 at different time interval with different magnifications



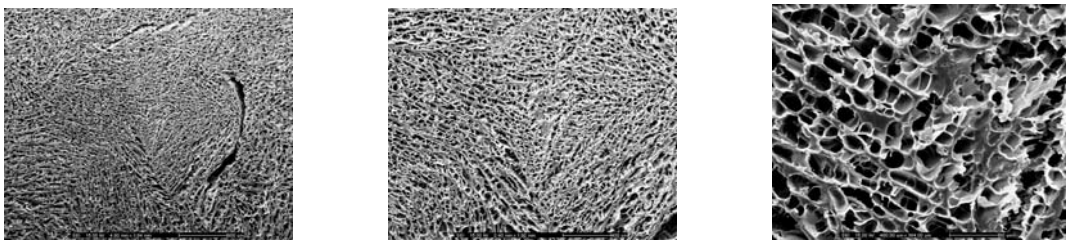
25X 50X 250X

(5min)



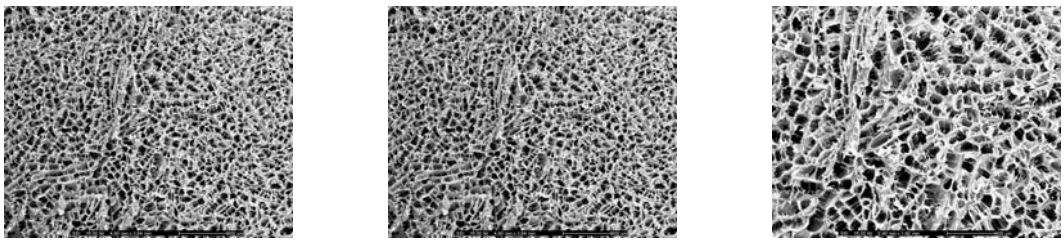
25X 50X 250X

(30 min)



25X 50X 250X

(240 min)



25X 50X 250X

(480 min)

Figure 40 SEM micrographs of tablet containing 75-mg indomethacin and 25% xanthan gum after dissolution test in phosphate buffer pH 6.2 at different time interval with different magnifications

8.2 The influence of types and amounts of diluents

Figures 41 and 42 are the scanning electron micrograps of indomethacin tablet containing 35% talcum and 35% lactose. Porosity of the SD tablet containing 35% talcum and 35% lactose was increased as the longer dissolution time was performed.

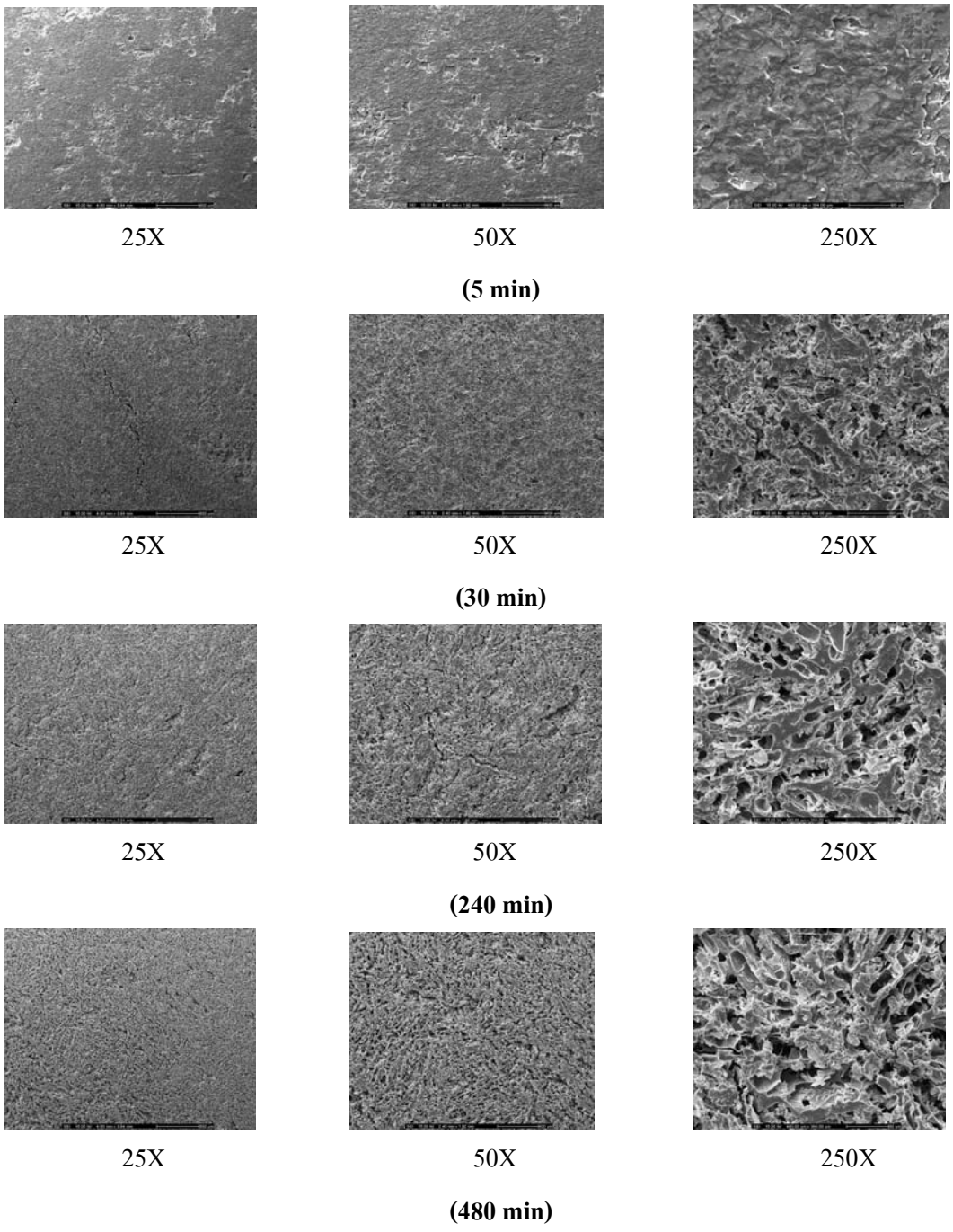
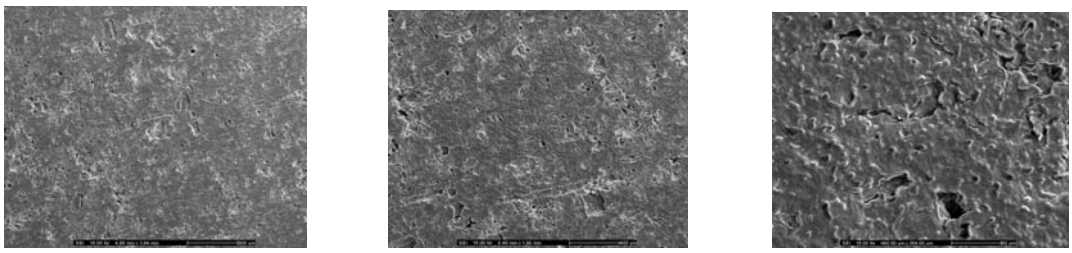
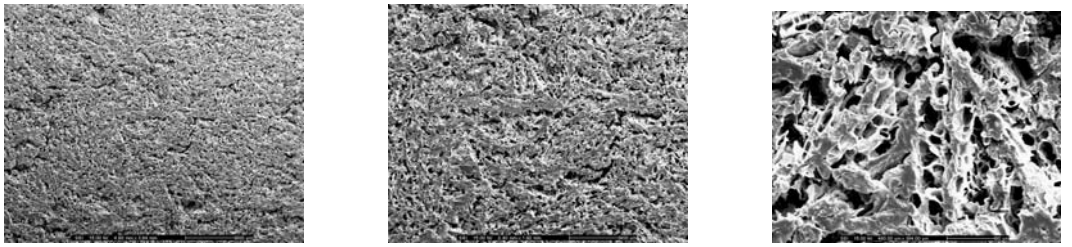


Figure 41 SEM micrographs of tablet containing 75-mg indomethacin, 5% xanthan gum and 35% talcum after dissolution test in phosphate buffer pH 6.2 at 480 min at different time interval with different magnifications



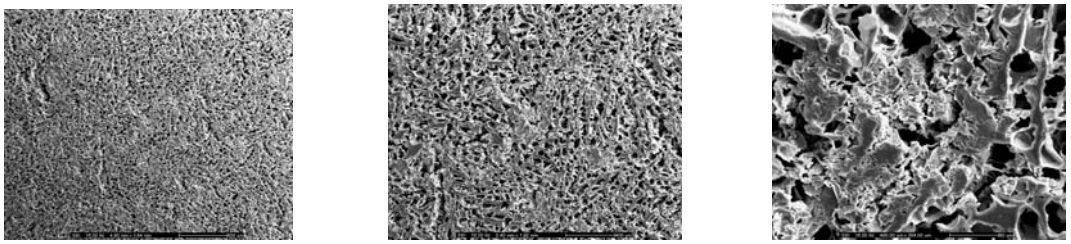
25X 50X 250X

(5 min)



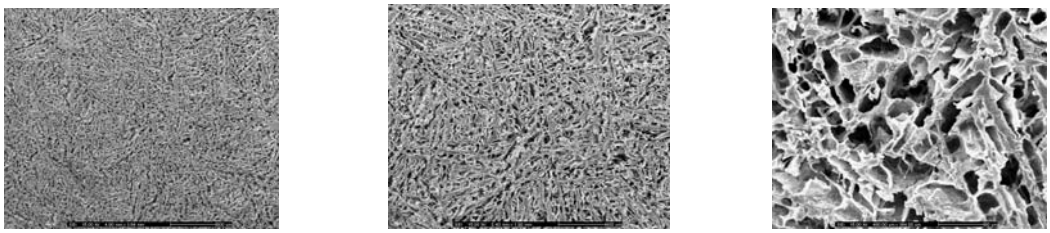
25X 50X 250X

(30 min)



25X 50X 250X

(240 min)



25X 50X 250X

(480 min)

Figure 42 SEM micrographs of tablet containing 75-mg indomethacin, 5% xanthan gum and 35% lactose after dissolution test in phosphate buffer pH 6.2 at 480 min at different time interval with different magnifications

8.3 The influence of amounts of indomethacin

Some pores and crack on tablet were evident in cross-section micrograph of 300-mg indomethacin tablet (Fig. 43). Durable shape of tablet containing 300-mg indomethacin was observed after dissolution test, but tablet containing 25-mg indomethacin exhibited high surface erosion.

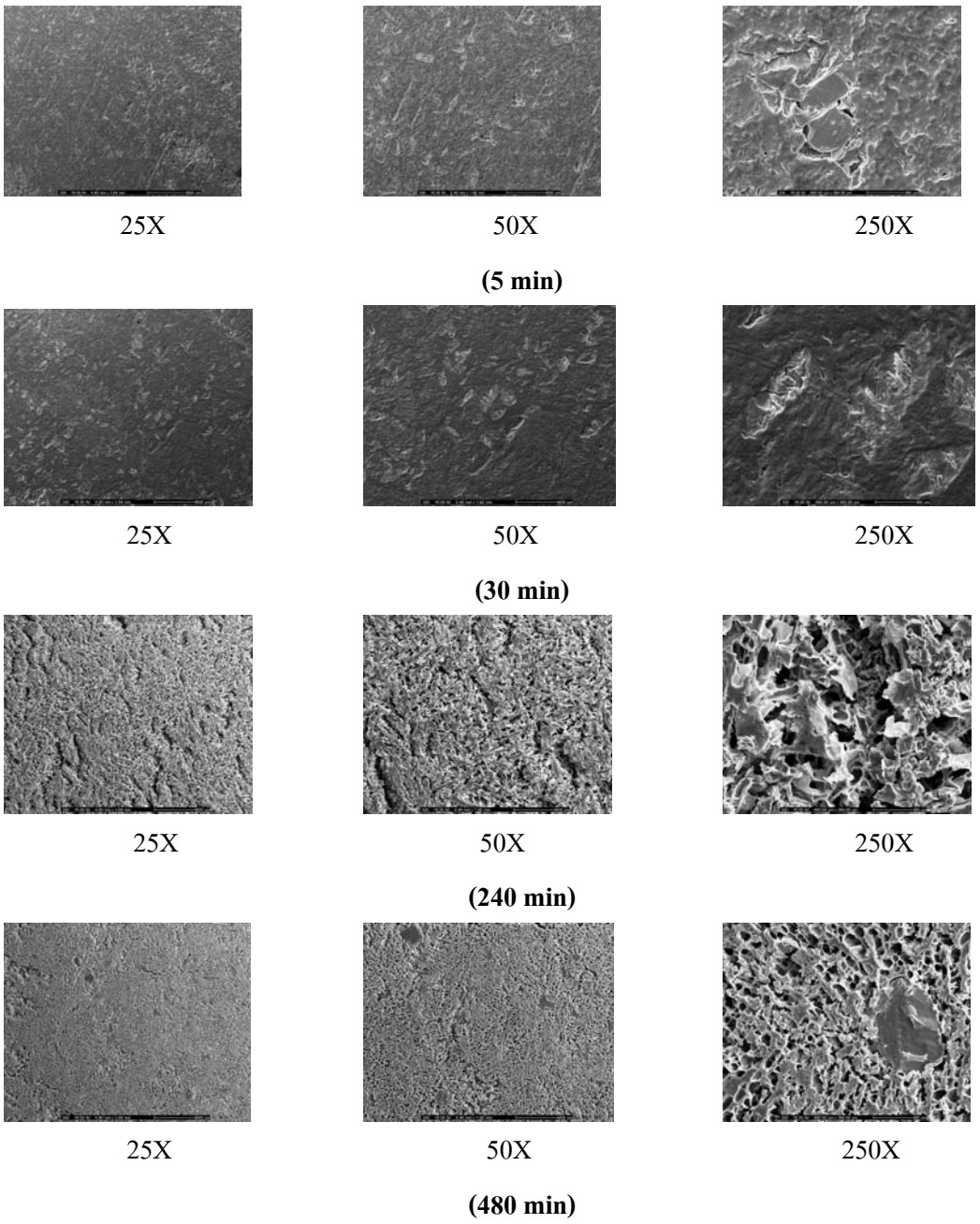
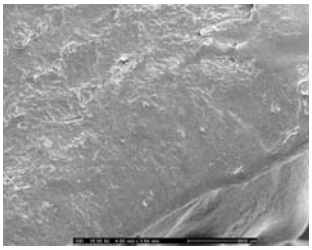


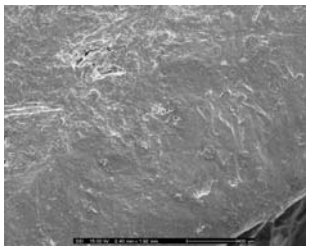
Figure 43 SEM micrographs of tablet containing 300-mg indomethacin and 5% xanthan gum after dissolution test in phosphate buffer pH 6.2 at 480 min at different time interval with different magnifications

8.4 The influence of coating

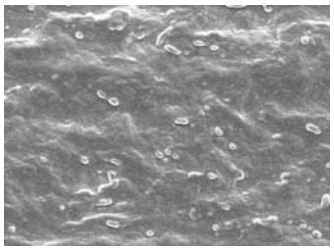
The surface morphology and cross-section of indomethacin tablet containing 75-mg indomeathcin and 5% xanthan gum coated with Eudragit L100 before and after dissolution test are shown in Figs. 44-47. The distinct and continuous coated layer was observed. The surface morphologies were dependent on time. The distinct coated layer without cracks or pores was visualized before dissolution test and after dissolution test at 5 minutes. Some pores were also evident on the surface of coating membrane at 30 and 240 minutes. Slight drug release was found in the initial 90 minutes of pH change system of dissolution. However, coated film was completely dissolved in phosphate buffer pH 6.2 during 120 to 240 minutes of dissolution.



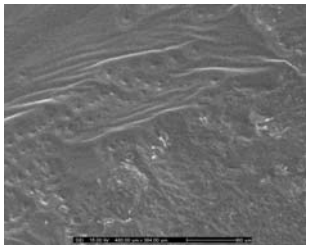
(A) 25X



(A) 50X

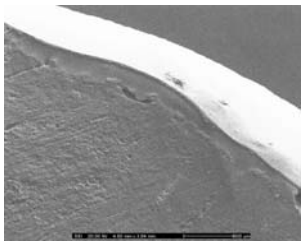


(A) 250X

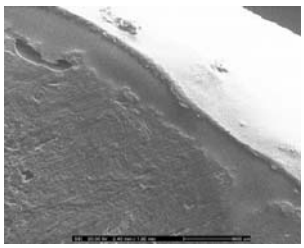


(B) Surface (25X)

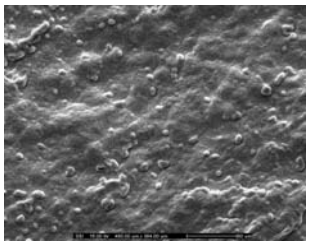
Figure 44 SEM micrographs of cross section (A) and surface (B) of solid dispersion tablet containing 75-mg indomethacin and 5% xanthan gum coated with Eudragit L100 after preparation with different magnifications



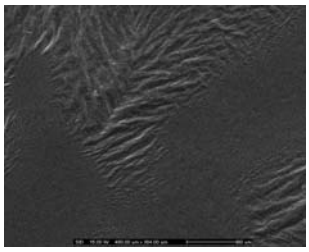
(A) 25X



(A) 50X



(A) 250X



(B) Surface (25X)

Figure 45 SEM micrographs of cross section (A) and surface (B) of solid dispersion tablet containing 75-mg indomethacin and 5% xanthan gum and coated with Eudragit L100 after dissolution test at 5 min with different magnifications

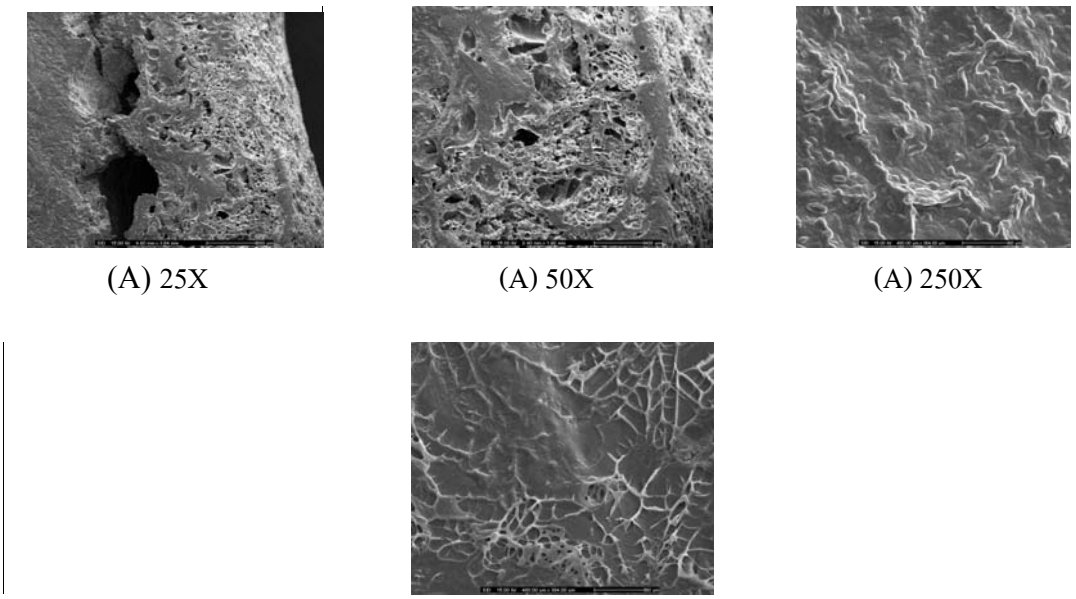
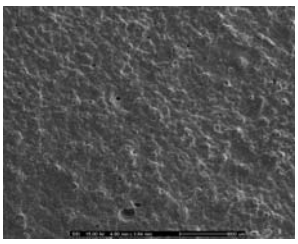
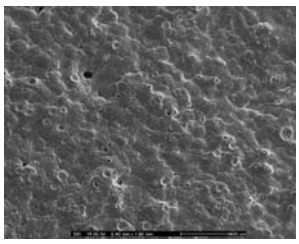


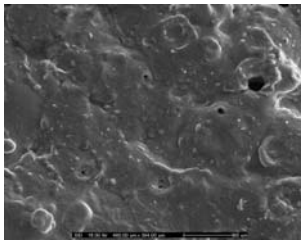
Figure 46 SEM micrographs of cross section (A) and surface (B) of solid dispersion tablet containing 75-mg indomethacin and 5% xanthan gum and coated with Eudragit L100 after dissolution test at 30 min with different magnifications



(A) 25X



(A) 50X



(A) 250X

Figure 47 SEM micrographs of tablet containing 75-mg indomethacin and 5% xanthan gum and coated with Eudragit L100 after dissolution test at 240 min with different magnifications

9. Content uniformity

The contents of tablets containing 75-mg indomethacin and 5%, 10%, 15% 20% and 25% xanthan gum are shown in Table 26. The percentage of drug contents of tablet containing different amount of xanthan gum conformed the specification of standard official USP 29 that the percentage of drug content for extended-release indomethacin capsule was not less than 90.0 percent and not more than 110.0 percent.

Table 26 Percentage of label amount of indomethacin in tablet containing different amount of xanthan gum (n=10)

Concentration of xanthan gum (%)	**% Label amount (n=10)**	**S.D.**
5	93.08	1.24
10	94.61	1.51
15	93.47	1.50
20	93.88	1.95
25	93.52	1.59

10. Analysis of the drug release data

To describe the drug release characteristic of the prepared matrix tablet, least square fitting the experimental dissolution data (cumulative drug release > 5% to 80%) to the mathematical expressions (power law, first order, Higuchi's and zero order) was carried out. The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using Model Selection Criterion (msc).

The r^2 from curve fitting was in range 0.9808 to 0.9989 and msc was in range 1.94 to 6.23. From curve fitting, the drug release from tablets containing different amount of HPMC, tablets containing 25-mg and 50-mg indomethacin were fitted well with first order model since r^2 and msc from curve fitting were higher than Higuchi's model and zero order curve fitting. The dissolution data of tablet containing different amount of xanthan gum, tablets containing of different amount of talcum in xanthan gum, tablets containing 75-mg and100-mg indomethacin, tablets with different size and different amount of xanthan gum and tablet coated with Eudragit L100 were fitted well on Higuchi's model since, r^2 and msc of curve fitting to Higuchi's model were higher than those fitting to first order and zero order. Dissolution data of tablet containing different amount of lactose in xanthan gum matrix and tablet containing 150-mg and 300-mg indomethacin could fit well on zero order model (Table 27). *In vitro* release data of tablets containing 75-mg indomethacin and 5% xanthan gum obtained from dissolution test with different rotational speed of basket exhibited the best fitted to Higuchi's model (Table 28). ND means "not determined" for cumulative drug release which was less than 5 % or more than 80% and that data points were not enough to be determined by curve fitting.

Table 27 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution profiles in phosphate buffer pH 6.2 to different release models.

Formula	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
Capsule containing 75-mg indomethacin	0.9913	4.16	0.9955	2.98	0.9811	3.51	0.9915	4.23
5 % HPMC	ND	ND	ND	ND	ND	ND	ND	ND
10 % HPMC	ND	ND	ND	ND	ND	ND	ND	ND
15 % HPMC	0.9973	4.71	0.9998	7.85	0.9861	3.48	0.9675	2.63
20 % HPMC	0.9915	3.23	0.8313	1.49	0.7813	1.23	0.6632	0.80
25 % HPMC	0.9881	4.01	0.9774	3.51	0.9880	4.14	0.9662	3.10
5 % xanthan gum	0.9985	5.95	0.8560	1.54	0.8996	1.90	0.7572	1.02
10 % xanthan gum	0.9944	4.73	0.9519	2.73	0.9896	4.26	0.9391	2.49
15 % xanthan gum	0.9816	3.45	0.8806	1.76	0.9449	2.54	0.8762	1.73
20 % xanthan gum	0.9955	5.46	0.8987	1.85	0.9597	2.81	0.9276	2.23
25 % xanthan gum	0.9913	4.98	0.8935	1.80	0.9562	2.68	0.9166	2.04
15 % talcum	0.9886	4.01	0.9396	2.50	0.9676	3.12	0.9206	2.23
25 % talcum	0.9902	4.33	0.9808	3.62	0.9660	3.05	0.9803	3.59
35 % talcum	0.9947	4.63	0.9909	4.30	0.9878	4.00	0.9847	3.78
45 % talcum	0.9985	5.95	0.9771	3.38	0.9985	6.10	0.9694	3.09
55 % talcum	0.9895	3.89	0.9436	2.43	0.9877	3.95	0.9607	2.79
15 % lactose	0.9898	4.13	0.9577	3.10	0.9597	3.26	0.9667	3.10
25 % lactose	0.9969	5.27	0.9956	5.12	0.9549	2.77	0.9965	5.33
35 % lactose	0.9989	6.23	0.9976	5.65	0.9301	2.30	0.9988	6.37
45 % lactose	0.9959	5.27	0.9981	5.87	0.9641	2.93	0.9991	6.64
55 % lactose	0.9897	3.83	0.9030	1.83	0.9886	3.97	0.9890	4.52

Table 27 (cont.) Comparison of degree of goodness-of-fit from curve fitting of drug dissolution profiles in phosphate buffer pH 6.2 to different release models.

Formula	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
25-mg indomethacin	0.9915	5.03	0.9567	2.34	0.8986	1.49	0.8570	1.14
50-mg indomethacin	0.9915	5.03	0.9427	2.06	0.9165	1.68	0.8256	0.95
75-mg indomethacin	0.9985	5.95	0.8560	1.54	0.8996	1.90	0.7572	1.02
100-mg indomethacin	0.9978	5.55	0.9794	3.52	0.9960	4.33	0.9133	2.08
150-mg indomethacin	0.9966	5.07	0.9921	4.45	0.9431	2.47	0.9960	5.12
300-mg indomethacin	0.9986	5.73	0.9986	6.03	0.9776	3.23	0.9986	5.99
Tablet containing 75-indomethacin and 5% xanthan gum coated with Eudragit L 100	0.9808	3.20	0.9824	3.54	0.9841	3.62	0.9599	2.72
Small tablet with 5% xanthan gum	0.9895	4.09	0.9793	3.54	0.9839	3.80	0.9460	2.59
Small tablet without xanthan gum	0.9984	5.76	0.9980	5.77	0.9988	3.51	0.9965	5.21
Medium tablet with 5% xanthan gum	0.9985	5.95	0.8560	1.54	0.8996	1.90	0.7572	1.02
Medium tablet without xanthan gum	0.9966	3.99	0.8468	1.08	0.9811	3.41	0.7082	0.43
Large tablet with 5% xanthan gum	ND	ND	ND	ND	ND	ND	ND	ND
Large tablet without xanthan gum	ND	ND	ND	ND	ND	ND	ND	ND

ND = Not Determined

Table 28 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution profiles of tablet containing 75-mg indomethacin and 5% xanthan gum in phosphate buffer pH 6.2 at various rotational speed of basket to different release models.

Rotational speed of basket (rpm)	**Power law**		**First order**		**Higuchi's**		**Zero order**	
	r^2	**msc**	**r^2**	**msc**	**r^2**	**msc**	**r^2**	**msc**
25	0.9952	4.75	0.9813	3.69	0.9873	4.08	0.9587	2.90
50	0.9823	3.63	0.9226	2.29	0.9469	2.67	0.8992	2.03
100	0.9979	5.25	0.8996	1.90	0.8560	1.54	0.7572	1.02
150	ND	ND	ND	ND	ND	ND	ND	ND

ND = Not Determined

The exponent *(n)* values for almost formula are shown in Table 29 and 30**.** The magnitude of the exponent *n* could indicate the release mechanism such as Fickian diffusion, case II transport, or anomalous transport. In the present study (cylindrical shape) the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of *n* between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation), commonly called anomalous non-Fickian transport (Lopes *et al*., 2007). The *k* values can be regarded as power law release constant with higher values leading to faster drug release. Mathematically, increase in *n* values higher than 1.0 would allow for a more desirable incremental release. To achieve delayed release pattern that was therapeutically useful, *n* values were expected to be higher and *k* values to be lower with a prerequisite of acceptable lag time (Wu *et al*., 2007).

The tablets containing different amount of xanthan gum, tablet containing different amount of talcum, tablet containing 75-mg and100-mg indomethacin, tablets with different size and tablet coated with Eudragit L100 tended to exhibit Fickian transport characteristics as corresponding values of *n* were lower than the standard value for declaring Fickian release behavior i.e. 0.45 (Biswal *et al*., 2008). *In vitro* release data of tablets containing different amount of lactose and tablets containing 150-mg and 300-mg indomethacin could best fit to zero order model with *n* value > 0.84 indicating Case-II transport of drug release (Vendruscolo *et al*., 2005). The *k* values of these tablets were low since the *n* values higher near 1.0. The *n* values of tablet containing different amount of HPMC, tablet containing 25-mg and 50-mg indomethacin were non-Fickian diffusion or nearly trented to Fickian diffusion. The release profiles of tablet containing 75-mg indomethacin and 5% xanthan gum performed using different rotational speeds of basket exhibited the Fickian transport characteristics as corresponding values of $n<0.45$.

Table 29 Estimate parameter from curve fitting of drug dissolution in phosphate buffer pH 6.2 to power law expression.

Formula	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
Capsule containing 75-mg indomethacin	0.1232 ± 0.0208	3.12 ± 1.03	0.31 ± 0.05
5 % HPMC	ND	ND	ND
10 % HPMC	ND	ND	ND
15 % HPMC	0.0811 ± 0.0175	2.43 ± 1.16	0.56 ± 0.05
20 % HPMC	0.0270 ± 0.0290	6.12± 1.31	0.47 ± 0.03
25 % HPMC	0.0221 ± 0.0061	-18.64 ± 12.80	0.48 ± 0.05
5 % xanthan gum	0.0198 ± 0.0011	24.39 ± 4.23	0.41 ± 0.02
10 % xanthan gum	0.0187 ± 0.0025	14.64 ± 4.70	0.42 ± 0.02
15 % xanthan gum	0.0225 ± 0.0041	46.32 ± 7.05	0.32 ± 0.03
20 % xanthan gum	0.0238 ± 0.0072	28.21 ± 9.38	0.43 ± 0.05
25 % xanthan gum	0.0162 ± 0.0091	15.94 ± 62.13	0.44 ± 0.11
15 % talcum	0.0532 ± 0.0063	23.68 ± 3.02	0.33 ± 0.02
25 % talcum	0.0122 ± 0.0021	-20.48 ± 12.47	0.28 ± 0.14
35 % talcum	0.0058 ± 0.0023	35.55 ± 16.84	0.64 ± 0.06
45 % talcum	0.0098 ± 0.0011	64.39 ± 4.23	0.31 ± 0.02
55 % talcum	0.0123 ± 0.0046	73.82 ± 19.39	0.43 ± 0.06
15 % lactose	0.0167 ± 0.0042	9.22 ± 8.78	0.52 ± 0.04
25 % lactose	0.0011 ± 0.0005	-37.21 ± 18.46	0.92 ± 0.07
35 % lactose	0.0008 ± 0.0002	-8.46 ± 10.99	0.97 ± 0.05
45 % lactose	0.0032± 0.0012	55.32 ± 10.12	0.91 ± 0.05
55 % lactose	0.0050 ± 0.0038	70.33 ± 39.05	0.58 ± 0.12
25-mg indomethacin	0.0084 ± 0.0090	5.13 ± 0.25	0.56 ± 0.02
50-mg indomethacin	0.0084 ± 0.0047	5.13 ± 0.25	0.56 ± 0.02
75-mg indomethacin	0.0198 ± 0.0011	24.39 ± 4.23	0.41 ± 0.02

Table 29 (cont.) Estimate parameter from curve fitting of drug dissolution in phosphate buffer pH 6.2 to power law expression.

Formula	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
100-mg indomethacin	0.0680 ± 0.0043	13.62 ± 0.55	0.43 ± 0.01
150-mg indomethacin	0.0003 ± 0.0003	-63.87 ± 43.60	1.13 ± 0.15
300-mg indomethacin	0.0005 ± 0.0004	40.03 ± 32.47	0.96 ± 0.12
Tablet containing 75-indomethacin and 5% xanthan gum coated with Eudragit L 100	0.0338 ± 0.0210	85.59 ± 22.17	0.44 ± 0.10
Small tablet with 5% xanthan gum	0.0123 ± 0.0115	14.49 ± 0.83	0.35 ± 0.04
Small tablet without xanthan gum	0.0035 ± 0.0028	9.80 ±1.13	0.29 ± 0.06
Medium tablet with 5% xanthan gum	0.0198 ± 0.0011	24.39 ± 4.23	0.41 ± 0.02
Medium tablet without xanthan gum	0.0074 ± 0.0272	5.12 ± 0.19	0.33 ± 0.07
Large tablet with 5% xanthan gum	ND	ND	ND
Large tablet without xanthan gum	ND	ND	ND

ND = Not Determined

Table 30 Estimate parameter from curve fitting of drug dissolution from tablet containing 75-mg indomethacin and 5% xanthan gum in phosphate buffer pH 6.2 at various rotational speed of basket to power law expression.

Rotational speed of basket (rpm)	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
25	0.0312 ± 0.0075	4.97 ± 3.18	0.37 ± 0.03
50	0.0804 ± 0.0081	2.16 ± 1.81	0.29 ± 0.02
100	0.0108 ± 0.0081	34.39 ± 4.55	0.41 ± 0.02
150	ND	ND	ND

ND = Not Determined

CHAPTER V

DISCUSSION

Hardness of tablet was increased as the amount of PEG4000 was increased because the amount of solid polyethylene glycol, such as PEG 4000, was higher in the system. System comprising 70:30 PEG4000:PEG400 was chosen as carrier for tablet since the tablet prepared by mold technique with this system could be easily removed from the mold and had suitable hardness for tablet dosage form. Hardness of tablet containing different amount of HPMC or xanthan gum was increased as the amount of both polymers was increased. Most remarkable property of xanthan gum was its capability of producing a large increased viscosity with a very small quantity of gum (Talukdar *et al*., 1998). The molecule of xanthan gum consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues (Tobyn *et al*., 1996). Xanthan solutions are highly viscous even at low polymer concentrations. This property is useful in many industrial applications, especially in the food industry where xanthan is used as a thickener, and to stabilize suspensions and emulsions (Remington's Pharmaceutical Sciences, 1990). It has been reported by many authors that xanthan gum can be used as an effective excipient for sustained-release systems (Talukdar *et al*., 1994; Tobyn *et al*., 1995). Processing variables at the laboratory and pilot scales can affect the hydration rate of xanthan gum matrices containing diclofenac sodium and hence rate of the drug release as described by Billa *et al*. (2000). Apparently, the hardness of tablet containing talcum and lactose was increased as the amount of these diluents was increased. Mater *et al*. (2008) found that incorporated lactose caused to increase the tablet hardness prepared with compression method. The enhancement of tablet hardness for tablet containing different amount of indomethacin was also due to the increasing amount of drug. This result signified that dissolved indomethacin showed property like binding agent since hardness of tablet was increased as the amount of this drug was increased. The amount of drug and filler also appeared to have significant impact on hardness and the two effects were approximately equal (Hercules Incorporated, 1997).

Drug content of the matrix tablets containing different amount of xanthan gum was uniformity as the labeled amount was in range 91.11 ± 0.01 and 93.13 ± 0.03% of indomethacin. This indicated the good homogeneity during blend solution of these systems before pouring into the mold.

Effect of polymer on the drug release from HPMC or xanthan gum matrix in solid dispersion system

Drug release from tablet without an addition of HPMC was faster than that of containing different amount of HPMC and capsule because the former tablet contained PEG as a carriers for increasing the solubility of indomethacin. Polyethylene glycols (PEGs) are one of the most widely used carriers to prepare solid dispersions due to their low melting point and their ability to provide the hydrophilic environment to enhance drug solubility (Trapani *et al*., 1999). The carriers are melted at elevated temperature and then the drugs are dissolved in molten carriers (Zerrouk *et al*., 2001). With this preparation technique, drug release from developed tablet was faster than capsule containing only indomethacin.

Drug release from tablet containing 5% HPMC was faster than did tablets containing 10%, 15%, 20%, 25% HPMC and capsule, respectively. High swelling capacity and gel formation of HPMC could retard the release of dissolved drug from the matrix. Relationship between drug release rate and HPMC concentration was previously reported by Fu *et al*., (2004). As also described by Ghimire *et al*. (2007), water insoluble drug released from matrix tablets and erosion properties of matrix tablet were found to be dependent upon the HPMC concentration however no direct correlation was found between erosion profile and drug release. Improvement of aqueous solubility has been investigated for water-insoluble natural active ingredients, such as rutin and quercetin, by solid dispersion technique using PEG, hydroxy propyl β cyclodextrin, PVP or disintegrating agent as the carrier. Furthermore, this system was developed as the sustained release tablet by direct compression. Dissolution of these substances was increased and could be prolonged the release (Lauro *et al*., 2002). Drug release from tablet without an addition of xanthan gum was notably faster than that of tablet containing 5% xanthan gum, that of capsule and those of tablets containing other amounts of xanthan gum, respectively. Xanthan gum at high concentration, on exposure to dissolution fluids, it hydrated and formed a viscous gel layer that

slowed down further seeping-in of dissolution fluids towards the core of the matrix tablet (Vendruscolo *et al*., 2005). Xanthan gum might also increase the viscous gel layer around the matrix core. In addition, the synergism attributed to the intermolecular hydrogen-bonding between acid group of indomethacin and OH-group of xanthan gum could be occurred (Walker and Wells, 1982). By comparison at the same amount of 5%, 10%, 15%, 20% and 25%, the indomethacin release from matrix system containing xanthan gum was slower than those containing HPMC. Such a burst effect with HPMC for matrices was also reported by other investigations (Rao and Devi, 1988). It was important to note that this initial rapid release of the drug from the hydrophilic matrix system was often therapeutically undesirable. More amount of HPMC was needed than xanthan gum to get a similar sustained release profile of acetaminophen in the same medium (Talukdar *et al*., 1998). Drug release from capsule containing only powder of 75-mg indomethacin was slower than that of all tablets containing HPMC. Additionally, drug release from capsule containing 75-mg indomethacin was slower than tablet containing 10%, 15%, 20% and 25% xanthan gum because indomethacin powder in capsule is a poorly soluble drug (5 μg/mL) (Wang *et al*., 2007 c).

Effect of types and amounts of diluents on the drug release

Incorporation of talcum into xanthan gum matrix minimized the drug dissolution and retarded the drug release in phosphate buffer pH 6.2. Enhanced amount of talcum decreased the amount of carriers. This result indicated that the amount of carrier significantly affected the drug release. Similar result has been mentioned by Uhumwangho *et al*. (2007) who investigated the effect of hydrophobic agents (i.e., talc or magnesium stearate) on the drug release profiles of the melt granulations. This mentioned study thus sought for a simple approach for effectively modifying drug release from granules. Such granules could ultimately be encapsulated or tableted for multi-unit dose applications. The release rates of paracetamol powder from the melt granules were retarded after the incorporation of a hydrophobic agent particularly while the talc or magnesium stearate content was more than 30%w/w. Pawar *et al*. (2004) described the ibuprofen-talc agglomerates prepared by using dichloromethane-water as the crystallization system. Talcum was retarded the rate of water penetration and reduced the rate of disentanglement of polymer.

Typically, lactose should increase the tablet porosity and stimulated the water penetration into the inner parts of the matrix. This study expected to increase the drug release from xanthan gum matrix by incorporation the hydrophilic filler, such as lactose. However, all tablets after addition of incorporated different amount of lactose into xanthan gum matrix exhibited percent drug release less than 40%. The drug release decrement for tablet containing different amount of lactose was due to a diminishment of drug carrier amount. Similar result has been mentioned by Perissutti *et al*. (2001) for utilization a ram extruder to prepare directly a fast release dosage form of carbamazepine with uniform shape and density, comprising polyethylene glycol 4000 (PEG) as a low melting binder. They concluded that an addition of lactose in this system reduced the dissolution rate.

Effect of amount of drug on the drug release

Since the amount of PEG4000 and PEG400 were decreased as the amount of indomethacin was increased, the release rate of drug from matrices was decreased. Similar result has been mentioned for the controlled release system using biodegradable and biocompatible foams to modulate the release of tetracycline (Sendil *et al*., 2000), which the drug loading showed an inverse effect on the release rate of tetracycline. When the amount of drug loaded into foams increased, the release rate decreased. As the drugs loading was increased, the interaction of drug crystals with the dissolution medium was decreased due to decreased surface to volume ratio of the drug, and due to occlusion of the pores by the drug crystals leading to a lower release rate. Although it appeared to be contrary to the general expectation for release of a drug from a polymer matrix or capsule, the situation here was very different.

Effect of pH of dissolution medium on the drug release

Drug release from tablets in HCl buffer pH 1.2 was very low but it was increased during pH of medium was increased to 6.2. Therefore, the drug dissolution was a function of drug solubility, at various pH ranges. Effect of type and concentration of vehicles on the dissolution rate of indomethacin from liquid solid compacts was previously reported (Javadzadeh *et al*., 2005). The amount of drug release at pH 7.2 (SIF) was greater than that released at pH 1.2 (SGF). This might be the high solubility of indomethacin at high pH value (indomethacin solubility in

SGF = 0.004 g/1000 g and solubility in SIF = 0.768 g/1000g). The reason for an increase in dissolution rate of indomethcin from liquisolid compact could be explained with solubility data (Javadzadeh *et al*., 2005). The release of indomethacin from matrix tablets containing pectin alone or combination with calcium acetate in phosphate buffer pH 6.2 was slower than that in tris buffer pH 7.4 or phosphate buffer pH 7.4. Since, indomethacin is a weak acidic drug, its solubility can increase with increasing pH. Thus, the higher drug release of pectin-based matrix tablets in buffer pH 7.4 was evident (Sungthongjeen *et al*., 2004). Suh *et al*. (1996) reported the physicochemical phenomena and thermodynamic properties of naproxen in Poloxamer 409 (PF-127) and the effect of micellar solubilization on the release of naproxen from the vehicle into the receptor medium under various conditions. The medium pH significantly affected the release of naproxen due to its effect on the extent of micellar entrapment of naproxen. The greatest release was observed at pH 6.3 which was higher than other pH of medium. Drug release kinetics were indicated to depend on the solubility of the drug and also the pH of the dissolution medium. For a particular drug, change in the internal structure of the surface hydrated layer may affect the extent to which different mechanisms of drug release contributed toward the overall release kinetics (Hodsdon *et al*., 1994).

Effect of mold size and amount of xanthan gum on the drug release

Xanthan gum could enhance the viscous gel layer around the matrix core. Therefore, drug release from tablets containing 5% xanthan gum was slower than tablet without xanthan gum at different size of tablet. The total amount of PEG4000 and PEG400 was increased as the tablet size was increased since the amount of drug was fixed at 75-mg/tablet therefore the drug release from large tablet was faster than medium and small tablets, respectively. Carriers enhanced the solubility of poor soluble drug by enhancement of the wettability and dispersibility of drug because the possible formation of a metastable dispersion could promote a greater solubility of drug in a faster dissolution rate (Ahmad *et al*., 2001).

Effect of hydrodynamic force on the drug release

The rate of indomethacin release at 150 rpm rotational speed of basket was faster than that at 100 rpm, 50 rpm and 25 rpm, respectively. This was due to more rapid erosion of matrix at

higher stirring rates because of the increased rate of detachment of polymer chains away from the matrix surface. This led to the thinner layer of gel forming at surface of the dosage form at higher agitation rate (Goole *et al*., 2007). Release rate of nitrendipine from hydroxypropylmethylcellulose phthalate (HP-55) microsphers was increased as the rotational speed of the paddle was increased (Yang *et al*., 2004). The release of diclofenac sodium from lipophilic matrix tablets in phosphate buffer solution pH 5.8 increased with higher rotation speed (Kincl *et al*., 2003). Similar resulted has been reported for the release increment of chlorpheniremine maleate from HPMC matrix tablet with increasing rotational speed (Krogel *et al*., 1999).

Effect of tablet coating on the drug release

Eudragit L 100 is the commercial name of an enteric polymer of methacrylic acid-methylmethacrylate that belongs to a class of reversible soluble/insoluble polymers (Dourado *et al*., 2002). Enteric-coated systems are designed to provide a protection to tablets in the stomach (Sinha *et al*., 2003). In this study, tablet was coated with Eudragit L 100 to protect indomethacin to irritate the stomach and deliver this drug to small intestine. Furthermore, the film coat would protect the carrier, PEG 4000 and PEG 400, not to be disturbed with HCl buffer pH 1.2 before the tablet was moved into the intestine. The indomethacin tablet coated with Eudragit L 100 demonstrated the low initial release of drug in acidic state (HCl buffer pH 1.2) of pH change system. Eudragit L 100 is a pH-dependent polymer which dissolves in medium with pH > 6 and is less soluble in medium with pH 1.2. Eudragit L100 contains an acid group such as methacrylic acid and methyl methacrylate in chemical structure. Both methacrylic acid and methyl methacrylate affected the solubility of Eudragit L 100 (Dourado *et al*., 2002; Akhgari *et al*., 2005). The release of drug was gradually increased upto 90% in phosphate buffer pH 6.2 because Eudragit L 100 could dissolve in this environmental pH.

Drug release from tablet coated with Eudragit L 100 was compared to that of tablet without Eudragit L 100 coating in pH change system. The release from tablet without Eudragit L 100 coating was very low but the drug release was fast increased as the pH of medium was enhanced to 6.2 and the drug released was constant after 4 hrs. In contrast, the initial release of tablet coated with Eudragit L 100 was very low but the drug was gradually released and could be

prolonged in phosphate pH 6.2. This result signified that Eudragit L100 film could be used for deliver drug to small intestine and drug was subsequently gradually liberated.

Water uptake and Erosion

During the tablet was immersed in an aqueous medium, liquid penetrated into the tablet and a gel was formed due to uncoiling of xanthan gum molecules and the formation of hydrogen bonds with water molecules (Talukdar *et al*., 1994). Tablet containing highest amount of xanthan gum exhibited the maximum swelling ratio. Therefore a high degree of swelling was due to the high water uptake and the small degree of erosion. Normally, percent erosion of matrices increased progressively with time (Sinha *et al*., 2002). In contrast, the tablet containing lowest amount xanthan gum exhibited the lowest swelling ratio and high degree of erosion. Nature of the polymer played an important role in this swelling process of the matrix tablets (Billa *et al*., 2000). The rate of water-uptake after hydrophilic gel-formation demonstrated a close relationship with the concentration of polymer forming the gel. Wan *et al*. (1992) mentioned that the rate of water penetration into hydrophilic matrix could be determined by the balance of forces promoting water entry and the viscous force opposing it (Matsuo *et al*., 1996). As a result, the diameter of the tablet increased progressively and a distinct gel-sol boundary developed. Swelling of polymeric matrices could be employed to compare their water uptake capacities (Baumgartner *et al*., 2008). Swelling of the matrix, as indicated by a transition of the polymer from glassy to rubbery state, was an important parameter in the determination of release characteristic of the matrix system. A correlation of polymer swelling to drug release could be conducted to predict drug release mechanisms for different types of polymer matrices (Talukdar *et al*., 1994). Dissolution rate and, ultimately, drug availability could be controlled by the rate of matrix swelling, drug diffusion through the gel layer and/or matrix erosion (Yeole *et al*., 2008). Therefore, there was the relationship between the release of drug closely with percent water uptake and erosion (Vendruscolo *et al*., 2005).

Morphological studies

The results from visual observation of tablet containing different amount of xanthan gum indicated that the matrices appeared to swell and form a viscous gel mass after contacting with the

medium. The photographs indicated a dark yellow at solid core of tablet swelling and soft yellow at gel layer because indomethacin was a pale yellow to yellow-tan crystalline powder. Clearly, the intensity of the yellow color indicated the dissolved drug concentration. The color was related to the position inside the gel layer. A series of photographs of the matrix base showed that the gradient of color in the gel layer depended on the drug loading and swelling time (Colombo *et al*., 2000). Swelling and erosion rates were comparable and that the two mechanisms were both effective in the control of drug release process (Maggi *et al*., 2001). The presence of two concentric layers could be apparently of system containing high amount of hydrophilic polymers. The external part had a consistence similar to a gel and the inner core was not solid but completely wetted. Initial tablet swelling indicated the high hydration of all tablets containing xanthan gum. When a matrix containing a swellable glassy polymer such as xanthan gum contacted with a solvent, a progressive change from the glassy to the rubbery state led to a swelling process as also described by Siepmann *et al*., (2002). The matrix exhibited a rigid and elastic structure after utilizing higher amount xanthan gum. Hydrogels are sometimes called infinitely large molecules or super macromolecules. One of the unique properties of hydrogels was their ability to maintain original shape during and after swelling due to isotropic swelling; in fact, swelling changed only the size of the original hydrogel while maintaining the original shape. In the case of NaCMC systems at pH 1, ionic interactions between the drug and the polymer probably caused the maintenance of a solid and rigid structure of the matrix during the dissolution test (Conti *et al*., 2007 b). In contrast, tablet containing different amount of xanthan gum could not maintain a shape of tablet owing to the high swelling capacity of xanthan gum and the rapidly swelling during immersion in the dissolution.

Radial dimension change

Considerable swelling and gel formation were apparently noticed, especially when the high amount xanthan gum was incorporated in PEG matrix. An addition of a certain amount hydrophilic polymer increased the surface wettability and, consequently, the water penetration into the matrix was subsequently promoted. The radial dimension change of tablet containing 5% xanthan gum could not determine because the tablet was gradually eroded and completely dissolved. Xanthan gum had the higher swellability index when it was added into formulations

containing poorly soluble drug (Ernest *et al*., 2007). Moreover, the amount of xanthan gum had a positive effect on percent diameter change since the percent diameter change increased as the amount of xanthan gum was increased.

Texture analysis

The texture profiles of tablets containing different amount of xanthan gum before and after dissolution test at different time interval were obtained by force-displacement measurements. The force required for probe to penetrate into the swollen tablet decreased with time as the swelling proceeded and gel strength was reduced. Similar result has been reported for the relationship between the physical properties of a xanthan matrix in the absence or presence of calcium ions and its influence on the release of pentoxifylline (Baumgartner *et al*., 2007). Force transition regions in a force–displacement textural profile of a swollen tablet has been defined earlier by Pillay and Fassihi (2000) and Durig and Fassihi (2002). The total work of penetration calculated as the area under the force–displacement curve indicating matrix stiffness or rigidity (Jamzad *et al*., 2005). The total tablet thickness and swelling front movement using force-displacement profiles provided more evidence that the rate and extent of gel formation was significantly influenced by the nature of excipient used (Baumgartner *et al*., 2008). Total work of penetration of tablet containing different amount of xanthan gum at different time points depicted the change in work of penetration versus time as the exposure to swelling medium was extended and hydration was increased. A sharp decrease in work of penetration reflected the initial high rate of hydration of tablets which incidentally coincided with high rate of water uptake and gel formation. All formulations showed lower values for work of penetration during 2 hrs to 8 hrs. In fact, the obtained results confirmed that the system containing a gel with a lower strength was greater susceptible to erosion and chains disentanglement as mentioned previously (Conti *et al*., 2007 a). Total work of penetration of tablet containing 25% HPMC and tablet containing different amount of xanthan gum were decreased with time. Therefore, the use of texture analysis on the swollen tablet also provided a good approach to understand drug release kinetic and the mechanism of drug delivery from a swellable matrix system. Total work of penetration of tablet containing different amount of polymer before dissolution test increased with increasing amount of polymers. The hardness of tablet determined with typical hardness tester was also increased as

the amount of polymer was increased. The polymer/water concentration gradients also resulted in textural and physicomechanical changes in the gel layer of matrix tablets which could be accurately detected by textural analysis (Durig *et al*., 2002). Li *et al*. (2007) studied the correlation between drug dissolution and polymer hydration of pseudoephedrine hydrochloride matrix tablet using a texture analyzer. Linear correlations were observed among drug dissolution, polymer content and parameters of texture analysis including hydrogel thickness and area under the curve (AUC_{TA}) for formulations containing hydrophilic polyethylene oxide (PEO). In addition, the results from textural analysis indicated that the total work of penetration (WT) was higher for matrix with polymer blend compared to HPMC-only matrix in water and phosphate buffer pH 6.8 (Tiwari *et al*., 2007). The total work of penetration was a measure of matrix stiffness or rigidity, indicating that the matrix blend system exhibited higher matrix gel strength compared to HPMC-only system. The higher gel strength in polymer blend matrix could be attributed to the differences in hydration of HPMC in a presence of anionic polymers or to the interaction between the polymers.

Total work of penetration of dry tablet (0 h) containing 25% HPMC was decreased with increasing time. Similarly, total work penetration of dry tablet (0 h) containing different amount of xanthan gum was decreased with increasing time. By comparison, total work penetration of dry tablet containing 25% xanthan gum was slighty higher than tablet containing 25% HPMC at 5 minutes. This might be due to the inward movement of the fully hydrated region as well as increase in total thickness of swollen tablet. The rate and extent of gel formation were significantly influenced by the nature of employed excipients (Jamzad *et al*., 2004).

The differential scanning calorimetry (DSC)

The DSC thermogram of lactose exhibited two endothermic peaks. The first endothermic corresponded to the loss of water of crystallization and the second endothermic peak corresponded to the melting of lactose followed by its decomposition. This thermal behavior of lactose has been previously reported by Larhrib *et al*. (2003). Differential scanning calorimetry (DSC) was conducted to indicate the molecular dispersion of indomethacin into carrier matrix. The DSC thermogram of solid dispersion system (indomethacin, PEG4000, PEG400 and 25% xanthan gum or 25% HPMC) exhibited all major peaks of each component indicating the

mixtures to be compatible. DSC data for pure HPMC and xanthan gum exhibited melting point at 56.2 ˚C and 73 ˚C, respectively. The DSC thermogram of system contained HPMC and xanthan gum showed a melting point at 50.7˚C and 49.8˚C, respectively. The thermograms of the solid dispersion showed the characteristic peak of the carrier matrix, without drug peak indicating that the drug was completely dissolved in the carrier. Alteration of this drug in PEG-based SD system has been reported previously by Zheng *et al*. (2005). However, additional peaks were observed around 50˚C, which suggested the drug was completely dissolved in the PEG carrier (Verheyen *et al*., 2001). Thermograms of the PEG-based system showed the characteristic peak of the carrier matrix around 50˚C, but without the drug endothermic melting peak, indicating that the drug was changed into amorphous structure. By comparison, thermograms of tablet containing talcum or lactose and tablet without talcum or lactose were not different. This result indicated that the hydrophobicity and hydrophilicity of fillers did not significantly affect the DSC thermograms. Previous study developed by Verma *et al*. (2005 b) claimed that talcum and lactose did not affect the drug structure after blending these fillers with drug. The exothermic peak of tablets containing 75-mg indomethacin exhibited at 24.7 ˚C after reverse run to -30 ˚C. Because system containing 75-mg indomethacin contained a high amount of carrier, the carrier was recrystallized which the exothermic peak was occurred as previously reported by Newa *et al*., (2007). The exothermic peak in system containing 300-mg indomethacin could be not detected. Because the carrier improved solubility of high amount indomethacin, the carrier not remained for recrystallization.

Cross section and surface topography of tablets

Characteristic change for tablet surface morphology was observed under SEM of tablet containing xanthan gum or HPMC. The differences in appearance of tablet surfaces were understandable in terms of the different dissolution time. Tablet containing highest amount of HPMC showed no pores or sponge like structure after drug dissolution but drug release from this tablet was increased with time. However, the tablet containing highest amount of xanthan gum showed larger pore formation after drug dissolution. Drug release from this tablet was increased with time. This result demonstrated a close relationship with the pore former since the increased level of pore and porosity of the surface promoted the increase of drug diffusion and the opening of the channels. This was reflected in the release studies, wherein the release increased with the

increase in level of pore former (Verma *et al*., 2003 a). Other factors like closer contact between the hydrophilic carrier and the drug might also be influence in enhancing drug solubility and/or dissolution rate observed with the solid dispersion particles. Therefore, dissolved drug molecules could diffuse through this pore so that the kinetic of drug release should be the diffusion-controlled release (Sankalia *et al*., 2008). Ahuja *et al*. (2007) described the dissolution enhancement of a poorly soluble model drug, rofecoxib, using solid dispersion approach. Diverse carriers *viz*. polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire®44/14), polyvinylpyrollidone K25 (PVP), poloxamers (Lutrol®F127 and F68), polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotropes (urea, nicotinamide) were investigated for the purpose to dissolution enhancement of rofecoxib. Solid state characterization revealed the partial loss of drug crystallinity which could bring about significant change in the drug dissolution rate. Tablet containing lowest amount of xanthan gum showed apparently the eroded surfaces, because the amount of xanthan gum was not enough to produce a gel layer and adequate. SEM images of tablet containing highest amount of HPMC exhibited the eroded surface during dissolution test and contained some pores after dissolution test at 480 min. Most likely, the morphological change was due to a leaching out of the water soluble polymers, HPMC, and the release of the indomethacin. This morphological characteristic of matrix has been previously claimed by Strubing *et al*. (2007).

SEM photograph of tablet containing 35% talcum or 35% lactose after release test at 240 min exhibited any pores after release test. These pores were occurred form the diffusion of drug due to the opening of the channels. Therefore, any pores increased with time in the surface were observed. In contrast, the drug release was decreased as the amount of talcum or lactose was increased. Consequently, the use of talcum or lactose in the tablet containing 5% xanthan gum diminished the drug dissolution and retarded the drug release.

Surface of tablet containing 300-mg indomethacin after dissolution test at 5 and 30 min were smooth and homogeneous. Some pore and tablet crack were evident after dissolution test at 240 min and 480 min. As the drug loading was increased, the interaction of drug crystals with the dissolution medium was decreased since the surface to volume ratio of the drug was decreased and the occlusion of the pores by the drug crystals led to a lower release rate (Sendil *et al*., 2000).

The distinct and continuous coated layer was noticed from tablet coated with Eudragit L100. The distinct coated layer without cracks or pores was visualized before dissolution test and after dissolution test at 5 minutes. Some pores were also evident on the surface of coating film at 30 and 240 minutes. Indomethacin could be leached out of through the film during dissolution testing. Enteric-coated systems showed no drug release in the first 90 minutes in the simulated gastric environment. It also showed negligible drug release in the initial 90 minutes of dissolution. Film from Eudragit L 100-coated tablet was completely dissolved in phosphate buffer pH 6.2 after dissolution time at 240 minutes. Drug gradually could released from tablet coated with Eudragit L 100 and it could be prolonged in phosphate pH 6.2. Practically, drug release behavior of various films in the digestive tract are presented in Fig. 48.

Analysis of the drug release data

To analyze the *in vitro* release data, the curve fitting of drug dissolution profiles to various kinetics models were carried out to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. Fickian diffusional release and a case-II relaxational release, are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (Cox *et al*., 1999).

From curve fitting to power law equation, the *n* values of tablet containing different amount of HPMC, tablets containing 25-mg and 50-mg indomethacin indicated that the release mechanism of these tablets were close to anomalous transport. Therefore, mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble drugs being released predominantly by diffusion with a limited contribution from matrix erosion and anomalous diffusion resulting from the relaxation of the macromolecular polymer chains (Hardy *et al*., 2007).

The release kinetics of tablets containing different amount of xanthan gum, tablets containing different amount of talcum in xanthan gum matrix, tablet containing 75-mg and 100-mg indomethacin, tablets with different size and different amount of xanthan gum and tablet coated with Eudragit L100 adequately followed a square root of time according to the Higuchi's model since Fickian diffusion occurred via the porous network formed when indomethacin dissolved from the inert matrix. During contaction between xanthan gum matrix and dissolution medium, the macromolecular chains swelled at the tablets surface and formed a gel layer around a dry-like core. Drug diffusion occurred at the core-gel interface then through this gel (Chambin *et al*., 2003). Erosion of swollen layer and dissolution of the matrix itself were also observed. The drug release data were explored for the type of release mechanism followed. For controlled or sustained release formulations, diffusion, swelling and erosion were the three most important rate controlling mechanisms. The drug release from the polymeric system was mostly by diffusion and was best described by Fickian diffusion.

In vitro release data of tablets containing different amount of lactose in xanthan gum matrix and tablets containing 150-mg and 300-mg indomethacin exhibited the best fitted to zero order model with *n* value close to 0.84 hence they exhibited as Case-II transport (Vendruscolo *et al*., 2005). These results were in agreement with the ones published by Sujja *et al*. (1998) that established correlation among the swelling, erosion and drug release in hydrophilic matrices elaborated from natural gums as xanthan, karaia and locust bean gum. The *n* values of tablets containing 75-mg indomethacin and 5% xanthan gum obtained from dissolution test with different rotational speed of basket were fitted well with Higuchi's model. Therefore, the release mechanism of these tablets were close to Fickian transport.

CHAPTER VI

CONCLUSION

Solid dispersion was used to improve the aqueous solubility of indomethacin and this solid dispersion was fabricated into tablet by mold technique. System comprising 70:30 PEG 4000 :PEG 400 was the suitable carrier for indomethacin. Indomethacin sustained-release matrix tablet containing HPMC or xanthan gum as matrix former could prolong the drug release at least for 8 hrs. The presence of a swelling soluble excipient like xanthan gum with different amount affected the release profile due to the change in swelling at the tablet surface. The hardness of tablet was increased as the amount of xanthan gum or HPMC was increased. However, an increased amount of talcum or lactose decreased the amount of carriers in the system, therefore the drug release from this system was decreased. This result indicated that the amount of carriers had significant parameter for the drug release behavior. Decreasing the drug release from tablet containing higher amount of indomethacin was also due to a decrease in the amount of drug carrier. Drug release from the large tablet was faster than the smaller tablet because the amount of PEG was increased as the tablet size was increased. In addition, type and amount of excipient had an influence on the indomethacin release. Drug release was increased as the thinner layer of gel forming at surface of the dosage form at higher agitation rate. Therefore, the rate of indomethacin release after using high rotational speed was faster than that using slower rotational speed.

The swelling of tablet containing xanthan gum was measured by their ability to absorb water and their swelling, whereas the erosion property of the tablet was measured from the mass loss. The variation of the amount of polymer led to a quite different swelling and erosion behaviour. The increased tablet radial dimension from polymer swelling was found since the surface wettability and, consequently, the water penetration into the matrix was subsequently promoted. The polymer/water concentration gradients also resulted in textural and physicomechanical changes in the gel layer of matrix tablets which could be accurately detected by textural analysis. Indomethacin was presented as an amorphous state in the solid dispersion at the drug-to-polymer according to the results of DSC. The thermograms of the solid dispersion

showed the characteristic peak of the carrier matrix, without drug peak indicating that the drug was completely dissolved in the carrier.

Since the amount of PEG4000 and PEG400 were decreased as the amount of indomethacin was increased, the release rate of drug from matrices was decreased. In this study, the prepared matrix tablet was coated with Eudragit L 100 to protect indomethacin to irritate the stomach and to deliver this system to the small intestine. Furthermore, the film coat would protect the carrier, PEG 4000 and PEG 400, not to be disturbed with HCl buffer pH 1.2 before the tablet was moved into the intestine. Eudragit L100 could dissolve in phosphate buffer pH 6.2. Therefore, initial drug release from tablet coated with Eudragit L 100 was very low but the drug was gradually released and could be prolonged in phosphate buffer pH 6.2.

In conclusion, successful solubilization of indomethacin was achieved using solid dispersion techniques. System comprising 7:3 PEG4000:PEG400 was chosen as drug carrier for tablet preparation. The tablet was prepared with this system by melting and mold technique. Tablet containing 5% xanthan gum as hydrophilic polymer could prolong the release of indomethacin from tablet. Tablet coated with Eudragit L100 could prolong drug release in pH change system followed Higuchi’s model.

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APPENDIX

APPENDIX I

Preparation of dissolution medium for dissolution

Preparation of phosphate buffer pH 6.2 using as dissolution medium

Phosphate buffer pH 6.2 was prepared by dissolving 6.8045 g of potassium dihydrogen orthophosphate and 0.344 g of sodium hydroxide in distilled water to obtain 1000 mL.

Preparation of HCl buffer pH 1.2 using as dissolution medium

HCl buffer pH 1.2 was prepared by dissolving 2 g of sodium chloride and 7 mL in hydrochloric acid in distilled water to obtain 1000 mL.

Preparation of buffer pH change using as dissolution medium

Buffer of pH change was prepared by dissolving 2 g of sodium chloride and 7 mL of hydrochloric acid in distilled water to obtain 1000 mL. Then 2.5850 g of sodium hydroxide, 3.06 g of potassium dihydrogen orthophosphate and 4.005 g of di-sodium hydrogen orthophosphate were added to 900 mL of HCl buffer pH 1.2 of dissolution time at 90 minutes.

Preparation of phosphate buffer pH 7.5 using as solvent for determination of content uniformity

Phosphate buffer pH 7.5 was prepared by dissolving 6.81 g of potassium dihydrogen orthophosphate and 1.63 g of sodium hydroxide in distilled water to obtain 1000 mL.

APPENDICES II

Calibration curve of indomethacin in different dissolution medium

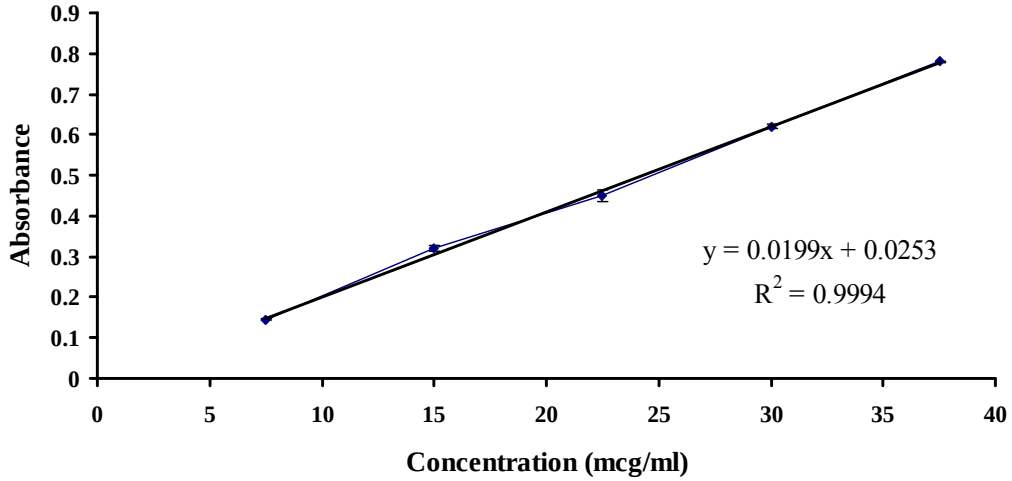

Figure 48 Calibration curve of indomethacin in phosphate buffer pH 6.2

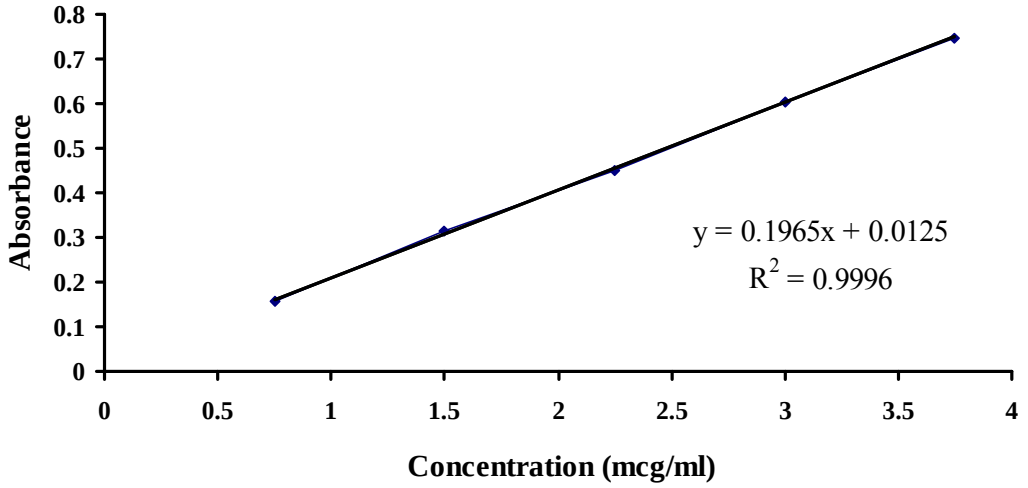

Figure 49 Calibration curve of indomethacin in HCl buffer pH 1.2

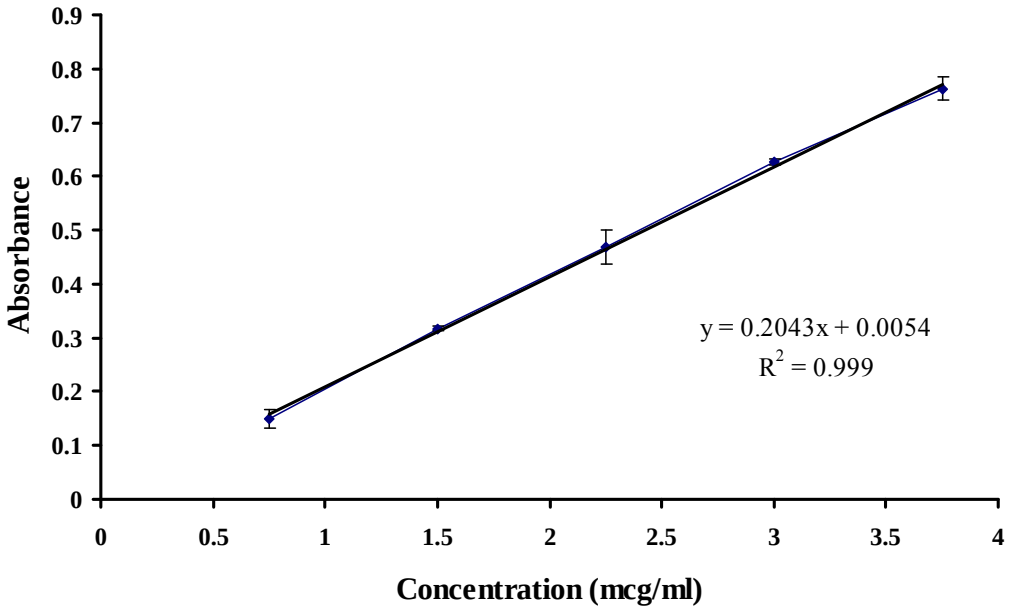

Figure 50 Calibration curve of indomethacin in HCl buffer pH 1.2 after adjustment the pH into pH 6.2

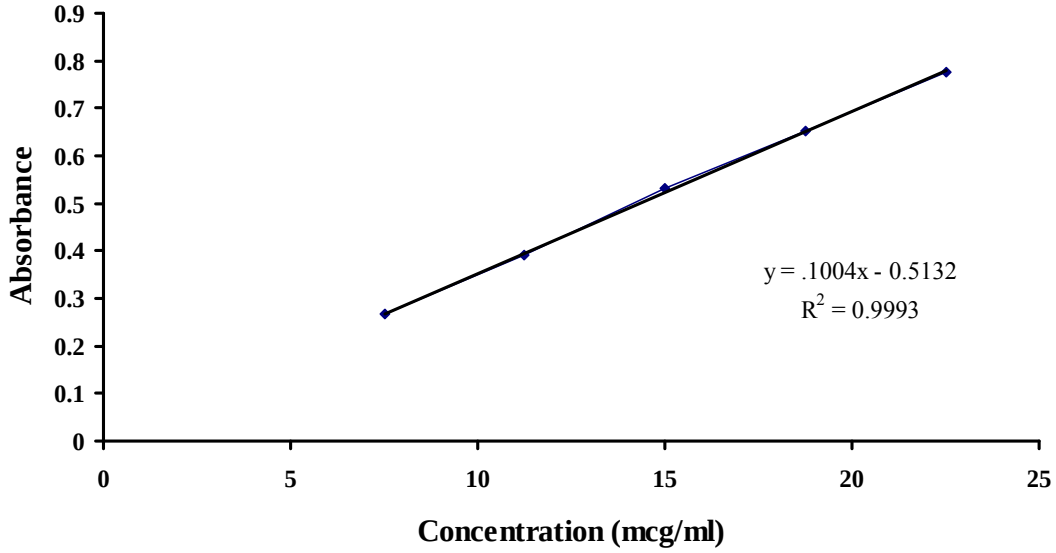

Figure 51 Calibration curve of indomethacin in solvent containing phosphate buffer pH 7.5 combind with methanol

APPENDICES III

The percentage of cumulative release of indomethacin at different condition of dissolution test

Table 31 The percentage of cumulative release of indomethacin from matrix containing different amount of HPMC in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

75-mg indomethacin+0% HPMC						75-mg indomethacin+5% HPMC					
TIME (min)	1	2	3	mean	S.D.	TIME (min)	1	2	3	mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	50.01	51.70	60.50	52.50	4.28	5	24.62	26.99	30.05	27.22	2.22
15	85.50	88.29	86.41	87.47	1.87	15	64.78	60.65	63.92	63.12	1.77
30	97.31	96.01	94.72	94.36	3.02	30	87.60	83.35	84.55	85.17	1.79
45	98.21	100.04	100.07	97.90	1.65	45	91.49	83.40	91.31	88.73	3.77
60	98.99	101.43	100.38	99.12	1.37	60	90.43	89.72	92.34	90.83	1.10
90	101.34	103.91	102.85	101.57	1.43	90	93.45	96.00	96.65	95.37	1.38
120	98.87	98.93	98.95	98.88	0.05	120	98.44	106.11	100.79	101.78	3.20
150	95.04	95.10	95.12	95.05	0.05	150	94.61	93.28	99.92	95.94	2.86
180	97.29	97.34	97.36	97.30	0.05	180	96.86	95.57	100.94	97.79	2.28
210	99.39	99.44	99.46	99.39	0.05	210	98.96	97.29	99.192	98.48	0.84
240	98.26	98.32	98.33	98.27	0.05	240	97.83	97.78	102.28	99.30	2.11
300	98.42	98.47	98.49	98.43	0.05	300	97.99	97.16	101.37	98.84	1.82
360	100.80	100.86	100.88	100.81	0.05	360	100.37	99.13	99.32	99.61	0.54
420	100.26	100.31	100.33	100.26	0.05	420	99.83	99.77	101.25	100.28	0.68
480	100.72	100.77	100.79	100.72	0.05	480	100.29	99.88	103.30	101.15	1.52

(continued)

(B)

75-mg indomethacin + 10% HPMC						75-mg indomethacin + 15% HPMC					
TIME (min)	1	2	3	mean	S.D.	TIME (min)	1	2	3	mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	21.21	16.82	16.22	18.08	2.22	5	12.77	14.78	14.58	14.04	0.90
15	50.14	40.73	34.74	41.87	6.33	15	28.03	35.00	31.66	31.56	2.84
30	78.77	72.57	64.58	71.97	5.80	30	46.28	56.66	53.21	52.05	4.31
45	87.13	89.03	80.48	85.55	3.66	45	61.07	71.09	67.61	66.59	4.15
60	89.36	100.74	85.48	91.85	6.47	60	69.14	80.13	77.98	75.75	4.75
90	87.19	96.63	92.69	92.17	3.86	90	74.74	88.03	84.56	82.44	5.62
120	92.09	97.43	97.05	95.52	2.43	120	78.03	91.58	86.83	85.48	5.61
150	94.86	100.66	92.43	95.98	3.45	150	80.90	92.52	89.36	87.59	4.90
180	96.84	99.60	94.06	96.83	2.26	180	82.80	93.00	89.48	88.43	4.22
210	98.72	101.86	94.72	98.43	2.92	210	84.01	92.61	91.20	89.27	3.76
240	97.59	99.40	94.84	97.28	1.87	240	84.36	92.51	92.63	89.83	3.86
300	99.48	102.89	96.90	99.76	2.45	300	84.12	90.32	91.15	88.53	3.13
360	99.74	99.08	98.66	99.16	0.44	360	87.85	90.27	91.65	89.92	1.57
420	99.59	99.73	99.12	99.48	0.26	420	87.45	89.44	91.77	89.56	1.76
480	99.70	102.62	101.01	101.11	1.19	480	89.82	89.43	91.88	90.38	1.07

(C)

75-mg indomethacin +20% HPMC						75-mg indomethacin +25% HPMC					
TIME (min)	1	2	3	Mean	S.D	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	11.00	10.34	11.75	11.03	0.57	5	4.69	4.79	4.40	4.63	0.16
15	20.52	18.60	14.10	17.74	2.69	15	9.69	12.38	8.76	10.28	1.53
30	37.57	37.23	25.14	33.31	5.78	30	12.97	20.28	11.74	15.00	3.77
45	54.38	53.26	35.28	47.64	8.75	45	15.09	22.60	14.57	17.42	3.67
60	61.51	62.55	44.06	56.04	8.48	60	17.19	25.07	16.07	19.44	4.00
90	65.24	66.80	50.61	60.88	7.29	90	19.08	26.73	17.64	21.15	3.98
120	68.41	69.96	54.98	64.45	6.72	120	21.02	28.56	20.39	23.32	3.71
150	70.73	72.38	59.75	67.62	5.60	150	24.47	31.69	23.31	26.49	3.70
180	70.50	74.08	62.62	69.06	4.78	180	27.31	32.96	20.67	26.98	5.02
210	73.53	75.19	63.97	70.90	4.94	210	29.21	34.63	26.29	30.04	3.45
240	75.20	76.18	65.58	72.32	4.78	240	31.32	36.80	28.67	32.27	3.38
300	76.30	78.25	69.42	74.66	3.79	300	31.81	37.49	30.55	33.28	3.01
360	75.04	80.67	72.90	76.20	3.27	360	36.09	41.30	35.88	37.76	2.50
420	78.47	83.39	77.22	79.70	2.66	420	39.70	44.86	38.44	41.00	2.78
480	83.16	85.78	80.26	83.06	2.25	480	44.54	49.10	42.96	45.53	2.60

Table 32 The percentage of cumulative release of indomethacin from matrix containing different amount of xanthan gum in tablet into phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

75-mg indomethacin +0% xanthan gum						75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	50.01	51.70	60.50	52.50	4.28	5	12.77	15.35	21.84	16.65	3.81
15	85.50	88.29	86.41	87.47	1.87	15	28.03	29.45	34.78	30.75	2.90
30	97.31	96.01	94.72	94.36	3.02	30	46.28	50.38	54.29	50.32	3.27
45	98.21	100.04	100.07	97.90	1.65	45	51.29	57.90	56.96	55.39	2.91
60	98.99	101.43	100.38	99.12	1.37	60	59.40	65.66	58.58	61.21	3.16
90	101.34	103.91	102.85	101.57	1.43	90	62.57	72.64	77.46	70.89	6.20
120	98.87	98.93	98.95	98.88	0.05	120	65.79	74.58	79.53	73.30	5.67
150	95.04	95.10	95.12	95.05	0.05	150	67.99	78.07	81.98	76.01	5.89
180	97.29	97.34	97.36	97.30	0.05	180	70.43	80.17	84.13	78.24	5.75
210	99.39	99.44	99.46	99.39	0.05	210	71.57	82.93	85.88	80.13	6.16
240	98.26	98.32	98.33	98.27	0.05	240	71.86	84.86	87.75	81.49	6.91
300	98.42	98.47	98.49	98.43	0.05	300	75.87	86.52	90.33	84.24	6.11
360	100.80	100.86	100.88	100.81	0.05	360	81.21	88.35	91.80	87.12	4.41
420	100.26	100.31	100.33	100.26	0.05	420	84.53	91.42	93.04	89.66	3.69
480	100.72	100.77	100.79	100.72	0.05	480	88.66	94.47	95.23	92.79	2.93

(continued)

(B)

75-mg indomethacin +10% xanthan gum						75-mg indomethacin +15% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	0	0	0	0	0	5	0	0	0	0	0
15	4.07	4.02	4.61	4.23	0.26	15	1.22	0.52	1.08	0.94	0.30
30	4.39	4.58	5.94	4.97	0.68	30	1.63	1.78	1.98	1.80	0.14
45	4.57	5.17	7.93	5.89	1.46	45	3.11	2.98	3.57	3.22	0.25
60	6.84	7.00	10.01	7.95	1.45	60	3.94	4.12	4.61	4.22	0.28
90	8.26	8.73	11.86	9.61	1.59	90	5.37	5.38	5.62	5.46	0.11
120	9.57	10.06	13.70	11.11	1.84	120	6.67	6.76	7.15	6.86	0.21
150	10.84	11.45	16.00	12.76	2.30	150	7.95	8.27	8.52	8.25	0.23
180	12.56	12.93	17.35	14.28	2.17	180	9.60	9.96	10.12	9.89	0.21
210	14.51	14.88	18.82	16.07	1.95	210	10.62	11.22	11.03	10.96	0.24
240	16.33	16.05	20.41	17.60	1.99	240	11.21	12.15	12.00	11.79	0.41
300	17.87	17.77	21.92	19.19	1.93	300	12.03	12.82	12.74	12.53	0.35
360	19.40	19.29	23.33	20.67	1.87	360	13.20	14.17	13.65	13.67	0.39
420	19.98	20.15	24.10	21.41	1.90	420	13.42	14.66	14.39	14.16	0.53
480	21.31	22.15	25.32	22.93	1.72	480	13.82	15.24	14.80	14.62	0.59

(C)

75-mg indomethacin +20% xanthan gum						75-mg indomethacin +25% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	2.26	4.91	4.81	3.99	1.22	5	0.13	0.18	-0.28	0.01	0.20
15	1.57	2.37	1.87	1.94	0.32	15	1.08	0.35	0.44	0.63	0.32
30	2.58	2.23	2.44	2.41	0.14	30	2.20	1.24	1.45	1.63	0.40
45	3.75	3.40	3.20	3.45	0.22	45	3.05	2.71	2.87	2.88	0.13
60	5.19	4.64	4.60	4.81	0.26	60	4.28	3.69	3.81	3.93	0.25
90	6.98	6.24	6.10	6.44	0.38	90	5.13	4.56	4.79	4.83	0.23
120	8.22	7.31	7.39	7.64	0.41	120	6.32	5.69	5.86	5.96	0.26
150	9.12	8.56	8.65	8.78	0.24	150	7.33	6.89	6.90	7.04	0.20
180	9.81	9.36	9.70	9.62	0.19	180	8.33	8.28	8.33	8.31	0.02
210	10.93	11.38	11.00	11.10	0.19	210	8.88	9.07	9.17	9.04	0.11
240	11.11	10.22	10.49	10.61	0.37	240	9.55	9.50	9.62	9.56	0.04
300	11.81	11.18	11.53	11.51	0.25	300	10.58	10.10	10.31	10.33	0.19
360	16.49	13.24	12.20	13.98	1.82	360	11.33	10.83	11.25	11.14	0.21
420	14.00	13.73	13.93	13.89	0.11	420	11.58	11.50	11.98	11.69	0.20
480	15.05	14.22	13.99	14.42	0.45	480	12.10	11.95	12.22	12.09	0.11

Table 33 The percentage of cumulative release of indomethacin from matrix containing 5% xanthan gum and different amount of talcum in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

75-mg indomethacin +5% xanthan gum+0%talcum						75-mg indomethacin +5% xanthan gum+15%talcum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	12.77	15.35	21.84	16.65	3.81	5	0.38	0.34	0.68	0.47	0.18
15	28.03	29.45	34.78	30.75	2.90	15	2.76	2.05	3.44	2.75	0.69
30	46.28	50.38	54.29	50.32	3.27	30	8.61	8.91	9.39	8.97	0.39
45	51.29	57.90	56.96	55.39	2.91	45	13.81	16.35	16.78	15.65	1.60
60	59.40	65.66	58.58	61.21	3.16	60	17.04	20.79	20.09	19.31	1.99
90	62.57	72.64	77.46	70.89	6.20	90	20.37	22.38	22.46	21.74	1.18
120	65.79	74.58	79.53	73.30	5.67	120	22.73	24.31	23.02	23.36	0.84
150	67.99	78.07	81.98	76.01	5.89	150	24.59	25.53	25.13	25.08	0.46
180	70.43	80.17	84.13	78.24	5.75	180	26.84	27.81	28.01	27.55	0.62
210	71.57	82.93	85.88	80.13	6.16	210	28.62	29.30	28.91	28.94	0.34
240	71.86	84.86	87.75	81.49	6.91	240	30.68	31.00	30.85	30.84	0.15
300	75.87	86.52	90.33	84.24	6.11	300	32.51	33.18	33.11	32.93	0.36
360	81.21	88.35	91.80	87.12	4.41	360	35.76	35.99	36.60	36.12	0.43
420	84.53	91.42	93.04	89.66	3.69	420	38.24	38.90	39.04	38.73	0.42
480	88.66	94.47	95.23	92.79	2.93	480	40.66	41.78	41.85	41.43	0.66

(continued)

(B)

75-mg indomethacin +5% xanthan gum+25%talcum						75-mg indomethacin +5% xanthan gum+35%talcum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	0.14	0.04	0.10	0.99	0.27	5	-0.01	0.01	-0.43	-0.14	0.25
15	1.44	1.15	1.75	1.44	0.30	15	0.04	0.27	0.16	0.16	0.11
30	3.50	3.93	4.23	3.89	0.36	30	1.52	1.31	1.28	1.37	0.13
45	5.70	7.01	6.26	6.33	0.65	45	3.17	2.69	2.88	2.91	0.24
60	7.55	8.03	7.99	7.86	0.26	60	4.83	3.97	4.59	4.46	0.43
90	10.49	10.32	10.07	10.29	0.21	90	7.71	6.20	8.10	7.33	1.00
120	12.56	12.56	11.57	12.23	0.57	120	10.30	9.96	10.74	10.34	0.39
150	14.10	14.49	13.03	13.87	0.75	150	12.20	10.13	13.02	11.78	1.48
180	15.49	15.72	14.36	15.19	0.72	180	13.99	11.60	14.84	13.48	1.68
210	16.70	17.03	16.43	16.72	0.30	210	15.76	13.29	16.60	15.22	1.72
240	19.41	19.54	18.32	19.09	0.67	240	17.13	16.42	17.93	17.16	0.75
300	19.77	20.45	19.15	19.79	0.64	300	21.87	18.40	20.28	20.19	1.73
360	22.48	22.84	21.61	22.31	0.62	360	25.76	23.06	23.71	24.18	1.41
420	26.47	26.93	24.44	25.95	1.32	420	29.05	24.35	25.44	26.28	2.45
480	30.67	31.87	31.20	31.25	0.59	480	29.95	25.97	26.87	27.60	2.08

(C)

75-mg indomethacin +5% xanthan gum+45%talcum						75-mg indomethacin +5% xanthan gum+55%talcum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	-0.12	-0.07	-0.22	-0.14	0.07	5	-0.41	-0.45	-0.63	-0.50	0.11
15	0.023	-0.03	-0.18	-0.06	0.10	15	0.08	-0.25	0.29	0.04	0.27
30	0.81	0.66	0.56	0.68	0.12	30	0.92	1.16	1.52	1.20	0.30
45	1.89	1.81	1.74	1.81	0.07	45	2.42	2.85	2.56	2.61	0.22
60	3.02	2.91	2.88	2.93	0.07	60	3.19	3.90	3.05	3.38	0.45
90	5.13	5.10	5.23	5.15	0.06	90	4.82	4.80	5.05	4.89	0.13
120	7.08	7.83	7.91	7.61	0.45	120	6.46	6.87	6.78	6.70	0.21
150	9.59	9.29	9.10	9.32	0.24	150	7.83	8.24	8.02	8.03	0.20
180	10.65	11.42	10.85	10.97	0.39	180	8.77	9.08	9.21	9.02	0.22
210	12.11	12.96	12.16	12.41	0.47	210	9.90	10.02	10.10	10.01	0.10
240	13.26	14.36	13.37	13.66	0.60	240	12.02	11.59	11.04	11.55	0.49
300	15.29	16.68	15.44	15.80	0.76	300	14.18	13.90	13.28	13.79	0.46
360	17.49	18.80	17.80	18.03	0.68	360	14.63	14.64	13.71	14.33	0.53
420	19.47	20.67	19.68	19.94	0.63	420	15.80	15.55	15.26	15.53	0.27
480	20.61	20.95	20.87	20.81	0.17	480	17.10	16.39	16.24	16.58	0.45

Table 34 The percentage of cumulative release of indomethacin from matrix containing 5% xanthan gum and different amount of lactose in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

75-mg indomethacin +5% xanthan gum+0%lactose						75-mg indomethacin +5% xanthan gum+15%lactose					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	12.77	15.35	21.84	16.65	3.81	5	3.16	2.24	2.77	2.72	0.45
15	28.03	29.45	34.78	30.75	2.90	15	3.40	3.03	3.64	3.36	0.30
30	46.28	50.38	54.29	50.32	3.27	30	6.98	6.54	6.87	6.80	0.23
45	51.29	57.90	56.96	55.39	2.91	45	11.54	10.58	11.72	11.28	0.61
60	59.40	65.66	58.58	61.21	3.16	60	14.53	11.09	14.68	13.43	2.03
90	62.57	72.64	77.46	70.89	6.20	90	18.03	16.79	17.95	17.59	0.69
120	65.79	74.58	79.53	73.30	5.67	120	20.14	19.32	20.22	19.90	0.49
150	67.99	78.07	81.98	76.01	5.89	150	22.63	22.35	22.28	22.42	0.18
180	70.43	80.17	84.13	78.24	5.75	180	24.20	23.43	23.28	23.64	0.49
210	71.57	82.93	85.88	80.13	6.16	210	25.21	24.02	25.65	24.96	0.84
240	71.86	84.86	87.75	81.49	6.91	240	26.59	26.17	27.79	26.85	0.84
300	75.87	86.52	90.33	84.24	6.11	300	29.76	28.95	31.41	30.04	1.25
360	81.21	88.35	91.80	87.12	4.41	360	33.87	32.56	36.28	34.24	1.88
420	84.53	91.42	93.04	89.66	3.69	420	38.66	37.79	40.62	39.02	1.44
480	88.66	94.47	95.23	92.79	2.93	480	41.96	39.52	43.45	41.64	1.98

(continued)

(B)

75-mg indomethacin +5% xanthan gum+25%lactose						75-mg indomethacin +5% xanthan gum+35%lactose					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	1.86	1.58	2.05	1.83	0.23	5	0.12	-0.02	-0.24	-0.04	0.18
15	3.67	3.07	3.69	3.48	0.35	15	0.49	0.31	0.26	0.35	0.12
30	4.23	4.84	4.37	4.48	0.31	30	1.45	1.89	1.78	1.71	0.23
45	5.74	5.33	5.80	5.62	0.25	45	3.04	3.27	3.17	3.16	0.11
60	7.80	7.74	8.01	7.85	0.14	60	4.24	5.31	5.60	5.05	0.71
90	9.17	9.54	9.84	9.52	0.33	90	5.43	6.83	7.04	6.43	0.87
120	11.44	12.65	11.65	11.92	0.64	120	7.33	8.62	8.66	8.20	0.75
150	14.53	13.24	14.04	13.94	0.65	150	10.16	10.70	10.91	10.59	0.38
180	15.85	15.56	15.87	15.76	0.17	180	11.77	12.64	13.16	12.53	0.70
210	17.43	16.82	16.82	17.02	0.35	210	12.53	14.34	15.26	14.04	1.38
240	18.65	17.19	19.33	18.39	1.09	240	16.15	16.66	17.99	16.93	0.94
300	23.19	23.51	23.28	23.33	0.16	300	18.81	20.25	21.72	20.26	1.45
360	26.92	26.66	27.37	26.98	0.36	360	22.92	24.54	25.08	24.18	1.12
420	31.46	31.40	31.47	31.44	0.04	420	25.84	28.36	28.91	27.70	1.63
480	34.24	33.08	35.06	34.13	0.99	480	29.54	33.38	31.68	31.52	1.92

(C)

75-mg indomethacin +5% xanthan gum+45%lactose						75-mg indomethacin +5% xanthan gum+55%lactose					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	-0.47	-0.36	-0.54	-0.46	0.09	5	-0.13	-0.24	-0.22	-0.19	0.05
15	-0.23	-0.21	-0.29	-0.24	0.03	15	-0.03	-0.02	-0.08	-0.04	0.03
30	0.74	1.00	0.70	0.81	0.16	30	0.69	0.42	1.69	0.93	0.66
45	2.15	2.19	1.81	2.05	0.20	45	1.45	1.17	2.70	1.77	0.81
60	4.89	4.47	4.62	4.66	0.20	60	2.44	2.09	3.79	2.77	0.89
90	5.97	5.40	5.87	5.75	0.30	90	3.26	2.87	5.80	3.98	1.59
120	7.43	6.84	7.50	7.26	0.36	120	-0.87	4.69	6.96	3.59	4.03
150	8.92	8.69	8.86	8.82	0.11	150	5.55	5.09	7.65	6.10	1.36
180	10.13	9.60	10.00	9.91	0.27	180	6.62	8.06	8.67	7.78	1.05
210	11.34	10.72	10.96	11.01	0.30	210	8.40	8.81	9.18	8.80	0.38
240	12.71	12.00	12.53	12.41	0.36	240	8.82	9.34	10.67	9.61	0.95
300	14.98	14.12	15.14	14.75	0.54	300	11.05	9.83	12.03	10.97	1.09
360	17.68	16.48	18.38	17.51	0.96	360	13.56	11.89	14.51	13.32	1.32
420	20.30	19.61	21.27	20.39	0.83	420	15.56	14.16	16.13	15.28	1.01
480	23.18	22.17	23.11	22.82	0.56	480	15.78	14.59	16.97	15.78	1.19

Table 35 The percentage of cumulative release of indomethacin from matrix containing 5% xanthan gum and different amount of drug in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

25-mg indomethacin+5% xanthan gum						50-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	21.81	22.73	21.16	21.90	0.64	5	26.54	22.46	17.38	22.13	3.74
15	48.91	51.39	48.78	49.69	1.20	15	54.00	54.13	49.71	52.61	2.05
30	62.93	66.76	65.67	65.12	1.61	30	67.96	69.99	65.86	67.94	1.68
45	68.56	72.92	77.38	72.95	3.60	45	73.12	78.13	72.65	74.63	2.48
60	72.89	78.37	84.04	78.44	4.55	60	78.25	81.44	79.37	79.69	1.32
90	80.40	83.50	91.13	85.01	4.50	90	83.45	88.65	86.23	86.11	2.12
120	87.23	90.49	94.16	90.62	2.83	120	88.31	93.21	90.43	90.65	2.00
150	91.52	93.06	96.84	93.80	2.23	150	89.10	95.24	93.80	92.71	2.62
180	95.69	100.63	100.74	99.02	2.35	180	90.37	96.05	95.45	93.96	2.54
210	99.75	102.35	101.92	101.34	1.13	210	90.95	97.26	97.33	95.18	2.99
240	102.47	104.11	102.92	103.17	0.69	240	93.60	98.35	97.86	96.60	2.13
300	103.27	105.66	104.88	104.60	0.99	300	94.66	98.83	98.67	97.39	1.92
360	104.02	106.62	106.50	105.71	1.19	360	96.58	99.55	99.40	98.51	1.36
420	105.98	108.00	107.55	107.18	0.86	420	98.00	100.12	99.96	99.36	0.96
480	107.53	108.84	108.91	108.43	0.63	480	99.40	100.75	100.56	100.24	0.59

(continued)

(B)

75-mg indomethacin +5% xanthan gum						100-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	12.77	15.35	21.84	16.65	3.81	5	1.55	1.64	2.59	1.93	0.47
15	28.03	29.45	34.78	30.75	2.90	15	8.90	7.74	7.86	8.16	0.51
30	46.28	50.38	54.29	50.32	3.27	30	21.53	20.65	19.92	20.70	0.65
45	51.29	57.90	56.96	55.39	2.91	45	30.90	30.35	29.07	30.11	0.76
60	59.40	65.66	58.58	61.21	3.16	60	35.53	36.06	36.71	36.10	0.48
90	62.57	72.64	77.46	70.89	6.20	90	46.38	44.74	44.40	45.18	0.86
120	65.79	74.58	79.53	73.30	5.67	120	53.69	54.88	51.26	53.28	1.50
150	67.99	78.07	81.98	76.01	5.89	150	58.98	57.19	54.41	56.86	1.87
180	70.43	80.17	84.13	78.24	5.75	180	65.85	62.51	58.53	62.30	2.99
210	71.57	82.93	85.88	80.13	6.16	210	70.27	68.24	64.89	67.80	2.21
240	71.86	84.86	87.75	81.49	6.91	240	72.24	71.30	66.83	70.12	2.35
300	75.87	86.52	90.33	84.24	6.11	300	80.33	81.30	73.90	78.51	3.28
360	81.21	88.35	91.80	87.12	4.41	360	84.81	84.03	82.71	83.85	0.86
420	84.53	91.42	93.04	89.66	3.69	420	89.00	88.61	90.34	89.32	0.74
480	88.66	94.47	95.23	92.79	2.93	480	91.26	91.12	90.88	91.09	0.15

(C)

150-mg indomethacin+5% xanthan gum						300-mg indomethacin+5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	-0.17	-0.15	-0.71	-0.34	0.26	5	-0.80	-0.94	-0.78	-0.84	0.07
15	0.38	0.84	-0.07	0.38	0.37	15	-0.74	-0.78	-0.74	-0.75	0.01
30	1.62	1.97	1.26	1.62	0.28	30	-0.35	-0.49	-0.45	-0.43	0.06
45	2.70	3.08	2.52	2.77	0.23	45	0.06	-0.11	-0.14	-0.06	0.09
60	3.76	4.49	4.19	4.15	0.29	60	0.39	0.11	0.74	0.41	0.25
90	7.61	8.20	8.69	8.17	0.43	90	2.30	1.86	1.94	2.03	0.19
120	10.29	10.01	11.00	10.43	0.41	120	2.55	2.45	2.46	2.49	0.04
150	11.33	10.29	11.53	11.06	0.55	150	3.87	3.73	3.70	3.77	0.07
180	13.63	9.87	13.69	12.40	1.78	180	6.09	5.02	5.22	5.44	0.46
210	16.82	14.11	15.91	15.61	1.12	210	6.13	6.08	6.27	6.16	0.08
240	18.89	15.57	17.74	17.40	1.37	240	7.03	7.19	7.50	7.24	0.19
300	23.73	18.55	22.94	21.74	2.27	300	9.21	9.43	9.95	9.53	0.30
360	28.05	21.30	27.26	25.54	3.01	360	10.96	11.70	12.56	11.74	0.65
420	32.15	24.29	31.81	29.42	3.62	420	12.74	14.21	14.48	13.81	0.76
480	36.46	29.60	34.17	33.41	2.84	480	14.41	16.51	16.07	15.66	0.90

Table 36 The percentage of cumulative release of indomethacin from xanthan gum matrix tablet containing 75-mg indomethacin and different amount of xanthan gum in HCl buffer pH 1.2 using basket method at 100 rpm

75-mg indomethacin +0% xanthan gum						75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	3.99	3.09	3.70	3.35	0.47	5	4.69	3.69	4.17	3.93	0.68
15	6.53	6.79	6.16	6.28	0.71	15	6.69	4.80	6.14	6.06	0.69
30	2.92	4.83	4.13	3.38	1.01	30	2.98	2.47	2.79	2.95	0.67
45	1.79	1.81	1.92	1.69	0.20	45	1.90	1.98	1.98	1.95	0.10
60	1.49	1.46	1.44	1.39	0.10	60	1.91	1.93	1.92	1.91	0.04
90	1.28	1.39	1.37	1.29	0.07	90	1.85	1.92	1.88	1.90	0.03
120	1.21	1.32	1.26	1.24	0.08	120	1.85	2.14	2.19	1.99	0.15
150	1.16	1.28	1.19	1.21	0.07	150	2.39	2.04	1.92	2.16	0.22
180	1.16	1.41	1.15	1.20	0.12	180	2.01	2.13	2.02	2.02	0.06
210	1.14	1.30	1.15	1.17	0.07	210	1.96	2.00	1.95	1.96	0.02
240	1.11	1.29	1.15	1.16	0.07	240	1.95	1.94	1.94	1.93	0.02
300	1.11	1.25	1.14	1.15	0.06	300	1.94	1.93	1.92	1.92	0.03
360	1.10	1.20	1.14	1.13	0.05	360	1.91	1.93	1.91	1.90	0.03
420	1.09	1.20	1.12	1.12	0.05	420	1.87	1.91	1.88	1.87	0.02
480	1.08	1.17	1.10	1.11	0.04	480	1.85	1.88	1.87	1.86	0.01

Table 37 The percentage of cumulative release of indomethacin from tablet with different size in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

Small tablet of 75-mg indomethacin +0% xanthan gum						Small tablet of 75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	0.80	0.71	0.47	0.66	0.13	5	0.61	0.82	0.62	0.68	0.09
15	0.31	0.52	0.31	0.38	0.10	15	1.37	1.41	1.48	1.42	0.04
30	1.52	1.71	1.63	1.62	0.07	30	3.53	3.91	3.61	3.69	0.16
45	2.24	2.27	2.22	2.24	0.02	45	5.66	5.81	6.05	5.84	0.16
60	2.61	2.56	2.65	2.61	0.03	60	7.76	8.20	8.50	8.15	0.30
90	4.28	3.96	3.97	4.07	0.14	90	11.76	11.24	13.45	12.15	0.94
120	5.60	5.44	5.29	5.44	0.12	120	18.25	17.85	17.42	17.84	0.34
150	6.74	6.75	6.78	6.76	0.01	150	25.04	25.02	24.96	25.01	0.03
180	7.91	7.94	7.50	7.78	0.20	180	28.18	27.74	27.41	27.77	0.31
210	9.09	9.34	9.43	9.29	0.14	210	31.78	31.65	31.34	31.59	0.18
240	10.38	10.26	10.65	10.43	0.16	240	34.75	33.85	33.57	34.06	0.50
300	12.73	13.05	13.18	12.99	0.19	300	39.37	39.57	39.11	39.35	0.18
360	14.61	14.92	14.85	14.79	0.13	360	43.54	43.65	42.77	43.32	0.39
420	17.36	17.43	17.53	17.44	0.06	420	47.63	48.07	47.88	47.86	0.18
480	19.01	18.91	19.00	18.97	0.04	480	50.11	50.20	49.51	49.94	0.30

(continued)

(B)

Medium tablet of 75-mg indomethacin +0% xanthan gum						Medium tablet of 75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	50.01	51.70	60.50	52.50	4.28	5	12.77	15.35	21.84	16.65	3.81
15	85.50	88.29	86.41	87.47	1.87	15	28.03	29.45	34.78	30.75	2.90
30	97.31	96.01	94.72	94.36	3.02	30	46.28	50.38	54.29	50.32	3.27
45	98.21	100.04	100.07	97.90	1.65	45	51.29	57.90	56.96	55.39	2.91
60	98.99	101.43	100.38	99.12	1.37	60	59.40	65.66	58.58	61.21	3.16
90	101.34	103.91	102.85	101.57	1.43	90	62.57	72.64	77.46	70.89	6.20
120	98.87	98.93	98.95	98.88	0.05	120	65.79	74.58	79.53	73.30	5.67
150	95.04	95.10	95.12	95.05	0.05	150	67.99	78.07	81.98	76.01	5.89
180	97.29	97.34	97.36	97.30	0.05	180	70.43	80.17	84.13	78.24	5.75
210	99.39	99.44	99.46	99.39	0.05	210	71.57	82.93	85.88	80.13	6.16
240	98.26	98.32	98.33	98.27	0.05	240	71.86	84.86	87.75	81.49	6.91
300	98.42	98.47	98.49	98.43	0.05	300	75.87	86.52	90.33	84.24	6.11
360	100.80	100.86	100.88	100.81	0.05	360	81.21	88.35	91.80	87.12	4.41
420	100.26	100.31	100.33	100.26	0.05	420	84.53	91.42	93.04	89.66	3.69
480	100.72	100.77	100.79	100.72	0.05	480	88.66	94.47	95.23	92.79	2.93

(C)

Large tablet of 75-mg indomethacin +0% xanthan gum						Large tablet of 75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	28.99	29.01	30.54	29.51	0.72	5	24.69	23.69	24.17	24.75	0.52
15	81.99	84.07	82.36	82.80	0.90	15	76.69	74.80	76.14	75.31	2.20
30	95.05	95.73	96.14	95.64	0.44	30	88.98	88.47	87.79	88.34	0.15
45	100.92	100.83	100.78	100.84	0.05	45	89.90	90.58	89.98	90.27	0.73
60	102.21	101.76	102.37	102.11	0.26	60	92.91	91.93	91.92	93.04	0.58
90	102.95	103.06	103.14	103.05	0.07	90	92.85	93.92	94.08	94.54	0.28
120	103.61	103.78	103.77	103.72	0.08	120	93.85	94.01	93.69	94.86	2.37
150	104.42	104.56	104.60	104.52	0.07	150	96.39	96.04	94.92	96.45	1.66
180	104.85	105.25	105.47	105.19	0.25	180	97.01	98.13	97.02	97.35	1.72
210	105.69	105.98	106.23	105.97	0.22	210	97.11	98.11	97.02	98.34	1.11
240	106.45	106.75	106.83	106.68	0.16	240	97.89	98.01	97.32	98.51	1.33
300	107.16	107.69	107.65	107.50	0.23	300	98.99	99.93	99.59	99.03	0.93
360	108.11	108.33	108.36	108.27	0.10	360	101.34	101.95	101.67	101.23	0.61
420	108.80	108.85	108.98	108.87	0.07	420	102.44	103.01	102.67	102.19	0.15
480	109.43	109.61	109.68	109.57	0.10	480	103.98	103.21	104.05	103.75	0.68

Table 38 The percentage of cumulative release of indomethacin from matrix tablet in phosphate buffer pH 6.2 using basket method at different rotational speed

(A)

75-mg indomethacin +5% xanthan gum using rotational speed at 25 rpm						75-mg indomethacin +5% xanthan gum using rotational speed at 50 rpm					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	2.83	3.13	3.10	3.02	2.13	5	9.65	10.34	9.77	9.92	0.29
15	4.75	5.17	5.22	5.04	3.21	15	14.92	20.22	22.35	19.16	3.12
30	6.98	6.87	7.32	7.72	3.28	30	18.23	24.45	25.16	22.61	3.11
45	10.85	11.08	11.28	11.06	4.17	45	20.20	26.35	26.77	24.44	3.00
60	12.26	13.21	13.80	13.09	2.63	60	22.36	27.71	27.98	26.02	2.58
90	15.82	16.83	16.80	16.48	2.46	90	23.14	31.28	30.47	28.30	3.66
120	18.19	18.99	18.47	18.54	3.33	120	24.92	34.21	33.12	30.75	4.14
150	20.83	21.32	21.90	21.34	2.43	150	26.96	36.86	35.13	32.98	4.31
180	23.88	25.07	24.44	24.46	3.48	180	28.46	39.31	37.21	34.99	4.70
210	26.69	27.62	27.51	27.27	3.41	210	30.10	41.30	39.05	36.82	4.83
240	29.52	30.68	30.35	30.18	2.48	240	31.50	42.31	41.42	38.41	4.89
300	35.57	36.33	35.58	36.49	2.82	300	33.51	45.47	43.95	40.98	5.31
360	37.98	37.70	38.17	38.61	3.48	360	35.57	48.09	46.32	43.33	5.53
420	40.19	40.09	41.33	40.86	4.48	420	36.91	50.22	48.44	45.19	5.89
480	41.78	41.67	43.53	42.46	3.48	480	50.05	52.90	51.51	51.48	1.16

(continued)

(B)

75-mg indomethacin +5% xanthan gum using rotational speed at 100 rpm						75-mg indomethacin +5% xanthan gum using rotational speed at 150 rpm					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
5	12.77	15.35	21.84	16.65	3.81	5	52.12	60.70	59.60	57.48	3.80
15	28.03	29.45	34.78	30.75	2.90	15	87.71	62.98	89.53	80.07	12.11
30	46.28	50.38	54.29	50.32	3.27	30	89.94	64.62	93.33	82.63	12.81
45	51.29	57.90	56.96	55.39	2.91	45	91.48	67.72	94.33	84.51	11.92
60	59.40	65.66	58.58	61.21	3.16	60	92.63	71.45	95.17	86.42	10.63
90	62.57	72.64	77.46	70.89	6.20	90	93.32	75.20	95.83	88.12	9.19
120	65.79	74.58	79.53	73.30	5.67	120	94.33	77.60	97.28	89.74	8.66
150	67.99	78.07	81.98	76.01	5.89	150	94.97	81.13	98.59	91.56	7.52
180	70.43	80.17	84.13	78.24	5.75	180	95.98	83.88	99.21	93.02	6.59
210	71.57	82.93	85.88	80.13	6.16	210	96.61	85.51	100.39	94.17	6.31
240	71.86	84.86	87.75	81.49	6.91	240	97.57	89.05	101.85	96.16	5.32
300	75.87	86.52	90.33	84.24	6.11	300	98.20	91.88	102.83	97.64	4.48
360	81.21	88.35	91.80	87.12	4.41	360	99.19	98.24	103.81	100.41	2.43
420	84.53	91.42	93.04	89.66	3.69	420	99.85	99.50	105.68	101.68	2.83
480	88.66	94.47	95.23	92.79	2.93	480	103.74	102.16	106.69	104.20	1.87

Table 39 The percentage of cumulative release of indomethacin from matrix tablet containing 75-mg indomethacin and 5% xanthan gum in pH change using basket method at 100 rpm

75-mg indomethacin +5% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00
5	1.30	0.96	0.82	1.02	0.20
15	1.75	1.26	1.19	1.40	0.24
30	1.37	1.16	1.20	1.24	0.08
45	1.27	1.22	1.32	1.27	0.04
60	1.56	1.98	1.67	1.74	0.17
90	1.86	1.95	1.59	1.80	0.15
120	13.17	15.71	14.29	14.39	1.04
150	14.86	14.03	14.96	14.62	0.41
180	24.95	37.33	62.70	41.66	15.71
210	87.16	84.89	80.68	84.24	2.68
240	81.73	70.69	78.56	76.99	4.63
300	73.24	90.10	75.32	79.56	7.50
360	74.44	82.17	76.59	77.73	3.25
420	75.61	79.60	75.18	76.80	1.99
480	76.87	77.53	73.51	75.98	1.76

Table 40 The percentage of cumulative release of indomethacin from matrix tablet containing 75-mg indomethacin and 5% xanthan gum coated with Eudragit L 100 in pH change using basket method at 100 rpm

75-mg indomethacin +5% xanthan gum coated with Eudragit L 100					
TIME (min)	**1**	**2**	**3**	**Mean**	**S.D.**
0	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
5	**0.02**	**0.04**	**0.00**	**0.02**	**0.01**
15	**0.13**	**0.28**	**0.10**	**0.17**	**0.08**
30	**0.41**	**0.42**	**0.39**	**0.41**	**0.01**
45	**0.47**	**0.51**	**0.50**	**0.49**	**0.01**
60	**0.61**	**0.59**	**0.62**	**0.61**	**0.01**
90	**0.54**	**0.62**	**0.69**	**0.62**	**0.06**
120	**26.35**	**21.45**	**24.14**	**23.98**	**2.00**
150	**31.48**	**29.15**	**30.82**	**30.48**	**0.97**
180	**36.10**	**35.83**	**38.88**	**36.93**	**1.37**
210	**46.65**	**42.20**	**44.72**	**44.52**	**1.82**
240	**58.51**	**56.28**	**56.97**	**57.25**	**0.93**
300	**60.14**	**59.51**	**60.01**	**59.89**	**0.27**
360	**71.00**	**67.05**	**69.14**	**69.06**	**1.61**
420	**78.50**	**76.50**	**78.26**	**77.76**	**0.89**
480	**84.70**	**82.27**	**90.14**	**85.70**	**3.29**

APPENDICES IV

The percentage of water uptake and erosion of indomethacin matrix tablet containing different amount of xanthan gum

Table 41 The percentage of water uptake of indomethacin matrix tablet containing different amount of xanthan gum

(A)

75-mg indomethacin +10% xanthan gum at 30 min				**75-mg indomethacin +15% xanthan gum at 30 min**			
Sample	Wet weight (g)	Remining dry weight (g)	% Water uptake	Sample	Wet weight (g)	Remining dry weight (g)	% Water uptake
1	2.8077	0.8772	220.07	1	2.3373	0.8597	171.87
2	2.9025	0.8735	232.28	2	2.5135	0.8435	197.98
3	3.0138	0.8677	247.33	3	2.4396	0.833	192.86
Mean	2.908	0.8728	233.23	Mean	2.4301	0.8454	187.57
S.D.	0.0842	0.0039	11.15	S.D.	0.0722	0.0109	11.29
75-mg indomethacin +10% xanthan gum at 60 min				**75-mg indomethacin +15% xanthan gum at 60 min**			
1	3.7229	0.835	345.86	1	3.7384	0.8314	349.65
2	3.5423	0.8555	314.06	2	3.7641	0.8376	349.39
3	3.8174	0.8697	338.93	3	4.0397	0.8267	388.65
Mean	3.6942	0.8534	332.95	Mean	3.8474	0.8319	362.56
S.D.	0.1141	0.0142	13.65	S.D.	0.1363	0.0044	18.44
75-mg indomethacin +10% xanthan gum at 120 min				**75-mg indomethacin +15% xanthan gum at 120 min**			
1	4.2336	0.8192	416.796875	1	4.6941	0.7405	533.90
2	4.1546	0.8095	413.2303891	2	4.4567	0.7513	493.19
3	4.2173	0.8022	425.7167789	3	4.9522	0.7377	571.30
Mean	4.2018	0.8103	418.5813477	Mean	4.701	0.7431	532.80
S.D.	0.0340	0.0069	5.25139595	S.D.	0.2023	0.0058	31.89
75-mg indomethacin +10% xanthan gum at 240 min				**75-mg indomethacin +15% xanthan gum at 240 min**			
1	6.7659	0.7867	760.0355917	1	5.5792	0.7430	650.90
2	5.878	0.7848	648.980632	2	5.2965	0.6998	656.85
3	5.8583	0.755	675.9337748	3	5.3931	0.7577	611.77
Mean	6.1674	0.7755	694.9833329	Mean	5.4229	0.7335	639.84
S.D.	0.4232	0.0145	47.29668955	S.D.	0.1173	0.0245	19.99
75-mg indomethacin +10% xanthan gum at 360 min				**75-mg indomethacin +15% xanthan gum at 360 min**			
1	7.0551	0.7102	893.3962264	1	6.7883	0.7102	855.82
2	6.879	0.7312	840.7822757	2	6.0864	0.6535	831.35
3	6.7762	0.7216	839.0521064	3	6.3299	0.6787	832.65
Mean	6.9034	0.721	857.7435362	Mean	6.4015	0.6808	839.94
S.D.	0.1151	0.0085	25.22015215	S.D.	0.2909	0.0231	11.24
75-mg indomethacin +10% xanthan gum at 480 min				**75-mg indomethacin +15% xanthan gum at 480 min**			
1	7.4971	0.688	989.6947674	1	6.6528	0.6758	884.43
2	7.3078	0.6951	951.3307438	2	7.901	0.609	1197.37
3	9.0527	0.7021	1189.374733	3	8.0058	0.6251	1180.72
Mean	7.9525	0.6950	1043.466748	Mean	7.5198	0.6366	1087.50
S.D.	0.7817	0.0057	104.3545387	S.D.	0.6145	0.0284	143.75

(continued)

(B)

75-mg indomethacin +20% xanthan gum at 30 min				75-mg indomethacin +25% xanthan gum at 30 min			
Sample	Wet weight (g)	Remining dry weight (g)	% Water uptake	Sample	Wet weight (g)	Remining dry weight (g)	% Water uptake
1	2.4134	0.8144	196.34	1	2.544	0.7196	253.52
2	2.424	0.8064	200.59	2	2.7267	0.6619	311.95
3	2.248	0.8211	173.77	3	3.3185	0.6934	378.58
Mean	2.3618	0.8139	190.23	Mean	2.8630	0.6916	314.68
S.D.	0.0805	0.0060	11.76	S.D.	0.3305	0.0235	51.08
75-mg indomethacin +20% xanthan gum at 60 min				**75-mg indomethacin +25% xanthan gum at 60 min**			
1	3.2832	0.8021	309.32	1	2.9485	0.7261	306.07
2	3.0018	0.7856	282.10	2	2.8408	0.6068	368.16
3	3.4478	0.8113	324.97	3	3.705	0.6658	456.47
Mean	3.2442	0.7996	305.46	Mean	3.1647	0.6662	376.90
S.D.	0.1841	0.01063	17.71	S.D.	0.3842	0.0487	61.71
75-mg indomethacin +20% xanthan gum at 120 min				**75-mg indomethacin +25% xanthan gum at 120 min**			
1	4.3203	0.7336	488.91	1	4.259	0.6275	578.72
2	4.2857	0.7502	471.27	2	4.8961	0.5967	720.52
3	4.4456	0.782	468.49	3	4.4062	0.6568	570.85
Mean	4.350	0.7552	476.22	Mean	4.5204	0.627	623.37
S.D.	0.0686	0.0208	9.04	S.D.	0.2723	0.0245	68.77
75-mg indomethacin +20% xanthan gum at 240 min				**75-mg indomethacin +25% xanthan gum at 240 min**			
1	5.0503	0.6662	658.07	1	4.8027	0.5498	773.53
2	4.9161	0.715	587.56	2	5.261	0.5333	886.49
3	5.026	0.663	658.06	3	5.3402	0.5918	802.36
Mean	4.9974	0.6814	634.57	Mean	5.1346	0.5583	820.80
S.D.	0.0583	0.0237	33.23	S.D.	0.2369	0.0246	47.92
75-mg indomethacin +20% xanthan gum at 360 min				**75-mg indomethacin +25% xanthan gum at 360 min**			
1	6.1965	0.6671	828.87	1	5.3261	0.4626	1051.34
2	6.7404	0.6847	884.43	2	5.1394	0.4266	1104.73
3	6.3836	0.6794	839.59	3	5.9913	0.5062	1083.58
Mean	6.4401	0.6770	850.96	Mean	5.4856	0.4651	1079.88
S.D.	0.2256	0.0073	24.06	S.D.	0.3656	0.0325	21.95
75-mg indomethacin +20% xanthan gum at 480 min				**75-mg indomethacin +25% xanthan gum at 480 min**			
1	8.0309	0.6023	1233.37	1	6.3388	0.4333	1362.91
2	7.2656	0.6189	1073.95	2	5.3106	0.3492	1420.79
3	7.6537	0.6549	1068.68	3	5.7431	0.4538	1165.55
Mean	7.6500	0.6253	1125.33	Mean	5.7975	0.4121	1316.42
S.D.	0.3124	0.0219	76.42	S.D.	0.4215	0.0452	109.26

Table 42 The percentage of erosion of indomethacin matrix tablet containing different amount of xanthan gum

(A)

75-mg indomethacin +10% xanthan gum at 30 min				**75-mg indomethacin +15% xanthan gum at 30 min**			
Sample	Remining dry weight (g)	Original dry weight (g)	% Erosion	Sample	Remining dry weight (g)	Original dry weight (g)	% Erosion
1	0.7196	0.9037	20.37	1	0.8144	0.8893	8.42
2	0.6619	0.88	24.78	2	0.8064	0.8909	9.48
3	0.6934	0.8915	22.22	3	0.8211	0.8802	6.71
Mean	0.6916	0.8917	22.45	Mean	0.8139	0.8868	8.20
S.D.	0.0235	0.009	1.80	S.D.	0.0060	0.0047	1.14
75-mg indomethacin +10% xanthan gum at 60 min				**75-mg indomethacin +15% xanthan gum at 60 min**			
1	0.7261	0.8801	17.49	1	0.8021	0.9102	11.87
2	0.6068	0.8735	30.53	2	0.7856	0.893	12.02
3	0.6658	0.8816	24.47	3	0.8113	0.9095	10.79
Mean	0.6662	0.8784	24.16	Mean	0.7996	0.9042	11.56
S.D.	0.0487	0.0035	5.32	S.D.	0.01063	0.0079	0.54
75-mg indomethacin +10% xanthan gum at 120 min				**75-mg indomethacin +15% xanthan gum at 120 min**			
1	0.6275	0.8917	29.62	1	0.7336	0.8749	16.15
2	0.5967	0.9054	34.09	2	0.7502	0.8785	14.60
3	0.6568	0.902	27.18	3	0.782	0.9147	14.50
Mean	0.627	0.8997	30.30	Mean	0.7552	0.8893	15.087
S.D.	0.0245	0.0058	2.86	S.D.	0.0208	0.0179	0.75
75-mg indomethacin +10% xanthan gum at 240 min				**75-mg indomethacin +15% xanthan gum at 240 min**			
1	0.5498	0.8574	35.87	1	0.6662	0.8727	23.66
2	0.5333	0.8718	38.82	2	0.715	0.9071	21.17
3	0.5918	0.8844	33.08	3	0.663	0.8785	24.53
Mean	0.5583	0.8712	35.92	Mean	0.6814	0.8861	23.12
S.D.	0.0246	0.0110	2.34	S.D.	0.0237	0.0150	1.42
75-mg indomethacin +10% xanthan gum at 360 min				**75-mg indomethacin +15% xanthan gum at 360 min**			
1	0.4626	0.8882	47.91	1	0.6671	0.907	26.44
2	0.4266	0.914	53.32	2	0.6847	0.9218	25.72
3	0.5062	0.8917	43.23	3	0.6794	0.9153	25.77
Mean	0.4651	0.8979	48.15	Mean	0.6770	0.9147	25.98
S.D.	0.0325	0.0114	4.12	S.D.	0.0073	0.0060	0.33
75-mg indomethacin +10% xanthan gum at 480 min				**75-mg indomethacin +15% xanthan gum at 480 min**			
1	0.4333	0.9083	52.29	1	0.6023	0.8691	30.69
2	0.3492	0.8878	60.66	2	0.6189	0.8876	30.27
3	0.4538	0.8806	48.46	3	0.6549	0.9036	27.52
Mean	0.4121	0.8922	53.80	Mean	0.6253	0.8867	29.49
S.D.	0.0452	0.0117	5.09	S.D.	0.0219	0.0140	1.40

(continued)

(B)

75-mg indomethacin +20% xanthan gum at 30 mins				75-mg indomethacin +25% xanthan gum at 30 mins			
Sample	Remining dry weight (g)	Original dry weight (g)	% Erosion	Sample	Remining dry weight (g)	Original dry weight (g)	% Erosion
1	0.8597	0.9109	5.62	1	0.8772	0.9107	3.67
2	0.8435	0.8981	6.07	2	0.8735	0.9098	3.98
3	0.833	0.8863	6.01	3	0.8677	0.8998	3.56
Mean	0.8454	0.8984	5.90	Mean	0.8728	0.9067	3.74
S.D.	0.0109	0.0100	0.20	S.D.	0.0039	0.0049	0.17
75-mg indomethacin +20% xanthan gum at 60 mins				**75-mg indomethacin +25% xanthan gum at 60 mins**			
1	0.8314	0.9152	9.15	1	0.835	0.9242	9.65
2	0.8376	0.8932	6.22	2	0.8555	0.9246	7.47
3	0.8267	0.9001	8.15	3	0.8697	0.9272	6.20
Mean	0.8319	0.9028	7.84	Mean	0.8534	0.9253	7.77
S.D.	0.0044	0.009	1.21	S.D.	0.0142	0.0013	1.42
75-mg indomethacin +20% xanthan gum at 120 mins				**75-mg indomethacin +25% xanthan gum at 120 mins**			
1	0.7405	0.8888	16.68	1	0.8192	0.9279	11.71
2	0.7513	0.899	16.42	2	0.8095	0.9199	12.00
3	0.7377	0.9059	18.56	3	0.8022	0.9039	11.25
Mean	0.7431	0.8979	17.23	Mean	0.8103	0.9172	11.65
S.D.	0.0058	0.0070	0.95	S.D.	0.0069	0.0099	0.30
75-mg indomethacin +20% xanthan gum at 240 mins				**75-mg indomethacin +25% xanthan gum at 240 mins**			
1	0.7430	0.9181	19.07	1	0.7867	0.9325	15.63
2	0.6998	0.9017	22.39	2	0.7848	0.9167	14.38
3	0.7577	0.9211	17.73	3	0.755	0.9132	17.33
Mean	0.7335	0.9136	19.73	Mean	0.7755	0.9208	15.78
S.D.	0.0245	0.0085	1.95	S.D.	0.0145	0.0083	1.20
75-mg indomethacin +20% xanthan gum at 360 mins				**75-mg indomethacin +25% xanthan gum at 360 mins**			
1	0.7102	0.8915	20.33	1	0.7102	0.9055	21.56
2	0.6535	0.8885	26.44	2	0.7312	0.9122	19.84
3	0.6787	0.9097	25.39	3	0.7216	0.9097	20.67
Mean	0.6808	0.8965	24.05	Mean	0.721	0.9091	20.69
S.D.	0.0231	0.0093	2.66	S.D.	0.0085	0.0027	0.70
75-mg indomethacin +20% xanthan gum at 480 mins				**75-mg indomethacin +25% xanthan gum at 480 mins**			
1	0.6758	0.92	26.54	1	0.688	0.9184	25.08
2	0.609	0.8887	31.47	2	0.6951	0.9082	23.46
3	0.6251	0.9207	32.10	3	0.7021	0.9229	23.92
Mean	0.6366	0.9098	30.04	Mean	0.6950	0.9165	24.15
S.D.	0.0284	0.0149	2.48	S.D.	0.0057	0.00615	0.68

APPENDICES V

Percentage of diameter change of 75-mg indomethacin tablets containing different amount of xanthan gum

Table 43 Percentage of diameter change of 75-mg indomethacin tablets containing different amount of xanthan gum in phosphate buffer pH 6.2

(A)

75-mg indomethacin +10% xanthan gum						75-mg indomethacin +15% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
30	5.00	6.00	6.00	5.66	0.47	30	6.00	6.00	7.00	6.33	0.47
60	7.00	7.00	8.00	7.33	0.47	60	8.00	7.00	7.50	7.50	0.40
90	9.00	11.00	10.00	10.00	0.81	90	10.00	11.00	12.00	11.00	0.81
120	10.50	12.00	11.00	11.16	0.62	120	11.00	12.00	13.00	12.00	0.82
240	11.50	12.00	11.00	11.50	0.41	240	13.00	12.00	13.00	12.66	0.47
360	17.00	18.00	19.00	18.00	0.81	360	18.00	18.50	19.00	18.50	0.40
480	18.00	20.00	21.00	19.66	1.24	480	20.00	21.50	21.00	20.83	0.62

(B)

75-mg indomethacin +20% xanthan gum						75-mg indomethacin +25% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	0.00	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
30	6.50	7.50	7.00	7.00	0.40	30	7.00	7.50	8.50	7.67	0.62
60	8.50	9.00	7.50	8.33	0.62	60	11.00	9.00	7.50	9.16	1.43
90	10.50	13.00	12.00	11.83	1.02	90	15.00	13.00	12.00	13.33	1.24
120	12.00	14.00	13.00	13.00	0.81	120	16.00	14.00	13.00	14.33	1.24
240	13.50	14.50	13.00	13.67	0.62	240	17.00	14.50	13.00	14.83	1.64
360	18.50	20.00	19.00	19.17	0.62	360	21.00	20.00	19.00	20.00	0.81
480	20.50	22.00	21.00	21.16	0.56	480	22.00	23.50	21.00	22.16	1.02

APPENDICES VI

6. Total work of penetration of tablet containing different amount of xanthan gum or 25% HPMC at different time points

Table 44 Total work of penetration of tablet containing different amount of xanthan gum at different time points in phosphate buffer pH 6.2

(A)

75-mg indomethacin +10% xanthan gum						75-mg indomethacin +15% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	6.99	7.86	8.51	7.97	0.32	0	9.03	9.54	9.32	9.27	0.03
30	6.04	5.12	7.87	6.01	0.79	30	3.23	3.12	4.25	3.67	0.71
60	2.45	1.97	2.15	2.12	0.30	60	1.35	1.72	1.69	1.68	0.23
90	1.79	1.91	1.72	1.80	0.02	90	1.56	1.47	1.39	1.47	0.02
120	0.44	0.46	0.41	0.45	0.02	120	0.32	0.35	0.33	0.34	0.01
240	0.38	0.35	0.34	0.36	0.03	240	0.31	0.34	0.28	0.31	0.04
360	0.21	0.18	0.24	0.22	0.01	360	0.10	0.15	0.14	0.13	0.03
480	0.18	0.19	0.17	0.18	0.02	480	0.09	0.11	0.09	0.10	0.02

(B)

75-mg indomethacin +20% xanthan gum						75-mg indomethacin +25% xanthan gum					
TIME (min)	1	2	3	Mean	S.D.	TIME (min)	1	2	3	Mean	S.D.
0	10.55	11.00	10.15	10.83	0.81	0	13.02	12.97	13.99	13.58	0.08
30	2.89	3.12	2.78	3.00	0.90	30	1.01	0.91	0.88	0.97	0.27
60	1.27	1.21	1.18	1.25	0.52	60	0.45	0.50	0.61	0.58	0.11
90	0.99	1.01	1.02	1.03	0.13	90	0.51	0.59	0.55	0.57	0.10
120	0.30	0.36	0.31	0.33	0.04	120	0.20	0.25	0.18	0.20	0.09
240	0.26	0.25	0.30	0.27	0.01	240	0.08	0.15	0.09	0.12	0.09
360	0.10	0.08	0.09	0.10	0.01	360	0.01	0.02	0.03	0.08	0.04
480	0.03	0.07	0.18	0.09	0.08	480	0.09	0.04	0.02	0.05	0.02

Table 45 Total work of penetration of tablet containing 25% HPMC at different time points in phosphate buffer pH 6.2

75-mg indomethacin +25% HPMC					
TIME (min)	**1**	**2**	**3**	**Mean**	**S.D.**
0	**11.44**	**11.38**	**11.60**	**11.56**	**0.16**
30	**3.11**	**3.35**	**2.69**	**3.00**	**0.37**
60	**1.01**	**0.97**	**1.06**	**1.03**	**0.13**
90	**0.80**	**0.65**	**0.69**	**0.73**	**0.18**
120	**0.30**	**0.48**	**0.38**	**0.39**	**0.22**
240	**0.08**	**0.04**	**0.03**	**0.05**	**0.20**
360	**0.06**	**0.04**	**0.04**	**0.04**	**0.20**
480	**0.03**	**0.02**	**0.04**	**0.03**	**0.30**

APPENDICES VII

DSC thermograms

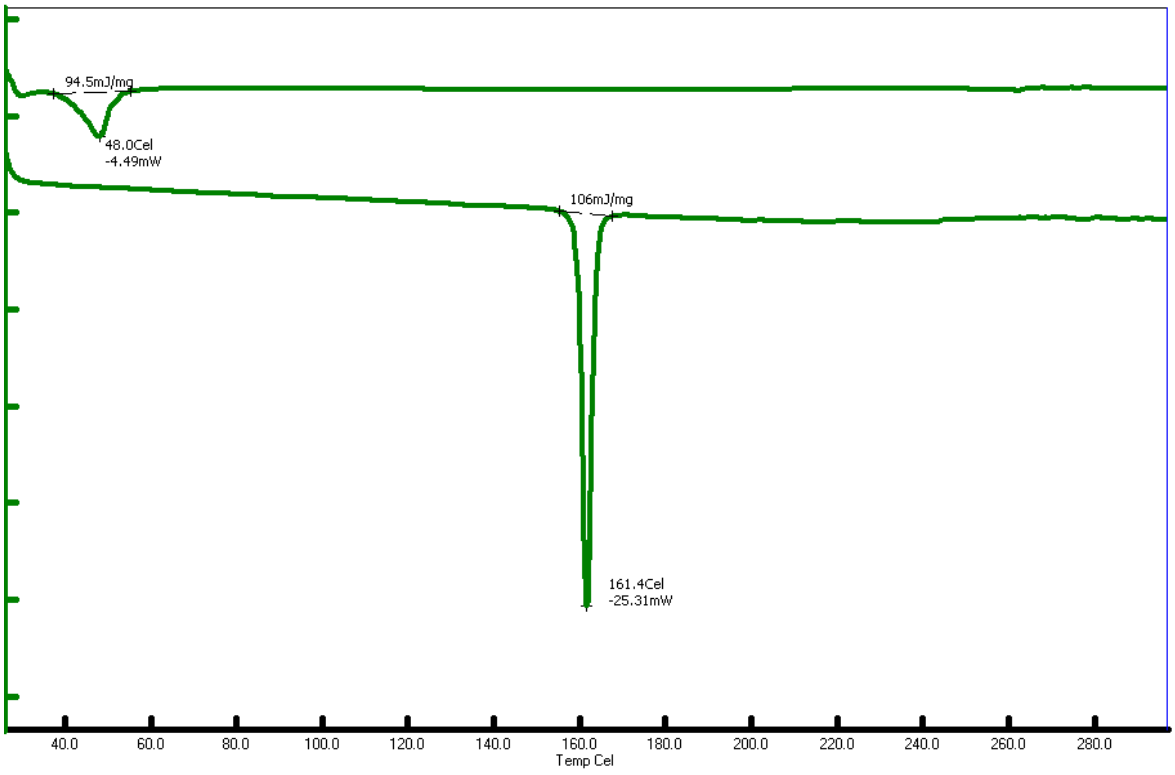

Figure 52 DSC thermograms of indomethacin tablet containing PEG 4000: PEG 400 and 75-mg indomethacin

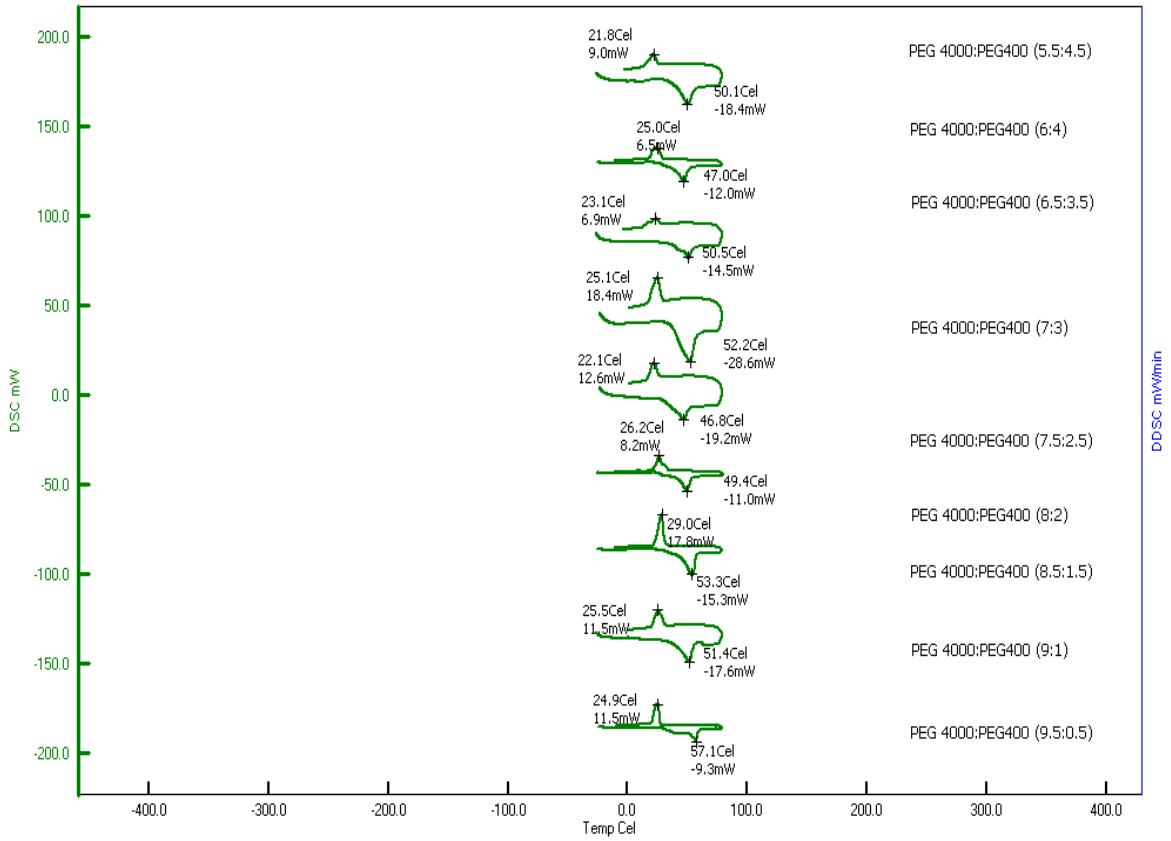

Figure 53 DSC thermograms from reverse run of DSC study of systems containing different ratio of PEG 4000: PEG 400 (5.5:4.5, 6:4, 6.5:3.5, 7:3, 7.5:2.5, 8:2, 8.5:1.5, 9:1 and 9.5:0.5)

APPENDICES VIII

The percentages of labeled amount of $C_{19}H_{16}ClNO_4$ (indomethacin) of matrix tablet containing different amount of xanthan gum

Table 46 The percentages of cumulative release of $C_{19}H_{16}ClNO_4$ (indomethacin) of matrix tablet containing different amount of xanthan gum in phosphate buffer pH 6.2 using basket method at 100 rpm

(A)

75-mg indomethacin +5% xanthan gum		**75-mg indomethacin +10% xanthan gum**	
Sample	% cumulative release	Sample	% cumulative release
1	95.62	1	96.17
2	93.45	2	93.05
3	94.13	3	92.98
4	95.27	4	95.16
5	94.09	5	97.01
6	94.98	6	96.34
7	94.74	7	94.11
8	95.05	8	95.33
9	95.11	9	92.76
10	95.31	10	93.14
Mean	93.08	Mean	94.61
S.D.	1.24	S.D.	1.51

(continued)

(B)

75-mg indomethacin +15% xanthan gum		75-mg indomethacin +20% xanthan gum	
Sample	% cumulative release	Sample	% cumulative release
1	92.11	1	96.55
2	94.09	2	92.13
3	94.99	3	92.52
4	93.25	4	95.66
5	91.13	5	96.98
6	92.46	6	93.17
7	93.09	7	92.33
8	95.11	8	93.12
9	92.33	9	95.26
10	96.17	10	91.09
Mean	93.47	Mean	93.88
S.D.	1.50	S.D.	1.95

(C)

75-mg indomethacin +25% xanthan gum	
Sample	% cumulative release
1	94.63
2	93.02
3	95.78
4	92.22
5	94.19
6	93.89
7	91.09
8	92.44
9	96.08
10	91.89
Mean	93.52
S.D.	1.59

BIOGRAPHY

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PRESENTATION	Anongnart Mesnukul and Thawatchai Phaechamud. "Indomethacin-Polyethylene glycol tablet fabricated with mold technique" The MSAT-5 Conference, Miracle grand Hotel, Thailand. September 18-19, 2008.