INFLUENCE OF TYPE AND CONTENT OF EXCIPIENT AND COMPRESSION FORCE ON THE RELEASE OF INDOMETHACIN FROM A LOW VISCOSITY GRADE OF HYDROXYPROPYL METHYLCELLULOSE MATRIX TABLETS

KOSON SAETING

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ABSTRACT

This study's aim was to examine the influence of the compression force of a tableting machine, and the type and content of excipient on the release of indomethacin from matrix tablets containing a low viscosity grade of hydroxypropyl methylcellulose (HPMC) as matrixing agent. Indomethacin matrix tablets with HPMC to excipient (lactose or microcrystalline cellulose) ratios of 0:77, 17:60, 37:40, 57:20, and 77:0 were prepared by direct compression method at the compression forces of 300, 600 and 900 kg. The experimental data were in-putted to various kinetic models in order to explore the mechanism of drug release. The results showed that although the compression force had a significant effect on tablet hardness, its effect on drug release from HPMC matrix tablets was minimal. The compression force also did not alter the drug release mechanism. The type and content of excipient influenced the extent and rate of drug release. The formulations containing an insoluble excipient (microcrystalline cellulose) released indomethacin at a slower rate and to a lesser extent than those containing a soluble excipient (lactose). Increasing the proportion of lactose in the tablet resulted in an increase in the release of indomethacin in the dissolution medium. However, the presence of microcrystalline cellulose changed the release profile to a small extent. Moreover, excipient type and content used in the tablet formulations, influenced the drug release mechanism. The release mechanism of indomethacin from each tablet formulation can be described by either the Hixson-Crowell cube root kinetics equation or Peppas's equation.

KEY WORDS: MATRIX TABLET/ COMPRESSION FORCE/ EXCIPIENT/ RELEASE KINETIC

224 p.

อิทธิพลของชนิดและปริมาณของสารเพิ่มปริมาณ และแรงตอกต่อการปลดปล่อยตัวยาอินโดเมทาซินจากยาเม็ดเมทริกซ์ที่ใช้ไฮดรอกซีโพรพิลเมททิลเซลลูโลสความหนืดต่ำเป็นสารก่อเมทริกซ์
(INFLUENCE OF TYPE AND CONTENT OF EXCIPIENT AND COMPRESSION FORCE ON THE RELEASE OF INDOMETHACIN FROM A LOW VISCOSITY GRADE OF HYDROXYPROPYL METHYLCELLULOSE MATRIX TABLETS)

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บทคัดย่อ

งานวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาอิทธิพลของแรงตอก ชนิดและปริมาณของสารช่วยในตำรับต่อการปลดปล่อยตัวยาอินโดเมทาซินจากยาเม็ดเมทริกซ์ที่มีไฮดรอกซีโพรพิลเมททิลเซลลูโลสความหนืดต่ำเป็นสารก่อเมทริกซ์ ยาเม็ดเมทริกซ์ที่ประกอบด้วยไฮดรอกซีโพรพิลเมททิลเซลลูโลสและสารช่วยในสัดส่วน 0:77, 17:60, 37:40, 57:20 และ 77:0 ทำการตอกยาเม็ดโดยวิธีการตอกตรง ด้วยแรงตอก 300, 600 และ 900 กิโลกรัม ตามลำดับ นำข้อมูลที่ได้จากการศึกษาไปเปรียบเทียบกับต้นแบบของจลนศาสตร์ต่างๆ เพื่อหากลไกการปลดปล่อยตัวยาอินโดเมทาซินจากยาเม็ดเมทริกซ์ ผลการศึกษาพบว่า แม้ว่าแรงตอกจะมีอิทธิพลต่อความแข็งของยาเม็ดที่เตรียมได้ แต่มีอิทธิพลต่อการปลดปล่อยตัวยาน้อย และแรงตอกไม่มีผลต่อการเปลี่ยนแปลงกลไกในการปลดปล่อยตัวยา นอกจากนี้ยังพบว่าชนิดและปริมาณของสารช่วยในตำรับมีอิทธิพลต่อปริมาณและอัตราการปลดปล่อยตัวยา โดยตำรับที่ประกอบด้วยไมโครคริสตัลลีนเซลลูโลสซึ่งเป็นสารช่วยที่ละลายน้ำได้น้อยมีการปลดปล่อยตัวยาด้วยอัตราเร็วที่ช้ากว่าและปลดปล่อยได้น้อยกว่าเมื่อเปรียบเทียบกับตำรับที่ประกอบด้วยสารช่วยที่ละลายน้ำได้อย่างแลคโตส และการเพิ่มสัดส่วนของแลคโตสในตำรับมีผลให้การปลดปล่อยตัวยาเพิ่มสูงขึ้น อย่างไรก็ตามการเพิ่มปริมาณของไมโครคริสตัลลีนเซลลูโลสก็มีผลให้การปลดปล่อยตัวยาเพิ่มขึ้นเล็กน้อย นอกจากนี้ทั้งชนิดและปริมาณของสารช่วยในตำรับยังมีผลต่อกลไกในการปลดปล่อยตัวยา โดยกลไกการปลดปล่อยตัวยาของยาเม็ดเมทริกซ์ในแต่ละตำรับสามารถอธิบายโดยใช้ Hixson-Crowell cube root kinetics equation และ Peppas’s equation.

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LIST OF ABBREVIATIONS

%	percent
°C	degree Celsius
µg	microgram(s)
µl	microliter(s)
ANOVA	analysis of variance
cm	centimeter(s)
cps	centipoise
EDTA	ethylenediamine tetra-acetate
e.g.	exempli gratia, for example
et al.	et alii, and others
etc.	et cetera
Eq.	equation
Fig.	Figure
g	gram(s)
HCl	hydrochloric acid
hr(s)	hour(s)
i.e.	id est (that is)
kg	kilogram(s)
Lac	lactose
m	meter(s)
MCC	microcrystalline cellulose
mg	milligram(s)
min	minute(s)
ml	milliliter(s)
mm	millimeter(s)
NaOH	sodium hydroxide
nm	nanometer(s)

LIST OF ABBREVIATIONS (continued)

pH	negative logarithm of hydrogen ion activity
pKa	the negative logarithm of the dissociation constant
r^2	coefficient of determination
rpm	revolution per minute(s)
RSD	relative standard deviation
SD	standard deviation
sec	second(s)
USP	The United States Pharmacopoeia
UV	ultraviolet
w/w	weight by weight

CHAPTER I
INTRODUCTION

Some drugs are inherently long-lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate-release dosage forms. However, many other drugs are not inherently long-lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing often is inconvenient for the patient and can result in missed doses, made up doses, and patient noncompliance with the therapeutic regimen.

Sustained release (SR) oral dosage forms have become more important in therapy as a means of reduced dosing frequency, hence potentially improving patient compliance and consequently efficacy. The principal goal of SR dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of SR systems. The blood level of a drug reaches to the therapeutic concentrations as soon as possible with SR dosage forms and then this level maintains for a certain period time.

Among different technologies used in sustained release system, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, broad FDA acceptance, their favorable in vivo performance and applicability to drugs with wide range of physico-chemical properties (1-3). The hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into tablets (4,5). An important carrier material used for the preparation of hydrophilic matrix system is hydroxypropyl methylcellulose (HPMC), a semisynthetic derivative of cellulose, is a pH-independent hydrophilic material. It is the most commonly used polymers in hydrophilic matrix formulations, owing to their solubility in water, availability in a range of molecular weight/viscosity grades, cost effectiveness, FDA acceptance, and unique swelling/erosion characteristics which can be utilized in modulating drug

release profile. One of its most important characteristics is its swellability, which has a pronounced effect on the release kinetics of an incorporated drug. On contact with biological fluid water diffuses into the device, resulting in polymer chain relaxation with volume expansion. Then, the incorporated drug dissolves and diffuses out of the system.

There are several formulation factors which influence the drug release rate from hydrophilic based matrices. These factors include the drug loading, drug solubility, drug : polymer ratio, drug particle size, physicochemical properties of the polymer, processing conditions, the testing medium used, and the addition of different types and levels of excipients and release modulators (1,6,7). The limitation of information on process variables such as effects of compression force, types and levels of excipients in the formulation, etc. on drug release still remained in spite of its unavoidable necessity in fabrication of sustained release drug delivery systems. It is therefore valuable to seek a definite influence of compression force, type and level of excipient on the release of drug from matrix tablet.

In this study, indomethacin matrix tablets were made using different type and ratios of excipient (lactose and microcrystalline cellulose) by direct compression method. The compression were made at three different upper punch forces (300, 600 and 900 kg) after which their released patterns were determined in order to examine the effect of type and content of excipient and compression force on the release of indomethacin from hydroxypropyl methylcellulose matrix tablets and to develop extended release indomethacin matrix tablets.

The objectives of this study were as follows :

1. To understand the effect of type and content of excipients (lactose and microcrystalline cellulose) on the release of indomethacin from hydroxypropyl methylcellulose matrix tablets.
2. To understand the effect of compression force on the release of indomethacin from hydroxypropyl methylcellulose matrix tablets.
3. To understand the release mechanism of indomethacin from hydroxypropyl methylcellulose matrix tablets.

CHAPTER II
LITERATURE REVIEW

In evaluating drugs as candidates for sustained-release formulation, the disadvantages of such formulation that must be considered include the following:

1) Administration of sustained-release medication does not permit the prompt termination of therapy. Immediate changes in drug need during therapy, such as might be encountered if significant adverse effects are noted, cannot be accommodated.

2) The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

3) Sustained-release dosage forms are designed for the normal population, i.e., on the basis of average drug biologic half-lives. Consequently, disease state that alter drug disposition, significant patient variation, and so forth are not accommodated.

4) Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing many sustained-release dosage forms (8).

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 (9) :

Hydrophobic carriers :

- Digestible base (fatty compounds) : glycerides - glyceryltristearate, fatty alcohols, fatty acids, waxes - carnauba wax.
- Nondigestible base (insoluble plastics) : methylacrylate - methylmethacrylate, polyvinyl chloride, polyethylene, ethyl cellulose.

Hydrophilic polymers : methylcellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, sodium alginate, xanthan gum, polyethylene oxide and carbopols.

Matrix systems offer several advantages relative to other extended release dose forms :

- 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 continuously 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 (10).

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.

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) (10).

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 equation:

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

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

Cs - 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 this is the case for combination diffusion and dissolution systems (10).

1.1. Encapsulated dissolution control

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particle 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 dosage form, i.e. particle without a barrier membrane, to provide for immediate 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 a hydrophilic substance to a solution of colloid. Whether a drug is water sensitive or not, it can be microencapsulated if the drug is protected from the aqueous environment by coating with polymer.

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 simply 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 reduced 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 of penetration of the dissolution fluid into the matrix, porosity of the tablet matrix, the presence of hydrophobic additives.

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 (10) :

2.1. Reservoir devices

Are ER formulations where film coating constitutes the main factor in controlling drug release. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry (9).

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 (10).

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 remains constant (no change occurs in the characteristics of the polymer matrix (10).

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) (11).

g) Only the diffusion process occurs (12).

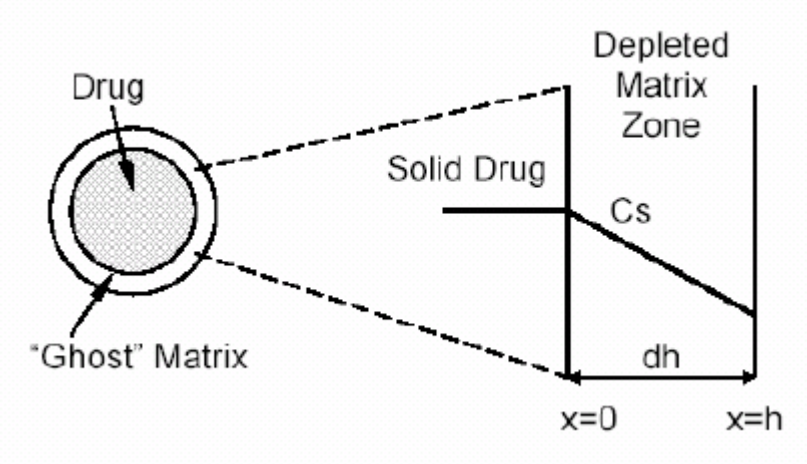

Figure 1. Schematic representation of a matrix release system

Release from a monolithic matrix system can be graphically depicted as in shown in Figure 1.

The release behavior for the system can be mathematically described by the following equation :

$$\frac{dM}{dh} = C_0 \cdot dh - \frac{C_s}{2} \qquad (2)$$

where

dM - change in the amount of drug released per unit area

dh - change in the thickness of the zone of matrix that has been depleted of drug

C_o - total amount of drug in a unit volume of matrix

C_s - saturated concentration of the drug within the matrix

Additionally, according to diffusion theory :

$$dM = \frac{D_m \cdot C_s}{h} \cdot dt \qquad (3)$$

where :

D_m - is the diffusion coefficient in the matrix

h - thickness of the drug-depleted matrix

dt - change in time

By combining equation 2 and equation 3 and integrating :

$$M = \left[C_s \cdot M_m \cdot \left(2C_o - C_s\right) \cdot t\right]^{1/2} \qquad (4)$$

When the amount of drug is in excess of the saturation concentration, then :

$$M = \left[2C_s \cdot D_m \cdot C_o \cdot t\right]^{1/2} \qquad (5)$$

Equation 4 and equation 5 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line.

Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix :

$$M = \left[D_s \cdot C_a \cdot \frac{\rho}{T} \cdot (2C_o - \rho \cdot C_a) \cdot t \right]^{1/2} \quad (6)$$

where:

ρ - porosity of the matrix

t - tortuosity

C_a - solubility of the drug in the release medium

D_s - diffusion coefficient in the release medium.

T - diffusional pathlength

For pseudo steady state, the equation can be written as :

$$M = \left[2D \cdot C_a \cdot C_o \cdot \frac{\rho}{T} \cdot t \right]^{1/2} \quad (7)$$

The total porosity of the matrix can be calculated with the following equation :

$$p = p_a + \frac{C_o}{\rho} + \frac{C_{ex}}{\rho_{ex}} \quad (8)$$

Where :

p - porosity

ρ - drug density

p_a - porosity due to air pockets in the matrix

ρ_{ex} - density of the water soluble excipients

C_{ex} - concentration of water soluble excipients

For the purpose of data treatment, equation 6 can be reduced to :

$$M = k \cdot t^{1/2} \qquad (9)$$

where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled.

If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters :

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug (10,11).

3. Diffusion and dissolution systems (Bimodal release)

In certain systems, there is a bimodal or anomalous release of 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 consideration 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 (13).

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 2).

- The “swelling front” separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the T_g 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 T_g that is above the respective environmental 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 (14).

- 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 release (14-18).

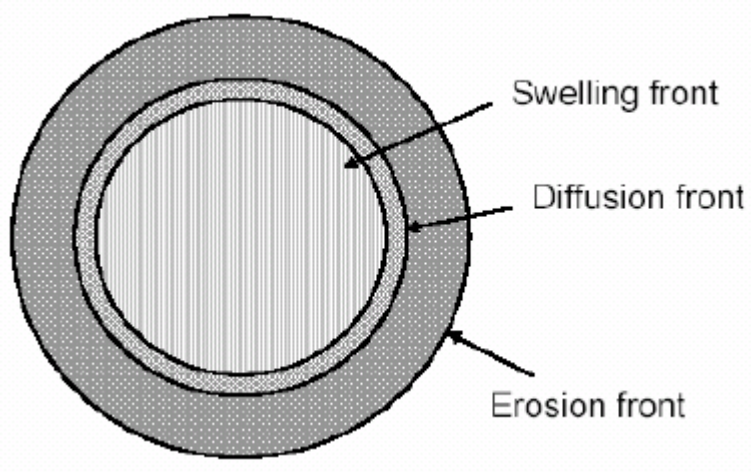

Figure 2. Fronts in bimodal release system

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gum do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices (19-21).

In 1985 Peppas introduced a semi-empirical equation describing the drug release behavior from anomalous-release, hydrophilic matrix systems :

$$Q = k \cdot t^n \qquad (10)$$

where:

Q - fraction of drug release in time (t)

t - time

k - rate constant (incorporates characteristics of polymer system and drug)

n - diffusional exponent

The value of n is indicative of the drug release mechanism. For n = 0.5, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For n = 1 drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For $0.5<n<1$ non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion (12).

In order to describe relaxational transport, Peppas and Sahlin (22) then modified equation 10 in order to account for relaxational transport :

$$Q = k_1 \cdot t^n + k_2 \cdot t^{2n} \qquad (11)$$

where:

k_1 - fickian diffusion constant

k_2 - relaxational mechanism constant

If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and equation 11 is transformed to:

$$Q = k_1 \cdot t^{0.5} + k_2 \cdot t \qquad (12)$$

The first term of this equation above accounts for diffusional phenomena, while the second term of this equation accounts for polymer erosion (12).

Drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, drug concentration and thickness of the gel layer governs the drug flux. Drug concentration in the gel depends on drug loading and solubility. Gel-layer thickness depends on the relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. Initially solvent penetration is more rapid than chain disentanglement, and a rapid build up of gel-layer thickness occurs. However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is observed since penetration and disentanglement rates are similar. Thus gel-layer thickness dynamics in swellable matrix tablets exhibit three

distinct patterns. The thickness increases when solvent penetration is the fastest mechanism, and it remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy-rubbery transition. In conclusion, the central element of the release mechanism is a gel-layer forming around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Drug release is controlled by drug diffusion through the gel layer, which can dissolve and/or erode.

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 (23).

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 of 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 (24).

A new ternary polymeric matrix system composed of pectin, HPMC, and highly water-soluble drugs such as diltiazem HC1 was developed by direct tablet compression (25). 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 (26). Diltiazem is contained in the hydrophilic polymer core, and two external layers serve to control the rate of hydration of the core, thereby restricting the surface area available for drug diffusion. New technology about HPMC matrices tablets was developed by Krogel *et al*. (27). They studied a multifunctional drug delivery system based on HPMC-matrices tablets placed within an impermeable polymeric cylinder (open at both ends). Depending on the configuration of the device, extend release, floating or pulsatile drug delivery systems could be obtained. The release behavior of different devices was investigated as a function of HPMC viscosity grade, HPMC content, type of drug (chlorpheniramine maleate or ibuprofen), matrix weight, position of the matrix within the polymer cylinder, addition of various fillers (lactose, dibasic calcium phosphate or microcrystalline cellulose) and agitation rate of the release medium. Three-layer matrix tablets of diclofenac sodium have been reported in which polyethylene oxide and HPMC together with diclofenac sodium were directly compressed into a three-layer matrix system (28).

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 a 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 (29). 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 (30).

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 of 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 compressed into 250-350 mg tablets (31).

Controlled parameters of the matrix tablets

Different factors that can influence drug release from hydrophilic matrices have been discussed and presented elsewhere (32,33). The release of dug from a matrix may be controlled by varying the following parameters.

1. Type of quantity of matrix material
2. Amount of drug incorporated in matrix
3. Solubility of drug
4. Particle size of drug
5. Matrix additive
6. pH of dissolution medium
7. Compression force
8. Matrix sharp
9. Tablet size

1. Type and quantity of matrix material

Various grades of commercially available HPMC differ in the relative proportion of the hydroxypropyl and methoxyl substitutions; increasing the amount of hydrophilic hydroxypropyl groups leads to a faster hydration: Methocel®K > Methocel®E > Methocel®F. Generally rapid hydrating Methocel®K grade is preferred, especially for highly soluble drugs where a rapid rate of hydration is necessary. It is important to note that an inadequate polymer hydration rate may lead to dose dumping, due to quick penetration of gastric fluids into the tablet core. In addition, as

viscosity of the HPMC increases, the drug release rate decreases mainly as a result of slower diffusion and extensive swelling (34).

In each grade, for a fixed polymer level, the viscosity of the selected polymer affects the diffusional and mechanical characteristics of the matrix. By comparing different Methocel®K viscosity grades, Nellore *et al*. (35) found that the higher viscosity gel layers provided a more tortuous and resistant barrier to diffusion, which resulted in slower release of the drug (metoprolol HCl). In addition, diffusional release of the water soluble drug metoprolol decreased with increasing HPMC incorporation. By varying the polymer level (Methocel® K4M 10-40%), they achieved different metoprolol in vitro release profiles.

Additionally when polymer concentration is low, the hydrated matrix would be highly porous with a low degree of tortuosity leading to low gel strength, rapid erosion of the matrix, and rapid diffusion of the drug from the matrix (7). It appears that the drug : polymer ratio is the most important factor affecting the rate and kinetics of the drug release from the matrix-based tablets. In general, an increase in the polymer concentration and ionic strength within the matrix causes an increase in viscosity of the gel as well as decrease in drug release rate (6,33).

In the study aimed to evaluate the relationship and influences of some formulation and technological factors, drug : HPMC ratio, particle size of the drug, particle size of HPMC and compression forces, on the drug release from matrices containing HPMC and diclofenac sodium model drug, Velasco *et al*. (6) found that the drug release and mechanism of diclofenac sodium release from HPMC K15M matrices were mainly controlled by the drug : HPMC ratio, although the dimension of the tablet also have to considered. This was because an increase in polymer concentration caused an increase in the viscosity of the gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusional path. The drug and HPMC particle size also influenced the drug release parameter, a lesser extent. Particle size has a significant effect on drug release when polymer content is low; however as polymer content increases its effect on release is diminished (36). Finally, the influence of the compression force can only be observed in the lag time and in the mechanical properties, with different results in the tablets produced with the lowest compression force (3kN). These results indicated that

the mechanical characteristics of the tablet did not play an important role in the drug release from HPMC matrices and other factors may be responsible. Reporting by Rekhi *et al*. (37) also confirmed this. Prez-Marcos *et al*. (38) used three varieties of carbomer and studied drug properties and release as a function of technological variable, type and proportion of polymer. They showed that in all cases, drug release profiles fitted Higuchi's model and showed strong dependence on proportion of polymer. Influence of the content of HPMC in the matrix tablet was investigated by Krogel *et al*. (27). Increasing the HPMC concentration from 10 to 40% (w/w), in their study decreased the ibuprofen release, probably because of the formulation of denser gel and slower erosion at the higher HPMC content.

Recently, Samani *et al*. (39) investigated the effect of polymer blends on release profiles of sodium diclofenac from matrices and the results showed that the drug release depends on the kind of polymer, its proportion in the formulation and its viscosity grade.

The release rate of a matrix type tablet is highly dependent on type and quantity of matrix material. Ford *et at*. (40) have investigated the effects of some formulation variable on the release rates of promethazine hydrochloride from hydroxypropyl methylcellulose tablet matrices. The major controlling factor appeared to be the promethazine : HPMC ratio and straight-line relationship existed between the Higuchi-type release rate and the reciprocal of the tablet content of HPMC. Increasing the particles size range of promethazine from 45-63 to 500-700 μm only produced a 12% increase in the drug release rate. Variation in compaction pressure from 93 to 1395 MNm^{-2} and the absence or presence of 0.75% magnesium stearate as lubricant appeared not to modify release rates at constant HPMC : Drug ratio. The other three grades (HPMC K4M, K15M and K100M) showed similar release rates despite the variation in their molecular size.

The studies on the release of adinazolam mesylate and HPMC, as well as the mechanism of drug release from HPMC-based matrix tablets by changing HPMC/lactose ratios and HPMC viscosity grade (Methocel®K100LV, K4M, K15M, K100M) by Sung *et al*. (41), found that the fastest release of adinazolam mesilate was achieved for the K100LV formulation. The K4M formulation exhibited a slightly greater drug release than K15M and K100M. Due to the lack of a significant

difference in the release profiles between K15M and K100M, the authors suggested a limiting HPMC viscosity of 15000cP, above which, if viscosity increased, the release rate would no longer decrease. In the case of ethylcellulose, the findings are completely different. The lower viscosity grades of ethylcellulose are more compressible than the higher viscosity grades, resulting in harder tablets and slower release (42). Moreover, the drug release rate was fast with the tablets made of the lower HPMC/lactose ratio and low HPMC viscosity grades, but slow with medium- and high-viscosity grade polymers. However the K15M and K100M formulations had identical drug release profiles. All the drug release data fit well the Higuchi expression. By comparing the drug and HPMC release data, it was concluded that diffusion of drug through the hydrate gel layer was the predominant drug release mechanism for most of the formulations studied.

In the studies involving the effect of HPMC/lactose ratio and HPMC viscosity grade on solute release and swelling of matrix tablets of Goa *et al*. (43), they used a semiquantitative optical imaging method of monitor the swelling of matrix with HPMC content from 20% to 80% (w/w) and four viscosity grades. They monitored simultaneously drug, lactose and HPMC release. Lactose and drug release rates were superimposed, indicating a similar diffusional release mechanism and no interaction with HPMC. HPMC/lactose ratio modulated drug release rate by altering drug diffusivity, a function of gel compression. In contrast, HPMC viscosity grade impacts matrix dissolution and gel layer thickness development below a critical molecular weight. For slowly dissolving matrices containing high viscosity grade (>4000 cps) HPMC, similar drug release rate are observed mainly due to the same drug diffusivity as a result of the identical gel composition and thickness. For fast dissolving matrices (less than 100 cps) swelling inhomogeneity is proposed as being responsible for a higher apparent drug diffusivity and release rate.

2. Amount of drug incorporated in matrix

The influence of the amount of drug incorporated in matrix is interesting and/or practical importance in the field of sustained release tablets. This can be a very important factor, as frequently it is desirable to produce several tablet concentration of

the same drug and matrix to provide a variety of dosage schedules. Thus the tablet concentration dependency must first be determined.

Uko-Nne *et al*. (44) showed that the effect of varying the concentration of theophylline in tablet was investigated using tablets containing 100.0, 200.0 and 300.0 mg of theophylline. In each case, the ratio of HPMC to dried molasses was kept constant. A presentative plot showing the amount drug released versus the square root of time as a function of drug concentration. It was observed that the release rate increased as the concentration of drug was increased. It could be assumed that increasing the amount of theophylline in the tablet would result in a corresponding increase in porosity by the same factor but would not affect other variables. It is evident from the rate equation that the slop should also increase by the same factor. On examination of the results, the slop of 200 mg tablet was 2.033 times that of the 100 mg tablet, and the 300 mg tablet was 2.663 times that of the 100 mg tablet. If the above assumption were correct, the factor should have been 2 and 3 times, respectively. The results obtained were close to theoretical values, and the deviations may indicate that other factor in the equation were changing with the amount of theophylline, or that the porosity was not proportional to formulation. As considered to 15% HPMC, 28.59% theophylline (the initial amount of drug in matrix), the release rate constants obtained were 2.779±0.310, 2.659±0.498 and 2.334±0.384 $min^{-1/2}$ for 100, 200 and 300 mg tablets, respectively, and were significantly different (P<0.05). The result indicated that the release rate constant is independent of drug concentration.

Kim *et al*. (25) have studied the influent of drug loading dose on release behavior. Tablets containing diltiazem gelatin granules equivalent to 5%, 12%, 20% and 24% diltiazem in 1:2 pectin : HPMC ratio blend were compressed at 2,000 lbs. and subjected to dissolution studies. The results indicated that the release rate and the fraction of drug release are significantly influenced by the drug-loading dose.

3. Solubility of drug

The solubility of the drug is an important variable to be considered when attempting to use the same matrix formulation for more than one drug. In monolithic systems typically an initial burst effect in release rate is observed especially when the drug solubility is high and loading dose in the matrix is large (6). It has also been

demonstrated that in addition to high drug solubility and dose a burst effect may be due to lack of critical polymer concentration threshold and distribution in the matrix (i.e. percolation threshold limit has to be met in all three dimensions of the tablet) (36).

The effect of drug solubility on the dissolution from the sustained release matrix tablet prepared with hydroxypropyl methylcellulose (HPMC) 2910 was investigated by Tahara *et al*. (45). The preparation of the sustained release matrix tablets of drugs were employed as follows : procaine hydrochloride anhydrous, acetaminophen, theophylline, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, and U-78875. In their study, seven model drugs which have various solubilities in the dissolution medium were used for preparation of tablets and dissolution studies were than performed. To determine the mechanism behind the sustained release, the filtration rate of the medium into the matrix tablet and the erosion rate of the matrix tablet were investigated. The model-independent moment parameters i.e. mean dissolution time (MDT), mean medium infiltration time (MIT), mean tablet erosion time (MET), mean swelling time (MSWT) and mean diffusion time (MDFT) as well as Higuchi-type model analysis which based on release mechanisms, were demonstrated for optimization of HPMC matrix tablets. Both in the model-independent and model analyses, the relationships obtained between drug solubility and release characteristics were similar. Regarding the poorly soluble drug, U-78875, the observed dissolution rate is slower than the erosion rate of the matrix tablet, which indicated that the main rate limiting factor for the dissolution is erosion of the matrix tablet. In the case of drugs whose solubilities are between 0.5 mg/ml (metyl-paraben, ethyl-paraben and propyl-paraben), dissolution rates are observed between the erosion rate of the matrix tablet and the infiltration rate of medium into the matrix tablet, and the dissolution rate increased by drug solubilities. Regarding highly soluble drugs, whose solubilities was more than 5 mg/ml (procain hydrochloride, acetaminophen, and theophylline), the dissolution rates was not influenced so much by drug solubility but show a similar rate of medium into the matrix tablet. The reported MDT and MDFT values were within the range 3.16-8.75 h and 1.11-6.70 h, respectively, except for U-78875. Also, MIT, MET and MSWT values as device matrix characteristic were 2.05, 12.05 and 10.00 h, respectively. The model-independent moment parameters, MDT, MIT, MET, MSWT and MDFT were

directly comparable to each other. Furthermore, these parameters would be applicable in comparing the device and dissolution characteristics of different types of formulation. These model-independent analytical approaches allow them to optimize the sustained release matrix formulation at the development stage.

Ford *et al*. (46) studied the release of theophylline from HPMC matrix in comparison with tetracycline hydrochloride and diazepam. The results showed the square root of time dissolution profiles of HPMC matrix tablets containing theophylline, tetracycline hydrochloride and diazepam. The theophylline profiles were linear in the time period 4-5 $min^{1/2}$ but thereafter showed positive deviations. The square of time profiles for tetracycline hydrochloride matrices were more complicated. Initial rapid release by 5 min^{-1} was followed by retardation in release rates and then by further increased in release rate. Square root of time kinetics therefore did not accurately describe the tetracycline release. The diazepam profiles displayed gradual increase in release rates in the time period up to 19 $min^{1/2}$ before linearity occurred.

4. Particle size of drug

Effect of drug particle size on release is important in the case of moderately soluble drugs (23). Hogan (5) indicated the influence of particle size on the drug release rate. In tablet matrix systems the tablet is in the form of compressed compact containing promethazine hydrochloride (250-500 μm), aminophylline (125-180μm), propranolol hydrochloride (125-180 μm) and HPMC K15M. The results showed that in the case of water-soluble aminophylline or propranolol HPMC-based tablets an increase in drug particle size did not significantly alter the release rate of the drug. A noticeable effect was seen only at a low drug : HPMC ratio and at a large drug particle size (above 250 μm), in this case, rapid dissolution of the water soluble drug would leave a matrix with low tortuosity and high porosity. Ford *et al*. (47) reported that the drug particle size was importance in the case of insoluble drugs, but for soluble drugs differences were only noticeable at low levels of HPMC and when the drug particle size was large.

Velasco *et al*. (6) have studied the effect of particle size of diclofenac sodium on release rates from HPMC matrix. The values of the kinetic constant k_2 increased significantly ($F = 17.43$, $P<0.05$) when the drug particle size decreased. The root time

release rate showed a different behavior, the value being higher in the formulation with the highest particle size of the drug (F = 4.49, P<0.05). Lag time increased significantly (F = 60.87, P<0.05) with increase in the drug particle size. The results showed that for a given effective surface area, diclofenac particle size influenced the release rate from HPMC tablets. The smallest particle size of drug dissolved more easily when dissolution medium penetrated through the matrix resulting in a greater role for diffusion. The larger particle size dissolved less readily and therefore was more prone to erosion at the matrix surface. A similar dependence was shown for a less soluble drug, indomethacin by Ford *et al*. (47).

The effect of some formulation variable from the release rate of oxazepam from HMPC was investigated by Tros de Llarduya *et al*. (48), the principle factors affecting this parameter was the drug particle size. It was observed in their study that the oxazepam dissolution rates (k) decreased as the particle size increased. The lag time (t_o) and the n values increased when the oxazepam particle size was 0.210-0.250 mm.

5. Matrix additive

5.1. Fillers

Other important factors in modulating drug release from monolithic matrix tablets include the type and quantity of excipients. It has been reported that the use of insoluble excipients such as dicalcium phosphate dihydrate in matrix tablets containing insoluble drug alprazolam and 40% HPMC K4M decreased the rate and extent of drug release compared with the same matrix containing soluble excipients like lactose (3). No explanation was provided regarding the effect of these excipients on the dynamics of hydration and front movements within the matrix as well as role of excipients on actual release mechanism(s) (49).

Nellore *et al*. (35) studied the effect of filler (57% of the tablet weight) on a metoprolol formulation at 20% Methocel® K4M level. They concluded that filler solubility had a limited effect on release rate. The release profiles showed a decrease of about 5-7% after 6h, as the filler was changed from lactose to lactose - microcrystalline cellulose then to dicalcium phosphate dehydrate - microcrystalline

cellulose. Addition of soluble fillers enhanced the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug, while insoluble fillers like dicalcium phosphate dihydrate got entrapped in the matrix. Also, it was assumed that the presence of a swelling insoluble filler like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface. Changing the filler from 100% dicalcium phosphate dihydrate to 100% lactose resulted in an increase in metoprolol release from Methocel® K100LV tablets at 4, 6 and 12 hr (37). This was explained by dissolution of lactose and the consequent reduction in the tortuosity and/or gel strength of the polymer. Similar dissolution profiles were obtained for filler concentration up to 48%. No dose dumping due to stress cracks (50) during gelling were observed in the case of insoluble fillers.

Hydroxypropyl methylcellulose (HPMC) matrix tablet containing melatonin (MT) was formulated as a function of HPMC viscosity, drug loading, type and amount of disintegrant, lubricant and glidant, and aqueous polymeric coating level and its was compared with two commercial product (51). The release characteristics of the HPMC matrix tablet were investigated in the gastric fluid for 2 hr followed by study in intestinal fluid. The surface morphology of an uncoated HPMC matrix tablet using scanning electron microscopy was crude, showing aggregated particles and rough crystals or pores, but it became smoother as the coating levels increased. As the HPMC polymer viscosity increased, the release had a tendency to decrease. As the drug loading increased, the release rate slightly decreased. When polyplasdone® XL, Primojel® and Ac-Di-Sol® except Avicel® were incorporated in the HPMC matrix tablet, the release rate was markedly increased. There was no significant difference in release profiles when a mixture of lubricants and glidants (magnesium stearate, talc, and Cab-O-Sil®), except for magnesium stearate alone, was incorporated in to low and high viscosity grade of HPMC matrix tablets. As the coating level increased, the release rate gradually decreased, giving an increased lag time. The sustained-release HPMC matrix tablet with optimizing formulation may provide an alternative for oral controlled delivery of MT and is helpful in the future treatment of circadian rhythmic disorders.

The study presented the results of in vitro dissolution of controlled-release theophylline tablets using hydroxypropyl methylcellulose as a rate-retarding

polymer. The effects of the addition of diluents, and the surface area of matrix tablets on the theophylline release rate were investigated by Veiga *et al*. (52). The results of the effect of adding diluents (soluble or insoluble) was not demonstrated although some authors had shown that those products, in large enough quantities, bring about marked differences in the release rate of active principles. So, it can be concluded that, in this work, the amount of diluent (11% or 22%) was not adequate to alter the release kinetics of theophylline. The studies developed by Williams *et al*. (3) led to the conclusion that the type and level of excipient influenced the rate and extension of drug release.

Vargas *et al*. (53) investigated the effect of polymer level and diluent type on theophylline release from matrices. The formulation containing theophylline anhydrous, Methocel® K4M Premium, different diluents (Fast-Flo, Avicel® pH 101, and Emcompress®), and magnesium stearate were prepared by direct compression. The effect of diluent types on drug release from matrices containing 10% polymer were investigated. As depicted in their study, at the 10% polymer level, Avicel® pH 101 matrices could not maintain integrity, and all drug was released at 1 hr of dissolution testing. Fast-Flo (lactose) released all drug at 6 hr of dissolution testing, while Emcompress® matrices released only 68.1%. The results showed the percentage of drug release from matrices containing 30% polymer and different diluents. At 6 hr of dissolution testing, the percentage drug released from lactose matrix was 65.5% while the percentage drug released from Avicel® pH 101 and Emcompress® matrices was 56.3% and 55.3%, respectively. The data showed no significant difference between the three diluents up to 3 hr of dissolution testing. At 4 hr and 6 hr, there was a slight difference in drug release between matrices prepared with Fast-Flo (lactose) and matrices prepared with Avicel® pH101 or Emcompress®. No difference in drug release was observed between Avicel® pH 101 and Emcompress® matrices up to 6 hr. The same trend was true for matrices prepared with 40% polymer. Te divergence between dissolution profiles of the different diluent formulations may be explained by the difference in solubility of the diluents and their subsequent effects on the tortuosity factor. In addition, the results showed that at low polymer level (high diluent content), differences were more apparent between soluble and insoluble diluent. Less difference

can be seen in tablet formulation containing 30% Methocel® K4M and 40% Methocel® K4M.

Krogel *et al*. (27) investigated the types of filler (lactose, microcrystalline cellulose and dibasic calcium phosphate) in the matrix tablet. With the low viscosity grade HPMC E5, the drug was released the fastest from tablet containing the water-soluble filler , lactose, when compared to the water-insoluble fillers, microcrystalline cellulose and dibasic calcium phosphate. With the higher viscosity grade HPMC E4M, the difference in drug release with different fillers were similar.

Cao *et al*. (54) studied the effect of incorporating pharmaceutical excipients such as surfactant (55,56), disintegrants and solubilizers on the in vitro release profiles and the release mechanism of monolithic hydroxypropyl methylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered Tylenol® ER tablets. The types and amounts of pharmaceutical excipients in m-HPMC tablets were found to crucially control acetaminophen release characteristics. Release profiles were governed by water uptake and tablet erosion in aqueous media. Optimally formulated m-HPMC tablets showed distinct dual release characteristics in different dissolution media and in vivo bioavailabilities equivalent to commercially available bi-layered Tylenol® ER tablet.

The effect of varying the type of diluent (insoluble Calcium phosphate or water-soluble arabic gum) and the diluent/matrix ratio on the drug release behavior from both lipophilic (glyceryl behenate, Compritol) or hydrophilic (hydroxypropyl methylcellulose) matrix tablets were investigate by Furlanetto *et al*. (57). Ketoprofen (KETO), theophylline (THEO) and sodium sulphadiazine (NaSDZ) were selected as model drugs on the basis of their respectively very low, medium and high water-solubility, in order to evaluate the influence of this parameter as well. In the case of KETO tablets with HPMC as polymeric matrix where it is clear that the effect of the two type of diluent (CaP or A.G.) on the considered responses is not statistically important. In contrast, the change in level of the other factor (matrix/diluent ratio) was statistically significant. Interestingly, opposite results were obtained when using Compritol as matrix-forming material. In fact, in this case,

changes in the matrix/diluent (w/w) ratio were not important, whereas the diluent type was statistically significant. These different results can be explained on the basis of the different nature of the two matrices and of the lipophilic character of the drug. In fact, the dissolution and subsequent diffusion of KETO through the hydrophilic HPMC matrix tablets is particularly unfavorable and, therefore, the progressive replacement of HPMC by an inert diluent improves the drug release rate. Moreover the results indicated that this effect takes place with both the examined fillers, despite their different solubilities. Probably, the insoluble CaP acts by interfering with the gel structuring and hinders the gel-forming process of the matrix. On the other hand, the soluble A.G. acts as a channeling agent, by rapidly dissolving and easily diffusing outward (58). On the contrary, in the case of tablets with the lipophilic Compritol (due to the higher affinity of the hydrophobic KETO towards such matrix, through which the dissolved drug more easily diffuses) the type of diluent added was more important than the matrix/diluent ratio and it was the critical factor in determining the dug release rate. The presence of CaP or A.G. had opposite effects on the drug release rate. The former displayed a negative influence, by reducing the matrix erosion process and consequently hindering drug diffusion and release, whereas the latter had a positive effect, since, as in the case of HPMC tablets, its rapid dissolution allowed a decrease in tortuosity and/or an increase in the matrix porosity. With regard to the THEO tablets showed that in the case of the HPMC matrix, only the type of diluent was important and that, however, in contrast to the case of KETO tablets, the highest matrix/diluent ratio was the most effective combination. It can be reasonably hypothesized that NaSDZ, due to its good water-solubility, rapidly dissolves and then the presence of high amounts of the hydrophilic diluent could be not only unnecessary, but also have a competitive effect and reduce the drug dissolution rate from matrix tablets. Moreover, the unexpectedly similar results obtained with both HPMC and Compritol matrices, in spite of their opposite properties and the very high water-solubility of the drug, could probably be attributed to the excessive affinity of NaSDZ for the hydrophilic matrix; in fact, it can give rise to the formation of possible drug-polymer interactions which could in-turn reduce the drug release rate. Such hypothesis is supported by the demonstrated ability of HPMC to have hydrogen bonding interactions with various drug molecules (59-61). Sung *et al*. (41) demonstrated that

changes in HPMC : lactose ratio can be used to produce a wide range of drug release rates.

5.2. Polymeric excipients

Another method of influencing the solute release from matrix tablet is by replacing part of the original matrix by a second polymer. Freely and Davis (62) reported that non-ionic polymers did not alter drug release significantly from HPMC matrices; however, ionic polymers were capable of retarding the release of oppositely charged molecules. They studied the effect of polymeric additives (non-ionic polyethylene glycol 6000 or ethyl cellulose, cationic diethylaminoethyl dextran, anionic sodium carboxymethyl cellulose Na-CMC) on drug release (chlorpheniramine maleate, sodium salicylate and potassiumfenoxymethylpenicillin) from HPMC matrix (85%). Non-ionic polymers (15% of tablet weight) did not significantly alter the release rates. Na-CMC (50% replacement of HPMC) reduced the chlorpheniramine maleate release in pH 7 buffer (near zero order release), but not in an acidic medium. There was a complexation of the drug with the anionic polymer; which was not possible below pH 3, when Na-CMC was in its unionized insoluble form. As a result of the complexation, the gel erosion became the prominent release mechanism instead of diffusion. No interaction occurred between sodium salicylate and Na-CMC (both anionic). In the presence of diethylaminoethyl dextran, sodium salicylate release was slower at pH 7, but not altered at pH 1 (when the drug was present in its unionized form). Overall, the effect of ionic polymers incorporated into HPMC matrices on the release of oppositely charged drugs was small. Takka *et al*. (63) used the drug-polymer ionic complexation approach in designing oral dosage formulation for controlled release of buspirone. Anionic exchange polymers sodium carboxymethyl cellulose and methacrylic acid / ethylacrylate copolymer were recommended based on the complexation affinity and dispersability in the aqueous environment of the gastrointestinal tract. The weight ratio of buspirone to anionic exchange polymer varied between 4:1 and 1:6, preferably between 2:1 and 1:4. In addition to facilitating the controlled release of buspirone, the formulations increased the bioavailability and reduced the inter-individual variability. Therefore, the buspirone-ion exchange polymer HPMC tablets permitted enhanced targeting of therapeutic amounts and

effects of the drug. Takka *et al*. (64) studied the effect of the addition of anionic polymers (Eudragit® S, Eudragit® L 100-55, and Na-CMC) on the release of weakly basic propranolol hydrochloride from HPMC matrices. The interaction between propranolol hydrochloride and anionic polymers influenced the drug release. The HPMC : anionic polymer ratio also affected the drug release. The matrix containing HPMC : Eudragit® L 100-55 (1:1) produced pH-independent extended release tablets. Bonferoni *et al*. (65) used an optimization procedure to determine the HPMC : λ-carrageenan ratio (34:30) required for a pH-independent release of chlorpheniramine maleate. λ-Carrageenan was added to overcome the increase in diffusion path length and decrease in the release rate associated with HPMC systems. λ-carrageenan was subjected to erosion, which was higher at acidic pH.

The addition of some carboxymethylcellulose (CMC) to matrix tablet was also studied by Juarez *et al*. (66). Tablets of the model drug 4-aminopyridine with HPMC were prepared with different proportions of polymer content as well as with different proportions of admixed CMC in the range up to 35% (based on the total polymer content). Loading of CMC in the range of 10-40 mg/tablet, while keeping the content of drug 20 mg/tablet and HPMC 80 mg/tablet constant, significantly affected the release process. This results show the regression parameters of release curves of these matrices. The slop of the release profiles in HCl 0.1 N and those obtained from phosphate buffer indicated a trend to increasing values of the exponent *n*, as matrices increase their CMC content, as can be seen in this study. Greater proportions of CMC exhibited drug release profiles with a trend toward a relaxation/erosion controlled process. Release profiles of matrices releasing the drug in phosphate buffer are nearing zero-order when the CMC content is 40 mg/tablet. These results showed the same trend as reported previously for formulation of hydrosoluble active principles (67,68). However, the release profiles obtained in HCl 0.1 N are all related by diffusional mechanism, at any CMC content in the matrix tablets, in spite of the trend toward higher exponent *n* values. These exponent *n* values in a range between 0.46 and 0.6 can be considered normal for diffusion-controlled processes (67). The result showed that increasing concentration of CMC in the matrix tablets reduced the release rate of 4-aminopyridine in both HCl 0.1 N and phosphate buffer pH7.4 media. This reduction in release rate may be attributed to stronger hydrogen bonding between the carboxyl

groups on CMC and hydroxyl groups on the non-ionic HPMC leading to stronger crosslinking between the polymers (68). The potential contributions to such an effect due to an increase in the diffusional path length (40,67) and changes in surface areas of matrices because of the increase polymer content, are not explicitly considered in the analysis; however, they can be considered alternatives to modify release rates. No attempts were made to correct dissolution rates because of changes in surface area (69) since the goal of the study is more qualitative. The release rates in HCl were broadly triple the release rates in phosphate buffer. This increase in release rate was observed in spite of the fact that the dissolution of 4-aminopyridine/lactose tablets was similar and rapid in both media. These results anticipated an undesirably slower release of 4-aminopyridine after a pH change from HCl 0.1 N to phosphate buffer, which would lead to a fed fast effect in vivo.

6. pH of dissolution medium

Many drugs of weak bases or salts demonstrated pH-dependent solubility in the pH-range of the gastrointestinal tract. With controlled release dosage forms, a possible pH-independent release could resulted in vivo variability and bioavailability problems. Therefore, several attempts to overcome the problem of pH-independent solubility of weakly basic drugs have been studied. They were mostly based on the presence of the acidic excipients, such as water-soluble or water-insoluble polymers of organic acids, which either increase the permeability of the drug delivery systems by leaching out at higher pH values or which keep the pH within the system in the intestinal in low pH-range and thus resulted in high solubility of the drug. The objective of that study was to achieve a pH-independent release of a weakly basic drug from matrix tablets consisting of ethylcellulose, an insoluble, almost unswellable polymer, or HPMC, a swellable and water-soluble polymer, respectively (70). These two polymers were widely used matrix formers in controlled drug delivery systems. Verapamil hydrochloride is a useful model substance to test the formulation concept because of its distinct pH-dependent solubility. Due to this pH-dependent solubility, a remarkable difference in the resulting drug release from ethylcellulose and HPMC tablets was observed in 0.1 N HCl and phosphate buffer. In the case of ethylcellulose-based matrix tablets, 31% of the drug was release after 1 hr in 0.1 N HCl, whereas

only 11% were released in phosphate buffer. After 8 hr, 83% of the drug was released in 0.1 N HCl versus only 34% in phosphate buffer. This can be explained as follows; the release of an incorporated drug from an insoluble ethylcellulose matrix is predominantly diffusion-controlled. In the case of highly swellable HPMC matrix tablets, approximately 15 and 6% of the drug were released after 1 hr in 0.1 N HCl and phosphate buffer, respectively. After 8 hr, 61% of the drug was released in 0.1 N HCl, whereas only 23% were released in phosphate buffer. Therefore, two different approaches to overcome the problem of pH-dependent drug release are demonstrated in this paper. The first one used the enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS) as a pore-former at high pH values, the second one used organic acids such as furmaric, succinic, or adipic acid to create an acidic micro-environmental pH inside the polymer matrices. The first approach failed to achieve pH-independent drug release, whereas the addition of organic acids to both matrix former was found to maintain low pH values within the tablets during drug release in phosphate buffer pH 6.8 or 7.4. Thus, the micro-environment conditions for the dissolution and diffusion of the weakly basic drug were almost kept constant. The release of verapamil hydrochloride from tablets composed of ethylcellulose or hydroxypropyl methylcellulose (HPMC) and organic acids was found to be pH-independent

The studies of Siepmann *et al*. (14) were reported in the literature as to investigate the drug release kinetics from HPMC tablets. To test the applicability of the new model, experiments were conducted with various drugs (chlorpheniramine meleate, diclofenac sodium, and propranolol hydrochloride) in different release media (0.1 M NaCl, 0.1 M phosphate buffer pH 7.4, and deionized water). For propranolol hydrochloride, this indicated the negligible effect of the type of release medium on the concentration dependence of the diffusivity.

Chetty *et al*. used two types of diclofenac sodium commercially available wax tablets and developed hydroxypropyl methylcellulose (HPMC) matrix tablets to investigate the effect on release rate of varying pH, ionic concentration, composition of the dissolution medium. The effect of pH on dissolution rate was investigated at pH 5.0, 6.8, and 8.2 phosphate buffer (0.2 M) and 100 rpm agitation rate were used for all studies. The results showed that release from both preparations is extremely slow at

pH 5.0 with a maximum of 20% of drug dissolution at 20 hr for both preparations. Faster dissolution rates are displayed by both formulation at pH 6.8 and pH 8.2. Both preparations are similarly affected by pH changes, and so it can be concluded that drug dissolution is a function of drug solubility at the various pHs. The effect of pH is not caused by formulation variables. Indeed, the pH-dependent solubility of diclofenac sodium was well known and was documented. Diclofenac sodium is freely soluble above pH 6.0 in phosphate buffer. Hence, it is not surprising that the rate of dissolution at pH 5.0 is so slow or that release rates are about the same at pH 6.8 and pH 8.2

7. Compression force

The compaction pressure controls both the hardness of the tablet and the pore structure of the matrix, and should be sufficiently high for the tablet to maintain its integrity during the release of the drug.

Velasco *et al*. (6) reported that for HPMC tablets, although the compression force had a significant effect on tablet hardness, its effect on drug release from HPMC tablets was minimal (71). It could be assumed that the variation in compression force should be closely related to a change in the porosity of the tablets (72). However, as the porosity of the hydrated matrix is independent of the initial porosity, the compression force seems to have little influence on drug release (38). Rekhi *et al*. (37) reported that changes in compression force or crushing strength had minimal effect on drug release from HPMC matrix tablets once critical hardness was reached. Increased dissolution rates were observed when the tablets were found to be extremely soft, and this phenomena was attributed to a lack of powder compaction, as tablet hardness was only 3 kp. Ebube *et al*. (73) presented the effects of compression force on tablet hardness for the matrix formulations. As expected, the tablet hardness increased as compression force increased. The tablets showed a tendency to cap above the compression force of 3000 lb. Formulations containing only acetaminophen did not show any differences in tablet hardness as the ratio of hydroxypropyl methylcellulose (HPMC) to polyvinylpyrrolidone (PVP) were varied, and maximum hardness was reached at compression force of 4000 lb. Tablet hardness increased considerably in formulation containing pseudoephedrine. This could be because formulation

containing both acetaminophen and pseudoephedrine produced granules with smaller mean particle size than those containing acetaminophen. It is possible that during the tableting process, the fines filled the interstitial spaces between the coarse particles, which resulted in enhanced interparticular bonding between the particles.

Kabanda *et al*. (74) stated that tablet crushing strength can also influence the initial drug release phase. Thus, tablets made at the lowest crushing strength with Methocel® K4M showed the initial burst effect due to a partial initial disintegration. Once the polymer was swollen, the dissolution profiles became similar to those tablets compressed to a higher crushing strength. In a similar way of this study the variation in lag time and crushing strength according to the compression force was statistically significant ($P<0.05$ and $P<0.05$ respectively), and a difference between the 3 kN batches and the other batches (6, 9 and 12 kN) can be observed. Thus, at low applied compression force the lag time was lower, maybe because the gel layer was formed after drug release had commenced earlier than in the other batches. However, the results seem to indicate that once crushing strength is achieved with a certain applied compression force. This variable has little further effect in the initial release of the drug.

Ebube *et al*. (75) studied the effect of pseudoephedrine (PE) as a co-active, HPMC : HPC ratio, polymer loading, pH of the dissolution media, and compression force on acetaminophen(APAP) release. The effect of changes in compression force on the initial release of APAP from the compressed matrix tablets. Increasing the compression force from 2000 to 3000 lb slightly decreased the initial rate of APAP released after 60 min. Tablets compressed beyond 3000 lb showed tendency to cap and were not tested for in vitro drug release. Previous investigations have also indicated that changing the compression force had little effect on the dissolution rate of drugs from HPMC matrices (36, 76). In this present study, some formulations showed an initial burst of drug release from matrices compressed at 2000 lb. Therefore, the rest of the in vitro drug release studies were performed only on tablets compressed at a compression force of 3000 lb.

The effect of compression speed and force on the compaction properties of four viscosity grades of hydroxypropyl methylcellulose 2280 (HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M) have been studied by Nokhodchi *et al*. (72).

This study showed that at the different compression forces from 5 to 20 kN and compression speed from 15 to 500 mm/s, HPMC K100 was the easiest of four plasticity during compression than the other grades. However, when compacts were compared at zero porosity rather than equal forces, the highest viscosity grade (HPMC K100M) produced compacts of higher tensile strength compared to the other viscosity grades. The study also showed that the tensile strength of all viscosity grades of HPMC were affected by compression speed. The tensile strength of HPMC K100 was more sensitive to compression speed than the other viscosity grades. It must be kept in mind that when the compression speed of tableting machine is increased, the tensile strength of HPMC compacts decreased. Therefore, in order to obtain tablets with high tensile strength for sustained release drug delivery systems a low compression speed may be suitable. It was thus suggested that for compression of HPMC powder, the time during which the particulate system is under a compressive load may be an important influence.

8. Tablet shape

Influence of shape factors on kinetics of drug release from matrix tablets were investigated by several workers. A likely means of modifying the release kinetics from matrix system is to alter the geometry of the matrix. Rekhi *et al*. (37) showed that the size and shape of the tablet for the matrix system undergoing diffusion and erosion might impact the drug dissolution rate. Modification of the surface area for metoprolol tartrate tablets formulated with Methocel® K100LV from the standard concave shape (0.568 sq. in.) to caplet shape (0.747 sq. in.) showed an approximately 20-30% increase in dissolution at each time point. Based upon these results, the researchers concluded that for maximum uniformity of extended release characteristics, tablet matrices should be manufactured to be as spherical as possible, in order to produce the minimum release rate, with regard to tablet shape. Siepman *et al*. (15,17) showed that varying the aspect ratio (radius/height) of the HPMC tablets is a very easy and effective tool to modify the release rate of the matrix system. Release rate for tablets with the same volume was higher for flat shape (ratio = 20) than regular cylinders (ratio = 2) and almost rod-shaped cylinders (ratio = 0.2). The results were attributed to difference in tablet surface area. A mathematical model was proposed that could

employed in order to calculate the optimal aspect ratio and size of a cylindrical tablet required to achieve a specific release profile. The model takes into account Fickian diffusion of water in and drug out of the tablets and swelling; it does not take into account dissolution and it cannot be applied for water insoluble drugs, which are released by dissolution process. The mathematical model proposed above was then used to predict the dissolution rates of propranolol hydrochloride and chlorphenramine maleate (water soluble drugs) by Siepmann *et al*. (15).

In this present study, matrix tablets with one hole or multihole tablets were prepare by Cheng *et al*. (77). Hydroxypropyl methylcellulose (HPMC) was selected as the excipient. Theophylline and diltiazem hydrochloride were used as model drugs to investigate in vitro drug release from donut-shaped tablets. The purpose of this study was to evaluate how various parameters such as the hole size, number of holes, drug solubility, and stirring rate affected drug release from donut tablets. The results demonstrated the effect of the hole size on the theophylline released from tablets of the perorated design. Release profiles show that the drug released from the tablets with the 2-mm and 3-mm hole was more rapid than from the tablets without holes. The linear release percentage of donut tablets is up to 80-90%. In contrast, the linear release percentage of tablets without holes was only about 50%. The most important reason for this different was the releasing surface area. As to the tablets without holes, the release surface area decreased with time, thus led to the anomalous release kinetics, while the donut tablet released drug through the outer surface and through the inner surface of the hole. During the release process, the increase the inner surface area of the hole could compensated for the decrease of the outer surface area, thus provided a relatively constant surface area to release drug. On the other hand, the larger the hole size was, the longer the linear release would be. However, the release profiles of the tablet with the 1-mm hole was similar to the tablet without holes. This could be explained by the shape change of the tablet during the drug release process. Since HPMC was a hydrophilic polymer, the tablet was swollen in the early stage of the drug release process, so if the hole size was too small, the hole would be stemmed by the swollen polymer, thus led the release profiles similar to the tablet without holes.

9. Tablet size

For tablets having the same aspect ratio and drug concentration, Siepman *et al*. (17) found that the tablet size had a very strong influence on the release rate; within 24 hours, 99.8% was released from the small tablets, 83.1% from the medium size and 50.9% from the large tablets. It was hypothesized that the smaller tablets released drug more rapidly due to an increased surface area per volume. Additionally, it was concluded that larger diffusion pathways existed in the larger tablet leading to a decrease in drug release.

Hydroxypropyl methylcellulose (HPMC)

1. Physiochemical Properties

Hydroxypropyl methylcellulose (HPMC) was first synthesized in the laboratories of Dow chemical company in the late 1930's and commercially available in 1948. HPMC is manufactured by dissolving cellulose from wood pulp in sodium hydroxide solution and reacting this methyl chloride and propylene oxide. These reactants provide the methoxy and hydroxypropyl substitution, respectively, on the original cellulose polymer. The product is washed thoroughly with hot water, in which it is insoluble, so as to remove contaminants such as sodium chloride and unreacted starting materials. HPMC grades of low viscosity are made by a depolymerization process on higher viscosity materials. The product is dried, milled, and packed into final containers (3). HPMC is available in 4 different chemistries (E, F, J, and K series) based on the varying degrees of hydroxypropyl and methyl substitutions. The K series is premium series meaning it has the fastest hydration rate. The K100LV polymer thus has fast hydration, has a viscosity of 100 cps and is termed low viscosity as per the “LV” designation. HPMC K100LV is a hypromellose 2208 which meets the requirements of the USP and European Pharmacopoiea and has been certified kosher.

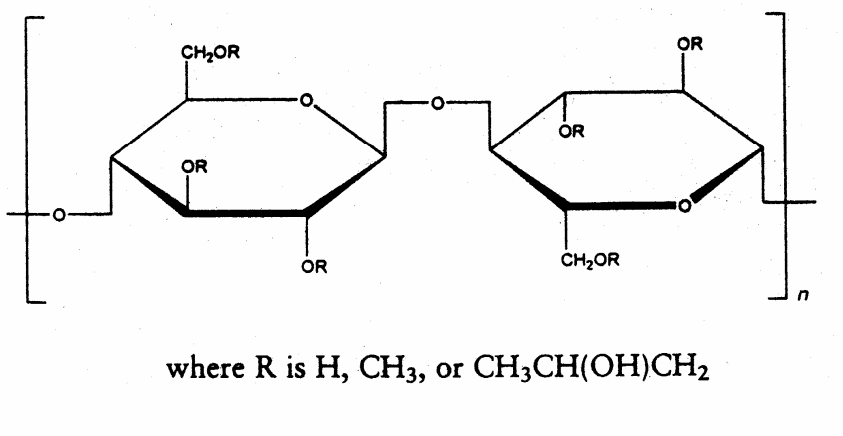

Figure 3. Structure of hydroxypropyl methylcellulose

1.1. Molecular weight : Approximately 10,000-1,500,000

1.2. Description

White to slightly off white powder, fibrous or granular powder

1.3. Melting point

Browns at 190-200 ^{0}C, chars at 225-230 ^{0}C. Glass transition temperature is 170-180 ^{0}C.

1.4. Specific gravity : 1.26

1.5. 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 mixture of methanol and dicholromethane. Certain grades of hydroxypropyl methylcellulose (HPMC) are soluble in aqueous acetone solutions, mixture of dicholromethane and propan-2-01, and other organic solvents.

2. Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agent. Since it is nonionic, hydroxypropyl methylcellulose will not form complex with metallic salts and ionic organic to form insoluble precipitates.

3. Applications

HPMC is used for many years as a food additive, where it frequently serves as a thickness or as an emulsifier for oil-and water-based systems. Purified grades of HPMC are also used use in personal care products, such as shampoo (4). The majority of HPMC used in pharmaceutical products is tablet film-coating formulations. The first application of HPMC for film coating appeared in the Abbott laboratories in 1962, HPMC is also used to a used as a tablet binder, a viscosity modifier for eye drops, and a thickening agent for oral liquid preparations. HPMC is dissolved in some organic solvents and also in water over the entire biological pH range.

Indomethacin

Indomethacin is a 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 (78).

1. Chemical names : Indomethacin is 1- (4-Ch1orobenzoyl)-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 (79).

2. Formula : $C_{19}H_{16}ClNO_4$

3. Molecular weight : 357.81

4. Chemical structure :

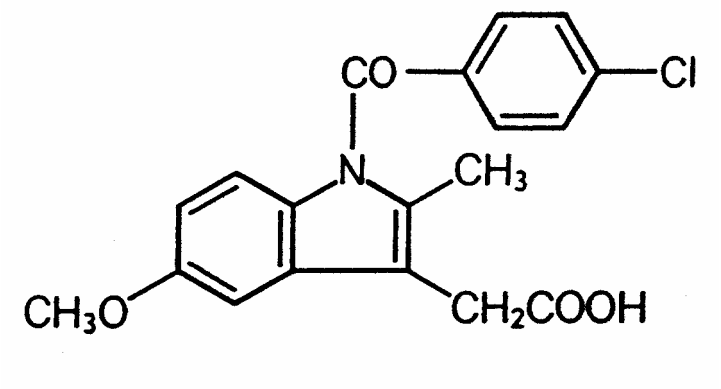

Figure 4. Structure of indomethacin.

5. Physical properties

5.1. Appearance

A white to yellow - tan, odorless or almost odorless, crystalline powder. Melting point is about 158 ^{O}C to 162 ^{O}C (79).

5.2. Crystal properties

Indomethacin is known to exist in several polymorphic forms which are different in melting point and solubility (79). Most authors refer to these polymorphs as From 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 (80).

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 (78,79). Its solubility data have been reported in Table 1 (80).

5.4. Dissociation constant

pKa equals 4.5 for the carboxyl group of indomethacin (79,80).

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 (80). 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 (80).

Table 1. Solubility data of indomethacin (80).

Solvent	Temp (^{O}C)	Solubility
Water	25	0.40 mg/100 ml[a]
Water	25	0.52 mg/100 ml[b]
Water	25	0.88 mg/100 ml[c]
Water	RT	Practically insoluble
Phosphate buffer pH 5.6	25	3.00 mg/100 ml[a]
Phosphate buffer pH 5.6	25	5.00 mg/100 ml[b]
Phosphate buffer pH 6.2	25	11.00 mg/100 ml[a]
Phosphate buffer pH 6.2	25	16.00 mg/100 ml[b]
Phosphate buffer pH 7.0	25	54.00 mg/100 ml[a]
Phosphate buffer pH 7.0	25	80.00 mg/100 ml[b]
Ethyl alcohol (95%)	RT	1 in 50
Chloroform	RT	1 in 50
Ether	RT	1 in 50
Methanol	25	32.00 mg/g
Benzene	25	4.00 mg/g
n-Butanol	25	19.00 mg/g
Sec-Butanol	25	27.00 mg/g

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

7. Dosage and administration (81)

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

The 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 mouth, or rectally as a suppository. In acute gouty

arthritis a suggested dose is 50 mg three times daily and in dysmenorrhea 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 course 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 the first dose.

8. Adverse reactions (81)

8.1. General and toxic reactions

Side effects, which involve up to 60% of patients, are closely correlated with the strong anti-inflammatory potency of indomethacin. Gastric irritation including ulcers, bleeding and perforation, predominate central nervous system complications are related to cerebral edema. Headache is common. Hematological effects are reported, but are infrequent. Nephrotoxicity is important in pre-existing renal impairment. Ocular toxicity may follow long-term use.

8.2. Hypersensitivity reactions

Cross-reactivity with aspirin has been reported. The hazards of administering topical indomethacin to asthmatic patients should be widely known.

9. Pharmacokinetic

Indomethacin is readily and almost completely absorbed from the gastrointestinal tract in adults after oral administration. The peak plasma concentrations are reached about 2 hours after a dose (78). Therapeutic concentration in plasma is usually in the range 0 5 - 3 μg/ml (79).

Indomethacin is about 99% bound to plasma proteins. The plasma half-life in adults ranginy from 2.6 to 11.2 hours has been reported (78). It is subject to considerable enterohepatic circulation. Metabolic reactions include O-demethylation, N-deacetylation and glucuronic acid conjugation, the major metabolites being desmethylindomethacin (DMI), deschlorobenzoylindomethacin (DBI) and desmethyl-deschlorobenzoylindomethacin (DMBI) and their glucuronides. These substances,

together with unchanged indomethacin and its glucuronide, are excreted in both urine and in the faces in variable amounts (79).

Controlled release preparations of indomethacin

The controlled release indomethacin dosage forms have been prepared by various methods. Ethylcellulose as a direct compression controlled release matrix forming material has been used, and the effects of different viscosity grades of it on the physical characteristics of indomethacin tablets was studied by Upadrashta *et al*. (42). Lower viscosity grades of ethylcellulose were more compressible than higher viscosity grades, allowing production of harder tablets which resulted in controlled release of the drug over a longer time period. Hosny (82) reported that the release rate of indomethacin depended on the polycarbophil content of the tablet formulations. As the carbophil content increased, the release amount of indomethacin decreased. The effect of indomethacin and lactose on the swelling properties of various types of hydrophilic cellulose derivatives (methylcellulose, hydroxypropyl methylcellulose and hydroxypropylcellulose) was studied by Panomsuk *et al*. (83). The results showed that hydroxypropylcellulose produced a matrix with a high integrity. Indomethacin and lactose changed the swelling properties of the hydrophilic cellulose matrices.

Controlled release indomethacin microspheres, prepared by different techniques, have been studied extensively. Roy (84) and his co-works have used a multiple-emulsificaton technique to develop indomethacin-loaded microsphere. The in vitro drug release followed the first-order diffusion controlled dissolution, and more than 85% of the drug was released over 6 hours at pH 6.2 for all dissolution batches. The phase separation/coacervation technique was chosen by Albin *et al*. (85) to prepare highly insoluble microspheres based on polycations of a variety of polymers (mainly polysaccharides) that were FDA approved. Maximum plasma concentration obtained from the Ca-polygalacturonic acid salt formulation was significantly lower than the value of the non-formulated product. Giunchedi *et al*. (86) reported the encapsulation of indomethacin with cellulose acetate trimellitate, enteric polymer, using a spray drying technique. The in vitro drug release tests, carried out using a pH change method with a flow-through cell apparatus, showed a typical delayed drug release to the pH-dependent solubility of the polymer.

There are several references dealing with, the manufacture of controlled release indomethacin pellets. Dave *et al*. (87) studied the mechanism of indomethacin release from pellets prepared by counterion method and by ethylcellulose coated sugar pellets. It was found that zero order and square root model provided a good fit to both formulations. El-Mahrouk *et al*. (88) investigated the use of Eudragit® RL 100, Eudragit® RS 100 and bees wax as drug release controlling materials for indomethacin loaded seeds. They found that release rate profile of indomethacin from coated seeds was dependent upon the particle size of the seeds and the concentration as well as the type of Eudragit®.

A controlled release indomethacin micropellets, using gelatin as the matrix system which was rigidized with formalin, was developed by Sa *et al*. (89). The proportion of drug and gelatin as well as the concentration of formalin had the pronounced effect on the indomethacin release rate.

The possible application of ethylcellulose as a potential carriers for the preparation of prolonged release formulations of indomethacin using the solid dispersion technique was evaluated by Shaikh *et al*. (90). It was found that the amount of ethylcellulose had a greater effect than the viscosity grade of ethylcellulose on the magnitude of release of drug from the drug-polymer matrices.

Other preparations of controlled release indomethacin, including ethylcellulose microcapsules prepared by coacervation, granules prepared with hydrogenated soya phospholipid and cholesterol, beads prepared from alginate or agarose, and w/o/w multiple emulsion system were studied by Tirkkonen *et al*. (91), Nishihata *et al*. (92), Shirashi *et al*. (93), Haglund *et al*. (94) and Roy *et al*. (95), respectively. All of these preparations succeeded in controlling the release of indomethacin.

CHAPTER III
MATERIALS AND METHODS

Materials

1. Indomethacin BP (Lot number 020103, China)
2. Hydroxypropyl methylcellulose (HPMC) (Methocel® K100, Lot number SK05012N21, Dow chemical company, USA)
3. Agglomerated lactose monohydrate NF (Tablettose®, Lot number 9913 A4033, Meggle GmbH,Wasserburg, Germany)
4. Microcystalline cellulose NF (Ceolus®, Lot number 15A3, Asahi Kasei Chemicals Corporation, Japan)
5. Magnesium stearate NF (Lot number 90417M, Japan)
6. Colloidal silicon dioxide NF (Aerosil® 200, Lot number CO 60448, Degussa Belgium)
7. Sodium hydroxide (Lot number 1L216191N, Carlo Erba Reagenti, Italy)
8. Potassium Dihydrogen Orthophosphate (Lot number AF501339, Ajax Finechem, New Zealand)

Equipments

1. Dissolution test apparatus (Model VK 7000, Vankel, USA)
2. Single beam spectrophotometer (Model S 1000, Secoman, France)
3. Autosampler (Model VK8000, VanKel, USA)
4. Vacuum pump (Model Dou004b, Germany)
5. Instrument rotary tablet machine (Colton Model 216, Vector Corporation, USA)
6. Strain amplifier (DPM-612A, Kyowa Electronic instrument Co.Ltd., Japan)
7. Strip chart oscillographic recorder (Model SC274, Gould Instrument Inc., USA)

8. Diametral crushing strength, diameter and thickness tester (Pharmatest PTB311, D6452, Germany)
9. Friabilator (Phannatest PTFR-A, D6452, Germany)
10. Tumbling mixer (Rotomixer, Forster equipment Co. Ltd., U.K.)
11. Electronic precision balance (Model 1518 MPB-1, Sartorius, West Germany)
12. Standard sieve mesh No.40 and 80 (F.Hurt Retsch GmbH&Co., Germany)
13. pH meter (Model MP220, Mettler Toledo, Switzerland)

Methods

1. Preparation of drug-HPMC matrices

Each tablets containing 75 mg indomethacin were made using different type and content of excipients (lactose and microcrystalline cellulose). The fraction of drug, excipient, HPMC and Colloidal silicon dioxide NF that pass through a 40 mesh sieve are mixed in a rotomixer for 10 min. Magnesium stearate NF screened through a sieve number 80 and mixed for additional 5 min. Final blends were compressed by direct compression into concave tablet with a diameter of 9.5 mm and a weight of 350 mg. The compression were made at 3 different upper punch forces i.e. 300, 600 and 900 kg using rotary tablet press (colton press model 216, USA) equipped with strain amplifier (DPM-612A, japan), strip chart oscillo graphic recorder (model SC 274, USA). The formulations of indomethacin matrix tablets are showed in Table 2.

2. Evaluation of preparation

2.1. Weight variation of tablets

Weight variation test is determined by weighing 20 tablets individually. The average and their standard deviation are then calculated (96).

2.2. Tablet thickness, diameter and hardness

Ten tablets were randomly sampled and individually measured its thickness, diameter and hardness by using a multipurpose measuring device (Pharmatest PTB311, D6452, Germany). Their means and standard deviations were reported.

2.3. Tablet friability

The friability of tablets is determined using the procedure in the USP 29 method (96). Tablet friability test is determined by taking a sample of whole tablets corresponding to 6.5 g (about 19 tablets). Loss of tablet weight with respect to initial value is calculated as percent of friability.

2.4. Content uniformity

Transfer the content of 1 tablet to a 250 ml volumetric flask, and add 100 ml of a mixture of equal volumes of methanol and pH 7.5 phosphate buffer. Sonicate until the contents are dispersed, dilute with the methanol and pH 7.5 phosphate buffer mixture (1:1) to volume, mix and centrifuge. Transfer 2 ml of the clear solution into 25 ml volumetric flask. Then the volume was adjusted with the methanol and pH 7.5 phosphate buffer mixture (1:1). The absorbance of this solution was measured in 1 cm cell using UV/Visible spectrophotometer at the wavelength of 318 nm and the methanol and pH 7.5 phosphate buffer mixture (1:1) as the blank. The absorbance was compared with the standard curve and percent drug content was calculated.

3. Determination of drug release from HPMC matrix tablets

3.1. Standard curve preparation

Indomethacin was accurately weighed 50 mg, dissolved with methanol 3 ml and diluted to volume with phosphate buffer pH 6.2 in 250-ml volumetric flask. Appropriate dilutions were then made to obtained standard solutions of 16, 32, 48, 64 and 80 µg/ml. The absorbances of this solution were determined at the wavelength of 318 nm with UV spectrophotometer, using phosphate buffer pH 6.2 as a blank. The absorbances of indomethacin standard solutions were plotted against the concentrations.

3.2. In vitro release method

In vitro drug release was performed for the manufactured tablets according to the USP 29 drug release test method for indomethacin extended-release capsules, test 1 (96). A minimum of 6 tablets per batch were tested, using dissolution test apparatus I (basket method). A rotating speed of 75 rpm was performed at 37±0.5°C. The absorbance is determined at 318 nm for the drug release in 750 ml of

phosphate buffer pH 6.2. The automated dissolution set up comprises a dissolution apparatus, a six-channel peristaltic pump, a UV/visible spectrophotometer equipped with six 1-cm quartz cells.

4. Statistical analysis

Two-way analysis of variance (using the Minitab statistical package; ANOVA balanced design) was used to assess the statistical significant of the variables studied on the percent drug released at 1, 6, 12 and 24 hours.

Table 2. Different formulations of indomethacin tablet and indomethacin matrix tablet (mg).

Code	Indomethacin	HPMC	Lactose	Microcrystalline cellulose	Magnesium stearate	Colloidal silicon dioxide	Compression force
F1/300	75.000	269.750	-	-	3.500	1.750	300
F1/600	75.000	269.750	-	-	3.500	1.750	600
F1/900	75.000	269.750	-	-	3.500	1.750	900
F2/300	75.000	-	269.750	-	3.500	1.750	300
F2/600	75.000	-	269.750	-	3.500	1.750	600
F2/900	75.000	-	269.750	-	3.500	1.750	900
F3/300	75.000	59.750	210.000	-	3.500	1.750	300
F3/600	75.000	59.750	210.000	-	3.500	1.750	600
F3/900	75.000	59.750	210.000	-	3.500	1.750	900
F4/300	75.000	129.750	140.000	-	3.500	1.750	300
F4/600	75.000	129.750	140.000	-	3.500	1.750	600
F4/900	75.000	129.750	140.000	-	3.500	1.750	900
F5/300	75.000	199.750	70.000	-	3.500	1.750	300
F5/600	75.000	199.750	70.000	-	3.500	1.750	600
F5/900	75.000	199.750	70.000	-	3.500	1.750	900

Table 2. Different formulations of indomethacin tablet and indomethacin matrix tablet (mg). (cont.)

Code	Indomethacin	HPMC	Lactose	Microcrystalline cellulose	Magnesium stearate	Colloidal silicon dioxide	Compression force
F6/300	75.000	-	-	269.750	3.500	1.750	300
F6/600	75.000	-	-	269.750	3.500	1.750	600
F6/900	75.000	-	-	269.750	3.500	1.750	900
F7/300	75.000	59.750	-	210.000	3.500	1.750	300
F7/600	75.000	59.750	-	210.000	3.500	1.750	600
F7/900	75.000	59.750	-	210.000	3.500	1.750	900
F8/300	75.000	129.750	-	140.000	3.500	1.750	300
F8/600	75.000	129.750	-	140.000	3.500	1.750	600
F8/900	75.000	129.750	-	140.000	3.500	1.750	900
F9/300	75.000	199.750	-	70.000	3.500	1.750	300
F9/600	75.000	199.750	-	70.000	3.500	1.750	600
F9/900	75.000	199.750	-	70.000	3.500	1.750	900
F10/300	75.000	129.750	105.000	35.000	3.500	1.750	300
F10/600	75.000	129.750	105.000	35.000	3.500	1.750	600
F10/900	75.000	129.750	105.000	35.000	3.500	1.750	900

Table 2. Different formulations of indomethacin tablet and indomethacin matrix tablet (mg). (cont.)

Code	Indomethacin	HPMC	Lactose	Microcrystalline cellulose	Magnesium stearate	Colloidal silicon dioxide	Compression force
F11/300	75.000	129.750	70.000	70.000	3.500	1.750	300
F11/600	75.000	129.750	70.000	70.000	3.500	1.750	600
F11/900	75.000	129.750	70.000	70.000	3.500	1.750	900
F12/300	75.000	129.750	35.000	105.000	3.500	1.750	300
F12/600	75.000	129.750	35.000	105.000	3.500	1.750	600
F12/900	75.000	129.750	35.000	105.000	3.500	1.750	900

CHAPTER IV
RESULTS AND DISCUSSION

1. Preparation of drug-HPMC matrices

Each tablets containing 75 mg indomethacin were made using different compression forces, types of excipient and HPMC : excipient ratios.

2. Evaluation of preparation

2.1. Weight variation of tablets

The amount of 20 tablets were weighted individually for weight variation test. The average weight and their standard deviation were then calculated. It could be seen in Tables 3-6 that all the tablet weights variation was under 1.5%. The tablet weight variation was found minimum for all the formulations.

2.2. Tablet thickness, diameter and hardness

When only one set of tooling was employed in this study, the diameter of the tablet should remain constant regardless of the material being compressed if the radial deformation after compaction was insignificant. Tablet thickness was a function of tablet weight and compression force. At the given tablet weight, the increase in compression force result in the decrease thickness. It could be seen the variation of thickness at any compression force was negligible due to the uniformity of powder flow. The data are shown in Tables 3-6.

The hardness values of indomethacin tablets compressed at different compression forces are given in Tables 7-10. The hardness of the tablets increased with increasing compression force (Figs. 5-7). Increasing the amount of microcrystalline cellulose slightly increased tablet hardness under three applied compression force (Figs. 5 and 7). Both HPMC and microcrystalline cellulose exhibits the same deformation behavior (plastic and elastic behavior) (97) and have strong binding properties, causing by hydrogen bonds between hydrogen groups (72).

Therefore, replacing HPMC by microcrystalline cellulose has only negligible effects on the hardness. On the other hand, the tablet hardness decreased when the amount of lactose increased (Figs. 6 and 7). The decrease in tablet hardness may be due to a decrease in the compressibility of the matrix resulting from the higher lactose proportion. It was observed that tablet hardness was influenced by the type and content of excipient.

2.3. Tablet friability

The friability decreased with increasing compression force as shown in Tables 7-10. A limiting value of 1% for friability tests of tablets has been suggested by the USP 29 (96). Under three applied compression forces, indomethacin matrix tablets provided a friability of <0.5%. Small values in friability imply much less friability during transportation, which is important in terms of sustained release of tablets. However, capping was particularly observed in the indomethacin tablet containing lactose at the compression force of 900 kg.

2.4. Drug content

The content of indomethacin in HPMC matrix tablets was analyzed by using UV-spectrophotometer at the wavelength of 318 nm. The standard curve of indomethacin in the methanol and pH 7.5 phosphate buffer mixture (1:1) is shown in Figure 8. Indomethacin contents in various formulation are presented in Tables 7-10. The indomethacin contents obtained from all formulations were in the range of 86.94-95.89% and the relative standard deviations were 1.19-2.25.

Table 3. Weight variation, thickness and diameter of indomethacin matrix tablets without an excipient (lactose and microcrystalline cellulose).

Formulation	Weight, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)
F1/300	347.70 (4.43)	5.71 (0.05)	9.43 (0.00)
F1/600	347.95 (3.56)	5.42 (0.04)	9.42 (0.01)
F1/900	349.85 (4.64)	5.29 (0.02)	9.42 (0.01)

Table 4. Weight variation, thickness and diameter of indomethacin matrix tablets, using lactose as an excipient.

Formulation	Weigh, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)
F2/300	349.50 (3.30)	5.23 (0.41)	9.47 (0.06)
F2/600	349.00 (2.87)	4.97 (0.01)	9.45 (0.01)
F2/900	350.80 (2.91)	4.88 (0.07)	9.46 (0.01)
F3/300	351.10 (3.26)	5.38 (0.04)	9.45 (0.01)
F3/600	348.50 (2.95)	5.04 (0.06)	9.44 (0.01)
F3/900	349.80 (2.80)	4.89 (0.05)	9.45 (0.01)
F4/300	347.50 (2.16)	5.44 (0.04)	9.45 (0.01)
F4/600	346.20 (4.20)	5.18 (0.07)	9.44 (0.01)
F4/900	344.70 (4.39)	5.00 (0.03)	9.44 (0.01)
F5/300	347.70 (4.94)	5.68 (0.03)	9.44 (0.01)
F5/600	349.70 (3.43)	5.37 (0.02)	9.43 (0.01)
F5/900	347.55 (4.30)	5.17 (0.03)	9.43 (0.01)

Table 5. Weight variation, thickness and diameter of indomethacin matrix tablets, using microcrystalline cellulose as an excipient.

Formulation	Weigh, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)
F6/300	344.15 (4.39)	5.42 (0.01)	9.43 (0.01)
F6/600	346.35 (4.02)	4.99 (0.04)	9.42 (0.01)
F6/900	344.55 (2.33)	4.75 (0.02)	9.43 (0.00)
F7/300	347.35 (2.78)	5.60 (0.05)	9.45 (0.00)
F7/600	347.75 (2.63)	5.15 (0.05)	9.45 (0.01)
F7/900	347.75 (2.55)	4.93 (0.04)	9.43 (0.00)
F8/300	346.10 (4.54)	5.61 (0.03)	9.44 (0.01)
F8/600	345.50 (2.98)	5.16 (0.02)	9.39 (0.10)
F8/900	348.55 (2.96)	5.00 (0.04)	9.42 (0.01)
F9/300	346.40 (2.74)	5.60 (0.04)	9.42 (0.00)
F9/600	347.10 (4.42)	5.37 (0.03)	9.43 (0.01)
F9/900	348.65 (2.23)	5.17 (0.03)	9.41 (0.01)

Table 6. Weight variation, thickness and diameter of indomethacin matrix tablets, using lactose and microcrystalline cellulose as excipients.

Formulation	Weight, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)
F10/300	346.05 (2.60)	5.55 (0.03)	9.44 (0.01)
F10/600	346.25 (2.79)	5.17 (0.02)	9.43 (0.00)
F10/900	347.50 (2.19)	5.02 (0.03)	9.43 (0.00)
F11/300	352.15 (2.30)	5.65 (0.05)	9.44 (0.00)
F11/600	343.30 (2.96)	5.21 (0.03)	9.44 (0.00)
F11/900	347.40 (2.72)	5.12 (0.30)	9.43 (0.00)
F12/300	348.50 (2.96)	5.67 (0.03)	9.45 (0.01)
F12/600	350.35 (2.13)	5.18 (0.04)	9.44 (0.01)
F12/900	347.95 (2.21)	5.00 (0.01)	9.43 (0.00)

Table 7. Hardness, percent friability and percent drug content of indomethacin matrix tablets without an excipient (lactose and microcrystalline cellulose).

Formulation	Hardness, N (SD)	% Friability	% Drug content (SD)
F1/300	71.77 (6.03)	0.14	90.12 (0.48)
F1/600	131.24 (4.72)	0.03	90.48 (0.51)
F1/900	168.95 (5.44)	0.02	90.84 (0.39)

Table 8. Hardness, percent friability and percent drug content of indomethacin matrix tablets, using lactose as an excipient.

Formulation	Hardness, N (SD)	% Friability	% Drug content (SD)
F2/300	N/A_1	2.96	93.17 (0.55)
F2/600	29.62 (2.24)	1.51	92.83 (0.36)
F2/900	40.58 (4.42)	N/A_2	92.56 (0.41)
F3/300	17.65 (1.19)	2.81	94.38 (0.35)
F3/600	45.18 (4.48)	0.28	94.55 (0.42)
F3/900	74.16 (2.67)	0.17	94.82 (0.39)
F4/300	33.79 (2.40)	1.30	93.99 (0.48)
F4/600	75.27 (6.37)	0.17	93.58 (0.37)
F4/900	110.93 (4.92)	0.03	93.26 (0.19)
F5/300	45.84 (4.57)	1.02	93.52 (0.25)
F5/600	99.93 (7.11)	0.09	93.30 (0.29)
F5/900	149.66 (7.58)	0.23	93.17 (0.37)

N/A_1 = Tablets are too soft.

N/A_2 = Capping of tablets.

Table 9. Hardness, percent friability and percent drug content of indomethacin matrix tablets, using microcrystalline cellulose as an excipient.

Formulation	Hardness, N (SD)	% Friability	% Drug content (SD)
F6/300	95.00 (1.85)	0.12	93.86 (0.32)
F6/600	156.99 (7.21)	0.08	95.58 (0.37)
F6/900	218.81 (5.86)	0.05	95.89 (0.40)
F7/300	79.61 (3.80)	0.01	93.75 (0.45)
F7/600	154.60 (7.93)	0.00	94.99 (0.41)
F7/900	187.83 (13.60)	0.00	95.04 (0.39)
F8/300	77.51 (5.09)	0.00	89.85 (0.50)
F8/600	150.12 (5.63)	0.09	88.62 (0.45)
F8/900	183.68 (8.51)	0.01	87.50 (0.48)
F9/300	75.54 (10.19)	0.12	86.71 (0.49)
F9/600	100.17 (7.15)	0.12	86.94 (0.47)
F9/900	181.89 (6.26)	0.12	87.19 (0.45)

Table 10. Hardness, percent friability and percent drug content of indomethacin matrix tablets, using lactose and microcrystalline cellulose as excipients.

Formulation	Hardness, N (SD)	% Friability	% Drug content (SD)
F10/300	32.60 (3.93)	0.98	94.67 (0.29)
F10/600	94.05 (8.34)	0.03	93.64 (0.35)
F10/900	124.76 (6.07)	0.03	93.29 (0.37)
F11/300	39.82 (6.09)	0.46	93.08 (0.41)
F11/600	102.31 (5.97)	0.09	93.34 (0.35)
F11/900	147.31 (4.02)	0.08	93.66 (0.38)
F12/300	59.95 (4.05)	0.31	93.12 (0.34)
F12/600	132.48 (4.83)	0.05	93.23 (0.37)
F12/900	173.80 (6.65)	0.03	93.49 (0.33)

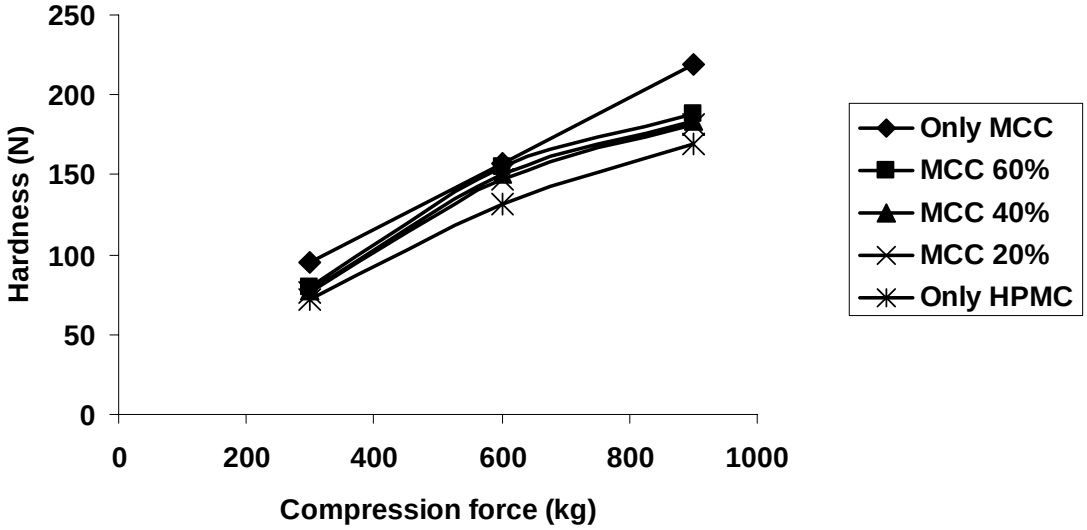

Figure 5. Effect of compression force on the hardness of microcrystalline cellulose and microcrystalline cellulose/HPMC tablets.

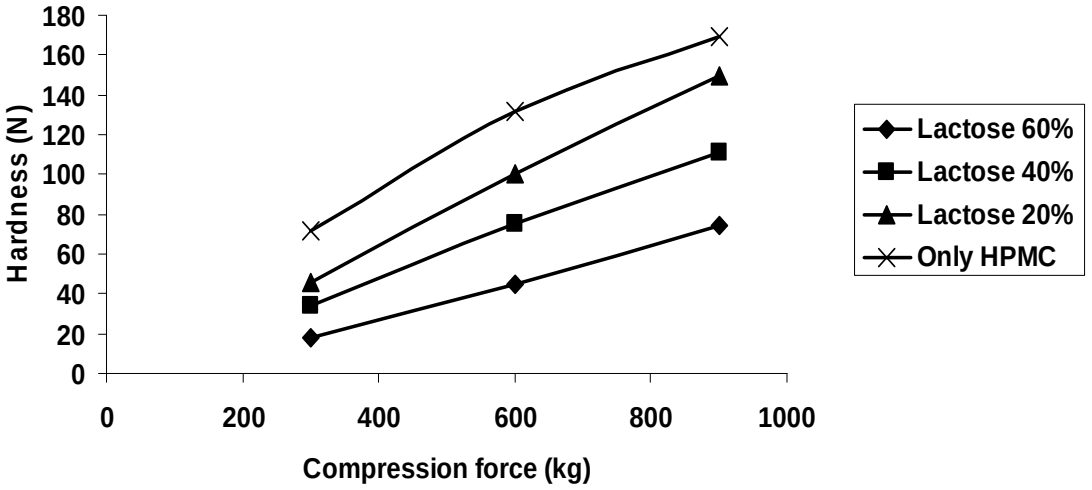

Figure 6. Effect of compression force on the hardness of lactose and lactose /HPMC tablets.

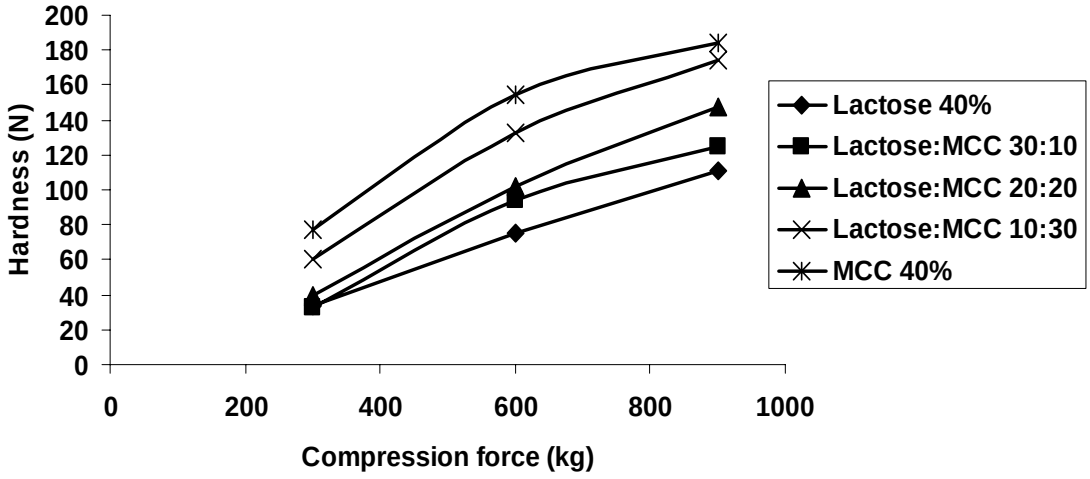

Figure 7. Effect of compression force on the hardness of lactose/microcrystalline cellulose/HPMC tablets containing HPMC 37%.

3. Determination of drug release from indomethacin-HPMC matrix tablets

The results of drug release from indomethacin tablets are shown in Tables A1-A36.

3.1. Standard curve of indomethacin

Standard curve of indomethacin in the methanol and pH 7.5 phosphate buffer mixture (1:1) and in pH 6.2 phosphate buffer were obtained from the standard solutions in the concentrations of 16-80 μg/ml. The concentrations and the corresponding absorbance at the wavelength 318 nm are presented in Table 11 and 12, respectively. Figure 8 and 9 show the relationship between the concentration of indomethacin in the media, which follow the Beer's law. Liner regression analysis was applied to obtain the best fit between the absorbance and drug concentrations. The linear regression coefficients were found to be 1 and 0.9999, respectively.

Table 11. UV absorbance of indomethacin in the methanol and pH 7.5 phosphate buffer mixture (1:1) at wavelength of 318 nm.

Concentration(mg/ml)	Absorbance
0.016	0.3073
0.032	0.6110
0.048	0.9131
0.064	1.2130
0.080	1.5248

Linear regression coefficient (r^2) = 1

Slope = 18.981

Intercept = 0.0027

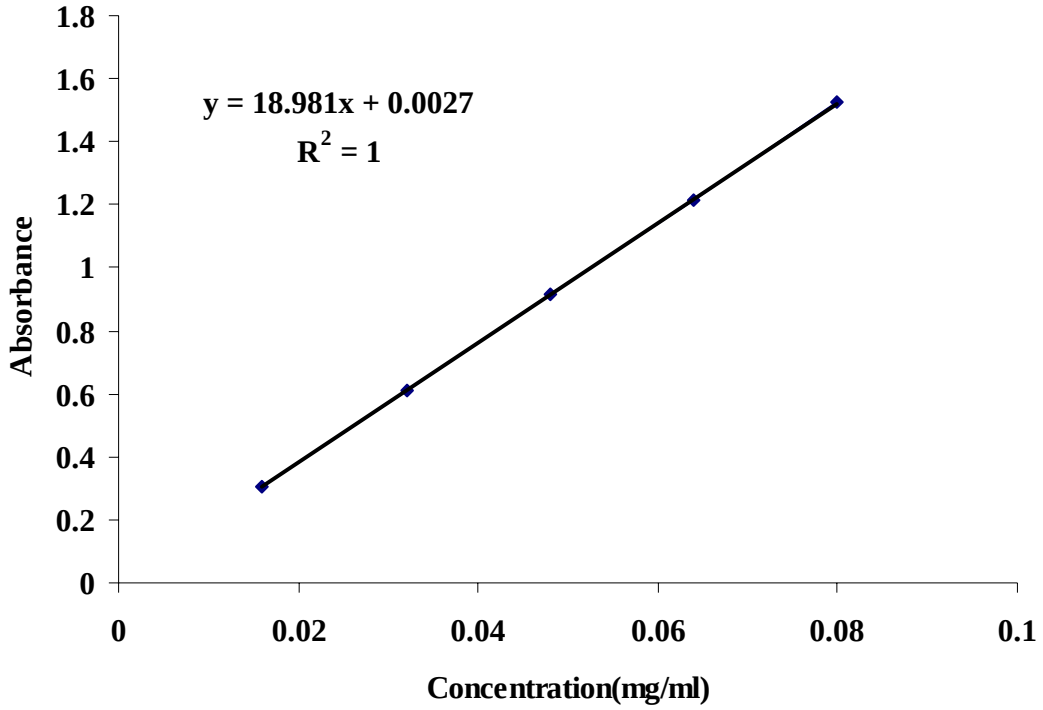

Figure 8. Standard curve of indomethacin in the methanol and pH 7.5 phosphate buffer mixture (1:1) at 318 nm.

Table 12. UV absorbance of indomethacin in pH 6.2 phosphate buffer at wavelength of 318 nm.

Concentration(mg/ml)	Absorbance
0.016	0.3115
0.032	0.6269
0.048	0.9564
0.064	1.2735
0.080	1.5865

Linear regression coefficient (r^2) = 0.9999

Slope = 19.979

Intercept = -0.008

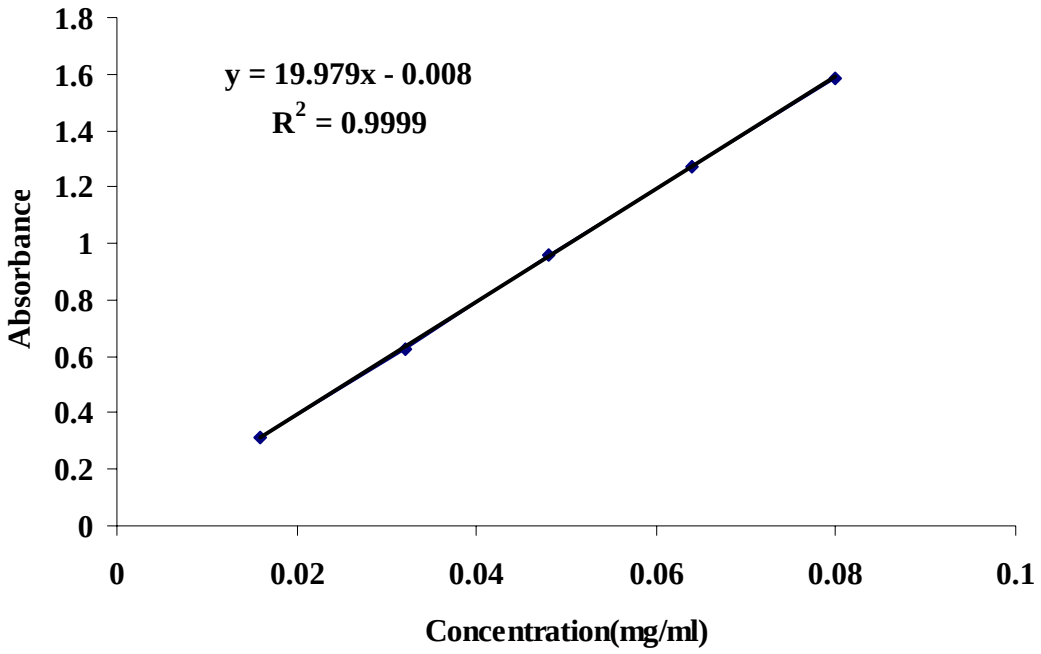

Figure 9. Standard curve of indomethacin in pH 6.2 phosphate buffer at 318 nm.

3.2. The effect of compression force on the release of indomethacin

Compression force is one among variables required in fabrication of controlled release drug delivery system with a predetermined-release rate. In addition, since the importance of sustained release technology primarily lies in the need for accurate control of the drug release rate during the duration of therapy, variability of release rate due to compression force could lead to serious problems. These problems would be hazardous particularly with drugs of narrow therapeutic indices. In this study of the influence of compression force on drug release rate the tablet matrices at various HPMC : excipient (lactose and microcrystalline cellulose) ratios were compressed at three different upper punch force (300, 600, and 900 kg) and their release rates were determined.

The release of indomethacin from HPMC matrix tablets containing lactose and microcrystalline cellulose as excipients at three different compression forces (300, 600, and 900 kg) are shown in Figures 10-21. As seen from these plots, little or no effect of compression force was observed for lactose (Figs. 10-13), microcrystalline cellulose (Figs. 14-17), lactose – microcrystalline cellulose (Figs. 18-20) or only HPMC formulations (Fig. 21). Literature reports (6,37) indicate similar findings, i.e. changes in compression force or crushing strength appear to have minimal effect on drug release from a matrix tablets once a critical hardness is achieved. Increase in dissolution was only observed when the tablets were too soft and may be attributed to the lack of powder compaction or consolidation ~3 kp. However, compression force is statistically factor on drug release from indomethacin tablets.

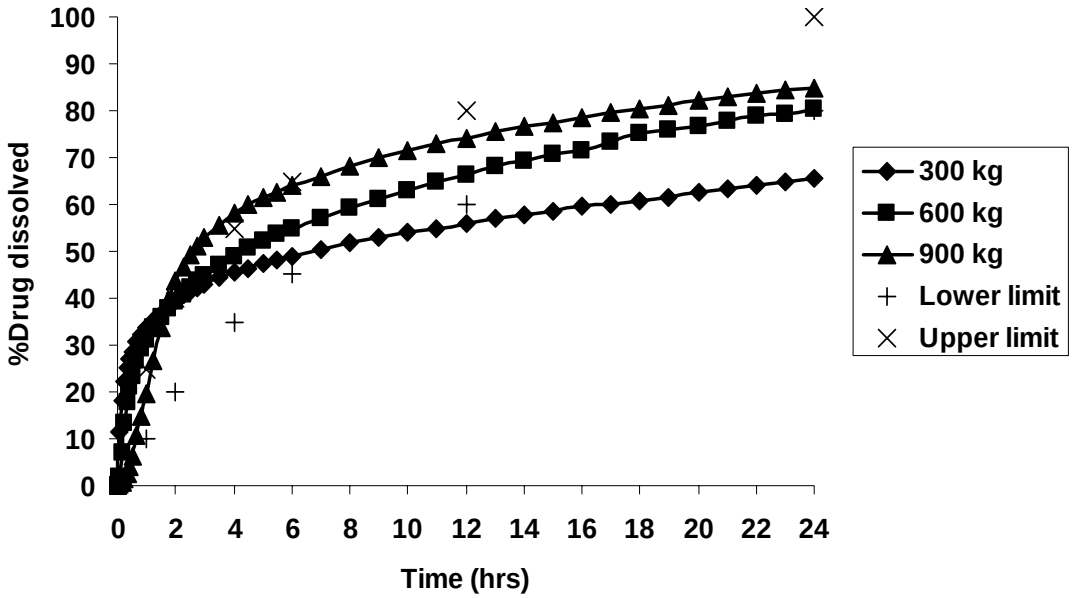

Figure 10. Effect of the compression force on the dissolution profiles of indomethacin tablets containing lactose as an excipient.

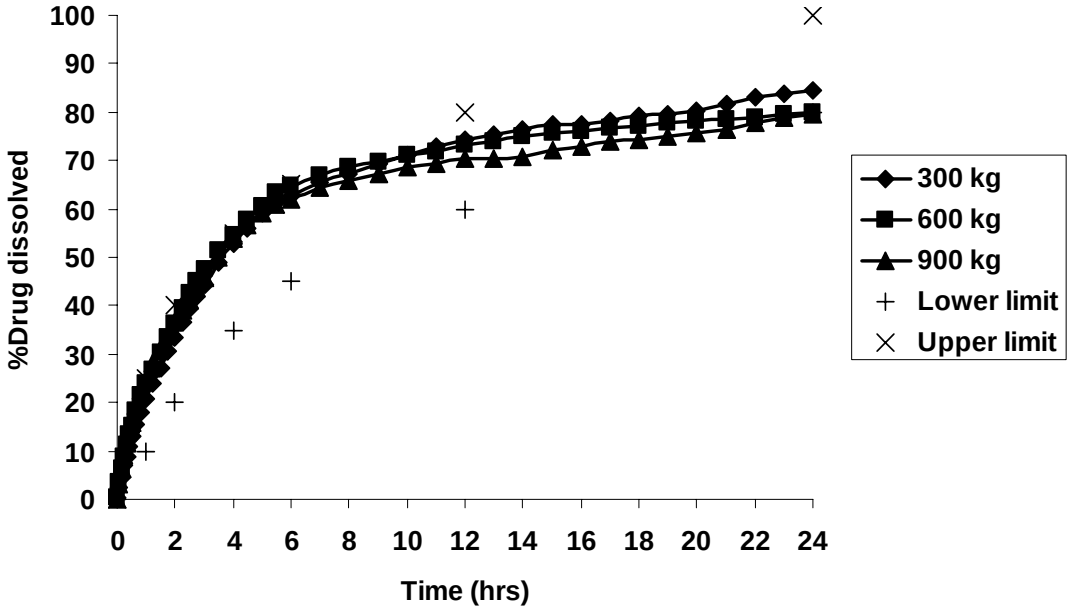

Figure 11. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose ratio of 17:60.

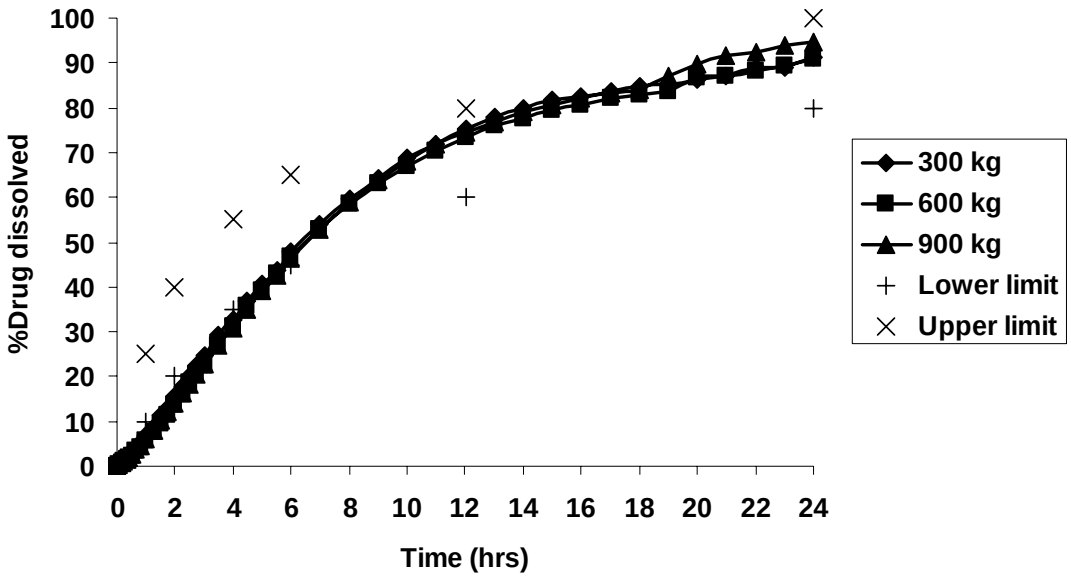

Figure 12. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose ratio of 37:40.

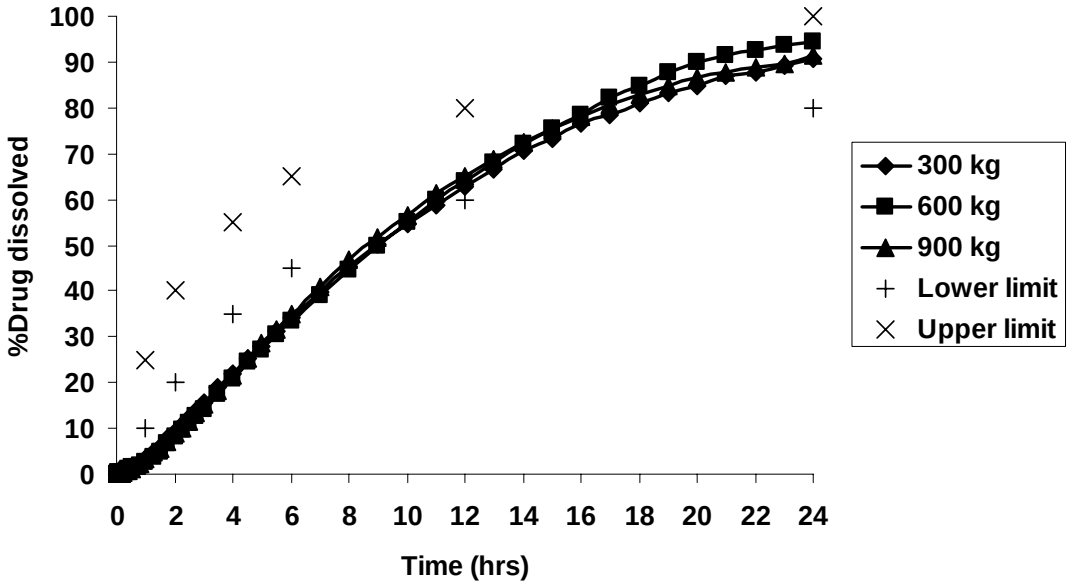

Figure 13. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose ratio of 57:20.

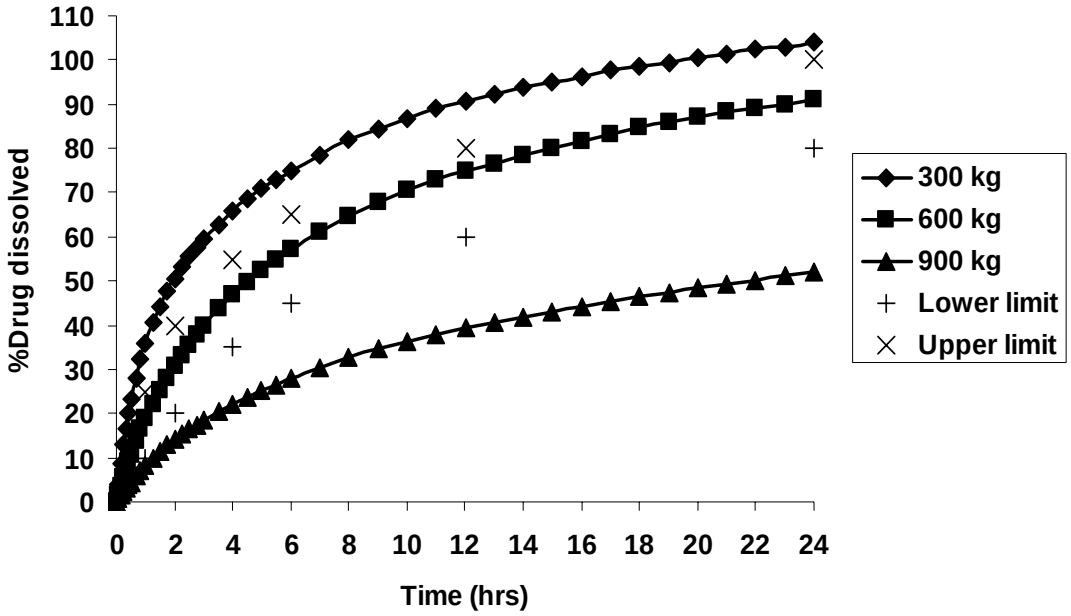

Figure 14. Effect of the compression force on the dissolution profiles of indomethacin tablets containing microcrystalline cellulose as an excipient.

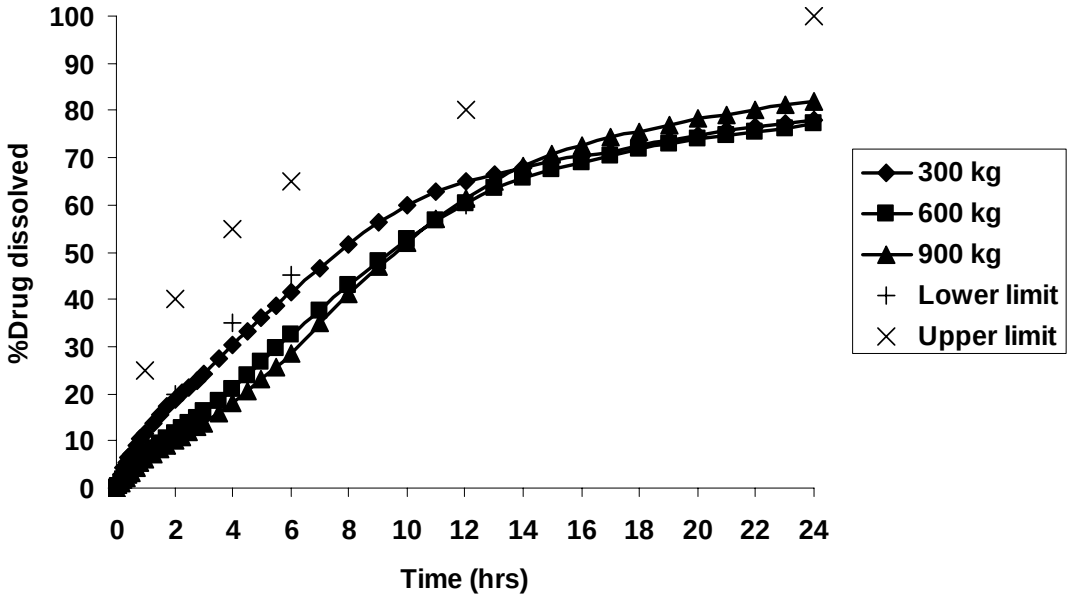

Figure 15. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : microcrystalline cellulose ratio of 17:60.

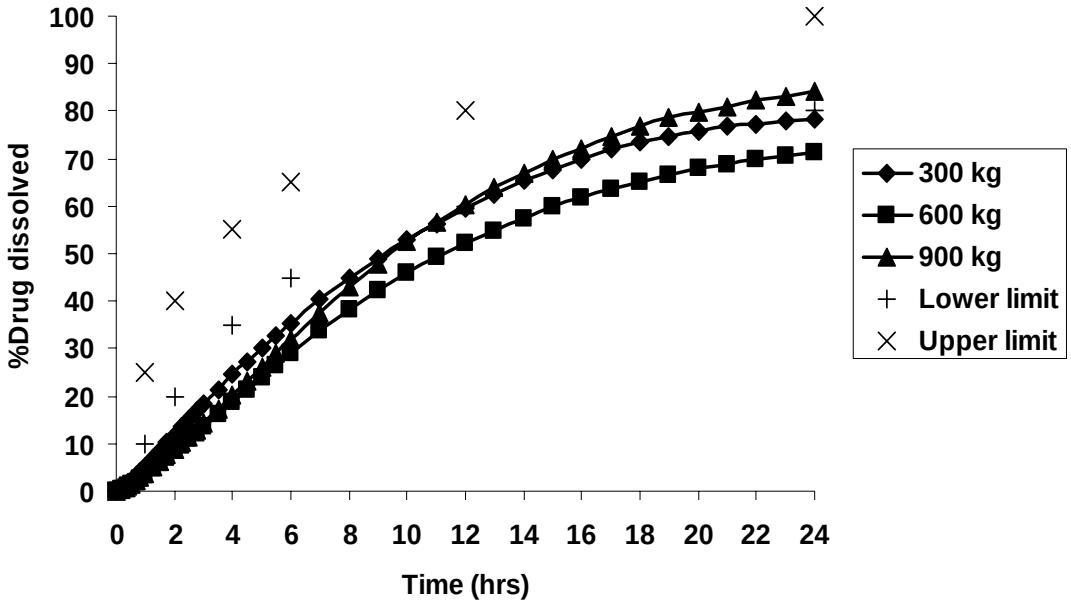

Figure 16. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : microcrystalline cellulose ratio of 37:40.

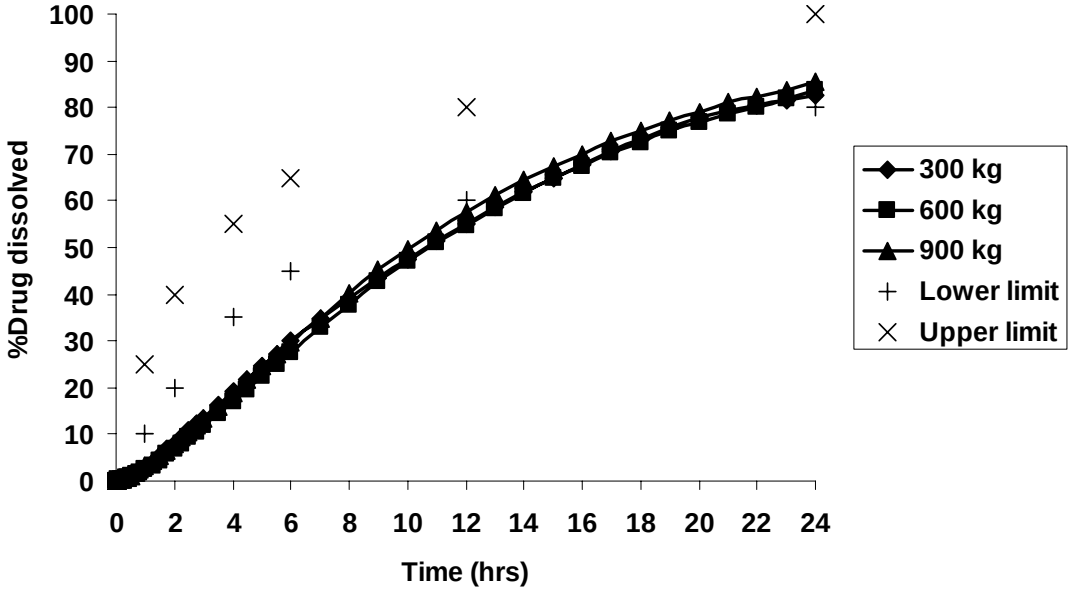

Figure 17. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : microcrystalline cellulose ratio of 57:20.

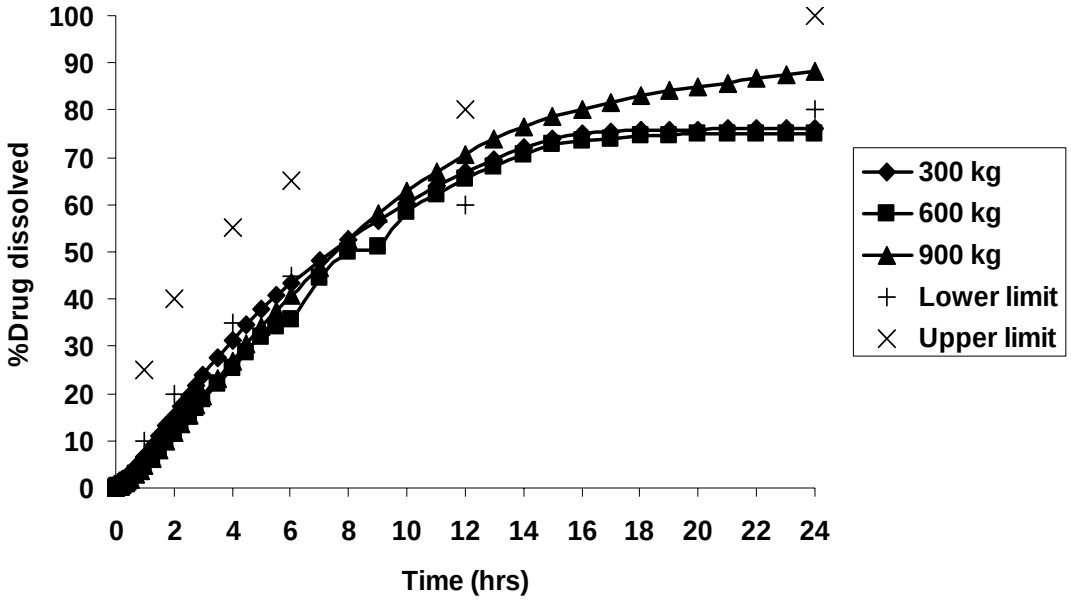

Figure 18. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose : microcrystalline cellulose ratio of 37:30:10.

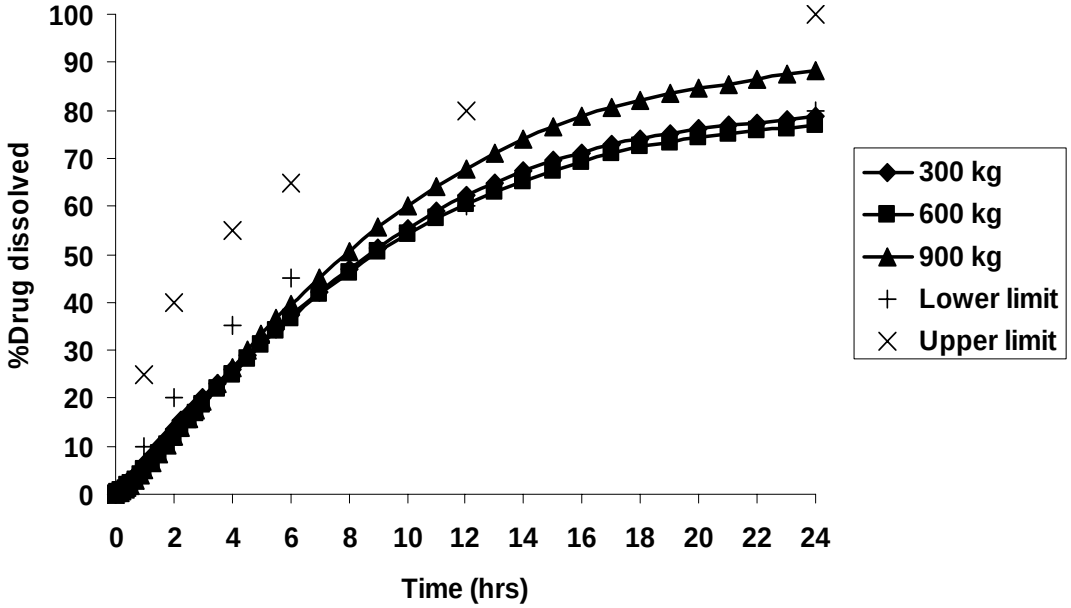

Figure 19. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose : microcrystalline cellulose ratio of 37:20:20.

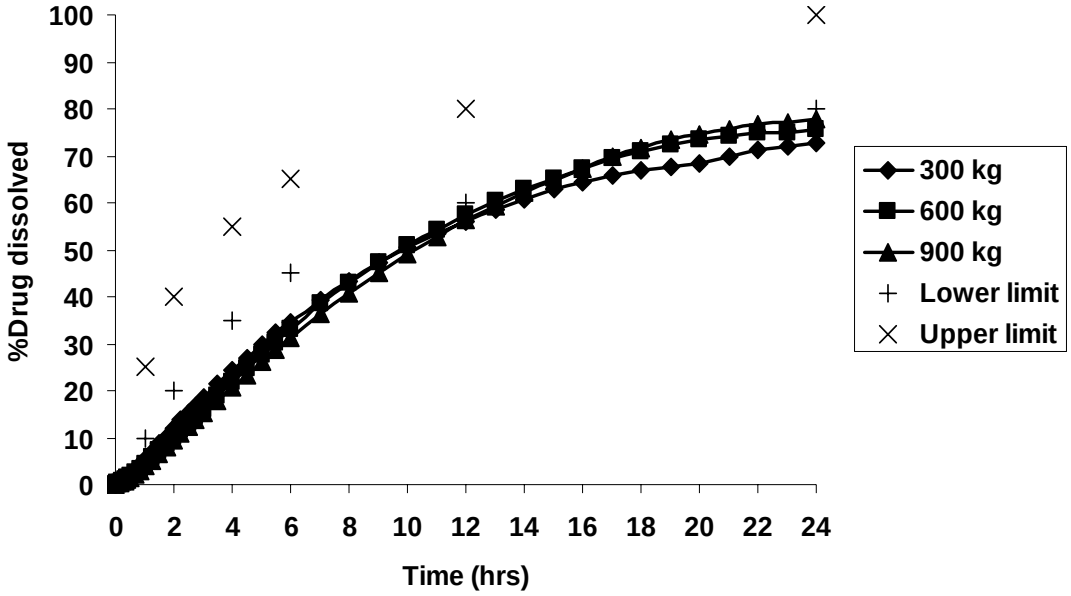

Figure 20. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose : microcrystalline cellulose ratio of 37:10:30.

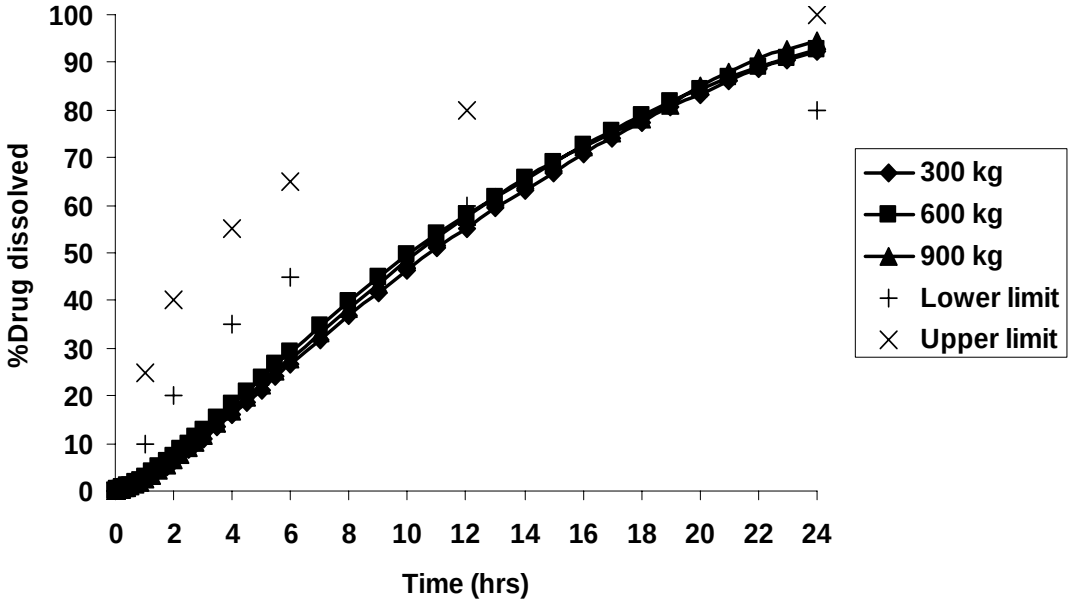

Figure 21. Effect of the compression force on the dissolution profiles of indomethacin matrix tablets containing only HPMC 77%, without lactose and microcrystalline cellulose.

3.3. The effect of type of excipient on the release of indomethacin

Figures 22-24 show that the formulations containing insoluble excipients microcrystalline cellulose (MCC) released indomethacin at a slower rate and to a lesser extent than those containing a soluble excipient lactose at all the time point (P<0.05). It could result from the hydrated gel layer was more permeable for drug release when a soluble excipient was contained in the formulation (3). The effect of changing from an insoluble (MCC) to soluble excipient (lactose) on indomethacin release was studied by holding the Methocel K100 level at 37% in all formulations. As shown in Figs. 25-27, change of excipient from 100% MCC (insoluble) to 100% lactose (soluble) resulted in an increase drug release. This may be due to dissolution of the lactose and the consequent reduction in the tortuosity and or gel strength of the polymer. These results confirm the findings of Lapidus and Lordi (37,98), that the increase in release rates was similar for both excipients (soluble / insoluble) up to the addition of 33% by weight of excipient (my study 40%). At a dilution level of greater than 50% level, however, a marked divergence occurs which may be explained by the differences in solubility of the excipient(s) and subsequent effects on the tortuosity factor. Moreover, the use of binary mixtures of lactose and microcrystalline cellulose in the tablet formulation produced drug release profiles of intermediate duration.

3.4. The effect of HPMC and excipient ratio on the release of indomethacin

In order to investigate the effects of excipients on the release rate of indomethacin, HPMC matrices as the inert matrix, lactose (a soluble excipient) and microcrystalline cellulose (an insoluble excipient) were chosen. Figures 28-33 show the effect of replacement of HPMC by lactose (Figs. 28-30) and microcrystalline cellulose (Figs. 31-33) on the release profile of indomethacin at various compression forces. Increasing the proportion of lactose in the tablet resulted in increased the release of indomethacin in dissolution medium at 1, 6, and 12 hr (P<0.05). This was due to the incorporation of lactose, which increased the interspace volume and porosity of the matrix and resulted in faster diffusion of drug from the matrix and an increased rate of erosion of the matrix tablet (45). Moreover, the relatively high amount of the soluble excipient in these tablet formulations led to the formation of the

hydrated gel layers with high drug permeability. In contrast, the higher concentration of HPMC especially in HPMC : lactose 77:0, will form a more resistant gelatinous layer to water penetration, drug diffusion and retard released than HPMC : lactose 17:60, 37:40 and 57:20 respectively. Indeed, HPMC swelling, which is appreciable in water, diminishes the rate of solvent penetration inside the polymer matrix, and hence a decrease in the rate of gel formation results with time. However, increasing the contents of microcrystalline cellulose in the tablet resulted in slightly increased indomethacin release in dissolution medium at all the time point ($P<0.05$). This could result from the presence of a swelling insoluble excipient like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface. Considering the results obtained, it was found that the proportion of the excipient modified the release rate of indomethacin. Moreover, analysis of variance indicated that change in proportion of excipient was a significant factor affecting drug release ($P<0.05$). Figs. 25-27 show the effect of replacement of lactose by microcrystalline cellulose on the release profile of indomethacin. In vitro release profiles of indomethacin showed that increase in the ratio of lactose/microcrystalline cellulose from 0:40 to 40:0 resulted in an increase in the release rate indomethacin.

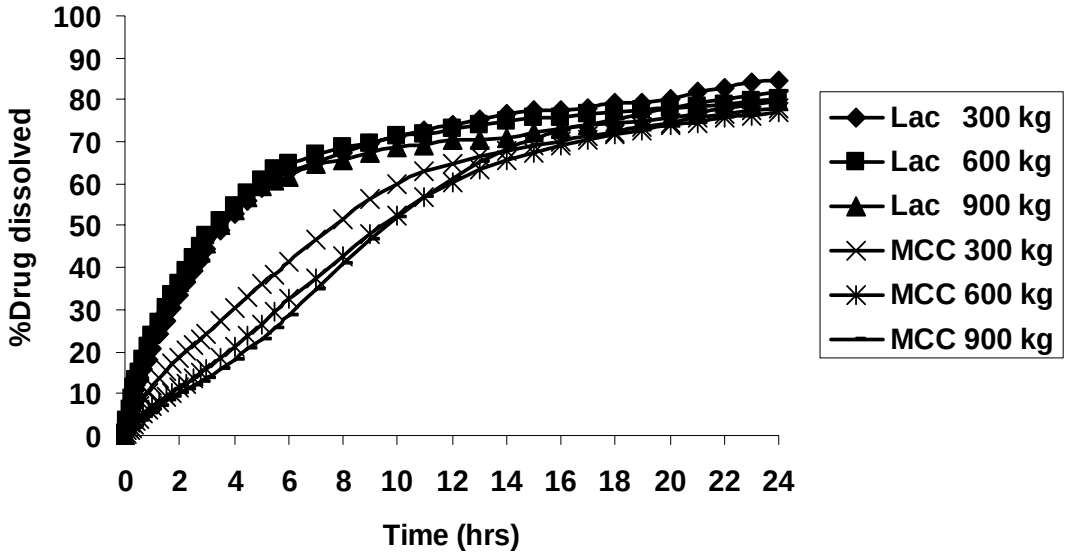

Figure 22. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose (Lac) and HPMC : microcrystalline cellulose (MCC) ratio of 17:60 at various compression forces.

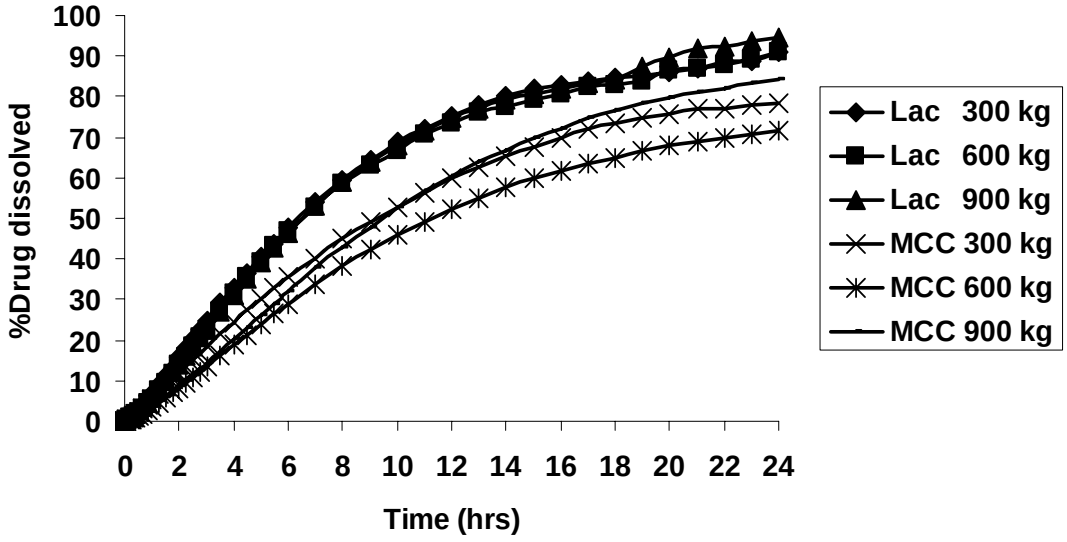

Figure 23. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose (Lac) and HPMC : microcrystalline cellulose (MCC) ratio of 37:40 at various compression forces.

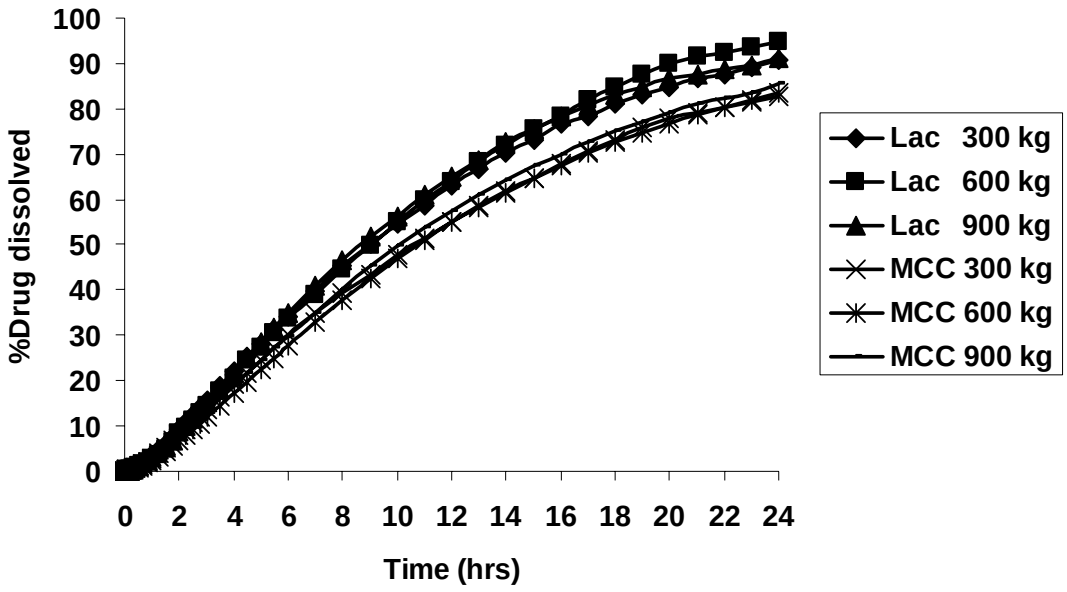

Figure 24. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC : lactose (Lac) and HPMC : microcrystalline cellulose (MCC) ratio of 57:20 at various compression forces.

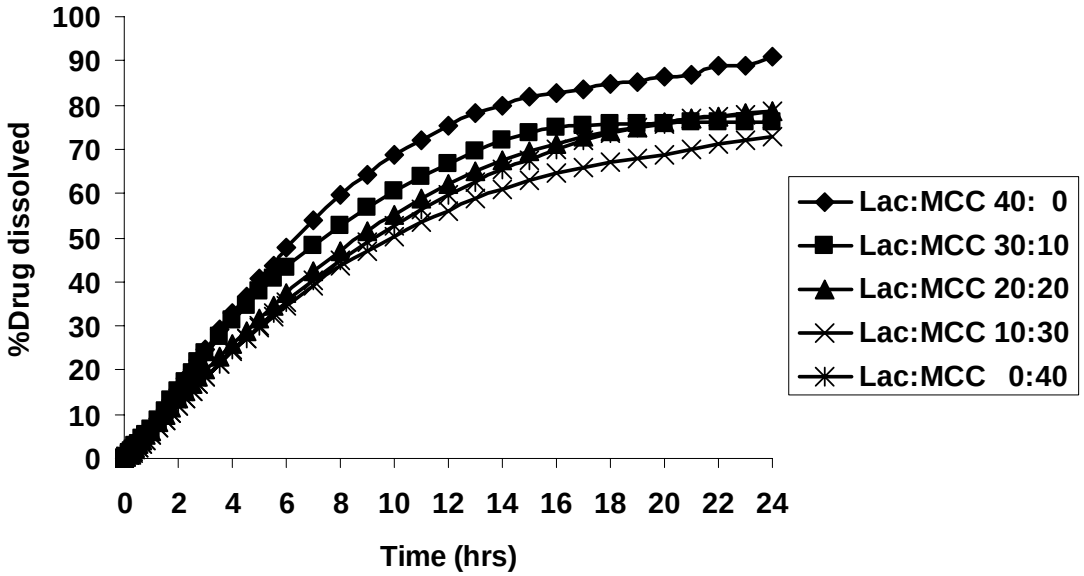

Figure 25. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC 37% and lactose (Lac) : microcrystalline cellulose (MCC) ratio of 40:0 to 0:40 at 300 kg compression force.

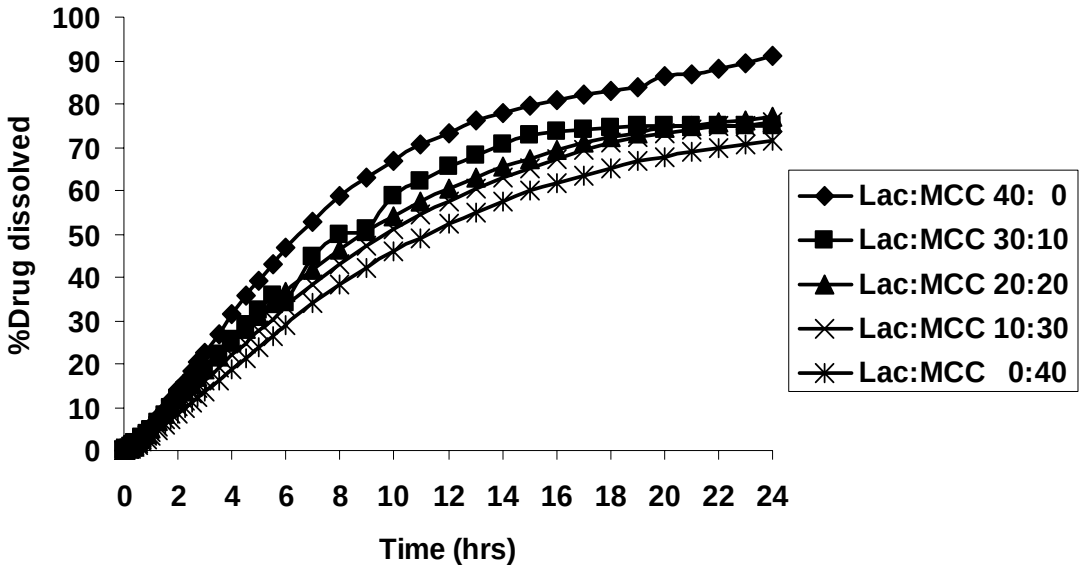

Figure 26. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC 37% and lactose (Lac) : microcrystalline cellulose (MCC) ratio of 40:0 to 0:40 at 600 kg compression force.

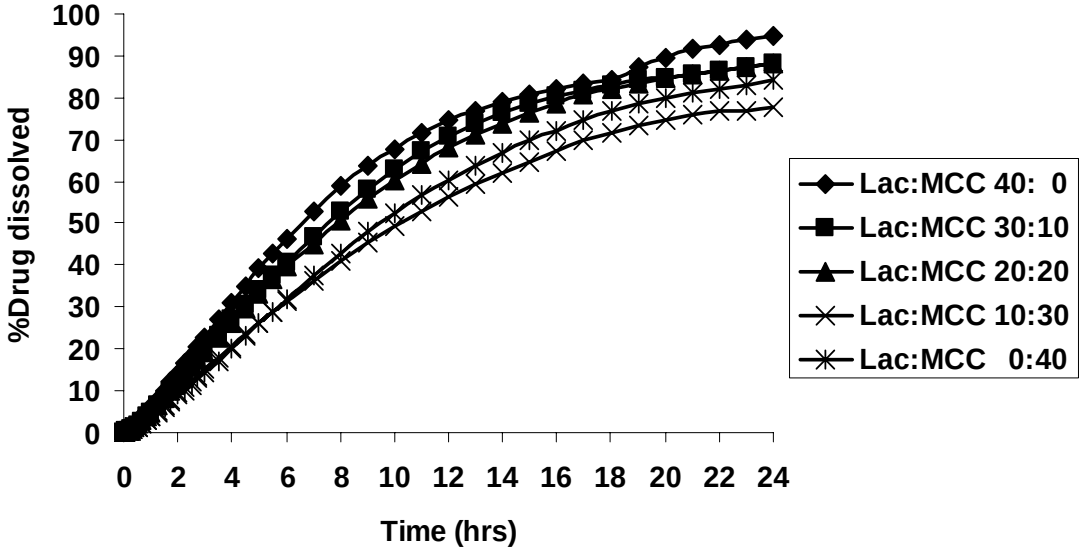

Figure 27. Comparison of the dissolution profiles of indomethacin matrix tablets containing HPMC 37% and lactose (Lac) : microcrystalline cellulose (MCC) ratio of 40:0 to 0:40 at 900 kg compression force.

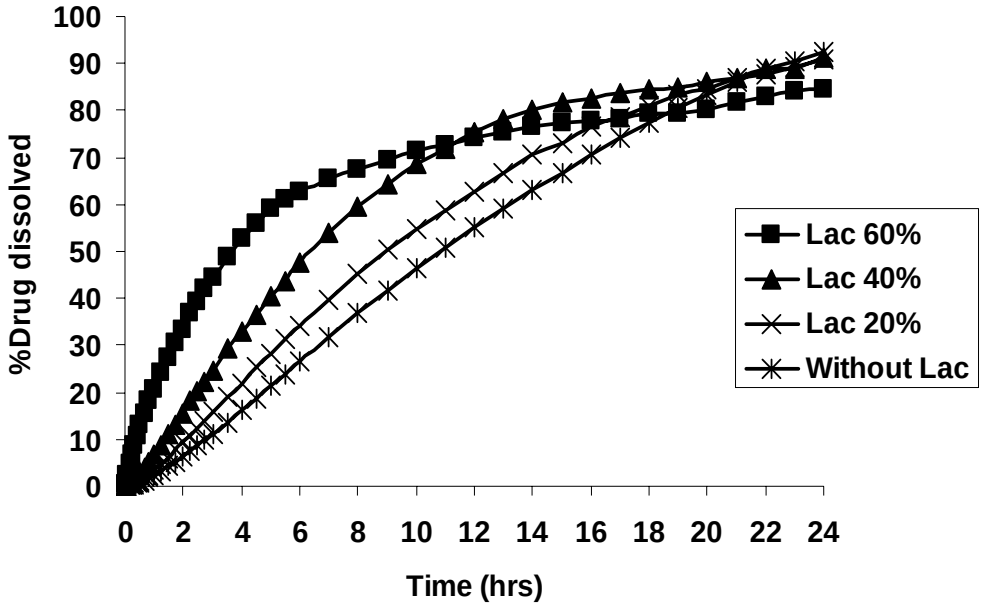

Figure 28. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of lactose (Lac) at 300 kg compression force.

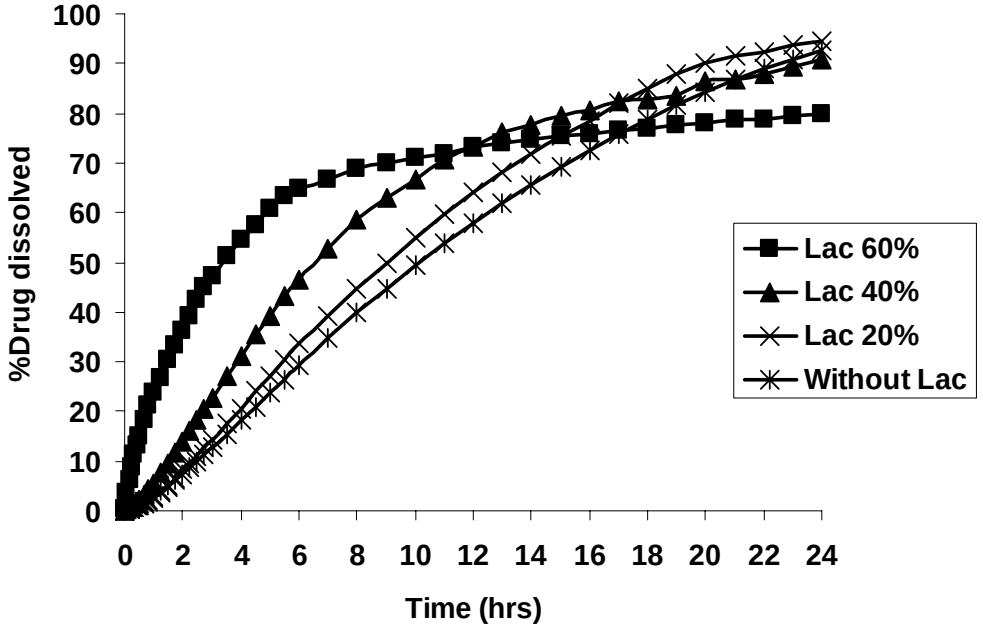

Figure 29. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of lactose (Lac) at 600 kg compression force.

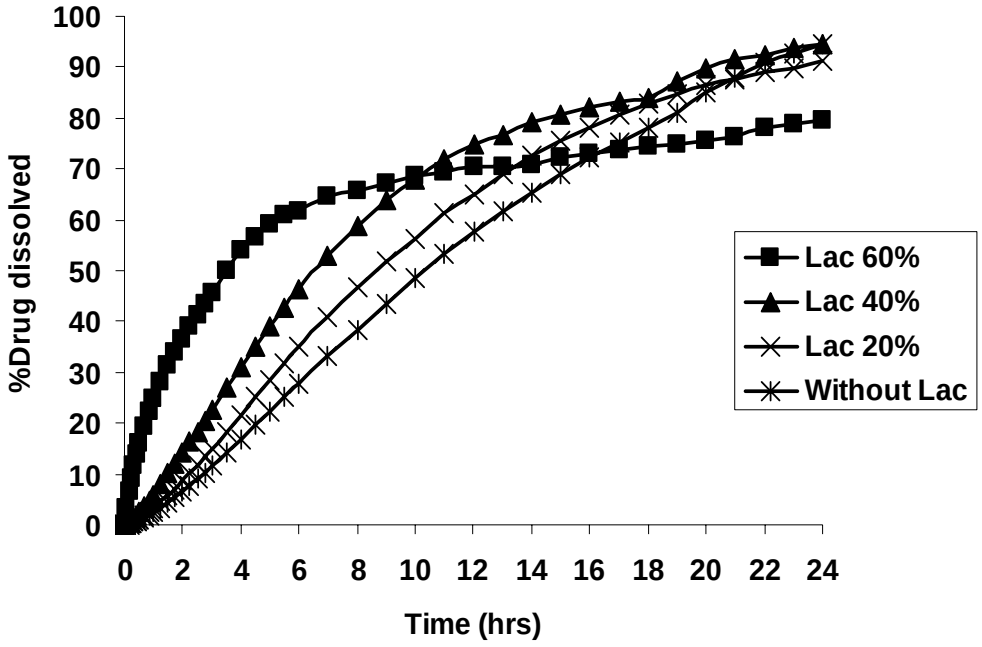

Figure 30. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of lactose (Lac) at 900 kg compression force.

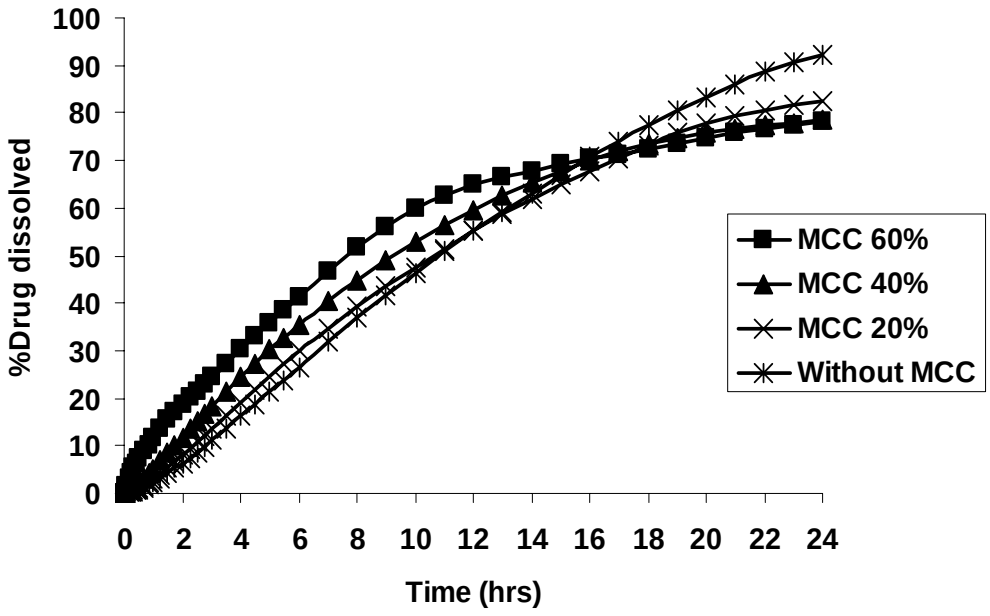

Figure 31. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of microcrystalline cellulose (MCC) at 300 kg compression force.

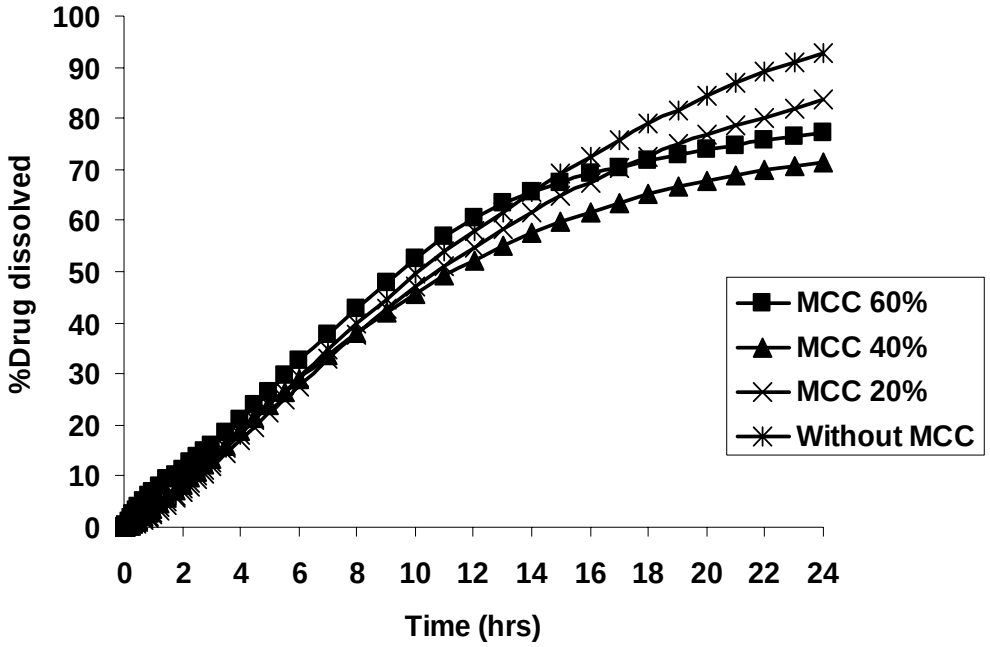

Figure 32. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of microcrystalline cellulose (MCC) at 600 kg compression force.

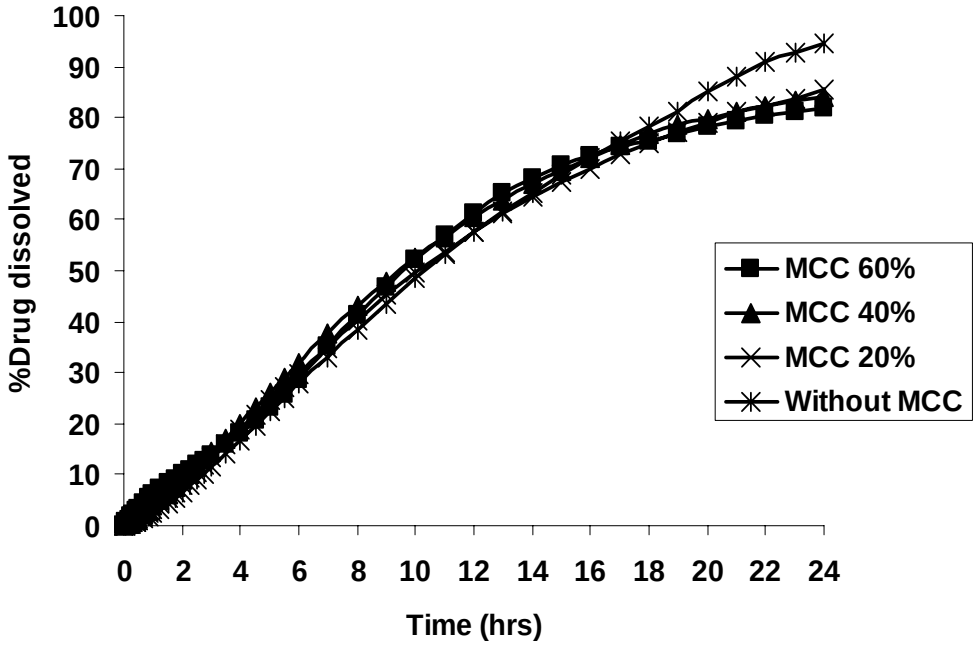

Figure 33. Comparison of the dissolution profiles of indomethacin matrix tablets in various contents of microcrystalline cellulose (MCC) at 900 kg compression force.

4. Mechanism and kinetics of drug release

The most common approach to determine the drug release mechanism of matrix tablets is to fit the well known equations of Hixson and Crowell (3) and Peppas (99,100). In addition, the release mechanism of many sustained release products can be described by the zero order kinetic in Eq. (17), Higuchi equation in Eq. (9) or apparent first order kinetic in Eq. (18) (101). Different mathematical models of indomethacin release from a tablet are proposed in order to describe the release mechanism based on the release data obtained from the formulations investigated.

Hixson-Crowell Cube Root Kinetics Equation

In the case of dissolution of a drug with poor aqueous solubility like indomethacin, dissolution occurs mainly after the erosion process, resulting in the release of drug particles from the matrix tablet, as represented by the Hixson-Crowell cube root kinetics equation (102) shown in Eq. (13),

$$\left[\frac{W_d}{W_i}\right]^{1/3} = 1\text{-}k_1t \qquad (13)$$

where W_d is dry weight of tablet at the designated time after immersion in the medium, W_i the initial dry weight of tablet, t the time, and k_1 the erosion rate constant for the tablet. From Eq. (13), when drug dissolution from particles is considerably slower than tablet erosion, dissolution profiles of the drug (Q_d) are more accurately represented by Eq. (14),

$$\left[1-\frac{Q_d}{A}\right]^{1/3} = 1\text{-}k_2t \qquad (14)$$

where Q_d is amount of drug dissolved at time t, A the total amount of drug present in the matrix, t time, and k_2 the apparent rate constant for the drug dissolution.

When Eq. (14) was plotted for each formulation, as shown in Figs. 34-42, a linear relationship was obtained from each formulation, indicating that the dissolution of indomethacin in those formulation occurred predominantly after release of the solid drug particles from the tablets, regardless of the excipient type used in the tablets. Table 13 shows the linear regression results of fitting the drug release data from each

formulation to the Hixson-Crowell cube root kinetics equation. The linear regression coefficient (r^2) of all formulations investigated ranged from 0.980 to 0.999 and indicated best fit of the release data according to the Hixson-Crowell cube root kinetics equation. The apparent rate constant for indomethacin dissolution (k_2) ranged from 0.019 to 0.053 hr^{-1}. This indicated the difference in dissolution rate of indomethacin from tablets containing different types of excipient (P<0.05). The rate of indomethacin dissolution from tablets containing water soluble excipient [Lactose (F3/300-F5/900) 0.025-0.053 hr^{-1}] was faster than the dissolution rate of indomethacin from tablets containing water insoluble excipient [Microcrystalline cellulose (F7/300-F9/900; 0.019-0.025 hr^{-1}]. The hydrated gel layers were more permeable for indomethacin release when the tablets contained soluble excipients, resulting in faster rates of dissolution. *Tahara et al.* reported similar results for the release of poorly water soluble drug, U-78875 (0.08 mg/ml in pH 6.8 medium), from a tablet containing a different substitution type of HPMC (HPMC 2910, 50 cPs) and lactose (45). Therefore, type and content of excipient had an influence on the dissolution rate of indomethacin.

Peppas's Equation

Peppas's transport equation has been developed to allow the influences of hydration and swelling on drug release. On the basis of Peppas's equation, Korsmeyer et al. derived a simple relationship, which may be used to describe drug release from polymeric systems in which release deviates from Fickian diffusion as expressed in Eq. (15) (99,100). Equation (16) was used to investigate the indomethacin release kinetics from tablet formulations containing different types and content of excipients.

$$\frac{M_t}{M_\infty} = kt^n \qquad (15)$$

$$\log\left[\frac{M_t}{M_\infty}\right] = \log k + n\log t \qquad (16)$$

where M_t/M_1 is the fraction of drug release, t the release time, k a constant incorporating structural and geometric characteristics of the controlled release device, and n the diffusional release exponent indicative of the mechanism of drug release for

drug dissolution. To characterize the release mechanism, the dissolution data were evaluated according to Eq. (16) (99,100,103). Figures 43-51 show a plot of the log fraction of drug dissolved as a function of time for each formulation. The linear regression results are given in Table 14. The linear regression coefficient (r^2) of all formulations investigated ranged from 0.986 to 0.999 and indicated best fit of the release data according to Eq. (16). According to Refs. (99,100,103), the value of the diffusional exponent, *n*, determined from the slope of those formulations containing different types and contents of excipient, ranged from 0.705 to 1.219. The difference in the diffusional release exponent value (*n*) may be due to the different contents of excipient used in the tablet formulations. Therefore, type and amount of excipient had an influence on the indomethacin release mechanism. The compression force did not alter the drug release mechanism.

Zero order kinetic

$$Q_t = Q_0 + k_0 t \qquad (17)$$

Where Q is the amount of drug dissolved in time t, Q is initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant.

The pharmaceutical dosage forms following this equation release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

Figures 70-78 show a plot of the fraction of drug dissolved as a function of time for each formulation. The linear regression results are given in Table 15. The linear regression coefficient (r^2) of all formulations investigated ranged from 0.956 to 0.999.

Higuchi equation

If a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line (101).

$$M = k_3 \cdot t^{1/2} \qquad (9)$$

Where M is the amount of drug release, k_3 the apparent rate constant for the drug dissolution.

Although the above equation is based on release from a single surface, it may be used to describe diffusion-controlled release from all surface tablets.

Figures 61-69 show a plot of the fraction of drug dissolved as a function of square root time for each formulation. The linear regression results are given in Table 16. The linear regression coefficient (r^2) of all formulations investigated ranged from 0.945 to 0.999.

First order kinetic

On assumption that the exponentially with time, drug release from most slow-release tablets could be described by apparent first order kinetics (44), thus

$$\log C_t = \log C_o - \frac{k_1 t}{2.303} \qquad (18)$$

where C_t is the amount of drug remaining in the matrix at time t; C_o initial amount of drug; and k_1 the first order release constant. Hence, a plot of the logarithm of the amount of drug remaining against time will be linear, if sink conditions are operative (101).

When Eq. (18) was plotted for each formulation, as shown in Figs. 52-60, a linear relationship was obtained from the all formulations (r^2 = 0.971-1.000). The linear regression results are given in Table 17.

The comparative linear regression analysis of release data between zero order kinetic, Higuchi equation and first order kinetic of indomethacin release from matrix tablets shows in Table 18. The indomethacin release from HPMC matrices followed first-order kinetics (r^2 = 0.995-1.000), except the formulation containing HPMC : Lactose ratio of 17:60 (F3/300-F3/900) that followed Higuchi equation (r^2 = 0.999). Also, the formulation containing only HPMC (F1/300-F1/900) and HPMC : MCC ratio of 17:60 (F7/300-F7/900) followed zero order kinetic equation (r^2 = 0.992-0.999).

Table 13. Results of linear regression for indomethacin release fitted to Hixson-Crowell Cube Root Kinetics Equation.

Formulation	Slope, k_2 (hr^{-1})	r^2	y-intercept
F1/300	-0.0220	0.9986	1.0311
F1/600	-0.0229	0.9993	1.0259
F1/900	-0.0231	0.9984	1.0329
F3/300	-0.0499	0.9927	0.9778
F3/600	-0.0529	0.9873	0.9719
F3/900	-0.0484	0.9817	0.9654
F4/300	-0.0342	0.9998	1.0122
F4/600	-0.0344	0.9995	1.0192
F4/900	-0.0340	0.9993	1.0178
F5/300	-0.0251	0.9997	1.0194
F5/600	-0.0259	0.9993	1.0267
F5/900	-0.0266	0.9990	1.0252
F7/300	-0.0250	0.9993	0.9858
F7/600	-0.0221	0.9953	1.0051
F7/900	-0.0218	0.9801	1.0124

Table 13. Results of linear regression for indomethacin release fitted to Hixson–Crowell Cube Root Kinetics Equation.(cont.)

Formulation	Slope, k_2 (hr^{-1})	r^2	y-intercept
F8/300	-0.0224	0.9989	1.0023
F8/600	-0.0186	0.9976	1.0065
F8/900	-0.0236	0.9986	1.0185
F9/300	-0.0208	0.9999	1.0141
F9/600	-0.0211	0.9993	1.0218
F9/900	-0.0222	0.9999	1.0192
F10/300	-0.0277	0.9951	0.9995
F10/600	-0.0265	0.9963	1.0117
F10/900	-0.0299	0.9997	1.0188
F11/300	-0.0261	0.9980	0.9978
F11/600	-0.0232	0.9973	1.0029
F11/900	-0.0279	0.9998	1.0134
F12/300	-0.0199	0.9950	0.9928
F12/600	-0.0218	0.9986	1.0073
F12/900	-0.0209	0.9995	1.0088

Table 14. Results of linear regression for indomethacin release fitted to Peppas's Equation.

Formulation	Slope, n	r^2	k
F1/300	1.1560	0.9971	0.5095
F1/600	1.1250	0.9967	0.5751
F1/900	1.1757	0.9973	0.5143
F3/300	0.7108	0.9967	1.3039
F3/600	0.6569	0.9964	1.3609
F3/900	0.6272	0.9916	1.3678
F4/300	1.0682	0.9944	0.8575
F4/600	1.1411	0.9941	0.7882
F4/900	1.1051	0.9982	0.8115
F5/300	1.1379	0.9925	0.6313
F5/600	1.1962	0.9934	0.5727
F5/900	1.2191	0.9942	0.5794
F7/300	0.7051	0.9993	1.0641
F7/600	0.8812	0.9945	0.8169
F7/900	0.9334	0.9864	0.7376

Table 14. Results of linear regression for indomethacin release fitted to Peppas's Equation.(cont.)

Formulation	Slope, n	r^2	k
F8/300	0.9736	0.9926	0.7744
F8/600	1.0179	0.9919	0.6358
F8/900	1.1155	0.9975	0.6174
F9/300	1.1001	0.9926	0.5904
F9/600	1.1662	0.9951	0.5109
F9/900	1.1393	0.9964	0.5703
F10/300	0.9747	0.9879	0.8727
F10/600	1.0160	0.9943	0.7797
F10/900	1.1245	0.9948	0.7321
F11/300	0.9376	0.9951	0.8340
F11/600	0.9942	0.9904	0.7683
F11/900	1.0824	0.9941	0.7465
F12/300	0.8667	0.9916	0.8426
F12/600	0.9012	0.9943	0.7369
F12/900	0.9751	0.9953	0.7179

Table 15. Results of linear regression for indomethacin release fitted to zero order kinetic equation.

Formulation	Slope, k_0	r^2	y-intercept
F1/300	4.9044	0.9989	-3.1919
F1/600	5.1420	0.9981	-2.2209
F1/900	5.2013	0.9992	-3.7687
F3/300	11.1810	0.9750	8.6005
F3/600	11.9570	0.9675	9.8204
F3/900	10.7730	0.9563	11.6120
F4/300	7.8068	0.9943	0.2273
F4/600	7.8801	0.9951	-1.4446
F4/900	7.7900	0.9967	-1.0466
F5/300	5.7112	0.9958	-1.4248
F5/600	5.8668	0.9974	-2.9629
F5/900	6.1725	0.9974	-3.2419
F7/300	5.6917	0.9924	6.2868
F7/600	5.0470	0.9986	1.5285
F7/900	5.1263	0.9930	-0.6680

Table 15. Results of linear regression for indomethacin release fitted to zero order kinetic equation.(cont.)

Formulation	Slope, k_0	r^2	y-intercept
F8/300	5.0808	0.9887	2.6317
F8/600	5.0994	0.9960	0.4809
F8/900	5.3638	0.9973	-1.3828
F9/300	4.7533	0.9944	-0.3935
F9/600	4.8419	0.9973	-2.2321
F9/900	5.1217	09978	-1.7729
F10/300	1.0352	0.9994	-1.2772
F10/600	5.9474	0.9903	1.0473
F10/900	6.8471	0.9966	-1.3402
F11/300	5.3954	0.9908	3.0397
F11/600	5.2145	0.9847	2.5750
F11/900	6.3329	0.9943	-0.0306
F12/300	4.4030	0.9816	5.6615
F12/600	4.8880	0.9906	2.0529
F12/900	4.6239	0.9927	2.1100

Table 16. Results of linear regression for indomethacin release fitted to Higuchi Equation.

Formulation	Slope, k_2	r^2	y-intercept
F1/300	25.771	0.9946	-35.143
F1/600	25.826	0.9956	-32.775
F1/900	26.576	0.9944	-35.985
F3/300	30.790	0.9987	-9.4515
F3/600	30.627	0.9990	-6.5622
F3/900	29.096	0.9993	-4.7059
F4/300	29.041	0.9931	-24.303
F4/600	30.081	0.9928	-27.876
F4/900	29.695	0.9917	-27.101
F5/300	25.841	0.9947	-28.247
F5/600	27.045	0.9943	-31.835
F5/900	26.878	0.9919	-30.315
F7/300	20.973	0.9869	-9.685
F7/600	21.363	0.9701	-17.898
F7/900	21.170	0.9449	-19.904

Table 16. Results of linear regression for indomethacin release fitted to Higuchi Equation.(cont.)

Formulation	Slope, k_2	r^2	y-intercept
F8/300	22.890	0.9969	-20.277
F8/600	21.449	0.9971	-22.823
F8/900	24.488	0.9882	-26.533
F9/300	22.951	0.9955	-25.430
F9/600	23.736	0.9925	-28.784
F9/900	23.885	0.9908	-27.118
F10/300	25.567	0.9979	-19.961
F10/600	26.585	0.9960	-26.697
F10/900	28.045	0.9939	-27.869
F11/300	22.893	0.9952	-18.412
F11/600	23.545	0.9972	-21.047
F11/900	26.378	0.9931	-24.859
F12/300	21.829	0.9992	-19.054
F12/600	23.828	0.9985	-24.889
F12/900	23.584	0.9986	-25.839

Table 17. Results of linear regression for indomethacin release fitted to first order kinetic equation.

Formulation	Slope, k_1	r^2	y-intercept
F1/300	-0.0334	0.9950	2.0588
F1/600	-0.0346	0.9967	2.0500
F1/900	-0.0350	0.9948	2.0607
F3/300	-0.0757	0.9976	1.9774
F3/600	-0.0799	0.9938	1.9682
F3/900	-0.0738	0.9903	1.9593
F4/300	-0.0514	0.9980	2.0275
F4/600	-0.0516	0.9976	2.0377
F4/900	-0.0511	0.9965	2.0359
F5/300	-0.0377	0.9978	2.0382
F5/600	-0.0390	0.9961	2.0496
F5/900	-0.0396	0.9963	2.0452
F7/300	-0.0376	0.9980	1.9877
F7/600	-0.0332	0.9896	2.0158
F7/900	-0.0324	0.9705	2.0250

Table 17. Results of linear regression for indomethacin release fitted to first order kinetic equation.(cont.)

Formulation	Slope, k_1	r^2	y-intercept
F8/300	-0.0339	1.0000	2.0130
F8/600	-0.0281	0.9995	2.0194
F8/900	-0.0355	0.9951	2.0365
F9/300	-0.0312	0.9989	2.0296
F9/600	-0.0317	0.9967	2.0409
F9/900	-0.0332	0.9961	2.0366
F10/300	-0.0419	0.9990	2.0095
F10/600	-0.0400	0.9957	2.0288
F10/900	-0.0448	0.9972	2.0372
F11/300	-0.0356	0.9997	2.0089
F11/600	-0.0351	0.9996	2.0143
F11/900	-0.0420	0.9981	2.0294
F12/300	-0.0303	0.9986	2.0015
F12/600	-0.0330	0.9997	2.0223
F12/900	-0.0319	0.9997	2.0258

Table 18. Correlation coefficients for release data of indomethacin from different formulations after fitting to Peppas, zero order, Higuchi and first order models.

Formulation	Peppas model	zero order model	Higuchi model	first order model
F1/300	0.9971	0.9989	0.9946	0.9950
F1/600	0.9967	0.9981	0.9956	0.9967
F1/900	0.9973	0.9992	0.9944	0.9948
F3/300	0.9967	0.9750	0.9987	0.9976
F3/600	0.9964	0.9675	0.9990	0.9938
F3/900	0.9916	0.9563	0.9993	0.9903
F4/300	0.9944	0.9943	0.9931	0.9980
F4/600	0.9941	0.9951	0.9928	0.9976
F4/900	0.9982	0.9967	0.9917	0.9965
F5/300	0.9925	0.9958	0.9947	0.9978
F5/600	0.9934	0.9974	0.9943	0.9961
F5/900	0.9942	0.9974	0.9919	0.9963
F7/300	0.9993	0.9924	0.9869	0.9980
F7/600	0.9945	0.9986	0.9701	0.9896
F7/900	0.9864	0.9930	0.9449	0.9705

Table 18. Correlation coefficients for release data of indomethacin from different formulations after fitting to Peppas, zero order, Higuchi and first order models.(cont.)

Formulation	Peppas model	zero order model	Higuchi model	first order model
F8/300	0.9926	0.9887	0.9969	1.0000
F8/600	0.9919	0.9960	0.9971	0.9995
F8/900	0.9975	0.9973	0.9882	0.9951
F9/300	0.9926	0.9944	0.9955	0.9989
F9/600	0.9951	0.9973	0.9925	0.9967
F9/900	0.9964	09978	0.9908	0.9961
F10/300	0.9879	0.9994	0.9979	0.9990
F10/600	0.9943	0.9903	0.9960	0.9957
F10/900	0.9948	0.9966	0.9939	0.9972
F11/300	0.9951	0.9908	0.9952	0.9997
F11/600	0.9904	0.9847	0.9972	0.9996
F11/900	0.9941	0.9943	0.9931	0.9981
F12/300	0.9916	0.9816	0.9992	0.9986
F12/600	0.9943	0.9906	0.9985	0.9997
F12/900	0.9953	0.9927	0.9986	0.9997

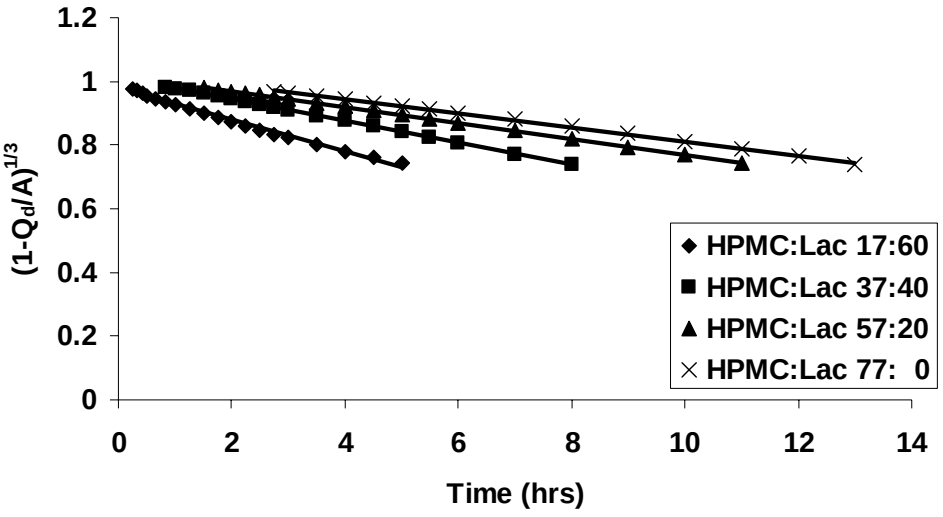

Figure 34. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose as a function (Lac) of time at compression force 300 kg.

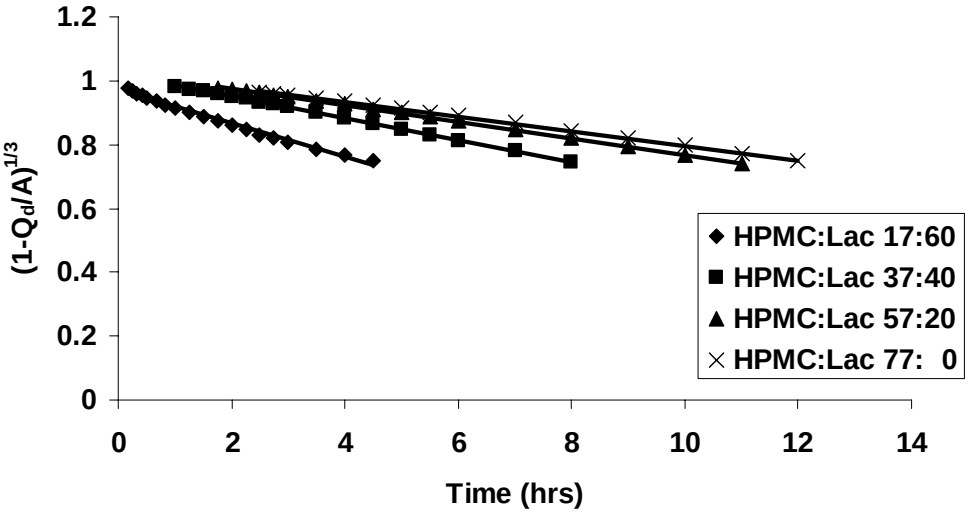

Figure 35. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 600 kg.

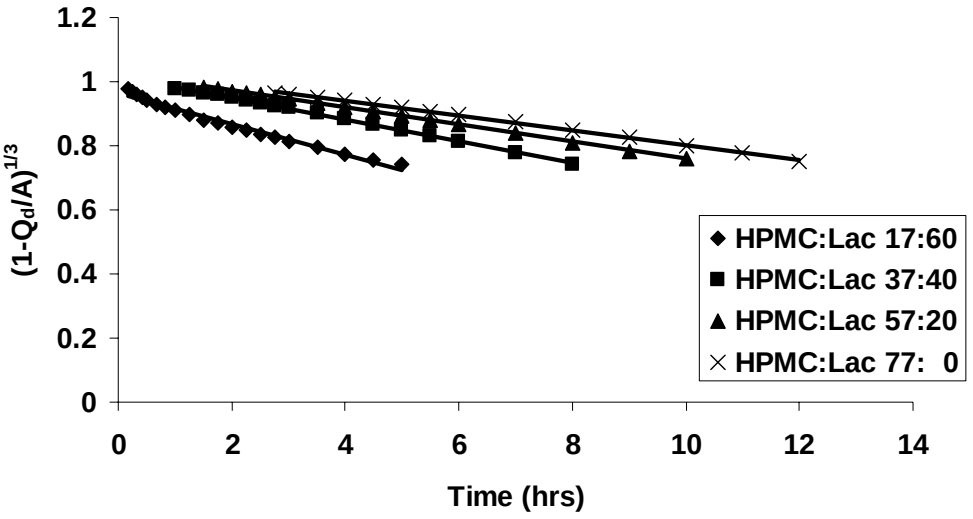

Figure 36. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 900 kg.

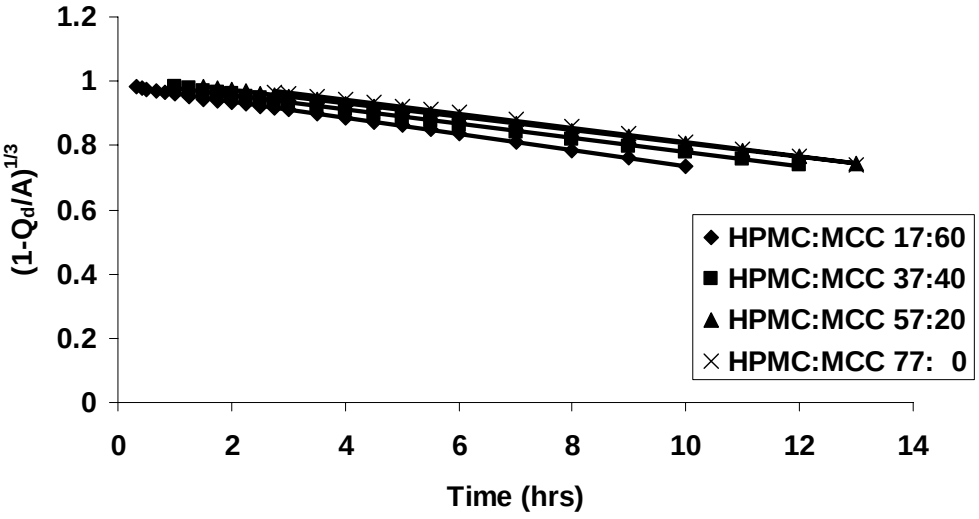

Figure 37. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

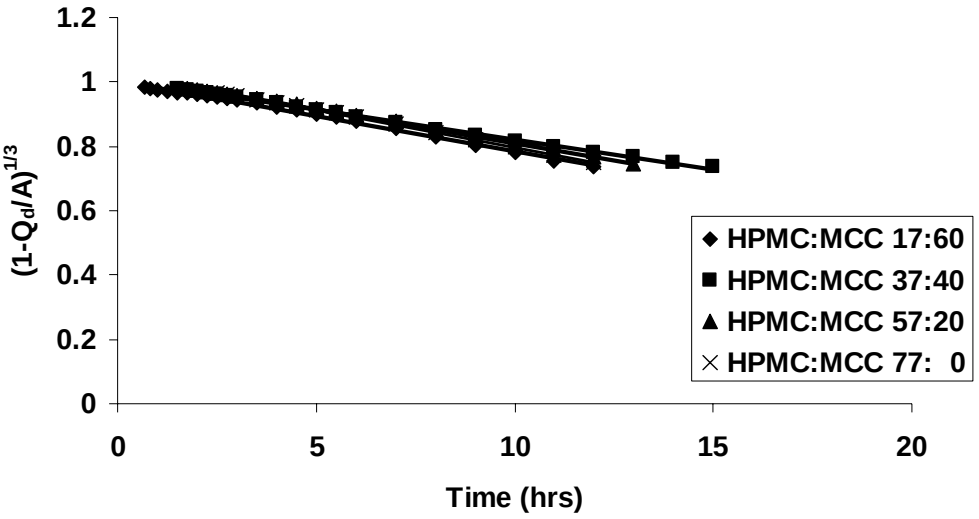

Figure 38. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

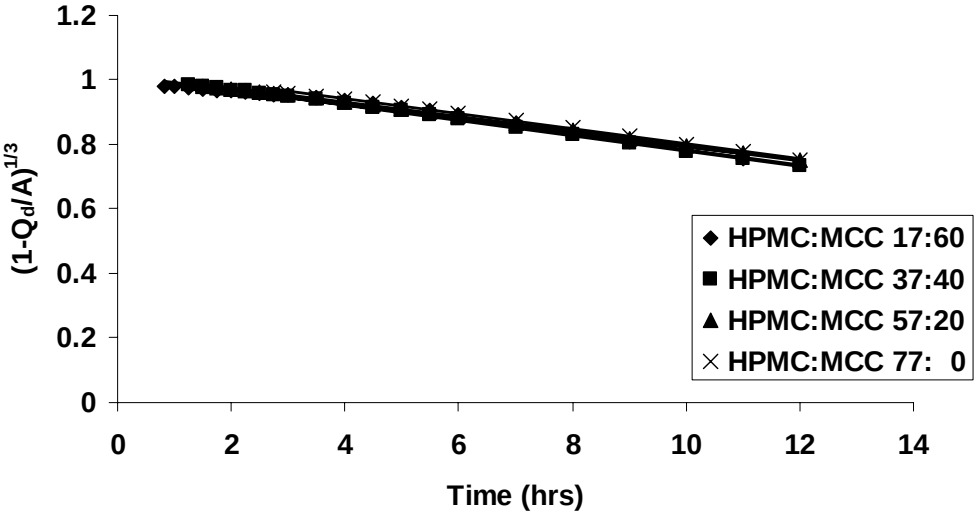

Figure 39. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

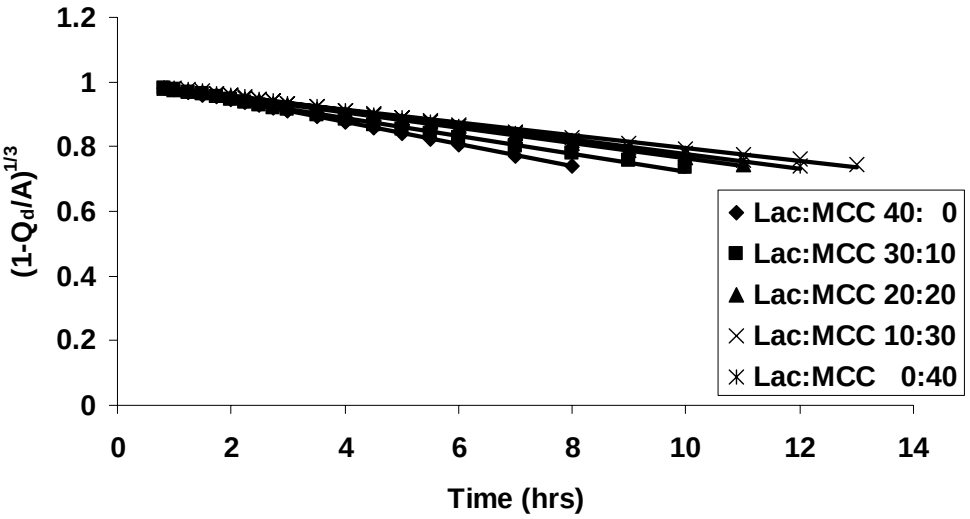

Figure 40. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

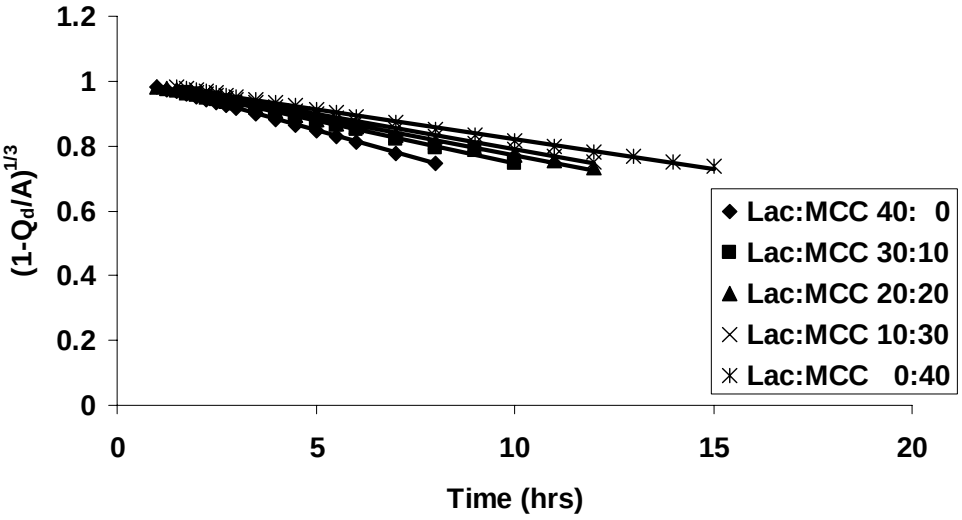

Figure 41. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

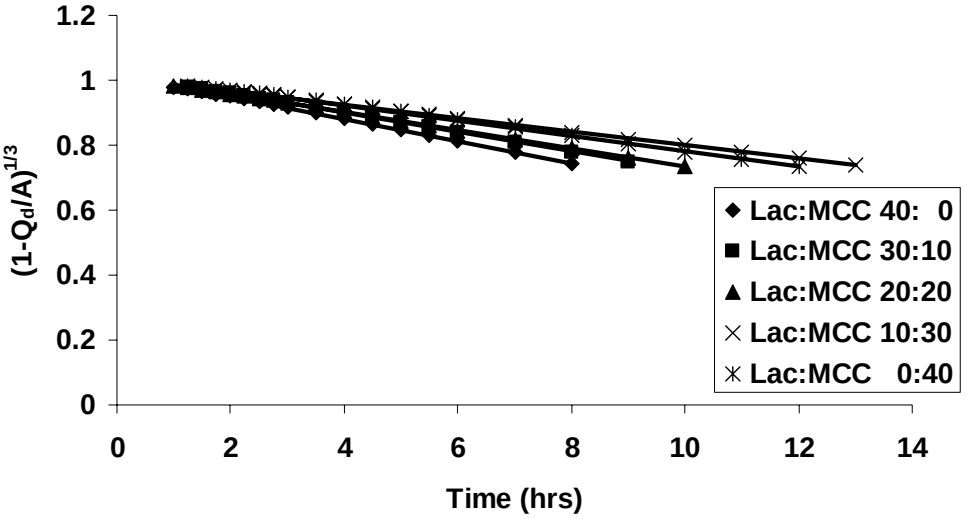

Figure 42. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

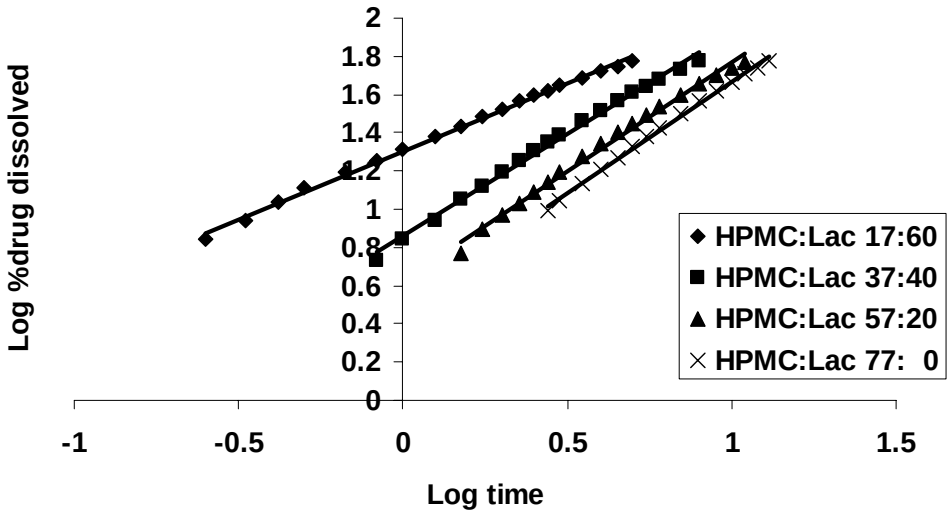

Figure 43. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Lactose (Lac) as a function of the logarithm of time at compression force 300 kg.

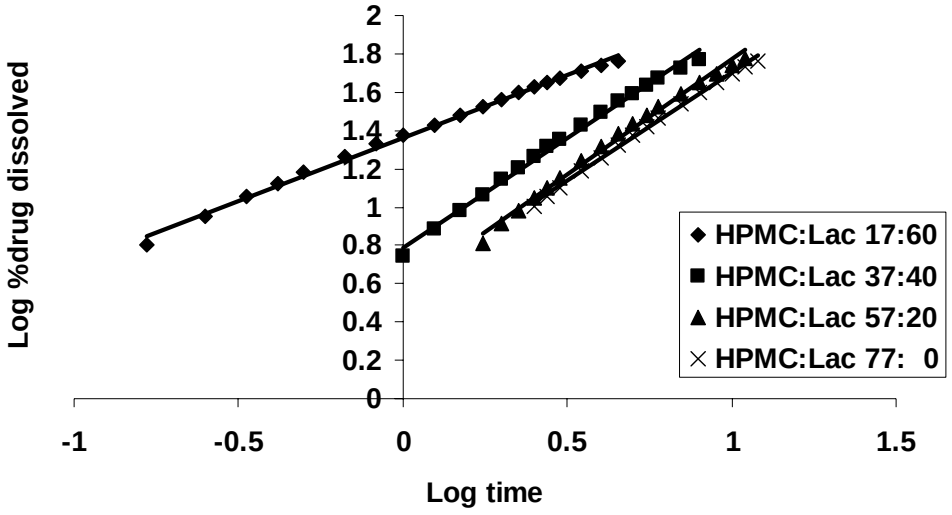

Figure 44. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Lactose (Lac) as a function of the logarithm of time at compression force 600 kg.

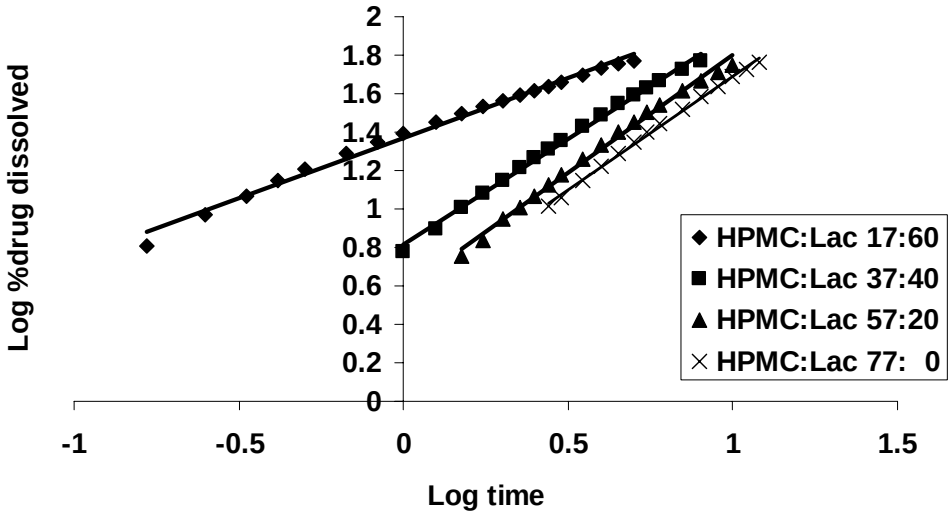

Figure 45. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Lactose (Lac) as a function of the logarithm of time at compression force 900 kg.

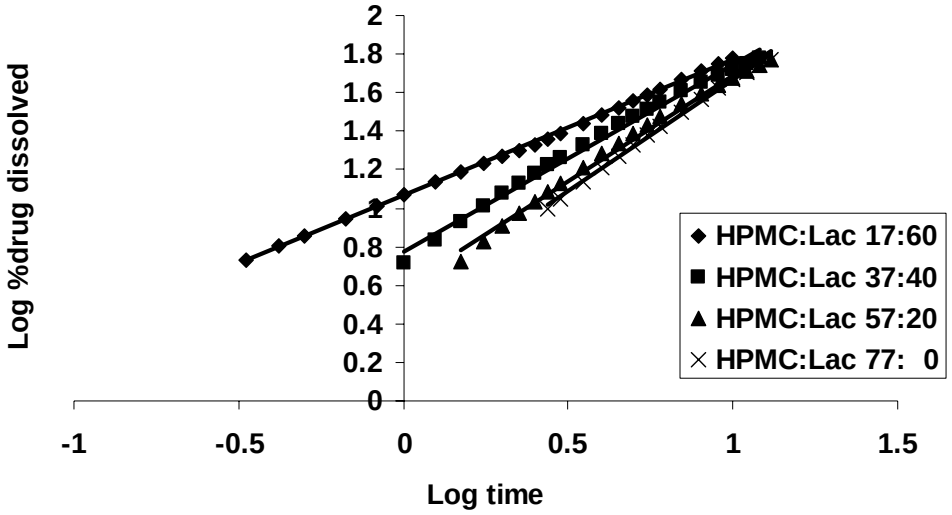

Figure 46. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 300 kg.

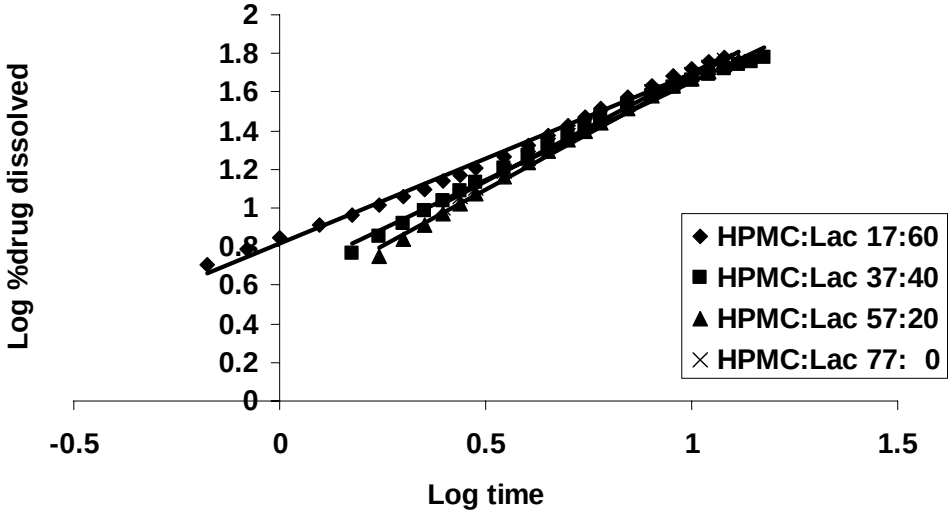

Figure 47. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 600 kg.

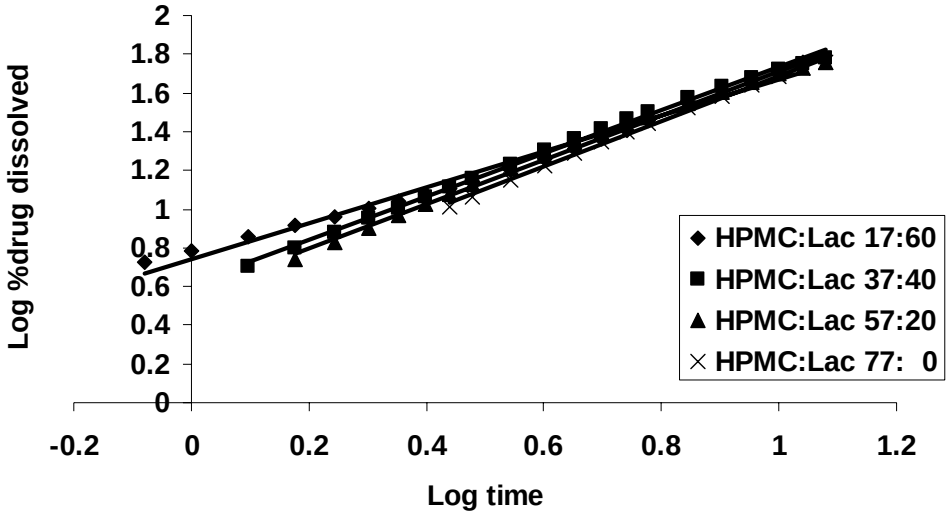

Figure 48. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : Microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 900 kg.

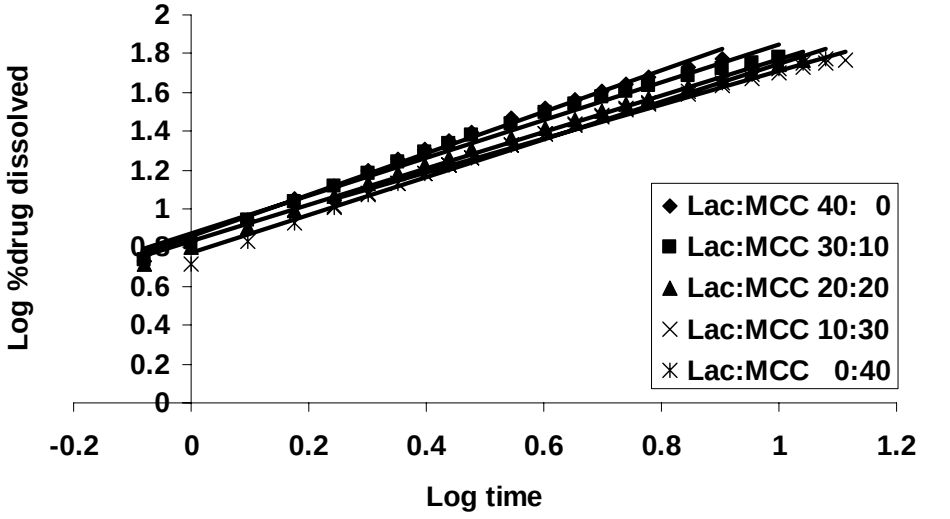

Figure 49. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 300 kg.

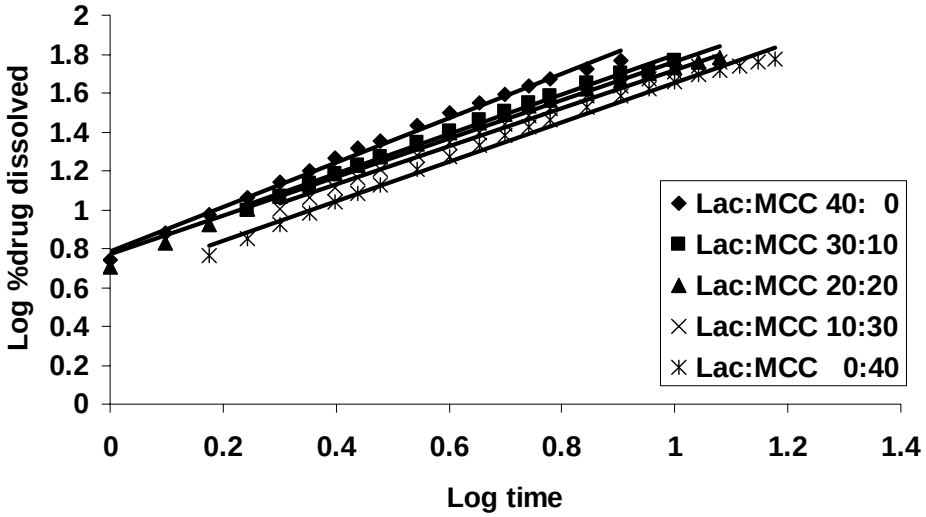

Figure 50. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 600 kg.

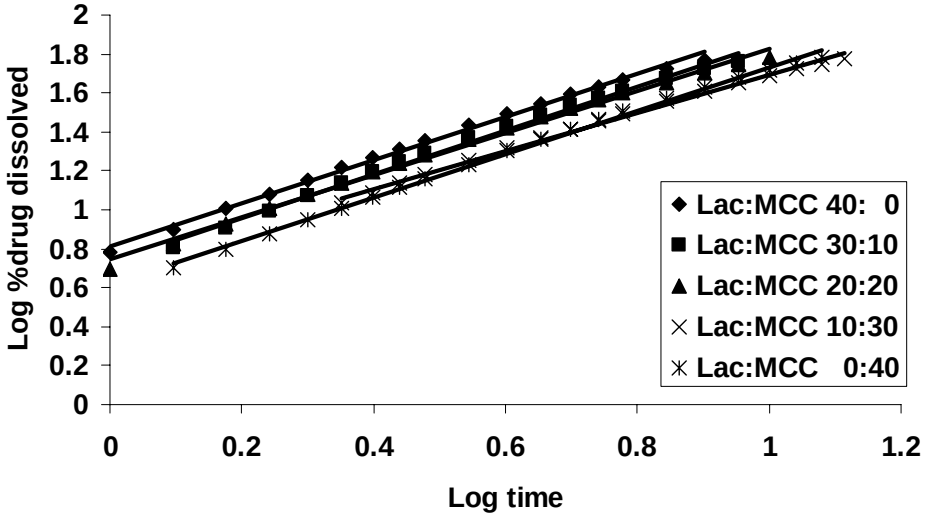

Figure 51. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of the logarithm of time at compression force 900 kg.

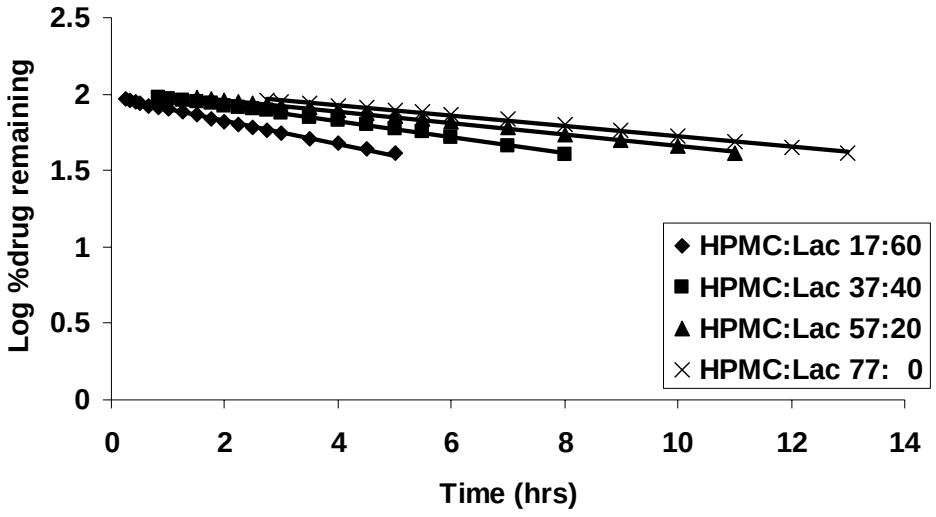

Figure 52. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 300 kg.

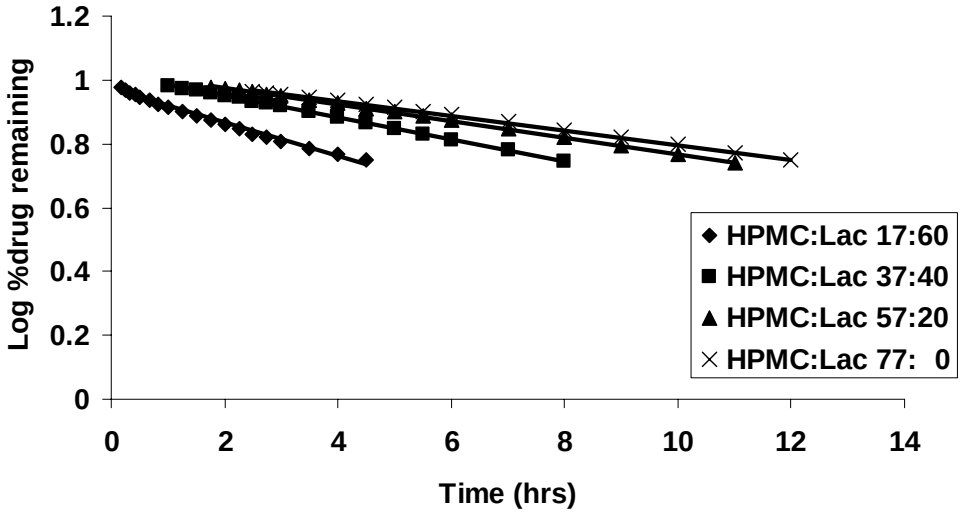

Figure 53. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 600 kg.

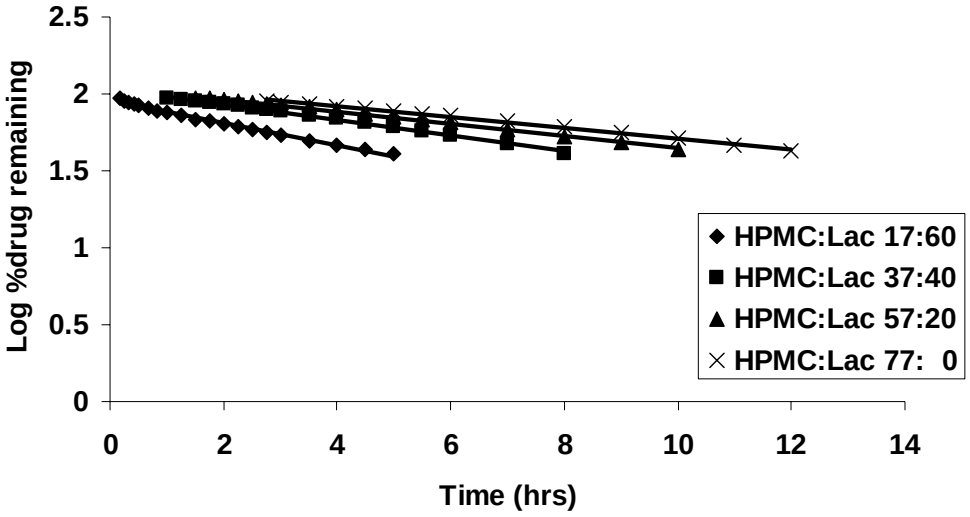

Figure 54. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 900 kg.

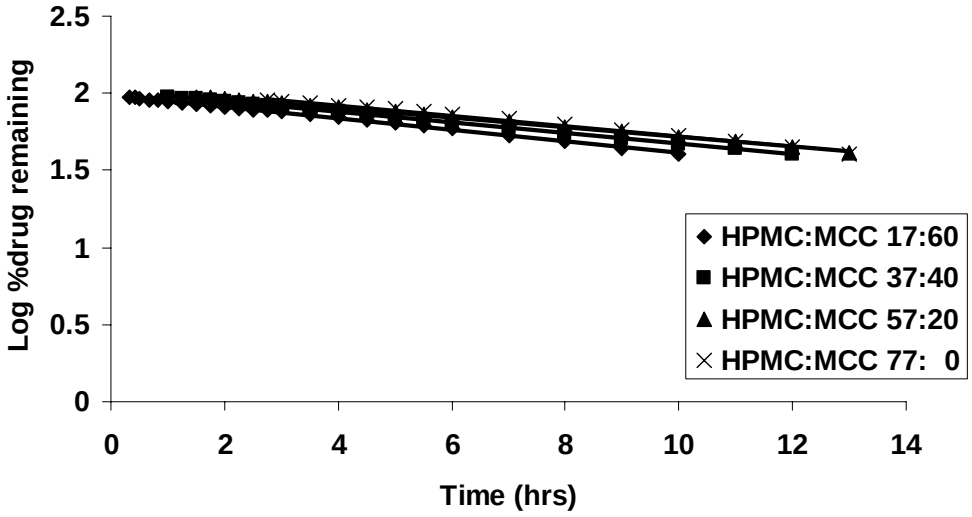

Figure 55. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

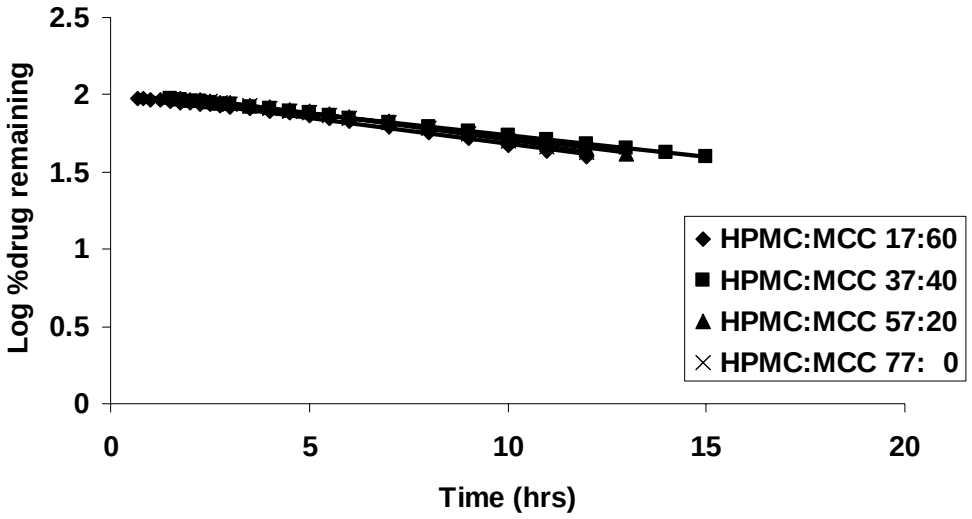

Figure 56. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

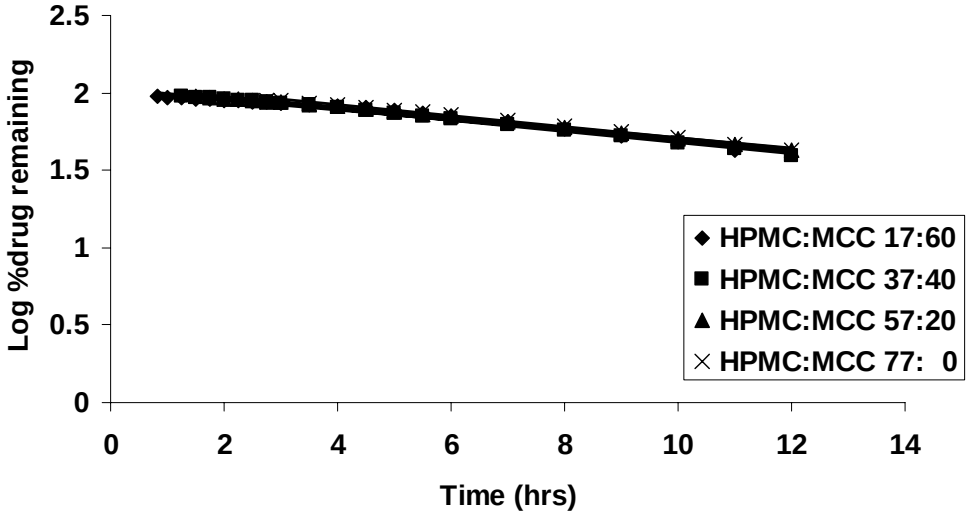

Figure 57. Plot of the log of percent indomethacin remaining from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

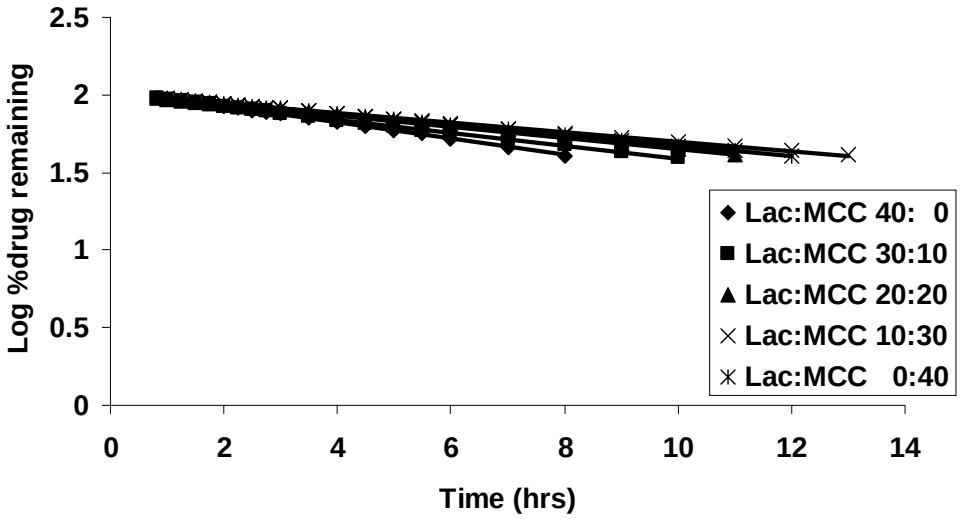

Figure 58. Plot of the log of percent indomethacin remaining from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

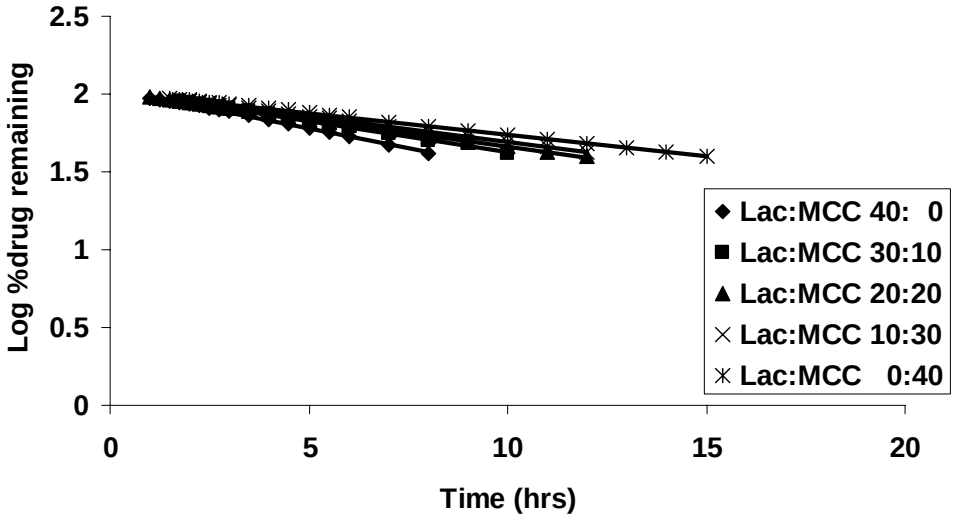

Figure 59. Plot of the log of percent indomethacin remaining from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

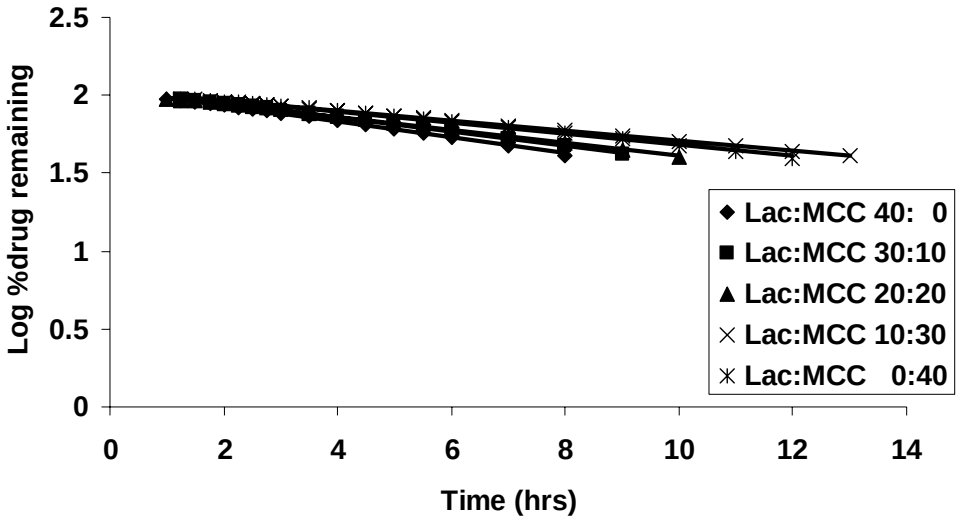

Figure 60. Plot of the log of percent indomethacin remaining from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

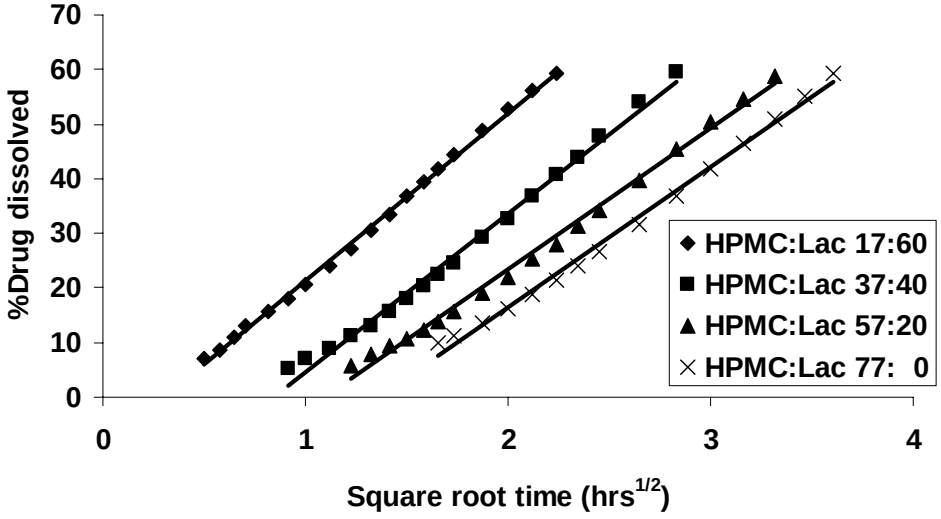

Figure 61. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of square root time at compression force 300 kg.

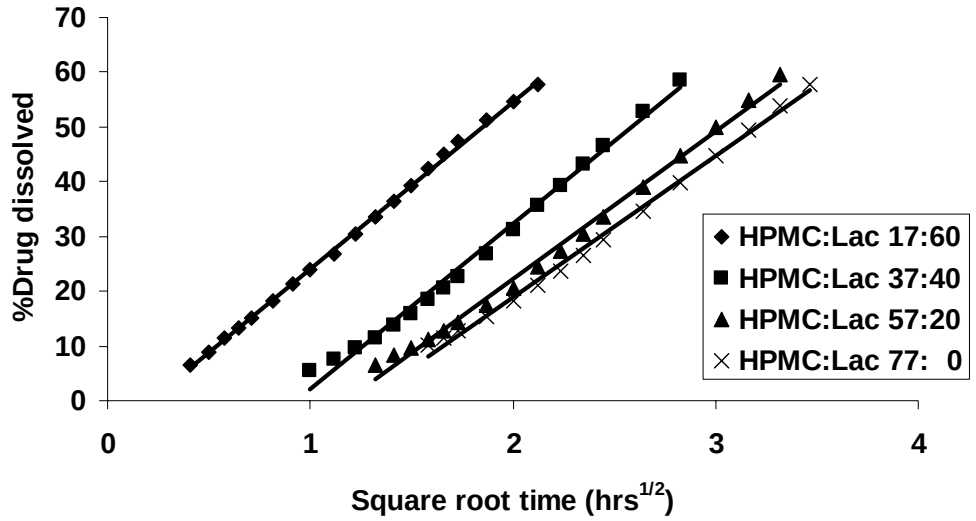

Figure 62. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of square root time at compression force 600 kg.

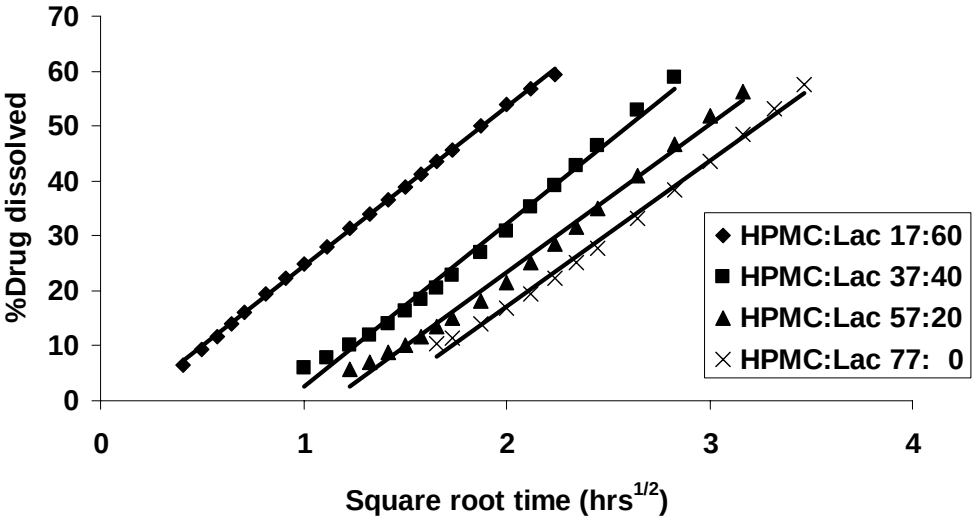

Figure 63. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of square root time at compression force 900 kg.

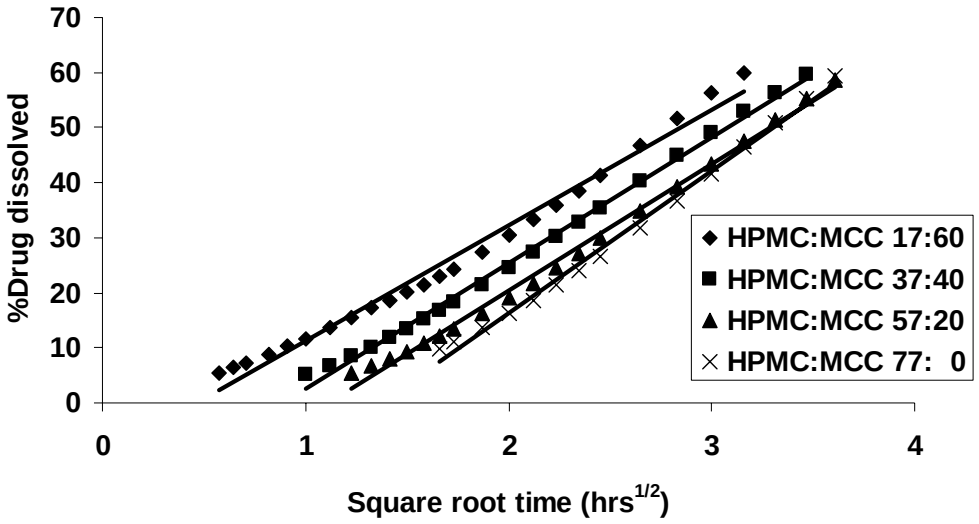

Figure 64. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of square root time at compression force 300 kg.

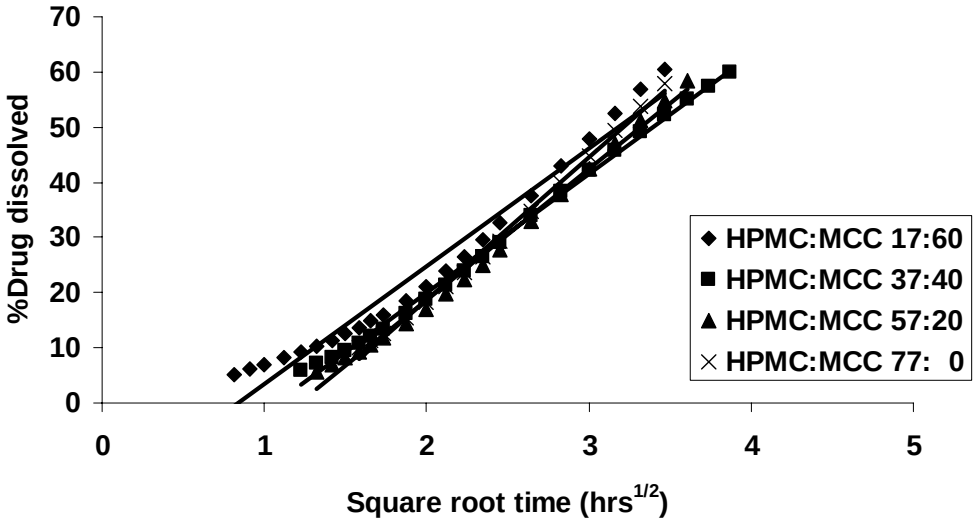

Figure 65. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of square root time at compression force 600 kg.

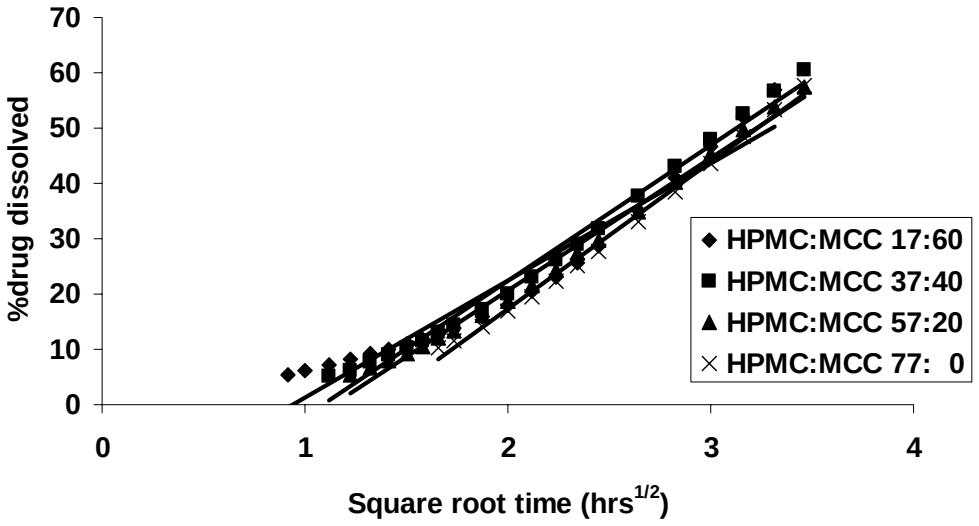

Figure 66. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of square root time at compression force 900 kg.

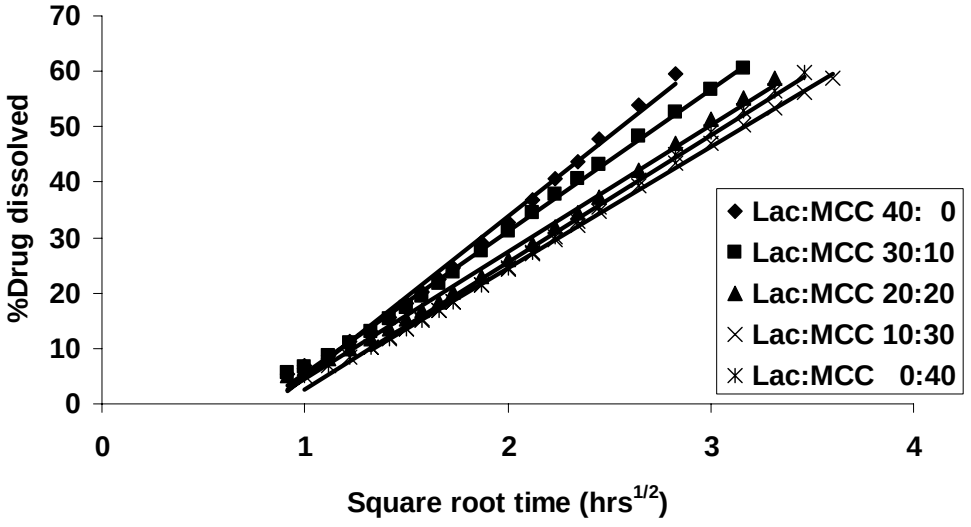

Figure 67. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of square root time at compression force 300 kg.

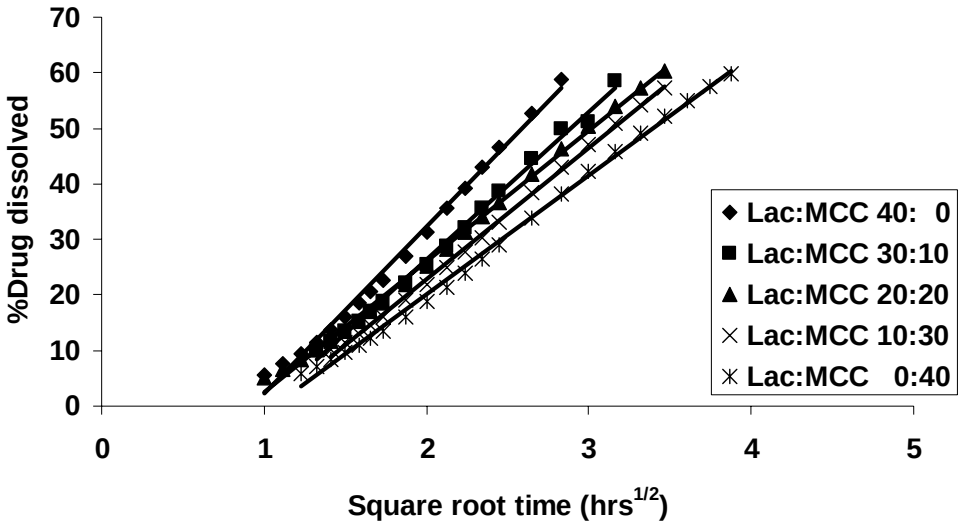

Figure 68. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of square root time at compression force 600 kg.

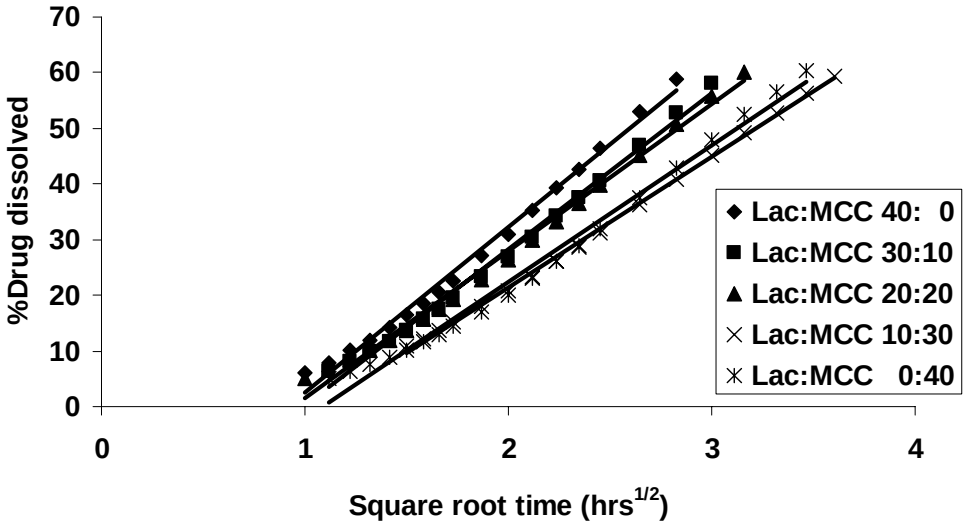

Figure 69. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of square root time at compression force 900 kg.

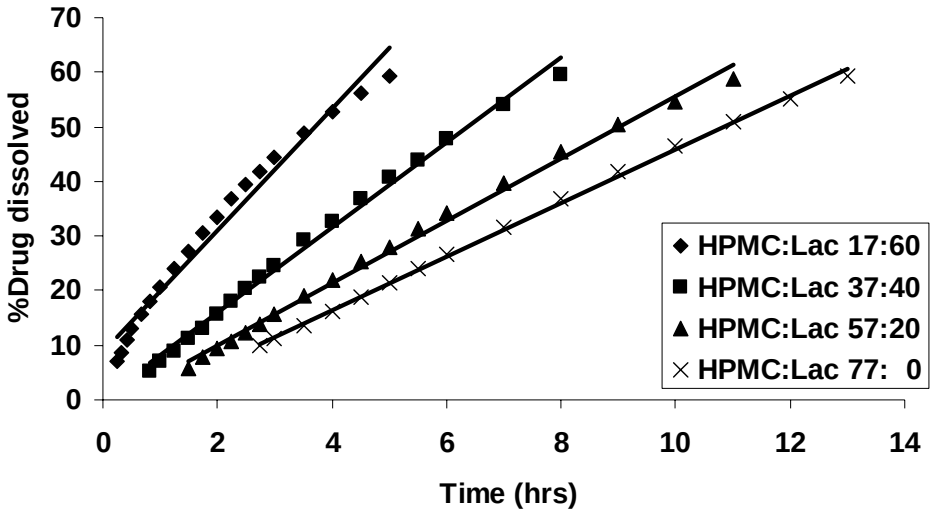

Figure 70. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 300 kg.

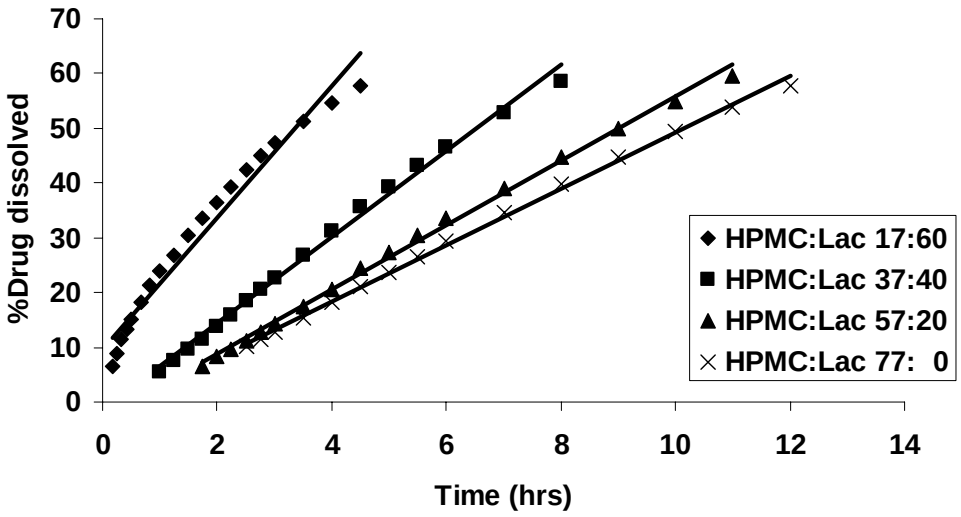

Figure 71. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 600 kg.

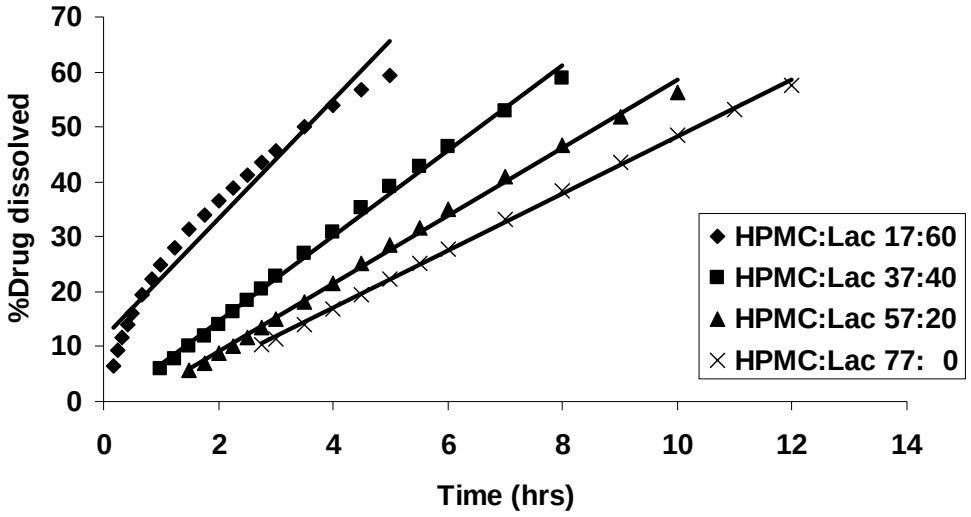

Figure 72. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : lactose (Lac) as a function of time at compression force 900 kg.

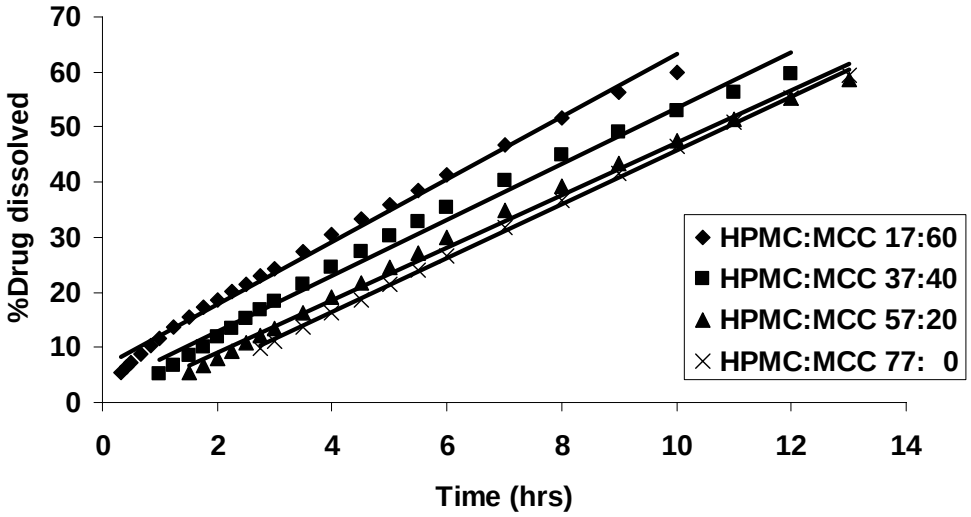

Figure 73. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

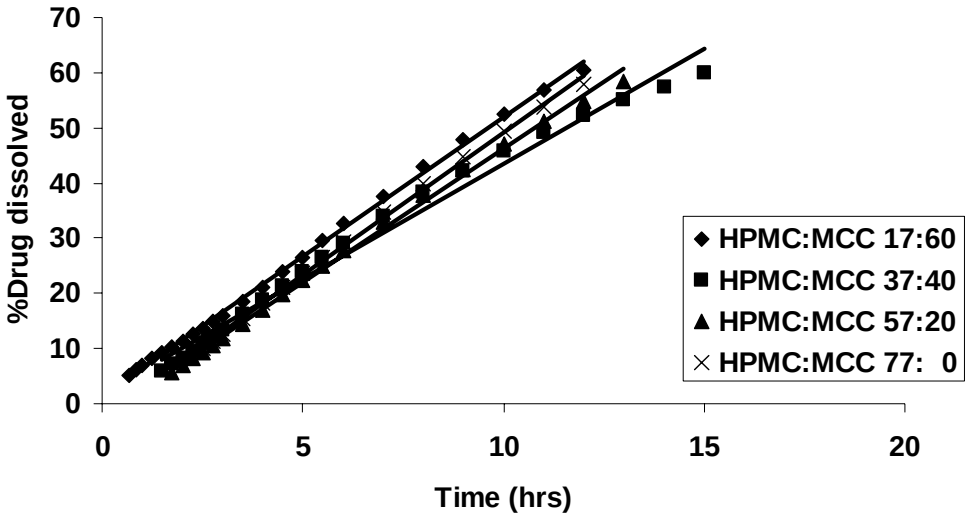

Figure 74. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

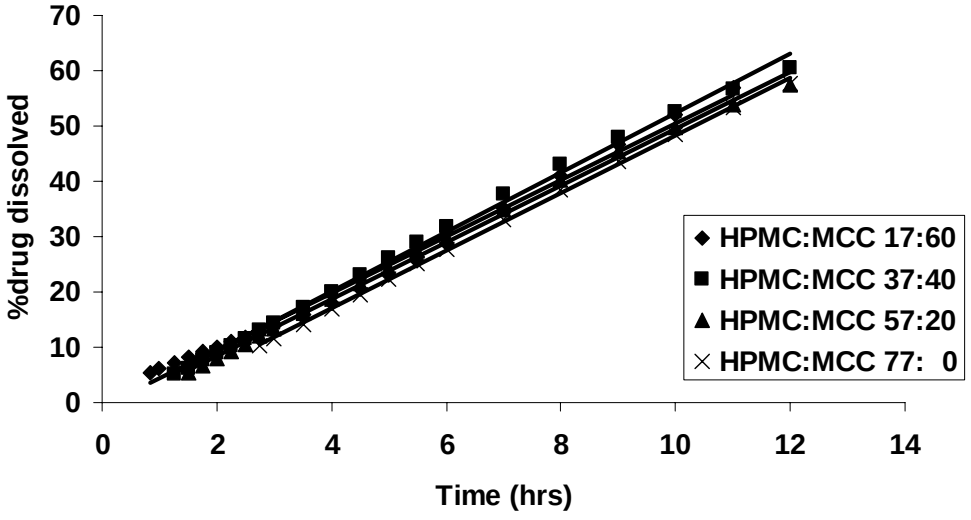

Figure 75. Plot of indomethacin released from matrix tablets containing various ratios of HPMC : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

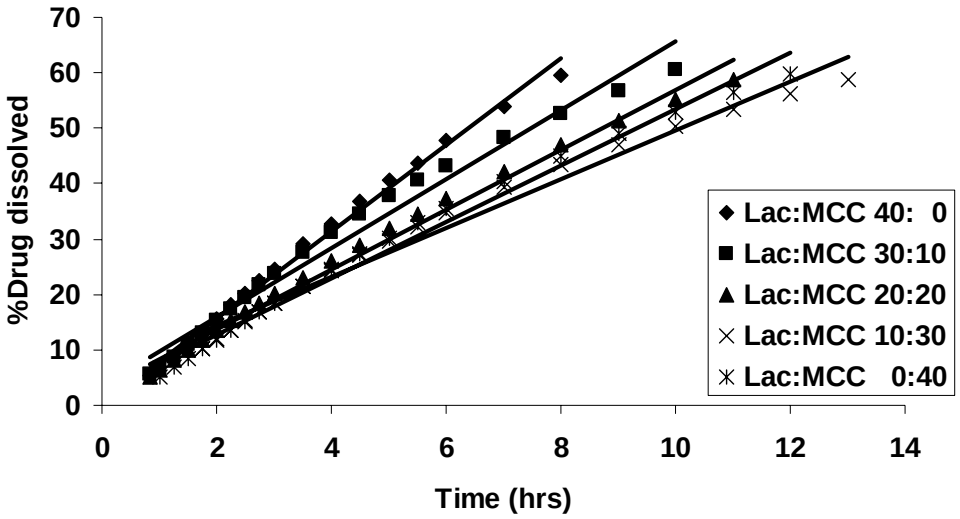

Figure 76. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 300 kg.

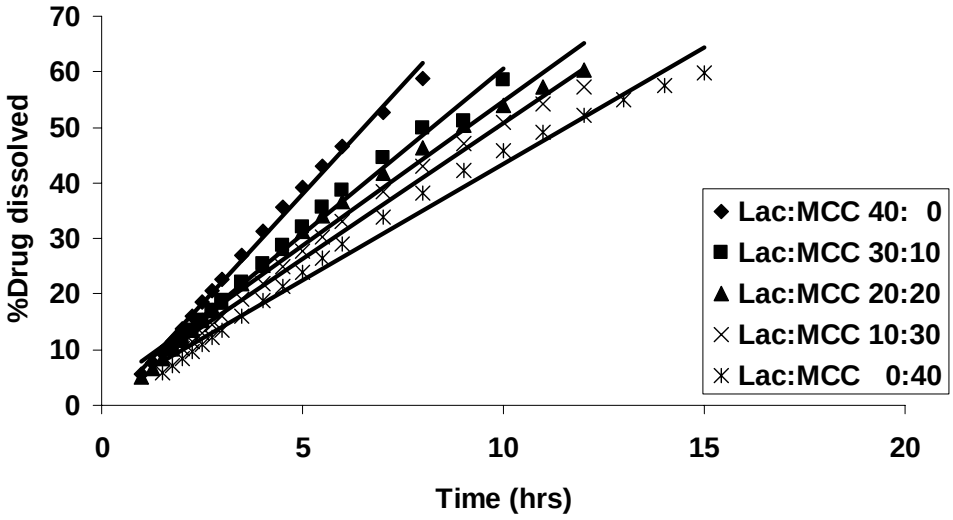

Figure 77. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 600 kg.

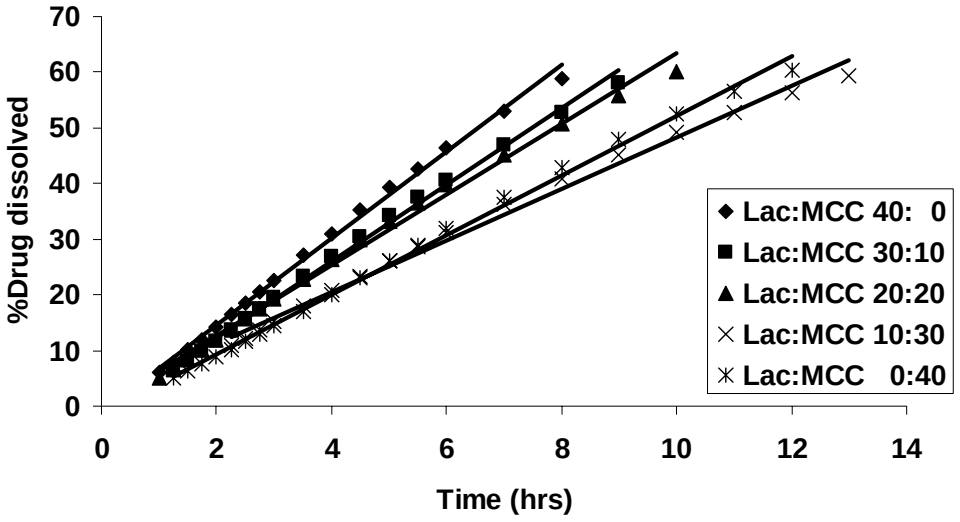

Figure 78. Plot of indomethacin released from matrix tablets containing HPMC 37% and various ratios of lactose (Lac) : microcrystalline cellulose (MCC) as a function of time at compression force 900 kg.

CHAPTER V
CONCLUSIONS

The results of the present study confirm that compression force had a significant effect on tablet friability and hardness. The friability decreased with increasing compression force. In contrast, the hardness of the tablets increased with increasing compression force. Increasing the amount of microcrystalline cellulose slightly increased tablet hardness under three applied compression force. Both HPMC and microcrystalline cellulose exhibits the same deformation behavior and have strong binding properties, causing by hydrogen bonds between hydrogen groups. Therefore, replacing HPMC by microcrystalline cellulose had only negligible effects on the hardness. On the other hand, the tablet hardness decreased when the amount of lactose increased. The decrease in tablet hardness may be due to a decrease in the compressibility of the matrix resulting from the higher lactose proportion. It was observed that tablet hardness was influenced by the type and content of excipient. Moreover, the compression force slightly affected drug release from HPMC tablets but did not alter the drug release mechanism.

The type and level of excipient influenced the extent and rate of drug release. The hydrated gel layer was more permeable for drug release when a soluble excipient was contained in the formulation, so the formulations containing microcrystalline cellulose (insoluble excipient) released indomethacin at a slower rate and to a lesser extent than those containing lactose (soluble excipient). Increasing the proportion of lactose in the tablet resulted in increased the release of indomethacin in dissolution medium. This was due to the incorporation of lactose, which increased the interspace volume and porosity of the matrix and resulted in faster diffusion of drug from the matrix and an increased rate of erosion of the matrix tablet. However, increasing the contents of microcrystalline cellulose in the tablet resulted in slightly increased indomethacin release in dissolution medium. The presence of a swelling insoluble excipient like microcrystalline cellulose changed the release profile to a small extent

due to a change in swelling at the tablet surface. In addition, type and content of excipient had an influence on the indomethacin release mechanism.

The release mechanism of indomethacin from each tablet formulation can be described by either the Hixson-Crowell cube root kinetics equation or Peppas's equation. Therefore, the dissolution of indomethacin occurs mainly after the erosion process, resulting in the release of drug particles from the matrix tablet. However, all of the formulations exhibited the best-fitted formulation into the first order kinetics except, the formulation containing HPMC to lactose ratio of 17:60 that followed Higuchi equation. Also, the formulation containing only HPMC and HPMC to MCC ratio of 17:60 followed zero order kinetic equation.

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APPENDIX

APPENDIX
EXPERIMENTAL DATA

Table A1. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.02	0.03	0.01	0.03	0.03	0.01	0.02	0.01
0.083	0.17	0.13	0.16	0.08	0.13	0.14	0.14	0.03
0.167	0.28	0.25	0.29	0.15	0.25	0.29	0.25	0.05
0.250	0.35	0.34	0.42	0.23	0.36	0.41	0.35	0.07
0.333	0.47	0.53	0.57	0.32	0.49	0.58	0.49	0.10
0.417	0.66	0.66	0.72	0.49	0.67	0.78	0.66	0.10
0.500	0.82	0.86	0.98	0.70	0.85	1.00	0.87	0.11
0.667	1.20	1.28	1.46	1.17	1.25	1.52	1.31	0.14
0.833	1.67	1.72	1.97	1.68	1.71	2.13	1.81	0.19
1.000	2.23	2.22	2.54	2.29	2.22	2.78	2.38	0.23
1.250	3.01	3.12	3.44	3.20	3.06	3.81	3.27	0.30
1.500	3.90	4.06	4.39	4.17	3.94	4.93	4.23	0.38
1.750	4.89	5.13	5.41	5.21	4.89	6.12	5.28	0.46
2.000	5.96	6.26	6.53	6.33	5.88	7.32	6.38	0.52
2.250	7.00	7.47	7.71	7.46	6.91	8.55	7.52	0.59
2.500	8.18	8.72	8.84	8.66	7.94	9.85	8.70	0.66
2.750	9.28	9.94	10.05	9.84	9.01	11.13	9.88	0.74
3.000	10.51	11.23	11.29	11.06	10.13	12.44	11.11	0.79
3.500	13.06	13.82	13.84	13.59	12.45	15.13	13.65	0.90
4.000	15.61	16.43	16.30	16.11	14.75	17.80	16.17	1.01

Table A1. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
4.500	18.19	19.08	18.79	18.69	17.05	20.51	18.72	1.13
5.000	20.86	21.80	21.38	21.31	19.39	23.25	21.33	1.26
5.500	23.48	24.47	23.86	23.89	21.73	26.06	23.92	1.41
6.000	26.22	27.15	26.48	26.53	24.15	28.88	26.57	1.53
7.000	31.41	32.52	31.51	31.74	28.85	34.28	31.72	1.76
8.000	36.42	37.79	36.57	36.85	33.60	39.56	36.80	1.95
9.000	41.35	42.85	41.50	41.83	38.24	44.46	41.71	2.05
10.000	46.15	47.58	46.05	46.55	42.80	49.30	46.41	2.14
11.000	50.79	52.18	50.49	51.27	47.27	53.74	50.96	2.15
12.000	55.07	56.52	54.54	55.67	51.39	57.84	55.17	2.19
13.000	59.08	60.84	58.70	60.07	55.56	61.65	59.32	2.14
14.000	62.79	64.86	62.40	63.92	59.24	65.13	63.06	2.16
15.000	66.23	68.43	66.04	67.79	63.35	68.58	66.74	1.98
16.000	69.76	72.73	69.94	71.43	67.82	72.21	70.65	1.83
17.000	73.04	76.34	73.49	74.74	71.56	75.27	74.07	1.72
18.000	76.08	80.06	76.94	77.95	75.31	78.23	77.43	1.70
19.000	78.92	83.19	80.36	81.06	78.76	80.75	80.51	1.62
20.000	81.93	86.09	83.19	84.39	81.71	83.05	83.39	1.64
21.000	84.17	89.09	86.24	86.27	85.13	85.79	86.12	1.66
22.000	86.86	91.27	89.07	89.27	87.42	88.26	88.69	1.57
23.000	89.24	93.36	91.15	91.44	88.96	89.60	90.63	1.68
24.000	91.19	94.07	92.95	92.51	91.09	91.92	92.29	1.13

Table A2. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.08	0.03	0.06	0.12	0.05	0.03	0.06	0.03
0.083	0.30	0.15	0.26	0.37	0.23	0.18	0.25	0.08
0.167	0.48	0.27	0.41	0.63	0.36	0.31	0.41	0.13
0.250	0.60	0.40	0.63	0.91	0.52	0.53	0.60	0.17
0.333	0.84	0.59	0.79	1.20	0.70	0.61	0.79	0.22
0.417	1.02	0.81	1.07	1.57	0.94	0.81	1.04	0.28
0.500	1.20	1.02	1.31	1.90	1.18	1.01	1.27	0.33
0.667	1.67	1.53	1.82	2.58	1.65	1.49	1.79	0.40
0.833	2.17	2.07	2.34	3.29	2.20	1.97	2.34	0.48
1.000	2.75	2.70	2.89	4.06	2.82	2.56	2.96	0.55
1.250	3.60	3.70	3.80	5.26	3.78	3.48	3.94	0.66
1.500	4.62	4.85	4.87	6.59	4.87	4.62	5.07	0.75
1.750	5.52	5.99	5.95	7.92	5.99	5.91	6.21	0.85
2.000	6.62	7.21	7.11	9.33	7.16	7.34	7.46	0.95
2.250	7.75	8.48	8.40	10.73	8.37	8.53	8.71	1.03
2.500	8.98	9.83	9.66	12.23	9.67	9.79	10.03	1.12
2.750	10.23	11.19	11.00	13.68	10.97	11.06	11.36	1.19
3.000	11.50	12.55	12.40	15.15	12.24	12.26	12.68	1.26
3.500	14.20	15.38	15.23	18.06	14.87	14.83	15.43	1.35
4.000	16.79	18.16	18.09	21.04	17.59	17.41	18.18	1.49
4.500	19.43	21.04	21.05	23.99	20.31	20.08	20.98	1.60

Table A2. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	22.11	23.90	23.98	27.07	23.00	22.65	23.79	1.76
5.500	24.75	26.68	26.85	29.96	25.73	25.16	26.52	1.87
6.000	27.41	29.37	29.72	33.20	28.49	27.72	29.32	2.10
7.000	32.46	34.48	35.16	39.34	33.71	32.63	34.63	2.53
8.000	37.51	39.38	40.27	45.28	39.05	37.83	39.89	2.83
9.000	41.93	44.20	45.12	50.71	43.79	42.70	44.74	3.13
10.000	46.39	48.86	49.86	55.74	48.60	47.38	49.47	3.30
11.000	50.78	53.29	54.50	60.07	52.90	51.70	53.87	3.30
12.000	54.80	57.18	58.76	63.97	56.77	55.71	57.87	3.28
13.000	59.08	61.29	62.77	66.98	60.64	59.63	61.73	2.88
14.000	63.07	65.15	66.70	70.92	64.22	63.55	65.60	2.91
15.000	66.85	68.71	70.26	73.95	67.38	67.24	69.07	2.70
16.000	70.55	72.14	73.92	77.09	70.75	70.82	72.55	2.56
17.000	73.79	75.12	77.19	79.86	73.84	74.32	75.69	2.40
18.000	77.19	78.35	80.76	82.87	76.75	77.42	78.89	2.42
19.000	80.07	81.15	83.42	85.38	79.39	80.47	81.65	2.29
20.000	82.57	83.83	86.07	88.19	82.35	83.45	84.41	2.28
21.000	85.42	86.03	88.52	90.28	84.63	86.14	86.84	2.13
22.000	87.99	88.63	90.91	92.52	86.75	88.03	89.14	2.15
23.000	89.70	90.75	92.85	93.65	88.48	90.22	90.94	1.96
24.000	91.94	92.36	93.87	95.61	89.58	92.20	92.59	2.02

Table A3. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.09	0.11	0.08	0.04	0.06	0.06	0.07	0.03
0.083	0.21	0.18	0.17	0.14	0.14	0.19	0.17	0.03
0.167	0.35	0.31	0.26	0.24	0.26	0.27	0.28	0.04
0.250	0.43	0.45	0.49	0.38	0.38	0.38	0.42	0.05
0.333	0.62	0.60	0.54	0.54	0.53	0.53	0.56	0.04
0.417	0.84	0.82	0.72	0.74	0.74	0.70	0.76	0.06
0.500	1.01	1.05	0.96	0.96	0.96	0.92	0.98	0.05
0.667	1.49	1.58	1.42	1.40	1.42	1.33	1.44	0.09
0.833	2.04	2.09	1.87	1.89	1.91	1.82	1.94	0.11
1.000	2.65	2.71	2.39	2.45	2.47	2.35	2.50	0.14
1.250	3.58	3.71	3.29	3.31	3.38	3.21	3.41	0.19
1.500	4.60	4.82	4.24	4.30	4.39	4.16	4.42	0.25
1.750	5.72	5.98	5.32	5.32	5.42	5.13	5.48	0.31
2.000	6.95	7.18	6.40	6.43	6.58	6.19	6.62	0.37
2.250	8.12	8.50	7.55	7.58	7.76	7.27	7.80	0.44
2.500	9.39	9.79	8.67	8.76	8.99	8.39	9.00	0.51
2.750	10.68	11.16	9.98	9.99	10.25	9.53	10.27	0.58
3.000	12.01	12.50	11.13	11.21	11.52	10.70	11.51	0.65
3.500	14.77	15.29	13.72	13.79	14.13	13.07	14.13	0.80
4.000	17.49	18.13	16.46	16.39	16.80	15.55	16.80	0.90
4.500	20.36	20.94	19.21	19.09	19.51	18.14	19.54	0.99

Table A3. %Drug dissolved of indomethacin from formulation containing only HPMC at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	23.25	23.80	22.01	21.79	22.29	20.75	22.32	1.09
5.500	26.04	26.52	24.73	24.43	25.00	23.41	25.02	1.12
6.000	29.07	29.23	27.52	27.10	27.70	26.12	27.79	1.19
7.000	34.64	34.49	32.95	32.38	32.98	31.34	33.13	1.26
8.000	40.25	39.52	38.17	37.70	38.27	36.58	38.42	1.31
9.000	45.72	44.53	43.18	42.98	43.42	41.72	43.59	1.38
10.000	50.78	49.28	48.00	48.14	48.36	46.71	48.55	1.37
11.000	55.49	53.65	52.62	53.03	53.03	51.44	53.21	1.34
12.000	59.68	57.76	56.78	57.79	57.46	56.04	57.59	1.23
13.000	63.41	61.62	60.81	62.19	61.33	60.14	61.58	1.14
14.000	66.96	65.17	64.53	66.06	65.20	64.15	65.35	1.03
15.000	70.39	68.63	68.01	69.76	68.69	67.70	68.86	1.03
16.000	73.69	71.95	71.17	73.07	72.12	71.06	72.18	1.04
17.000	76.54	75.26	74.41	76.27	75.05	74.15	75.28	0.96
18.000	79.29	78.11	77.20	79.37	78.09	77.08	78.19	0.98
19.000	81.83	80.97	80.00	82.35	81.20	79.88	81.04	0.98
20.000	85.77	85.30	84.12	86.44	85.00	83.68	85.05	1.03
21.000	88.66	87.89	87.32	89.00	87.88	87.09	87.97	0.74
22.000	91.52	90.78	90.31	92.26	90.23	89.86	90.83	0.90
23.000	93.51	92.72	92.66	94.29	91.97	91.58	92.79	0.99
24.000	94.85	94.31	94.43	96.13	94.09	93.52	94.56	0.89

Table A4. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.21	0.20	0.19	0.15	0.18	0.17	0.18	0.02
0.083	11.66	10.74	11.15	11.47	11.34	11.52	11.31	0.33
0.167	18.46	17.81	18.06	18.17	18.15	18.24	18.15	0.21
0.250	22.62	22.04	22.22	22.16	22.25	22.28	22.26	0.20
0.333	25.40	25.03	25.09	24.88	25.05	25.01	25.08	0.17
0.417	27.45	27.28	27.22	26.87	27.12	27.02	27.16	0.20
0.500	28.97	28.84	28.73	28.28	28.59	28.45	28.64	0.25
0.667	31.20	31.15	30.94	30.26	30.72	30.50	30.79	0.37
0.833	32.78	32.70	32.46	31.67	32.21	31.95	32.29	0.44
1.000	33.89	34.08	33.73	32.88	33.43	33.13	33.52	0.46
1.250	35.64	36.18	35.60	34.39	35.15	34.70	35.28	0.66
1.500	36.95	38.12	37.21	35.66	36.60	35.98	36.75	0.89
1.750	38.04	40.54	38.99	36.83	38.06	37.13	38.27	1.35
2.000	38.99	42.87	40.63	37.80	39.37	38.10	39.63	1.88
2.250	39.88	44.36	41.83	38.71	40.42	39.00	40.70	2.11
2.500	40.60	45.40	42.73	39.53	41.27	39.80	41.55	2.21
2.750	41.39	46.25	43.54	40.27	42.05	40.55	42.34	2.25
3.000	42.00	46.93	44.22	41.03	42.75	41.27	43.03	2.23
3.500	43.16	48.02	45.41	42.42	44.01	42.61	44.27	2.14
4.000	44.36	49.09	46.54	43.63	45.18	43.81	45.44	2.08
4.500	45.31	49.93	47.45	44.62	46.12	44.79	46.37	2.03

Table A4. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	46.31	50.70	48.31	45.52	47.01	45.72	47.26	1.96
5.500	47.16	51.29	49.03	46.38	47.80	46.58	48.04	1.86
6.000	48.25	52.01	49.89	47.27	48.70	47.52	48.94	1.77
7.000	49.84	53.20	51.27	48.85	50.19	49.10	50.41	1.62
8.000	51.36	54.31	52.58	50.33	51.58	50.59	51.79	1.47
9.000	52.60	55.35	53.74	51.64	52.81	51.88	53.00	1.37
10.000	53.66	56.32	54.74	52.67	53.83	52.92	54.02	1.34
11.000	54.67	57.15	55.67	53.72	54.82	53.96	55.00	1.26
12.000	55.72	58.15	56.71	54.82	55.88	55.05	56.05	1.23
13.000	56.70	58.96	57.59	55.72	56.78	55.97	56.95	1.18
14.000	57.47	59.75	58.40	56.62	57.62	56.83	57.78	1.15
15.000	58.35	60.47	59.20	57.52	58.47	57.73	58.62	1.08
16.000	59.16	61.40	60.07	58.31	59.30	58.52	59.46	1.14
17.000	59.90	62.05	60.72	58.89	59.93	59.14	60.11	1.15
18.000	60.49	62.80	61.43	59.64	60.64	59.85	60.81	1.16
19.000	61.34	63.52	62.18	60.32	61.38	60.58	61.55	1.17
20.000	62.29	64.38	63.07	61.24	62.29	61.50	62.46	1.14
21.000	63.13	65.13	63.87	62.08	63.11	62.34	63.28	1.11
22.000	63.86	66.02	64.69	62.87	63.91	63.12	64.08	1.15
23.000	64.50	66.51	65.25	63.48	64.49	63.74	64.66	1.10
24.000	65.32	67.24	65.98	64.13	65.21	64.43	65.38	1.12

Table A5. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.13	0.11	0.12	0.11	0.10	0.11	0.11	0.01
0.083	1.06	1.28	1.63	1.85	2.33	1.90	1.68	0.46
0.167	4.46	4.51	5.59	7.47	11.41	9.21	7.11	2.80
0.250	9.71	9.56	11.88	15.26	17.00	16.21	13.27	3.31
0.333	14.43	14.89	17.74	20.06	20.10	19.96	17.86	2.64
0.417	18.32	18.52	21.25	22.97	22.28	22.41	20.96	2.04
0.500	21.35	21.16	23.75	24.96	24.00	24.48	23.28	1.63
0.667	25.44	24.67	27.23	27.85	26.76	27.48	26.57	1.25
0.833	28.42	27.34	29.85	30.23	29.09	29.77	29.12	1.08
1.000	30.79	29.55	32.00	32.20	31.09	31.74	31.23	0.98
1.250	33.27	32.07	34.54	34.66	33.77	33.91	33.70	0.95
1.500	35.26	34.22	36.65	36.89	35.91	35.92	35.81	0.97
1.750	37.06	36.09	38.48	38.86	38.07	37.58	37.69	1.01
2.000	38.51	37.61	40.13	40.63	39.82	39.45	39.36	1.11
2.250	39.75	39.07	41.72	42.35	41.53	40.94	40.89	1.25
2.500	41.00	40.35	42.94	43.85	43.12	42.29	42.26	1.34
2.750	42.05	41.75	44.23	45.29	44.61	43.45	43.56	1.42
3.000	43.12	42.84	45.60	46.63	46.06	44.48	44.79	1.57
3.500	44.97	44.98	47.59	49.34	48.59	46.21	46.95	1.85
4.000	46.54	46.85	49.59	51.36	51.04	47.79	48.86	2.10
4.500	47.90	48.70	51.16	53.10	53.54	49.14	50.59	2.38

Table A5. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	49.20	50.53	52.73	55.07	55.49	50.15	52.20	2.66
5.500	50.35	51.96	54.00	56.72	57.06	51.36	53.58	2.83
6.000	51.43	53.23	55.40	58.16	58.67	52.22	54.85	3.07
7.000	53.24	55.31	57.35	61.02	61.69	54.03	57.11	3.58
8.000	55.00	57.15	59.42	63.95	64.28	55.80	59.27	4.04
9.000	56.58	58.79	61.24	66.38	66.47	57.44	61.15	4.38
10.000	58.06	60.41	62.90	69.27	68.75	59.11	63.08	4.87
11.000	59.60	61.79	64.89	71.32	71.13	60.62	64.89	5.22
12.000	60.72	63.29	66.61	73.13	73.07	61.94	66.46	5.51
13.000	61.79	64.87	68.32	74.49	75.22	63.33	68.00	5.74
14.000	62.93	66.00	69.44	76.11	76.81	64.82	69.35	5.90
15.000	63.86	67.15	70.72	77.40	78.47	66.01	70.60	6.11
16.000	64.76	68.12	71.85	78.34	79.88	66.97	71.65	6.23
17.000	66.47	70.07	73.78	80.06	82.18	68.48	73.51	6.40
18.000	67.68	71.34	75.12	81.54	84.31	70.06	75.01	6.65
19.000	68.58	72.77	76.26	82.10	85.58	71.04	76.06	6.62
20.000	70.01	73.69	77.15	82.51	86.04	71.69	76.85	6.32
21.000	70.83	74.41	78.07	83.70	87.64	72.88	77.92	6.57
22.000	71.50	75.19	78.98	84.81	88.93	73.60	78.84	6.81
23.000	72.28	75.40	79.68	85.33	89.55	74.29	79.42	6.80
24.000	72.99	76.21	80.74	86.51	90.81	75.57	80.47	6.95

Table A6. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.10	0.11	0.08	0.10	0.11	0.07	0.10	0.02
0.083	0.34	0.34	0.36	0.44	0.32	0.36	0.36	0.04
0.167	0.69	0.77	0.67	0.94	0.56	0.64	0.71	0.13
0.250	1.41	1.73	1.23	2.21	1.11	1.06	1.46	0.44
0.333	2.53	3.22	2.06	3.84	2.02	1.67	2.56	0.83
0.417	4.04	5.03	3.42	6.04	3.23	2.88	4.11	1.21
0.500	6.01	7.17	5.55	8.31	4.68	5.01	6.12	1.38
0.667	10.57	12.15	10.39	12.36	8.18	9.80	10.57	1.55
0.833	15.03	17.03	14.82	16.79	11.97	14.08	14.95	1.86
1.000	19.68	21.73	19.05	21.37	17.10	18.16	19.52	1.80
1.250	26.82	28.41	26.18	28.38	25.03	25.43	26.71	1.44
1.500	33.98	36.22	33.56	35.80	30.80	32.67	33.84	2.01
1.750	39.85	42.95	39.47	42.04	35.20	38.31	39.64	2.77
2.000	43.98	47.48	43.64	46.00	38.61	42.36	43.68	3.08
2.250	47.04	50.76	46.55	49.27	41.48	45.14	46.71	3.25
2.500	49.53	53.42	48.87	51.81	43.91	47.35	49.15	3.35
2.750	51.64	55.69	50.71	53.86	46.13	49.05	51.18	3.41
3.000	53.41	57.65	52.21	55.46	47.93	50.40	52.84	3.49
3.500	56.39	60.86	54.96	58.18	50.86	52.99	55.71	3.59
4.000	58.74	63.26	57.24	60.12	53.20	55.23	57.96	3.58
4.500	60.58	64.94	59.08	61.89	55.30	57.12	59.82	3.45

Table A6. %Drug dissolved of indomethacin from formulation containing lactose 77% (without HPMC) at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	62.25	66.52	60.67	63.10	57.22	58.72	61.41	3.32
5.500	63.57	67.83	61.90	64.19	58.68	59.92	62.68	3.28
6.000	64.80	68.94	63.14	65.47	60.09	61.21	63.94	3.19
7.000	66.88	70.77	65.24	67.74	62.57	63.40	66.10	3.02
8.000	68.87	72.92	67.05	69.41	64.54	65.09	67.98	3.11
9.000	70.88	74.75	69.21	70.93	66.66	67.36	69.96	2.93
10.000	72.34	76.09	70.65	72.19	68.32	68.84	71.40	2.83
11.000	74.01	77.88	72.07	73.65	70.16	70.13	72.98	2.91
12.000	75.19	78.80	73.30	74.76	71.69	71.47	74.20	2.72
13.000	76.55	80.39	74.20	76.40	73.27	72.14	75.49	2.96
14.000	77.80	81.54	75.35	77.45	74.82	73.29	76.71	2.90
15.000	78.43	81.82	76.03	78.40	75.98	74.10	77.46	2.70
16.000	79.57	82.95	77.26	78.97	77.02	75.36	78.52	2.64
17.000	80.62	83.71	78.36	80.12	78.49	76.58	79.65	2.45
18.000	81.37	84.49	79.05	80.70	79.28	77.23	80.35	2.49
19.000	82.25	85.10	79.78	81.22	80.81	78.00	81.19	2.40
20.000	83.08	85.81	80.78	82.28	81.58	79.10	82.10	2.27
21.000	83.88	86.13	81.68	82.93	83.06	80.19	82.98	2.01
22.000	84.72	86.99	82.33	83.10	84.12	80.77	83.67	2.14
23.000	85.35	87.46	82.92	83.89	85.05	81.41	84.35	2.10
24.000	85.93	87.76	83.38	84.25	86.28	81.92	84.92	2.13

Table A7. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.16	0.25	0.25	0.19	0.20	0.17	0.20	0.04
0.083	2.13	2.14	3.47	2.05	2.41	2.73	2.49	0.54
0.167	4.05	4.17	6.21	3.99	4.65	5.10	4.70	0.85
0.250	6.32	6.17	8.70	6.03	6.95	7.46	6.94	1.02
0.333	8.45	8.01	10.45	7.42	8.49	9.08	8.65	1.04
0.417	10.28	10.06	12.60	9.88	10.94	11.54	10.88	1.04
0.500	12.16	12.14	14.60	12.04	13.37	13.71	13.00	1.06
0.667	14.80	14.98	17.04	14.74	16.24	16.19	15.67	0.96
0.833	17.41	17.77	19.18	17.28	18.60	18.16	18.07	0.73
1.000	20.07	20.21	21.37	19.93	21.28	20.99	20.64	0.64
1.250	23.26	23.70	24.81	23.86	24.44	24.30	24.06	0.56
1.500	26.50	27.04	27.91	27.28	27.20	27.38	27.22	0.46
1.750	29.96	30.32	31.17	30.66	29.91	30.94	30.49	0.52
2.000	33.24	33.48	33.88	33.92	32.59	33.97	33.51	0.54
2.250	36.14	36.41	37.54	37.23	35.77	37.15	36.71	0.70
2.500	38.79	38.76	40.69	39.92	38.30	39.56	39.34	0.89
2.750	41.40	41.22	43.71	42.23	40.70	42.05	41.89	1.05
3.000	43.82	43.57	46.51	44.76	43.25	44.74	44.44	1.19
3.500	48.44	47.97	50.54	49.32	47.57	49.40	48.87	1.09
4.000	51.89	51.70	54.41	52.79	52.01	53.07	52.65	1.02
4.500	55.59	55.56	57.14	55.87	55.40	56.77	56.06	0.72

Table A7. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	59.02	58.89	59.98	58.43	58.31	60.68	59.22	0.93
5.500	61.32	61.13	61.34	60.53	59.73	63.44	61.25	1.24
6.000	63.11	62.78	62.84	62.06	61.04	65.00	62.81	1.31
7.000	65.85	65.00	65.52	64.30	63.56	68.23	65.41	1.61
8.000	67.85	67.21	67.02	66.33	65.62	70.01	67.34	1.52
9.000	70.28	69.64	69.48	68.21	67.12	71.78	69.42	1.62
10.000	72.01	71.57	71.03	69.91	69.00	73.98	71.25	1.73
11.000	73.42	72.91	72.63	71.15	70.93	75.47	72.75	1.66
12.000	75.18	74.30	73.74	72.71	72.21	77.00	74.19	1.74
13.000	76.52	75.43	75.17	72.96	73.13	78.23	75.24	2.01
14.000	77.14	76.31	76.38	74.60	74.93	79.58	76.49	1.79
15.000	78.40	77.04	77.27	75.76	75.94	80.17	77.43	1.65
16.000	78.75	78.16	77.27	76.01	76.04	79.31	77.59	1.39
17.000	78.97	78.04	78.14	76.22	76.72	80.23	78.05	1.46
18.000	80.19	79.36	79.30	77.59	77.93	81.11	79.25	1.33
19.000	80.73	79.69	79.64	77.73	78.12	81.09	79.50	1.35
20.000	81.58	80.85	80.26	78.14	78.17	81.73	80.12	1.61
21.000	83.51	82.30	82.09	79.97	80.01	83.02	81.82	1.50
22.000	84.52	83.24	83.04	81.01	81.23	84.61	82.94	1.55
23.000	85.47	84.76	84.35	82.38	82.02	84.88	83.98	1.43
24.000	86.31	84.47	84.93	82.92	82.56	86.12	84.55	1.57

Table A8. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.27	0.34	0.34	0.18	0.33	0.39	0.31	0.07
0.083	3.35	3.29	4.04	2.04	4.05	4.20	3.49	0.81
0.167	6.14	6.00	7.28	4.18	6.94	7.77	6.39	1.27
0.250	8.57	8.40	10.04	6.27	9.41	10.71	8.90	1.56
0.333	10.88	10.69	12.63	8.45	11.88	13.42	11.32	1.75
0.417	12.81	12.67	14.71	10.33	13.75	15.61	13.31	1.84
0.500	14.63	14.45	16.60	12.13	15.55	17.54	15.15	1.89
0.667	17.78	17.49	19.70	15.18	18.61	20.66	18.24	1.91
0.833	21.27	19.98	23.10	17.87	22.69	23.22	21.35	2.11
1.000	23.98	22.20	25.64	20.25	25.45	25.41	23.82	2.19
1.250	26.87	25.27	28.34	23.60	28.23	28.31	26.77	1.96
1.500	31.02	28.32	32.43	26.62	32.82	31.17	30.40	2.43
1.750	34.38	31.12	35.60	29.55	36.49	33.83	33.49	2.66
2.000	37.37	33.44	38.56	32.21	39.91	36.41	36.32	2.97
2.250	40.69	36.48	41.65	35.05	43.21	39.06	39.36	3.12
2.500	43.99	39.53	44.72	37.91	46.96	41.48	42.43	3.40
2.750	46.43	42.63	47.21	40.90	49.48	43.83	45.08	3.19
3.000	48.57	45.18	49.49	43.13	52.05	45.94	47.39	3.25
3.500	52.57	48.56	53.52	47.04	56.20	49.67	51.26	3.43
4.000	56.09	51.32	56.80	50.34	60.23	52.36	54.52	3.81
4.500	59.39	53.66	60.21	53.44	63.98	55.28	57.66	4.22

Table A8. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	62.48	56.05	63.40	56.60	67.34	58.07	60.66	4.47
5.500	65.35	58.58	66.33	58.86	70.67	60.23	63.34	4.88
6.000	66.94	60.36	67.66	60.06	72.09	61.05	64.69	4.94
7.000	69.06	62.19	70.00	61.96	74.35	63.01	66.76	5.13
8.000	71.11	64.09	72.07	64.13	76.14	64.86	68.73	5.09
9.000	72.20	65.04	73.14	65.38	77.13	65.93	69.80	5.06
10.000	73.54	66.60	74.58	66.86	78.57	67.21	71.23	5.04
11.000	74.24	67.12	75.44	67.62	78.79	68.21	71.90	4.90
12.000	75.29	68.55	76.60	69.44	79.81	69.44	73.19	4.68
13.000	75.99	68.99	77.40	70.64	80.27	70.39	73.95	4.57
14.000	76.81	69.83	78.15	71.93	81.01	71.27	74.83	4.45
15.000	77.37	70.54	79.05	72.94	81.10	72.79	75.63	4.14
16.000	77.59	71.27	79.29	73.36	81.13	73.00	75.94	3.95
17.000	78.46	71.89	80.18	73.87	81.91	74.00	76.72	4.02
18.000	78.56	72.20	80.37	74.51	81.95	74.34	76.99	3.86
19.000	79.14	72.75	81.14	75.26	82.73	75.24	77.71	3.89
20.000	79.64	73.11	81.53	75.49	83.16	75.77	78.12	3.92
21.000	79.89	73.90	81.90	76.63	82.50	76.78	78.60	3.38
22.000	80.05	74.15	82.17	76.81	82.91	77.07	78.86	3.42
23.000	80.74	75.13	82.84	77.38	83.40	77.68	79.53	3.31
24.000	81.15	75.41	83.32	77.86	83.63	78.50	79.98	3.27

Table A9. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.083	4.90	3.80	2.79	2.60	2.77	2.42	3.21	0.96
0.167	8.32	7.18	6.01	5.68	6.04	5.35	6.43	1.11
0.250	10.95	9.99	8.88	8.56	9.02	8.24	9.27	1.01
0.333	13.44	12.44	11.40	10.97	11.44	10.53	11.70	1.06
0.417	15.61	14.71	13.63	13.26	13.81	12.89	13.99	1.00
0.500	17.56	16.70	15.79	15.35	15.83	14.90	16.02	0.96
0.667	20.91	20.10	19.28	18.78	19.29	18.27	19.44	0.94
0.833	23.90	23.07	22.16	21.71	22.24	21.25	22.39	0.96
1.000	26.42	25.61	24.37	24.07	24.61	23.57	24.78	1.05
1.250	29.61	28.82	27.90	27.40	28.03	26.90	28.11	0.98
1.500	32.42	31.95	31.24	30.78	31.47	30.32	31.36	0.76
1.750	34.83	34.51	33.91	33.33	34.19	32.74	33.92	0.77
2.000	37.23	36.93	36.94	36.42	36.68	35.31	36.59	0.68
2.250	39.16	39.29	39.55	38.63	39.41	37.71	38.96	0.69
2.500	41.13	41.48	42.04	41.01	41.82	39.98	41.24	0.73
2.750	43.19	43.73	44.61	43.45	44.27	42.29	43.59	0.82
3.000	45.48	45.99	46.65	45.53	46.50	44.40	45.76	0.82
3.500	50.30	50.76	50.27	49.28	51.21	48.28	50.02	1.07
4.000	53.94	54.51	53.78	53.61	55.10	52.24	53.86	0.97
4.500	56.89	57.27	57.16	56.17	57.65	55.17	56.72	0.91

Table A9. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 17:60 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	59.18	59.61	59.47	58.92	60.04	58.36	59.26	0.58
5.500	60.68	61.03	60.90	60.60	61.38	60.30	60.82	0.37
6.000	62.03	62.21	62.54	61.36	61.98	60.78	61.82	0.64
7.000	64.28	64.38	65.35	64.70	64.48	64.05	64.54	0.45
8.000	65.84	65.61	66.99	65.92	65.38	64.84	65.76	0.72
9.000	67.34	67.02	68.43	67.45	66.70	66.46	67.23	0.70
10.000	69.02	68.37	69.68	68.69	67.72	67.69	68.53	0.77
11.000	70.15	69.23	70.31	69.24	68.31	68.17	69.24	0.89
12.000	70.71	71.37	71.80	70.35	69.37	69.30	70.48	1.02
13.000	71.30	70.38	71.33	70.34	69.45	69.34	70.36	0.86
14.000	72.06	70.80	72.51	71.07	69.53	69.63	70.93	1.22
15.000	73.15	72.02	73.62	72.37	70.88	71.11	72.19	1.09
16.000	74.25	72.93	74.29	73.00	71.61	71.71	72.97	1.17
17.000	74.95	73.59	75.30	74.09	72.22	72.88	73.84	1.19
18.000	75.42	74.08	75.61	74.52	72.74	73.43	74.30	1.12
19.000	76.10	74.80	76.29	75.02	73.49	73.75	74.91	1.16
20.000	77.12	75.61	76.82	75.75	74.10	74.67	75.68	1.17
21.000	77.99	76.50	77.50	76.40	75.01	75.29	76.45	1.17
22.000	79.18	77.69	79.59	78.29	76.20	76.99	77.99	1.29
23.000	80.57	78.75	80.22	78.98	76.92	77.73	78.86	1.40
24.000	81.28	79.25	81.12	79.83	77.21	78.54	79.54	1.56

Table A10. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.20	0.20	0.15	0.23	0.19	0.12	0.18	0.04
0.083	0.73	0.48	0.68	0.63	0.62	0.56	0.62	0.09
0.167	1.10	0.87	1.08	0.80	1.01	0.83	0.95	0.13
0.250	1.76	1.38	1.80	1.60	1.91	1.74	1.70	0.19
0.333	2.19	1.77	2.14	1.78	2.08	1.96	1.99	0.18
0.417	2.69	2.16	2.60	2.19	2.50	2.37	2.42	0.22
0.500	3.28	2.74	3.17	2.79	3.03	2.97	3.00	0.21
0.667	4.39	3.65	4.33	3.78	3.97	4.17	4.05	0.30
0.833	5.82	4.81	5.56	5.03	5.23	5.64	5.35	0.39
1.000	7.49	6.21	7.04	6.60	6.85	7.46	6.94	0.50
1.250	9.42	8.33	8.90	8.33	8.50	9.26	8.79	0.48
1.500	11.94	10.79	11.25	10.77	10.94	11.89	11.26	0.53
1.750	13.98	12.90	13.19	12.53	12.33	13.45	13.06	0.61
2.000	16.61	15.93	15.38	14.93	14.71	16.40	15.66	0.78
2.250	19.08	18.72	17.67	17.25	16.95	18.67	18.06	0.88
2.500	21.49	20.88	19.78	19.53	19.19	20.78	20.27	0.90
2.750	23.86	22.84	21.97	21.83	21.26	22.48	22.37	0.91
3.000	26.38	24.69	24.10	24.15	23.62	24.75	24.62	0.96
3.500	31.41	28.62	28.73	29.17	28.24	29.07	29.21	1.13
4.000	35.41	31.88	32.42	33.15	31.67	32.07	32.77	1.39
4.500	39.74	35.42	36.41	37.45	35.49	35.69	36.70	1.67

Table A10. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	43.93	38.69	40.47	41.71	39.37	39.57	40.62	1.93
5.500	47.60	41.76	43.95	45.10	42.08	42.10	43.77	2.29
6.000	51.78	45.22	47.70	49.77	46.10	45.98	47.76	2.55
7.000	58.74	51.11	53.46	56.41	52.09	51.96	53.96	2.99
8.000	64.60	56.56	58.92	62.25	57.59	57.37	59.55	3.19
9.000	69.55	61.47	63.43	67.08	62.03	62.06	64.27	3.29
10.000	73.90	66.21	68.19	71.36	66.32	66.57	68.76	3.19
11.000	77.19	70.21	71.12	74.36	69.20	69.62	71.95	3.16
12.000	80.65	73.05	74.59	77.74	72.46	73.23	75.29	3.24
13.000	83.32	76.02	76.80	80.38	75.66	75.90	78.01	3.14
14.000	85.19	78.00	78.89	82.11	77.76	77.86	79.97	3.04
15.000	86.89	79.93	80.93	83.53	79.49	79.78	81.76	2.92
16.000	87.69	80.95	82.22	84.50	80.30	80.42	82.68	2.91
17.000	88.44	81.50	83.22	85.77	82.00	81.34	83.71	2.84
18.000	89.07	82.63	84.54	86.41	82.94	82.46	84.67	2.62
19.000	89.77	83.12	84.68	86.73	83.44	82.95	85.11	2.68
20.000	90.52	84.15	86.63	87.69	84.26	84.18	86.24	2.57
21.000	91.49	84.61	86.89	88.98	85.16	84.64	86.96	2.78
22.000	92.86	86.69	89.24	90.62	87.04	87.05	88.92	2.47
23.000	93.03	87.01	88.95	89.79	87.36	86.72	88.81	2.39
24.000	95.16	87.39	92.51	92.78	89.24	89.43	91.08	2.87

Table A11. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.02	0.13	0.01	0.00	0.00	0.00	0.03	0.05
0.083	0.41	0.43	0.37	0.49	0.61	0.65	0.49	0.11
0.167	0.70	0.73	0.67	0.82	0.81	0.76	0.75	0.06
0.250	0.91	1.02	1.05	1.01	0.90	0.82	0.95	0.09
0.333	1.37	1.50	1.51	1.57	1.40	1.37	1.45	0.08
0.417	1.64	1.94	1.96	1.93	1.70	1.61	1.80	0.16
0.500	2.06	2.48	2.43	2.46	2.19	2.09	2.29	0.19
0.667	2.90	3.49	3.37	3.41	3.18	3.16	3.25	0.22
0.833	3.93	4.68	4.44	4.49	4.21	4.10	4.31	0.28
1.000	5.02	6.03	5.52	5.77	5.51	5.45	5.55	0.34
1.250	6.74	8.08	7.54	8.00	7.77	7.59	7.62	0.48
1.500	8.68	10.27	9.45	10.01	9.57	9.07	9.51	0.59
1.750	10.63	12.47	11.48	12.21	11.61	11.01	11.57	0.70
2.000	12.78	14.90	13.80	14.56	13.88	13.21	13.86	0.80
2.250	14.62	17.12	16.06	16.87	15.92	15.15	15.96	0.96
2.500	16.66	19.44	18.54	19.60	18.63	18.02	18.48	1.07
2.750	18.62	21.66	20.69	21.81	20.61	19.96	20.56	1.18
3.000	20.44	23.75	22.83	23.86	22.57	21.90	22.56	1.27
3.500	24.68	28.05	27.59	28.29	26.96	26.02	26.93	1.37
4.000	28.57	32.17	32.45	32.74	31.53	30.40	31.31	1.58
4.500	32.75	36.06	37.22	36.80	36.04	34.53	35.57	1.66

Table A11. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	36.44	39.39	41.70	39.96	39.98	38.29	39.29	1.78
5.500	40.08	42.79	46.25	43.33	44.05	42.27	43.13	2.04
6.000	43.59	45.98	50.49	46.38	47.50	46.24	46.70	2.26
7.000	49.33	51.75	58.17	51.71	52.82	53.08	52.81	2.94
8.000	54.71	57.39	64.49	57.09	58.30	60.08	58.68	3.34
9.000	58.77	61.98	68.78	61.42	62.47	64.88	63.05	3.42
10.000	62.52	66.01	72.32	65.25	66.13	68.67	66.82	3.34
11.000	66.35	69.63	75.85	69.00	70.11	72.25	70.53	3.23
12.000	69.82	72.83	78.43	71.68	72.25	74.63	73.27	2.97
13.000	71.84	75.45	81.23	74.64	75.41	77.56	76.02	3.15
14.000	74.33	77.11	82.43	76.55	76.90	78.69	77.67	2.72
15.000	76.23	78.47	83.97	78.56	78.94	80.15	79.39	2.58
16.000	77.50	79.82	85.18	79.54	80.49	81.77	80.72	2.59
17.000	79.47	81.14	86.85	81.42	82.03	82.78	82.28	2.50
18.000	80.19	81.49	86.81	81.97	83.01	84.00	82.91	2.31
19.000	81.30	82.42	87.19	82.71	83.77	84.35	83.62	2.05
20.000	83.31	85.81	89.70	85.45	87.09	87.75	86.52	2.19
21.000	83.34	85.82	92.08	85.90	86.63	88.04	86.97	2.93
22.000	84.52	87.11	92.19	86.01	88.97	89.43	88.04	2.73
23.000	87.12	88.09	93.10	88.43	90.03	89.17	89.32	2.10
24.000	87.92	89.15	94.99	89.76	91.42	92.21	90.91	2.53

Table A12. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.04	0.02	0.00	0.00	0.00	0.00	0.01	0.02
0.083	0.42	0.43	0.35	0.48	0.42	0.32	0.40	0.06
0.167	0.92	0.82	0.58	0.90	0.80	0.55	0.76	0.16
0.250	1.14	1.15	0.89	1.28	1.14	0.77	1.06	0.19
0.333	1.66	1.65	1.23	1.72	1.47	0.86	1.43	0.33
0.417	2.19	2.11	1.63	2.30	2.07	1.45	1.96	0.34
0.500	2.75	2.65	2.11	2.88	2.68	1.95	2.50	0.38
0.667	3.86	3.86	3.32	4.34	4.16	3.29	3.81	0.43
0.833	5.09	4.74	3.99	5.14	4.86	3.67	4.58	0.61
1.000	6.60	6.19	5.39	6.70	6.32	4.90	6.02	0.72
1.250	8.52	8.12	7.28	8.65	8.32	6.51	7.90	0.84
1.500	10.80	10.27	9.32	10.82	10.77	8.75	10.12	0.88
1.750	12.99	12.38	11.31	12.78	12.54	10.14	12.02	1.09
2.000	15.33	14.42	13.50	14.89	14.59	11.95	14.11	1.22
2.250	17.70	16.51	15.89	17.23	16.85	14.19	16.40	1.24
2.500	20.05	18.44	18.08	19.18	18.66	15.93	18.39	1.39
2.750	22.44	20.47	20.40	21.25	20.83	17.75	20.52	1.55
3.000	25.13	22.37	22.86	23.27	22.82	19.71	22.69	1.75
3.500	30.10	26.38	27.56	27.49	26.93	23.66	27.02	2.08
4.000	34.43	30.47	32.11	31.12	30.36	27.39	30.98	2.31
4.500	38.99	34.41	37.24	35.05	33.78	31.34	35.14	2.69

Table A12. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 37:40 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	43.72	38.31	41.34	38.88	37.44	35.45	39.19	2.93
5.500	47.84	42.07	45.31	42.29	40.42	38.42	42.73	3.39
6.000	51.80	45.63	49.03	45.77	44.01	41.61	46.31	3.62
7.000	58.30	51.83	56.57	52.42	50.44	48.16	52.95	3.81
8.000	63.97	57.09	62.84	59.06	55.88	53.97	58.80	3.95
9.000	68.68	62.20	68.10	64.55	60.76	58.76	63.84	4.00
10.000	72.23	66.37	71.97	68.64	64.98	63.14	67.89	3.73
11.000	76.09	70.14	76.08	71.92	68.91	67.59	71.79	3.62
12.000	78.90	72.94	78.69	74.48	71.94	70.98	74.66	3.41
13.000	81.17	75.59	80.56	76.14	74.07	73.32	76.81	3.31
14.000	83.28	77.45	82.59	78.05	76.74	76.22	79.06	3.08
15.000	84.84	79.03	83.67	79.47	78.27	78.40	80.61	2.88
16.000	85.98	80.75	84.99	80.47	79.77	79.91	81.98	2.76
17.000	87.33	82.15	86.50	81.45	80.72	82.03	83.36	2.81
18.000	87.65	82.78	87.05	82.46	81.69	83.06	84.12	2.55
19.000	91.13	85.69	91.00	84.03	84.70	86.92	87.25	3.12
20.000	94.16	88.18	93.04	87.03	86.57	88.77	89.63	3.20
21.000	96.65	89.85	94.42	89.41	88.40	91.31	91.67	3.21
22.000	96.87	91.25	95.66	89.72	89.23	91.89	92.44	3.14
23.000	98.45	91.76	97.41	90.99	90.74	93.33	93.78	3.36
24.000	99.16	93.18	97.48	92.07	91.81	93.88	94.60	3.03

Table A13. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.20	0.15	0.10	0.25	0.18	0.20	0.18	0.05
0.083	0.20	0.19	0.15	0.32	0.20	0.30	0.23	0.07
0.167	0.61	0.35	0.29	0.44	0.37	0.47	0.42	0.11
0.250	0.66	0.46	0.40	0.56	0.43	0.60	0.52	0.10
0.333	1.11	1.05	0.86	0.82	0.75	0.80	0.90	0.15
0.417	1.26	1.19	0.76	0.97	0.90	1.02	1.02	0.18
0.500	1.47	1.39	1.07	1.12	1.07	1.19	1.22	0.17
0.667	2.27	2.27	1.78	1.95	1.88	1.99	2.02	0.20
0.833	2.92	2.87	2.60	2.33	2.13	2.11	2.49	0.36
1.000	3.92	3.63	3.54	3.19	3.09	3.22	3.43	0.32
1.250	5.19	4.90	5.00	4.26	4.19	4.49	4.67	0.42
1.500	6.65	6.29	6.37	5.33	5.06	5.35	5.84	0.67
1.750	8.42	8.00	8.26	7.25	7.29	7.57	7.80	0.50
2.000	10.16	9.58	10.03	8.56	8.67	8.99	9.33	0.69
2.250	11.55	11.02	11.40	9.86	9.94	10.30	10.68	0.74
2.500	13.40	12.58	13.23	11.31	11.43	11.88	12.31	0.90
2.750	15.00	14.26	14.76	12.83	12.96	13.46	13.88	0.93
3.000	16.72	15.81	18.94	14.04	13.98	14.62	15.69	1.92
3.500	20.53	19.12	20.34	17.61	17.69	18.34	18.94	1.28
4.000	23.84	21.87	23.19	20.56	20.63	21.44	21.92	1.35
4.500	27.38	25.09	26.53	23.93	24.00	24.90	25.31	1.39

Table A13. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	30.52	27.60	29.97	26.24	26.46	27.54	28.06	1.79
5.500	34.18	30.45	33.62	29.03	29.51	30.71	31.25	2.15
6.000	37.53	33.33	36.38	31.96	32.37	33.69	34.21	2.25
7.000	43.57	38.75	41.83	37.21	38.19	39.21	39.79	2.41
8.000	49.66	43.72	49.23	42.11	43.32	44.05	45.35	3.24
9.000	54.83	48.75	54.27	46.81	48.66	48.45	50.30	3.38
10.000	59.65	52.79	57.87	51.41	53.58	52.87	54.70	3.27
11.000	63.78	56.98	61.69	55.51	57.68	56.85	58.75	3.24
12.000	68.10	61.15	65.53	59.53	62.46	60.37	62.86	3.32
13.000	71.74	64.65	69.19	63.73	66.38	63.76	66.58	3.26
14.000	75.14	68.28	73.00	67.83	70.65	67.86	70.46	3.06
15.000	78.37	70.89	75.46	70.53	73.40	70.57	73.20	3.20
16.000	81.52	73.98	78.11	74.19	77.29	74.53	76.60	2.96
17.000	83.08	75.88	80.22	76.11	79.10	76.64	78.51	2.84
18.000	85.04	77.71	82.00	79.57	82.16	79.61	81.02	2.59
19.000	86.87	80.14	84.51	81.80	84.40	81.84	83.26	2.44
20.000	88.09	81.17	85.83	83.80	86.16	83.18	84.71	2.47
21.000	89.82	83.88	87.72	85.79	88.03	85.83	86.85	2.10
22.000	90.84	85.44	88.07	86.79	88.64	86.58	87.73	1.90
23.000	91.58	86.54	90.14	87.94	89.87	88.76	89.14	1.78
24.000	92.86	88.33	91.34	89.30	92.51	90.72	90.84	1.78

Table A14. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.11	0.17	0.15	0.10	0.13	0.11	0.13	0.03
0.083	0.40	0.19	0.22	0.20	0.12	0.21	0.22	0.09
0.167	0.53	0.22	0.30	0.22	0.18	0.25	0.28	0.13
0.250	0.64	0.31	0.62	0.57	0.57	0.60	0.55	0.12
0.333	0.85	0.46	0.93	0.94	1.02	1.10	0.88	0.22
0.417	1.07	0.49	1.07	0.94	1.02	1.03	0.94	0.22
0.500	1.24	0.65	1.50	1.36	1.48	1.59	1.30	0.34
0.667	1.40	0.66	1.92	1.43	1.75	1.84	1.50	0.46
0.833	1.87	0.92	2.56	1.82	2.42	2.46	2.01	0.62
1.000	2.48	1.45	3.41	2.44	3.29	3.38	2.74	0.77
1.250	3.30	2.23	4.80	3.37	4.51	4.53	3.79	0.99
1.500	4.71	3.15	5.96	4.35	5.28	5.19	4.77	0.97
1.750	6.30	4.66	7.55	6.29	7.22	7.07	6.52	1.04
2.000	8.00	6.26	9.27	8.16	8.99	8.81	8.25	1.09
2.250	9.34	7.42	10.70	9.46	10.34	10.30	9.59	1.19
2.500	11.12	8.79	12.19	10.89	11.79	11.84	11.10	1.23
2.750	12.51	10.27	13.93	12.42	13.39	13.59	12.69	1.33
3.000	14.14	11.73	15.62	13.93	14.95	15.24	14.27	1.40
3.500	17.51	14.64	19.15	16.98	18.15	18.56	17.50	1.59
4.000	20.70	17.56	22.53	20.00	21.28	21.83	20.65	1.75
4.500	24.25	20.93	26.47	23.67	24.95	25.83	24.35	1.96

Table A14. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	27.47	23.69	29.58	26.17	27.72	28.75	27.23	2.09
5.500	30.79	26.63	32.70	28.97	31.03	31.82	30.32	2.19
6.000	34.16	29.77	36.12	31.97	34.35	35.27	33.61	2.34
7.000	39.89	35.11	41.75	37.25	40.19	40.72	39.15	2.48
8.000	45.57	40.25	46.98	42.82	46.08	46.28	44.66	2.60
9.000	50.85	45.03	52.46	47.85	51.57	52.13	49.98	2.94
10.000	55.96	49.85	57.44	53.00	56.30	56.59	54.86	2.88
11.000	61.16	54.56	61.85	57.74	61.50	61.50	59.72	2.95
12.000	66.14	58.83	66.05	62.27	65.21	65.31	63.97	2.89
13.000	69.91	62.71	70.05	66.72	69.39	69.87	68.11	2.93
14.000	74.70	67.25	73.33	70.32	72.48	73.75	71.97	2.75
15.000	77.89	71.08	77.51	73.20	75.31	76.90	75.32	2.70
16.000	81.30	74.76	79.50	76.89	78.45	80.07	78.50	2.36
17.000	84.21	78.17	84.12	80.02	81.77	83.61	81.98	2.47
18.000	87.93	81.18	85.84	83.91	84.15	86.18	84.87	2.33
19.000	90.97	83.88	88.89	86.66	87.42	88.67	87.75	2.40
20.000	92.71	86.15	90.78	88.90	89.45	91.93	89.99	2.37
21.000	94.09	88.40	92.96	89.49	91.45	93.22	91.60	2.25
22.000	95.02	89.11	92.81	91.94	91.97	93.78	92.44	2.01
23.000	96.68	90.66	93.84	93.09	92.48	94.98	93.62	2.08
24.000	97.08	92.13	94.45	93.67	93.12	97.07	94.59	2.07

Table A15. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.083	0.05	0.00	0.00	0.00	0.00	0.00	0.01	0.02
0.167	0.21	0.07	0.08	0.02	0.08	0.07	0.09	0.06
0.250	0.52	0.31	0.44	0.38	0.50	0.44	0.43	0.08
0.333	0.82	0.46	0.55	0.39	0.54	0.59	0.56	0.15
0.417	1.14	0.67	0.82	0.62	0.77	0.75	0.80	0.18
0.500	1.39	0.87	1.11	0.84	1.02	1.00	1.04	0.20
0.667	2.15	1.66	1.98	1.65	1.85	1.84	1.86	0.19
0.833	2.84	2.16	2.51	2.17	2.37	2.30	2.39	0.26
1.000	3.77	2.95	3.44	3.25	3.52	3.40	3.39	0.27
1.250	5.07	4.36	5.03	4.59	4.81	4.46	4.72	0.30
1.500	6.23	5.31	5.97	5.60	5.80	5.34	5.71	0.36
1.750	7.60	6.77	7.37	6.79	6.83	6.00	6.89	0.56
2.000	9.40	8.40	9.12	8.99	9.21	8.39	8.92	0.43
2.250	10.74	9.93	10.48	10.39	10.42	9.30	10.21	0.52
2.500	12.48	11.39	11.86	11.93	11.80	10.38	11.64	0.71
2.750	14.11	12.98	13.54	13.81	13.80	12.50	13.46	0.60
3.000	15.83	14.64	15.17	15.54	15.34	13.86	15.06	0.71
3.500	19.51	17.75	18.28	18.64	18.22	16.59	18.17	0.97
4.000	22.92	21.10	21.79	22.38	21.75	19.92	21.64	1.05
4.500	26.69	24.28	25.18	26.08	25.25	23.45	25.16	1.17

Table A15. %Drug dissolved of indomethacin from formulation containing HPMC : lactose ratio of 57:20 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	30.27	27.44	28.45	29.62	28.55	26.51	28.47	1.38
5.500	33.69	30.52	31.56	33.07	31.83	29.71	31.73	1.50
6.000	37.46	33.36	34.71	36.31	34.81	32.99	34.94	1.71
7.000	43.84	39.11	40.51	43.27	41.18	38.18	41.02	2.24
8.000	49.52	44.55	45.90	49.57	46.96	43.71	46.70	2.47
9.000	54.85	49.38	50.77	55.35	52.02	48.69	51.84	2.78
10.000	59.60	53.78	55.45	60.00	56.22	52.90	56.33	2.94
11.000	64.15	58.10	60.13	65.14	61.48	58.19	61.20	2.97
12.000	68.20	61.90	64.09	69.15	65.38	62.00	65.12	3.06
13.000	71.84	65.45	68.40	72.42	68.81	65.89	68.80	2.91
14.000	75.41	69.19	72.02	75.82	73.13	70.09	72.61	2.71
15.000	78.23	72.30	75.42	78.27	75.64	73.02	75.48	2.51
16.000	81.01	74.93	78.09	81.59	78.27	75.57	78.24	2.72
17.000	82.82	77.66	80.66	83.19	80.81	78.37	80.59	2.25
18.000	85.39	79.90	83.22	85.50	82.91	81.06	83.00	2.25
19.000	87.38	81.63	85.03	87.20	84.88	82.66	84.80	2.33
20.000	89.06	83.23	86.35	89.11	86.89	84.99	86.61	2.30
21.000	89.52	84.17	87.48	90.66	88.53	85.31	87.61	2.49
22.000	90.28	85.68	88.44	92.03	89.25	87.90	88.93	2.16
23.000	91.15	87.13	90.09	92.63	88.98	88.42	89.73	1.98
24.000	92.42	89.26	91.30	93.94	91.25	89.81	91.33	1.71

Table A16. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.16	0.14	0.15	0.13	0.14	0.15	0.14	0.01
0.083	4.08	6.42	2.66	2.61	5.48	2.65	3.98	1.65
0.167	9.20	12.95	6.20	5.78	11.26	6.10	8.58	3.04
0.250	13.34	18.49	9.94	9.93	16.35	9.94	13.00	3.73
0.333	16.67	23.30	13.21	13.24	20.78	13.22	16.74	4.39
0.417	19.69	27.21	16.58	15.80	24.55	16.39	20.04	4.80
0.500	22.77	30.74	19.79	17.88	28.00	19.31	23.08	5.20
0.667	28.03	36.14	25.32	21.27	33.44	24.31	28.08	5.69
0.833	32.28	40.34	30.13	24.80	37.79	28.80	32.36	5.80
1.000	36.11	43.68	34.07	28.22	41.28	32.61	35.99	5.70
1.250	40.83	47.47	38.98	32.90	45.35	37.46	40.50	5.32
1.500	44.74	50.58	43.00	37.22	48.69	41.56	44.30	4.86
1.750	48.42	53.29	46.40	41.32	51.57	45.13	47.69	4.38
2.000	51.45	55.57	49.50	44.99	54.05	48.37	50.66	3.87
2.250	54.11	57.74	52.08	48.07	56.33	51.08	53.23	3.56
2.500	56.51	59.62	54.31	50.98	58.29	53.48	55.53	3.22
2.750	58.43	61.34	56.46	53.37	60.12	55.69	57.57	2.96
3.000	60.37	62.96	58.40	55.60	61.82	57.70	59.48	2.75
3.500	63.52	65.90	61.75	59.43	64.86	61.17	62.77	2.43
4.000	66.29	68.49	64.59	63.49	67.52	64.32	65.78	1.97
4.500	68.64	71.01	67.21	66.95	70.06	67.15	68.50	1.71

Table A16. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	70.78	73.10	69.42	69.94	72.18	69.55	70.83	1.51
5.500	72.73	75.14	71.60	72.99	74.26	71.95	73.11	1.36
6.000	74.38	76.93	73.26	75.55	76.01	73.83	74.99	1.40
7.000	77.39	80.56	76.63	80.08	79.58	77.49	78.62	1.65
8.000	80.35	83.46	79.73	84.12	82.53	80.83	81.84	1.79
9.000	82.58	86.02	82.01	87.30	85.02	83.33	84.38	2.08
10.000	84.67	88.48	84.35	90.61	87.45	85.92	86.91	2.41
11.000	86.57	90.44	86.19	93.20	89.38	87.94	88.95	2.64
12.000	88.34	92.58	87.81	95.09	91.39	89.63	90.81	2.77
13.000	89.61	94.31	89.24	97.26	93.04	91.25	92.45	3.06
14.000	90.95	95.76	90.32	98.61	94.40	92.39	93.74	3.15
15.000	91.91	97.17	91.68	100.13	95.80	93.79	95.08	3.28
16.000	93.16	98.26	92.55	101.25	96.83	94.73	96.13	3.31
17.000	94.34	99.68	94.04	103.19	98.27	96.33	97.64	3.49
18.000	95.48	100.90	94.90	104.41	99.40	97.28	98.73	3.60
19.000	96.38	101.84	95.64	105.12	100.29	98.01	99.55	3.59
20.000	97.31	102.47	96.40	106.21	100.95	98.85	100.37	3.64
21.000	97.88	103.66	97.20	106.60	102.05	99.55	101.16	3.62
22.000	99.29	104.86	98.41	107.95	103.25	100.80	102.43	3.63
23.000	99.58	105.77	98.83	108.98	104.04	101.37	103.09	3.90
24.000	100.33	106.71	99.69	110.04	104.96	102.28	104.00	3.99

Table A17. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.14	0.15	0.09	0.15	0.11	0.11	0.13	0.03
0.083	1.63	1.18	1.22	2.76	1.79	1.64	1.70	0.57
0.167	3.31	2.46	2.53	5.92	4.08	3.80	3.68	1.28
0.250	4.87	3.73	3.82	8.81	6.37	5.57	5.53	1.90
0.333	6.81	4.95	4.74	11.78	8.60	7.15	7.34	2.61
0.417	8.53	6.44	5.57	14.29	10.76	8.84	9.07	3.15
0.500	10.05	7.95	6.67	16.35	12.87	10.71	10.77	3.49
0.667	12.47	10.37	8.38	19.87	16.82	13.91	13.64	4.21
0.833	14.87	12.90	9.86	23.38	20.42	16.82	16.38	4.95
1.000	16.99	14.98	11.30	26.51	23.77	19.67	18.87	5.64
1.250	19.65	17.78	13.31	30.76	28.03	23.51	22.17	6.54
1.500	22.21	20.31	15.16	34.68	32.08	26.60	25.17	7.39
1.750	24.77	22.45	17.14	38.26	35.86	29.46	27.99	8.10
2.000	27.50	24.41	18.93	41.65	39.06	32.18	30.62	8.72
2.250	30.43	26.31	20.64	44.66	41.89	34.71	33.11	9.19
2.500	33.07	28.06	21.98	47.90	44.79	36.97	35.46	9.86
2.750	35.33	29.65	23.47	50.91	47.38	39.26	37.67	10.43
3.000	37.64	31.09	24.91	53.75	49.70	41.39	39.75	10.93
3.500	41.27	33.92	27.67	58.99	54.27	45.59	43.62	11.90
4.000	44.60	36.40	30.37	62.87	58.15	49.23	46.94	12.46
4.500	47.54	38.65	32.97	66.01	61.36	52.32	49.81	12.77

Table A17. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	50.11	40.78	35.33	68.96	64.29	54.85	52.39	13.06
5.500	52.68	42.81	37.48	71.17	67.12	57.27	54.76	13.22
6.000	55.39	44.70	39.39	73.45	69.66	59.35	56.99	13.42
7.000	60.01	48.18	42.98	77.63	74.71	63.24	61.13	13.85
8.000	63.89	51.30	46.30	81.58	78.88	66.85	64.80	14.21
9.000	67.14	53.89	49.15	84.69	82.15	69.61	67.77	14.40
10.000	69.95	56.24	51.92	87.79	85.26	72.34	70.58	14.62
11.000	72.41	58.39	54.17	90.23	87.13	74.50	72.81	14.61
12.000	74.64	60.29	56.30	92.25	89.29	76.43	74.87	14.63
13.000	76.34	62.00	58.35	93.66	90.95	78.15	76.58	14.46
14.000	77.94	63.56	60.16	95.97	92.45	79.58	78.28	14.56
15.000	79.91	65.38	62.20	97.28	94.05	81.28	80.02	14.34
16.000	81.43	67.08	63.98	99.18	95.57	82.67	81.65	14.33
17.000	82.69	68.65	65.73	100.50	97.21	84.28	83.18	14.24
18.000	84.00	70.13	67.41	102.07	98.77	85.33	84.62	14.23
19.000	85.76	71.67	68.71	104.00	99.73	86.36	86.04	14.26
20.000	86.49	73.14	70.23	105.05	100.42	88.15	87.25	14.00
21.000	88.03	74.34	71.66	105.06	101.81	88.89	88.30	13.68
22.000	88.88	75.06	72.74	105.75	102.62	89.26	89.05	13.60
23.000	89.66	76.05	73.81	106.01	103.27	89.91	89.79	13.33
24.000	90.84	77.13	75.12	107.70	104.35	91.21	91.06	13.43

Table A18. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.06	0.14	0.08	0.07	0.05	0.07	0.08	0.03
0.083	1.03	1.08	1.04	0.69	0.68	0.64	0.86	0.21
0.167	1.90	2.26	1.98	1.38	1.27	1.18	1.66	0.44
0.250	2.69	3.26	2.88	2.07	1.84	1.75	2.42	0.62
0.333	3.47	4.16	3.68	2.73	2.42	2.33	3.13	0.75
0.417	4.22	4.96	4.48	3.38	2.97	2.91	3.82	0.85
0.500	4.96	5.71	5.39	4.00	3.52	3.52	4.52	0.96
0.667	6.20	7.18	6.99	5.22	4.63	5.04	5.88	1.07
0.833	7.46	8.40	8.44	6.37	5.61	6.45	7.12	1.17
1.000	8.65	9.58	9.70	7.57	6.66	7.77	8.32	1.20
1.250	10.08	11.19	11.44	9.26	8.16	9.56	9.95	1.23
1.500	11.40	12.62	13.02	11.00	9.52	11.25	11.47	1.25
1.750	12.65	13.93	14.59	12.59	10.86	12.71	12.89	1.29
2.000	13.86	15.17	15.84	14.00	12.07	14.02	14.16	1.29
2.250	14.96	16.29	17.18	15.25	13.42	15.21	15.39	1.28
2.500	16.02	17.40	18.31	16.50	14.54	16.31	16.51	1.28
2.750	17.07	18.39	19.37	17.60	15.45	17.37	17.54	1.32
3.000	18.01	19.59	20.40	18.68	16.39	18.29	18.56	1.38
3.500	19.81	21.63	22.34	20.67	18.13	20.13	20.45	1.48
4.000	21.33	23.42	24.12	22.47	19.76	21.97	22.18	1.55
4.500	22.79	25.08	25.58	24.10	21.15	23.68	23.73	1.61

Table A18. %Drug dissolved of indomethacin from formulation containing microcrystalline cellulose 77% (without HPMC) at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	24.28	26.78	27.02	25.72	22.44	25.15	25.23	1.71
5.500	25.60	28.36	28.25	27.21	23.62	26.40	26.57	1.79
6.000	26.88	30.31	29.59	28.61	24.76	27.61	27.96	2.01
7.000	29.32	33.62	32.13	31.21	26.86	29.81	30.49	2.37
8.000	31.57	36.58	34.13	33.40	28.70	31.69	32.68	2.68
9.000	33.56	38.87	35.85	35.27	30.36	33.43	34.56	2.85
10.000	35.28	40.93	37.43	36.95	31.83	35.04	36.24	3.02
11.000	36.89	42.80	39.13	38.43	33.19	36.55	37.83	3.19
12.000	38.32	44.29	40.41	39.89	34.58	37.92	39.24	3.21
13.000	39.71	45.75	41.64	41.30	35.74	39.23	40.56	3.30
14.000	41.23	47.28	42.88	42.61	36.82	40.36	41.86	3.44
15.000	42.57	48.50	44.19	44.03	37.95	41.32	43.09	3.50
16.000	43.83	49.79	45.40	45.47	38.98	42.15	44.27	3.63
17.000	45.00	50.99	46.43	46.82	39.85	42.89	45.33	3.78
18.000	46.16	52.14	47.46	47.93	40.91	43.50	46.35	3.87
19.000	47.37	53.29	48.58	49.15	41.74	44.16	47.38	4.04
20.000	48.39	54.44	49.61	50.15	42.64	44.75	48.33	4.18
21.000	49.35	55.44	50.51	51.19	43.53	45.36	49.23	4.28
22.000	50.40	56.53	51.32	52.12	44.27	45.96	50.10	4.43
23.000	51.31	57.75	52.59	53.21	45.22	46.49	51.10	4.62
24.000	52.30	58.81	53.34	54.02	45.89	47.18	51.92	4.75

Table A19. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.10	0.12	0.05	0.07	0.11	0.07	0.09	0.03
0.083	1.73	1.60	1.55	1.46	1.23	1.67	1.54	0.18
0.167	3.32	3.22	2.95	2.92	2.16	3.19	2.96	0.42
0.250	4.59	4.63	4.21	4.17	2.99	4.62	4.20	0.63
0.333	5.63	6.03	5.28	5.55	3.71	5.88	5.35	0.84
0.417	6.58	7.18	6.17	6.72	4.38	6.97	6.33	1.02
0.500	7.39	8.16	7.01	7.78	4.99	7.95	7.21	1.16
0.667	8.94	9.78	8.48	9.59	6.68	9.66	8.86	1.18
0.833	10.35	11.19	9.68	11.11	8.44	11.06	10.31	1.08
1.000	11.72	12.83	10.74	12.52	10.04	12.37	11.70	1.10
1.250	13.66	15.01	12.33	14.85	12.01	14.05	13.65	1.26
1.500	15.80	16.91	13.72	17.00	14.10	15.59	15.52	1.38
1.750	17.66	18.61	14.99	18.81	16.06	16.98	17.19	1.48
2.000	19.38	20.11	16.19	20.42	17.64	18.31	18.68	1.61
2.250	21.03	21.47	17.43	21.83	19.03	19.53	20.05	1.69
2.500	22.96	22.65	19.11	23.02	20.30	20.79	21.47	1.64
2.750	24.75	23.83	21.08	24.16	21.49	22.11	22.90	1.54
3.000	26.27	25.34	22.64	25.56	22.66	23.45	24.32	1.59
3.500	28.93	28.54	25.89	29.21	25.00	26.35	27.32	1.79
4.000	31.43	31.75	29.75	32.53	27.48	29.62	30.43	1.84
4.500	33.99	34.19	33.31	34.95	30.27	32.47	33.20	1.66

Table A19. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	36.62	36.66	36.65	37.29	33.19	35.21	35.94	1.51
5.500	39.14	39.08	39.63	39.64	35.59	37.99	38.51	1.55
6.000	41.75	41.59	42.74	42.11	39.29	40.54	41.34	1.23
7.000	46.97	47.12	48.58	46.84	45.79	45.01	46.72	1.22
8.000	51.97	52.10	53.84	51.34	51.02	49.44	51.62	1.45
9.000	56.72	56.69	58.75	55.88	55.43	53.63	56.18	1.69
10.000	60.51	60.07	62.24	59.98	59.03	57.78	59.94	1.49
11.000	63.50	62.71	64.80	62.97	61.71	61.08	62.80	1.32
12.000	65.51	64.61	66.72	65.25	63.77	63.54	64.90	1.18
13.000	67.22	66.17	68.22	67.00	65.43	65.36	66.57	1.12
14.000	68.57	67.34	69.35	68.37	66.63	66.72	67.83	1.10
15.000	70.05	68.65	70.74	69.68	67.82	68.11	69.18	1.16
16.000	71.24	69.77	71.72	70.88	68.72	69.24	70.26	1.19
17.000	72.27	70.64	72.71	71.93	69.60	70.27	71.24	1.24
18.000	73.45	71.79	73.70	73.18	70.74	71.44	72.38	1.22
19.000	74.73	72.88	74.83	74.48	71.78	72.56	73.54	1.30
20.000	75.84	73.91	76.01	75.46	72.81	73.82	74.64	1.31
21.000	77.03	74.90	77.15	76.62	73.81	74.96	75.75	1.38
22.000	77.91	75.65	78.09	77.35	74.42	75.98	76.57	1.45
23.000	78.79	76.57	78.85	78.32	75.23	76.67	77.41	1.47
24.000	79.46	77.18	79.66	79.04	75.81	77.34	78.08	1.54

Table A20. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.083	0.12	0.46	0.16	0.85	0.38	0.19	0.36	0.27
0.167	0.80	1.43	0.71	2.08	1.29	0.92	1.21	0.51
0.250	1.38	2.25	1.34	3.09	2.06	1.59	1.95	0.67
0.333	2.03	3.00	1.94	3.98	2.74	2.20	2.65	0.77
0.417	2.67	3.70	2.53	4.82	3.36	2.79	3.31	0.86
0.500	3.32	4.40	3.11	5.57	3.93	3.36	3.95	0.92
0.667	4.50	5.60	4.14	7.04	4.94	4.44	5.11	1.07
0.833	5.52	6.61	4.98	8.28	5.79	5.38	6.09	1.20
1.000	6.47	7.50	5.77	9.39	6.55	6.23	6.99	1.31
1.250	7.55	8.72	6.87	10.81	7.52	7.33	8.13	1.45
1.500	8.63	10.00	7.82	12.16	8.42	8.42	9.24	1.60
1.750	9.66	11.39	8.78	13.46	9.25	9.40	10.32	1.78
2.000	10.82	12.81	9.62	14.79	10.06	10.37	11.41	1.99
2.250	12.06	14.12	10.54	16.15	10.86	11.59	12.55	2.17
2.500	13.33	15.36	11.38	17.56	11.79	12.93	13.73	2.34
2.750	14.57	16.55	12.20	18.97	12.86	14.15	14.88	2.51
3.000	15.74	17.86	13.02	20.39	13.98	15.40	16.07	2.69
3.500	18.08	20.59	14.79	23.39	16.25	18.07	18.53	3.08
4.000	20.31	23.41	16.71	26.52	18.49	20.93	21.06	3.51
4.500	22.76	26.39	18.87	30.44	20.77	23.93	23.86	4.13

Table A20. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	25.29	30.29	20.97	33.38	23.09	26.72	26.62	4.59
5.500	28.84	33.47	23.15	36.05	26.29	30.25	29.68	4.69
6.000	32.00	36.10	25.38	39.13	29.40	33.85	32.64	4.88
7.000	36.51	41.42	29.97	45.03	33.80	38.92	37.61	5.39
8.000	41.84	46.79	35.18	50.62	38.71	44.03	42.86	5.55
9.000	46.97	51.98	40.43	55.39	43.72	49.22	47.95	5.45
10.000	51.77	56.55	45.89	59.44	48.14	53.94	52.62	5.09
11.000	55.99	60.24	51.04	62.70	52.36	58.30	56.77	4.53
12.000	59.43	63.32	56.14	64.94	56.07	62.25	60.36	3.75
13.000	62.11	65.89	60.70	66.81	58.93	65.71	63.36	3.23
14.000	64.09	67.52	64.21	68.32	60.95	68.09	65.53	2.94
15.000	65.73	69.14	67.19	69.93	62.73	70.26	67.50	2.90
16.000	67.27	70.60	69.43	71.09	64.19	71.88	69.08	2.88
17.000	68.30	71.81	71.19	72.41	65.48	73.30	70.42	2.96
18.000	69.53	72.99	72.68	73.61	66.73	74.77	71.72	3.00
19.000	70.41	74.05	73.95	74.52	67.76	75.95	72.77	3.06
20.000	71.32	74.97	75.35	75.57	68.93	76.95	73.85	3.06
21.000	71.93	75.54	76.18	76.33	69.71	77.94	74.61	3.12
22.000	72.80	76.66	77.40	77.28	70.59	78.69	75.57	3.15
23.000	73.27	77.46	78.36	77.71	71.36	79.48	76.27	3.20
24.000	74.43	78.15	78.95	78.73	72.47	80.44	77.20	3.06

Table A21. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.09	0.10	0.07	0.02	0.06	0.03	0.06	0.03
0.083	0.59	0.54	0.80	0.60	0.70	0.52	0.63	0.11
0.167	1.13	1.01	1.49	1.16	1.37	1.08	1.21	0.18
0.250	1.54	1.41	2.09	1.73	1.95	1.55	1.71	0.26
0.333	2.08	1.90	2.66	2.34	2.71	2.08	2.30	0.33
0.417	2.54	2.32	3.23	2.97	3.62	2.59	2.88	0.49
0.500	2.94	2.73	3.75	3.50	4.50	3.02	3.41	0.66
0.667	3.71	3.50	4.73	4.57	6.14	3.95	4.43	0.96
0.833	4.47	4.17	5.52	5.51	7.53	4.75	5.33	1.21
1.000	5.12	4.77	6.26	6.38	8.71	5.47	6.12	1.42
1.250	5.98	5.65	7.36	7.54	10.26	6.51	7.22	1.67
1.500	6.80	6.44	8.39	8.66	11.52	7.46	8.21	1.84
1.750	7.48	7.23	9.38	9.76	12.68	8.38	9.15	2.00
2.000	8.21	7.96	10.32	10.86	13.83	9.23	10.07	2.17
2.250	8.80	8.67	11.36	11.99	14.91	10.04	10.96	2.35
2.500	9.56	9.34	12.37	13.12	16.05	10.80	11.87	2.54
2.750	10.35	10.08	13.49	14.31	17.11	11.57	12.82	2.69
3.000	11.24	10.83	14.71	15.57	18.24	12.30	13.82	2.87
3.500	13.28	12.29	17.18	17.97	20.46	13.94	15.85	3.18
4.000	15.39	13.96	19.69	20.53	22.89	15.98	18.07	3.47
4.500	17.67	15.79	22.46	23.37	25.38	18.37	20.51	3.76

Table A21. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 17:60 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	20.03	17.76	25.34	26.24	27.94	21.02	23.06	4.01
5.500	22.64	19.80	28.26	29.31	30.59	23.66	25.71	4.29
6.000	25.19	22.02	31.44	33.06	33.73	26.37	28.64	4.78
7.000	31.35	26.70	38.52	40.16	40.66	32.65	35.01	5.64
8.000	38.30	31.86	45.16	45.97	46.03	39.60	41.15	5.66
9.000	43.43	38.91	50.84	51.00	51.19	45.35	46.79	5.08
10.000	48.86	44.21	56.28	55.94	56.12	50.93	52.06	4.95
11.000	54.28	50.07	60.94	60.29	60.25	55.56	56.90	4.34
12.000	59.06	55.44	64.96	64.03	64.20	59.84	61.26	3.76
13.000	63.66	60.08	68.15	67.32	67.23	63.85	65.05	3.09
14.000	67.38	63.77	70.17	70.32	69.90	67.21	68.13	2.55
15.000	70.26	66.63	72.18	72.65	71.95	70.25	70.65	2.21
16.000	72.60	68.73	74.07	74.37	73.37	72.41	72.59	2.04
17.000	74.35	70.54	75.36	75.88	74.98	74.12	74.21	1.91
18.000	75.64	71.84	76.95	77.12	76.12	75.50	75.53	1.92
19.000	76.76	73.36	78.13	78.41	77.24	76.94	76.81	1.81
20.000	78.37	74.70	79.44	79.84	78.43	78.36	78.19	1.82
21.000	79.26	75.69	80.44	80.84	79.50	79.43	79.19	1.83
22.000	80.50	76.88	81.60	81.78	80.33	80.73	80.30	1.78
23.000	81.18	77.71	82.24	82.63	81.27	81.75	81.13	1.77
24.000	81.80	78.68	82.74	83.43	82.16	82.74	81.93	1.68

Table A22. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.03	0.10	0.09	0.05	0.08	0.09	0.07	0.03
0.083	0.41	0.28	0.43	0.38	0.35	0.39	0.37	0.05
0.167	0.76	0.56	0.76	0.71	0.66	0.71	0.69	0.08
0.250	1.09	0.84	1.23	1.03	1.00	1.13	1.05	0.13
0.333	1.49	1.27	1.63	1.44	1.42	1.54	1.46	0.12
0.417	1.86	1.67	2.04	1.81	1.81	1.95	1.86	0.13
0.500	2.18	2.14	2.50	2.17	2.24	2.41	2.27	0.15
0.667	3.01	3.10	3.51	3.03	3.18	3.41	3.21	0.21
0.833	4.16	4.01	4.41	4.12	4.15	4.31	4.19	0.14
1.000	5.30	4.97	5.43	5.22	5.17	5.32	5.23	0.16
1.250	6.99	6.54	6.92	6.88	6.75	6.83	6.82	0.16
1.500	8.84	8.12	8.42	8.66	8.38	8.35	8.46	0.25
1.750	10.78	9.76	9.99	10.53	10.07	9.93	10.18	0.39
2.000	12.82	11.25	11.49	12.43	11.70	11.43	11.85	0.63
2.250	14.85	12.69	12.97	14.31	13.30	12.90	13.50	0.87
2.500	16.98	14.08	14.34	16.26	14.87	14.28	15.13	1.20
2.750	19.03	15.48	15.74	18.14	16.43	15.68	16.75	1.49
3.000	20.99	16.90	17.17	19.97	17.99	17.10	18.35	1.72
3.500	24.66	19.69	20.04	23.42	21.02	19.95	21.46	2.08
4.000	28.15	22.56	22.81	26.75	24.02	22.75	24.51	2.38
4.500	31.33	25.21	25.48	29.80	26.81	25.41	27.34	2.61

Table A22. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	34.38	27.95	28.17	32.77	29.61	28.12	30.17	2.76
5.500	37.20	30.61	30.69	35.55	32.28	30.67	32.83	2.86
6.000	39.77	33.20	33.31	38.13	34.87	33.28	35.43	2.85
7.000	44.63	38.08	38.23	42.99	39.76	38.19	40.31	2.83
8.000	49.03	42.72	42.96	47.45	44.36	42.90	44.90	2.70
9.000	52.82	46.94	47.30	51.35	48.50	47.21	49.02	2.48
10.000	56.19	50.80	51.48	54.84	52.32	51.31	52.82	2.18
11.000	59.24	54.54	55.27	58.07	55.90	55.09	56.35	1.87
12.000	62.31	58.00	58.79	61.23	59.28	58.59	59.70	1.69
13.000	64.85	61.01	62.17	63.89	62.26	61.88	62.68	1.42
14.000	67.26	63.65	64.93	66.36	64.87	64.61	65.28	1.30
15.000	69.28	66.13	67.66	68.49	67.30	67.28	67.69	1.09
16.000	71.26	68.62	69.99	70.60	69.62	69.65	69.96	0.91
17.000	72.64	71.09	71.95	72.25	71.69	71.74	71.89	0.53
18.000	73.94	73.09	73.58	73.73	73.43	73.46	73.54	0.29
19.000	74.79	74.44	74.97	74.70	74.66	74.84	74.73	0.18
20.000	75.81	75.69	76.20	75.78	75.85	76.07	75.90	0.19
21.000	76.36	76.82	77.24	76.48	76.81	77.14	76.81	0.35
22.000	76.59	77.32	77.82	76.77	77.26	77.70	77.24	0.49
23.000	76.91	78.20	78.58	77.23	77.97	78.49	77.90	0.68
24.000	77.25	78.70	79.31	77.61	78.49	79.16	78.42	0.83

Table A23. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.07	0.06	0.04	0.04	0.04	0.04	0.05	0.01
0.083	0.21	0.11	0.20	0.16	0.20	0.16	0.17	0.04
0.167	0.37	0.24	0.33	0.33	0.37	0.29	0.32	0.05
0.250	0.49	0.43	0.60	0.58	0.62	0.50	0.54	0.07
0.333	0.74	0.64	0.78	0.84	0.94	0.75	0.78	0.10
0.417	1.01	0.90	1.01	1.12	1.22	1.00	1.04	0.11
0.500	1.34	1.17	1.33	1.46	1.55	1.32	1.36	0.13
0.667	1.91	1.77	2.00	2.17	2.20	1.97	2.00	0.16
0.833	2.62	2.46	2.66	2.93	2.96	2.68	2.72	0.19
1.000	3.40	3.14	3.35	3.72	3.63	3.45	3.45	0.21
1.250	4.52	4.24	4.61	4.97	4.78	4.66	4.63	0.25
1.500	5.75	5.34	5.86	6.22	6.00	5.83	5.83	0.29
1.750	7.02	6.50	7.20	7.54	7.22	7.08	7.09	0.34
2.000	8.29	7.67	8.50	8.82	8.39	8.30	8.33	0.38
2.250	9.59	8.85	9.89	10.21	9.60	9.59	9.62	0.45
2.500	10.91	10.08	11.27	11.57	10.76	10.86	10.91	0.51
2.750	12.25	11.27	12.64	12.93	11.91	12.14	12.19	0.58
3.000	13.60	12.53	14.06	14.31	13.07	13.39	13.49	0.65
3.500	16.40	15.00	16.91	17.11	15.38	15.88	16.11	0.84
4.000	19.12	17.63	19.80	19.91	17.66	18.36	18.75	1.02
4.500	21.89	20.18	22.52	22.62	19.86	20.81	21.31	1.20

Table A23. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	24.60	22.83	25.30	25.33	22.13	23.28	23.91	1.35
5.500	27.39	25.42	27.96	27.96	24.62	25.74	26.52	1.44
6.000	30.06	27.96	30.67	30.44	26.88	28.14	29.03	1.57
7.000	35.11	32.82	35.56	35.78	31.07	32.74	33.85	1.91
8.000	39.63	37.35	39.89	40.52	34.91	37.03	38.22	2.15
9.000	43.71	41.46	43.81	44.59	38.46	41.04	42.18	2.30
10.000	47.42	45.17	47.62	48.11	41.72	44.73	45.80	2.43
11.000	50.76	48.70	50.94	51.50	44.70	48.06	49.11	2.55
12.000	53.81	51.97	54.00	54.49	47.52	51.08	52.15	2.62
13.000	56.60	54.89	56.89	57.43	50.09	53.87	54.96	2.74
14.000	59.13	57.56	59.48	60.12	52.44	56.24	57.50	2.85
15.000	61.51	59.84	61.92	62.92	54.60	58.42	59.87	3.04
16.000	63.30	61.76	63.68	65.03	56.30	60.14	61.70	3.14
17.000	65.51	63.75	65.50	66.90	57.96	61.61	63.54	3.28
18.000	67.08	65.16	67.25	68.21	59.49	63.08	65.05	3.28
19.000	68.61	67.04	68.76	69.80	61.22	64.52	66.66	3.24
20.000	69.83	68.08	70.07	71.01	62.51	65.64	67.86	3.23
21.000	70.82	69.11	71.01	71.90	63.55	66.62	68.84	3.19
22.000	71.72	70.07	72.18	72.96	64.45	67.37	69.79	3.28
23.000	72.64	70.93	72.94	73.72	65.32	68.09	70.61	3.28
24.000	73.47	71.77	73.79	74.65	66.03	68.89	71.43	3.34

Table A24. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.03	0.04	0.03	0.03	0.04	0.03	0.03	0.00
0.083	0.18	0.22	0.22	0.17	0.22	0.22	0.21	0.02
0.167	0.38	0.38	0.37	0.38	0.38	0.37	0.38	0.00
0.250	0.61	0.59	0.56	0.61	0.60	0.55	0.59	0.03
0.333	0.87	0.86	0.82	0.87	0.87	0.81	0.85	0.03
0.417	1.19	1.18	1.12	1.19	1.20	1.11	1.17	0.04
0.500	1.53	1.47	1.42	1.54	1.49	1.41	1.48	0.05
0.667	2.29	2.19	2.12	2.31	2.22	2.11	2.21	0.08
0.833	3.09	2.93	2.84	3.13	2.97	2.82	2.96	0.13
1.000	3.99	3.77	3.63	4.04	3.83	3.60	3.81	0.18
1.250	5.20	4.99	4.82	5.24	5.06	4.79	5.02	0.19
1.500	6.49	6.22	6.04	6.55	6.29	6.00	6.26	0.23
1.750	7.88	7.52	7.30	7.97	7.61	7.26	7.59	0.29
2.000	9.43	8.80	8.55	9.60	8.90	8.50	8.96	0.45
2.250	10.45	10.14	9.86	10.51	10.25	9.80	10.17	0.29
2.500	11.92	11.50	11.20	12.02	11.62	11.14	11.57	0.36
2.750	13.38	12.88	12.54	13.50	13.02	12.47	12.97	0.42
3.000	14.72	14.30	13.96	14.81	14.43	13.89	14.35	0.38
3.500	17.36	17.12	16.77	17.39	17.26	16.70	17.10	0.30
4.000	20.36	20.06	19.77	20.42	20.18	19.71	20.08	0.30
4.500	23.39	23.05	22.74	23.46	23.17	22.68	23.08	0.32

Table A24. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 37:40 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	26.31	26.00	25.71	26.38	26.11	25.65	26.03	0.30
5.500	29.32	28.96	28.61	29.39	29.10	28.54	28.99	0.35
6.000	32.22	31.90	31.51	32.27	32.06	31.43	31.90	0.36
7.000	37.96	37.70	37.13	37.97	37.92	37.02	37.62	0.43
8.000	43.24	43.00	42.58	43.26	43.17	42.49	42.96	0.34
9.000	48.22	47.90	47.44	48.26	48.08	47.35	47.87	0.39
10.000	52.92	52.51	52.00	52.99	52.71	51.90	52.50	0.46
11.000	57.11	56.71	56.14	57.16	56.94	56.02	56.68	0.49
12.000	60.88	60.51	59.87	60.91	60.77	59.74	60.45	0.52
13.000	64.19	63.85	63.26	64.23	64.08	63.14	63.79	0.48
14.000	67.23	66.86	66.39	67.29	67.05	66.29	66.85	0.43
15.000	69.99	69.69	69.32	70.04	69.84	69.24	69.69	0.34
16.000	72.37	72.13	71.81	72.41	72.26	71.75	72.12	0.28
17.000	74.84	74.67	74.61	74.89	74.69	74.60	74.72	0.12
18.000	76.78	76.68	76.89	76.84	76.59	76.93	76.78	0.13
19.000	78.35	78.37	78.90	78.41	78.16	79.01	78.53	0.34
20.000	79.51	79.68	80.37	79.55	79.40	80.51	79.84	0.48
21.000	80.68	80.86	81.54	80.71	80.59	81.68	81.01	0.48
22.000	81.69	82.02	82.93	81.70	81.65	83.11	82.18	0.66
23.000	82.65	82.98	83.92	82.67	82.60	84.11	83.16	0.68
24.000	83.63	84.02	85.10	83.65	83.58	85.32	84.22	0.79

Table A25. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.12	0.10	0.05	0.08	0.09	0.10	0.09	0.02
0.083	0.20	0.19	0.22	0.21	0.20	0.20	0.20	0.01
0.167	0.39	0.31	0.38	0.37	0.35	0.37	0.36	0.03
0.250	0.48	0.36	0.59	0.51	0.45	0.48	0.48	0.07
0.333	0.72	0.48	0.84	0.72	0.63	0.69	0.68	0.12
0.417	0.98	0.53	1.20	0.98	0.81	0.92	0.90	0.22
0.500	1.18	0.64	1.55	1.23	1.00	1.14	1.12	0.30
0.667	1.77	0.88	2.29	1.81	1.46	1.68	1.65	0.46
0.833	2.35	1.13	3.07	2.41	1.92	2.23	2.18	0.64
1.000	3.11	1.68	3.98	3.19	2.61	2.97	2.92	0.76
1.250	4.18	2.78	5.28	4.38	3.76	4.11	4.08	0.82
1.500	5.41	4.01	6.54	5.63	4.99	5.34	5.32	0.83
1.750	6.76	5.48	7.88	7.00	6.40	6.72	6.71	0.78
2.000	8.16	6.78	9.17	8.32	7.72	8.07	8.04	0.78
2.250	9.58	8.05	10.56	9.69	9.06	9.44	9.40	0.82
2.500	11.19	9.28	11.78	11.01	10.38	10.86	10.75	0.85
2.750	12.92	10.49	13.10	12.40	11.75	12.36	12.17	0.95
3.000	14.54	11.73	14.41	13.77	13.10	13.81	13.56	1.03
3.500	17.87	14.15	16.98	16.50	15.79	16.72	16.33	1.27
4.000	21.07	16.62	19.54	19.19	18.46	19.58	19.08	1.47
4.500	24.19	19.09	22.12	21.88	21.12	22.40	21.80	1.67

Table A25. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	27.16	21.66	24.72	24.57	23.80	25.18	24.51	1.80
5.500	30.16	24.17	27.20	27.18	26.43	27.92	27.18	1.95
6.000	33.37	26.76	29.78	29.92	29.17	30.82	29.97	2.16
7.000	38.20	31.63	34.52	34.72	34.00	35.64	34.78	2.15
8.000	42.51	36.08	39.20	39.25	38.47	40.08	39.26	2.10
9.000	46.33	40.41	43.68	43.53	42.71	44.19	43.47	1.93
10.000	50.10	44.58	48.11	47.73	46.84	48.22	47.60	1.82
11.000	53.47	48.75	52.29	51.70	50.82	52.00	51.50	1.60
12.000	56.60	52.67	56.25	55.44	54.55	55.53	55.17	1.42
13.000	59.59	56.31	59.86	58.91	58.02	58.84	58.59	1.29
14.000	62.21	59.78	63.37	62.18	61.29	61.89	61.79	1.19
15.000	64.79	63.04	66.74	65.33	64.40	64.84	64.86	1.21
16.000	67.29	66.15	69.80	68.26	67.35	67.63	67.75	1.22
17.000	69.91	69.16	72.70	71.12	70.23	70.42	70.59	1.22
18.000	72.42	72.11	75.34	73.80	73.00	73.07	73.29	1.16
19.000	74.84	74.91	77.59	76.23	75.56	75.55	75.78	1.02
20.000	76.90	76.89	79.68	78.29	77.59	77.59	77.82	1.05
21.000	78.47	78.45	80.84	79.65	79.05	79.06	79.25	0.90
22.000	79.68	79.79	82.00	80.87	80.32	80.29	80.49	0.85
23.000	80.79	80.90	83.14	81.99	81.43	81.41	81.61	0.86
24.000	81.87	81.75	84.16	82.99	82.38	82.41	82.59	0.89

Table A26. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.00	0.07	0.09	0.02	0.06	0.09	0.05	0.04
0.083	0.16	0.15	0.34	0.16	0.20	0.29	0.22	0.08
0.167	0.30	0.24	0.44	0.29	0.31	0.39	0.33	0.07
0.250	0.41	0.37	0.53	0.40	0.42	0.49	0.44	0.06
0.333	0.64	0.57	0.60	0.62	0.60	0.59	0.60	0.02
0.417	0.83	0.76	0.65	0.81	0.75	0.68	0.75	0.07
0.500	1.08	0.99	0.76	1.06	0.96	0.82	0.94	0.13
0.667	1.62	1.52	0.97	1.60	1.41	1.11	1.37	0.27
0.833	2.24	2.10	1.20	2.21	1.91	1.43	1.85	0.44
1.000	2.93	2.74	1.43	2.88	2.46	1.76	2.37	0.63
1.250	3.95	3.77	2.11	3.91	3.40	2.53	3.28	0.78
1.500	5.09	4.92	3.19	5.05	4.53	3.62	4.40	0.81
1.750	6.28	6.09	4.55	6.23	5.75	4.94	5.64	0.73
2.000	7.47	7.33	5.84	7.44	6.99	6.21	6.88	0.69
2.250	8.58	8.59	7.20	8.58	8.24	7.55	8.12	0.61
2.500	9.74	9.83	8.49	9.76	9.47	8.83	9.35	0.56
2.750	10.86	11.05	9.91	10.91	10.72	10.20	10.61	0.45
3.000	12.02	12.34	11.38	12.10	12.02	11.62	11.91	0.35
3.500	14.32	14.84	14.26	14.45	14.57	14.41	14.47	0.21
4.000	16.64	17.36	17.21	16.82	17.14	17.25	17.07	0.28
4.500	19.02	19.95	20.19	19.25	19.78	20.13	19.72	0.48

Table A26. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	21.47	22.53	23.17	21.74	22.43	23.01	22.39	0.68
5.500	23.97	25.09	26.07	24.25	25.06	25.83	25.04	0.83
6.000	26.51	27.64	28.94	26.79	27.68	28.62	27.70	0.96
7.000	31.48	32.67	34.31	31.78	32.78	33.90	32.82	1.12
8.000	36.48	37.65	39.41	36.77	37.80	38.97	37.85	1.16
9.000	41.22	42.40	44.11	41.52	42.53	43.68	42.58	1.15
10.000	45.75	46.73	48.46	46.00	46.92	48.03	46.98	1.08
11.000	50.04	50.91	52.45	50.26	51.08	52.07	51.13	0.96
12.000	53.89	54.75	55.94	54.11	54.83	55.64	54.86	0.81
13.000	57.48	58.31	59.36	57.69	58.37	59.10	58.38	0.74
14.000	60.74	61.43	62.72	60.91	61.58	62.40	61.63	0.79
15.000	63.84	64.55	65.74	64.02	64.67	65.44	64.71	0.76
16.000	66.78	67.34	68.37	66.92	67.46	68.11	67.50	0.63
17.000	69.42	69.97	71.03	69.56	70.10	70.77	70.14	0.64
18.000	71.93	72.46	73.43	72.06	72.57	73.19	72.61	0.60
19.000	74.08	74.87	75.71	74.28	74.88	75.50	74.89	0.64
20.000	75.86	76.76	77.62	76.09	76.75	77.41	76.75	0.70
21.000	77.83	78.78	79.37	78.07	78.69	79.22	78.66	0.61
22.000	79.27	80.26	80.91	79.52	80.18	80.75	80.15	0.65
23.000	80.80	82.15	82.30	81.14	81.85	82.26	81.75	0.63
24.000	82.82	83.85	84.28	83.08	83.70	84.17	83.65	0.59

Table A27. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.03	0.04	0.03	0.02	0.05	0.07	0.04	0.02
0.083	0.17	0.18	0.18	0.16	0.18	0.22	0.18	0.02
0.167	0.27	0.29	0.29	0.27	0.27	0.33	0.29	0.02
0.250	0.41	0.44	0.44	0.41	0.41	0.51	0.44	0.04
0.333	0.62	0.65	0.66	0.63	0.60	0.74	0.65	0.05
0.417	0.84	0.88	0.89	0.85	0.81	0.99	0.88	0.06
0.500	1.10	1.15	1.15	1.10	1.08	1.30	1.15	0.08
0.667	1.70	1.76	1.78	1.71	1.65	1.98	1.76	0.12
0.833	2.32	2.42	2.44	2.34	2.26	2.73	2.42	0.17
1.000	3.01	3.11	3.14	3.04	2.92	3.45	3.11	0.18
1.250	4.14	4.24	4.29	4.19	3.99	4.60	4.24	0.20
1.500	5.35	5.46	5.52	5.42	5.15	5.83	5.46	0.22
1.750	6.57	6.68	6.78	6.67	6.26	7.10	6.68	0.27
2.000	7.86	7.98	8.12	8.00	7.45	8.46	7.98	0.33
2.250	9.17	9.30	9.48	9.35	8.63	9.86	9.30	0.40
2.500	10.47	10.64	10.85	10.68	9.83	11.37	10.64	0.50
2.750	11.75	11.96	12.20	11.99	11.01	12.83	11.96	0.59
3.000	13.11	13.36	13.64	13.39	12.25	14.39	13.36	0.70
3.500	15.73	16.04	16.40	16.08	14.66	17.34	16.04	0.87
4.000	18.38	18.80	19.24	18.82	17.06	20.48	18.80	1.11
4.500	21.16	21.63	22.15	21.68	19.59	23.55	21.63	1.29

Table A27. %Drug dissolved of indomethacin from formulation containing HPMC : microcrystalline cellulose ratio of 57:20 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	23.96	24.46	25.10	24.59	22.05	26.62	24.46	1.49
5.500	26.80	27.32	28.03	27.51	24.65	29.60	27.32	1.62
6.000	29.15	29.83	30.47	29.79	27.24	32.50	29.83	1.71
7.000	33.90	34.90	35.35	34.35	32.53	38.35	34.90	1.95
8.000	39.11	40.14	40.59	39.56	37.76	43.69	40.14	1.99
9.000	44.38	45.27	45.78	44.89	42.85	48.44	45.27	1.85
10.000	49.16	49.81	50.42	49.77	47.34	52.36	49.81	1.64
11.000	53.37	53.80	54.47	54.04	51.35	55.75	53.80	1.45
12.000	57.32	57.56	58.26	58.03	55.20	58.96	57.56	1.29
13.000	61.16	61.19	61.96	61.93	58.84	62.06	61.19	1.22
14.000	64.58	64.46	65.31	65.44	62.01	64.93	64.46	1.26
15.000	67.64	67.38	68.23	68.48	65.10	67.46	67.38	1.20
16.000	70.41	70.08	70.88	71.21	68.02	69.88	70.08	1.12
17.000	73.16	72.70	73.50	73.96	70.74	72.12	72.70	1.15
18.000	75.35	74.94	75.64	76.05	73.24	74.40	74.94	1.01
19.000	77.59	77.11	77.79	78.27	75.53	76.36	77.11	1.01
20.000	79.54	79.05	79.64	80.13	77.78	78.15	79.05	0.91
21.000	81.48	80.98	81.47	81.96	80.02	79.98	80.98	0.82
22.000	82.73	82.25	82.66	83.14	81.48	81.22	82.25	0.75
23.000	84.09	83.71	84.16	84.55	82.72	83.00	83.71	0.71
24.000	85.75	85.41	85.78	86.13	84.62	84.74	85.41	0.61

Table A28. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.07	0.09	0.05	0.08	0.08	0.06	0.07	0.01
0.083	0.64	0.46	0.53	0.60	0.52	0.51	0.54	0.06
0.167	1.18	0.97	1.08	1.13	1.05	1.05	1.08	0.07
0.250	1.73	1.57	1.68	1.69	1.64	1.65	1.66	0.05
0.333	2.26	2.10	2.25	2.22	2.18	2.21	2.20	0.06
0.417	2.77	2.70	2.77	2.75	2.74	2.75	2.75	0.03
0.500	3.26	3.29	3.32	3.27	3.29	3.31	3.29	0.02
0.667	4.22	4.54	4.37	4.30	4.42	4.41	4.38	0.11
0.833	5.30	5.78	5.42	5.42	5.57	5.51	5.50	0.17
1.000	6.51	7.09	6.47	6.66	6.79	6.63	6.69	0.23
1.250	8.50	9.30	8.46	8.70	8.89	8.67	8.75	0.31
1.500	10.68	11.65	10.33	10.92	11.08	10.66	10.89	0.45
1.750	12.81	14.16	12.30	13.15	13.36	12.77	13.09	0.64
2.000	14.90	16.55	14.25	15.31	15.56	14.83	15.23	0.79
2.250	17.05	18.54	16.26	17.42	17.60	16.83	17.28	0.78
2.500	19.59	20.46	18.36	19.81	19.72	18.89	19.47	0.74
2.750	22.17	22.78	20.29	22.32	22.01	20.91	21.75	0.94
3.000	24.64	24.73	22.07	24.66	24.04	22.74	23.81	1.14
3.500	29.17	28.20	25.50	28.93	27.77	26.18	27.62	1.49
4.000	33.29	31.42	28.81	32.82	31.24	29.46	31.17	1.78
4.500	37.15	34.48	32.00	36.48	34.53	32.62	34.54	2.04

Table A28. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	40.72	37.42	35.22	39.90	37.70	35.77	37.79	2.18
5.500	43.74	40.06	38.14	42.82	40.50	38.62	40.65	2.24
6.000	46.29	42.60	40.97	45.37	43.12	41.38	43.29	2.14
7.000	50.89	47.47	46.16	50.04	48.00	46.49	48.17	1.91
8.000	54.98	52.01	50.93	54.24	52.48	51.20	52.64	1.64
9.000	58.79	56.06	55.24	58.11	56.54	55.45	56.70	1.45
10.000	62.31	59.86	59.23	61.70	60.32	59.39	60.47	1.26
11.000	65.37	63.46	62.92	64.89	63.80	63.06	63.92	1.00
12.000	67.99	66.48	66.07	67.61	66.76	66.17	66.85	0.79
13.000	70.45	69.26	69.16	70.15	69.53	69.19	69.62	0.55
14.000	72.65	71.57	71.73	72.38	71.88	71.69	71.98	0.43
15.000	74.23	73.64	73.71	74.08	73.81	73.69	73.86	0.24
16.000	75.23	74.74	74.84	75.11	74.89	74.82	74.94	0.19
17.000	75.62	75.18	75.56	75.51	75.39	75.47	75.45	0.16
18.000	75.90	75.59	75.84	75.82	75.73	75.78	75.78	0.11
19.000	75.96	75.69	75.88	75.89	75.81	75.83	75.84	0.09
20.000	76.00	75.70	76.05	75.93	75.86	75.96	75.92	0.12
21.000	76.10	75.73	76.09	76.01	75.91	76.00	75.97	0.14
22.000	76.05	75.85	76.10	76.00	75.96	76.04	76.00	0.09
23.000	76.08	75.86	76.12	76.03	75.98	76.06	76.02	0.09
24.000	76.10	75.94	76.15	76.06	76.03	76.10	76.06	0.07

Table A29. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.08	0.08	0.07	0.06	0.08	0.08	0.07	0.01
0.083	0.26	0.23	0.27	0.31	0.27	0.17	0.25	0.05
0.167	0.47	0.46	0.49	0.55	0.45	0.41	0.47	0.05
0.250	0.75	0.76	0.79	0.85	0.71	0.74	0.77	0.05
0.333	1.05	1.07	1.10	1.18	0.97	1.07	1.07	0.07
0.417	1.49	1.50	1.53	1.59	1.44	1.48	1.50	0.05
0.500	1.84	1.87	1.90	1.98	1.76	1.86	1.87	0.07
0.667	2.75	2.78	2.82	2.91	2.66	2.78	2.78	0.08
0.833	3.73	3.76	3.79	3.89	3.64	3.75	3.76	0.08
1.000	4.65	4.75	4.79	4.97	4.40	4.81	4.73	0.19
1.250	6.33	6.42	6.46	6.62	6.10	6.48	6.40	0.18
1.500	8.16	8.22	8.25	8.38	8.00	8.25	8.21	0.13
1.750	9.91	9.99	10.00	10.11	9.73	10.06	9.97	0.13
2.000	11.68	11.80	11.77	11.82	11.47	11.96	11.75	0.16
2.250	13.47	13.61	13.52	13.49	13.26	13.85	13.53	0.19
2.500	15.16	15.37	15.23	15.17	14.89	15.70	15.25	0.27
2.750	16.89	17.14	16.97	16.89	16.55	17.56	17.00	0.34
3.000	18.62	18.90	18.70	18.59	18.25	19.37	18.74	0.37
3.500	21.84	22.26	21.99	21.88	21.26	22.95	22.03	0.56
4.000	25.30	25.71	25.41	25.20	24.79	26.43	25.47	0.56
4.500	28.63	29.08	28.74	28.51	28.06	29.87	28.81	0.61

Table A29. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	31.94	32.41	32.08	31.87	31.34	33.22	32.14	0.63
5.500	35.42	35.80	35.45	35.12	35.00	36.54	35.55	0.56
6.000	31.91	35.58	35.24	38.24	24.91	39.58	34.24	5.29
7.000	44.39	44.81	44.46	44.19	43.89	45.58	44.55	0.59
8.000	49.77	50.13	49.87	49.70	49.30	50.76	49.92	0.49
9.000	49.46	52.33	52.00	54.22	44.04	55.53	51.26	4.10
10.000	58.43	58.92	58.50	58.13	57.88	59.84	58.62	0.70
11.000	61.89	62.54	62.02	61.64	61.12	63.69	62.15	0.89
12.000	65.08	65.80	65.16	64.60	64.27	67.16	65.34	1.03
13.000	67.87	68.75	67.97	67.29	66.88	70.42	68.20	1.26
14.000	70.41	71.40	70.50	69.68	69.32	73.30	70.77	1.44
15.000	72.25	73.38	72.38	71.52	71.00	75.49	72.67	1.60
16.000	73.12	74.31	73.22	72.23	71.82	76.60	73.55	1.73
17.000	73.60	74.85	73.75	72.80	72.19	77.21	74.07	1.79
18.000	74.12	75.37	74.20	73.11	72.79	77.79	74.56	1.82
19.000	74.29	75.57	74.37	73.26	72.92	78.05	74.74	1.87
20.000	74.39	75.65	74.45	73.32	73.05	78.12	74.83	1.86
21.000	74.48	75.75	74.53	73.36	73.16	78.24	74.92	1.88
22.000	74.60	75.87	74.63	73.41	73.31	78.37	75.03	1.89
23.000	74.65	75.90	74.66	73.42	73.40	78.38	75.07	1.87
24.000	74.68	75.92	74.69	73.46	73.44	78.39	75.10	1.86

Table A30. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.01	0.04	0.00	0.02	0.01	0.02	0.02	0.01
0.083	0.30	0.27	0.23	0.27	0.26	0.28	0.27	0.02
0.167	0.51	0.53	0.47	0.51	0.50	0.51	0.50	0.02
0.250	0.68	0.77	0.75	0.74	0.74	0.72	0.73	0.03
0.333	0.99	1.08	1.14	1.07	1.09	1.05	1.07	0.05
0.417	1.39	1.44	1.54	1.45	1.48	1.44	1.46	0.05
0.500	1.76	1.83	2.05	1.87	1.92	1.85	1.88	0.10
0.667	2.61	2.66	3.14	2.77	2.89	2.76	2.80	0.19
0.833	3.53	3.53	4.17	3.69	3.85	3.69	3.74	0.24
1.000	4.48	4.44	5.25	4.65	4.86	4.66	4.72	0.30
1.250	6.02	5.98	7.09	6.27	6.55	6.28	6.36	0.41
1.500	7.62	7.54	9.00	7.93	8.29	7.95	8.05	0.54
1.750	9.38	9.27	11.06	9.75	10.19	9.77	9.90	0.65
2.000	11.15	10.95	13.17	11.56	12.11	11.61	11.76	0.80
2.250	12.88	12.76	15.46	13.47	14.14	13.50	13.70	0.99
2.500	14.70	14.47	17.63	15.32	16.11	15.38	15.60	1.15
2.750	16.51	16.26	19.89	17.23	18.14	17.29	17.55	1.32
3.000	18.35	18.04	21.98	19.10	20.09	19.18	19.46	1.43
3.500	22.00	21.53	26.25	22.83	24.01	22.95	23.26	1.70
4.000	25.62	25.07	30.07	26.46	27.71	26.60	26.92	1.79
4.500	29.28	28.58	33.76	30.05	31.35	30.23	30.54	1.83

Table A30. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 30:10 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	32.83	32.12	37.42	33.62	34.95	33.80	34.12	1.88
5.500	36.40	35.43	40.86	37.03	38.39	37.27	37.56	1.89
6.000	39.79	38.85	43.34	40.21	41.33	40.44	40.66	1.54
7.000	46.13	45.13	49.28	46.42	47.46	46.67	46.85	1.41
8.000	51.97	50.94	55.12	52.24	53.29	52.50	52.68	1.42
9.000	57.65	56.49	60.20	57.71	58.64	58.00	58.11	1.24
10.000	62.44	61.17	64.97	62.44	63.39	62.76	62.86	1.26
11.000	66.66	65.37	69.15	66.64	67.58	66.96	67.06	1.25
12.000	70.27	68.87	72.50	70.13	71.04	70.48	70.55	1.19
13.000	73.49	72.24	75.56	73.38	74.21	73.70	73.76	1.09
14.000	76.12	74.85	77.90	75.93	76.69	76.25	76.29	1.00
15.000	78.15	77.41	80.10	78.27	78.94	78.45	78.55	0.91
16.000	79.92	79.27	81.50	79.99	80.55	80.15	80.23	0.75
17.000	81.26	80.81	83.11	81.50	82.07	81.61	81.73	0.79
18.000	82.72	82.15	84.22	82.81	83.33	82.95	83.03	0.70
19.000	84.00	83.12	85.09	83.83	84.33	84.05	84.07	0.64
20.000	84.96	84.03	85.79	84.70	85.14	84.94	84.93	0.57
21.000	85.53	85.16	86.69	85.64	86.02	85.73	85.79	0.52
22.000	86.57	85.97	87.24	86.44	86.76	86.59	86.59	0.41
23.000	87.72	86.88	87.88	87.34	87.59	87.55	87.49	0.35
24.000	88.34	87.90	88.97	88.28	88.55	88.39	88.40	0.35

Table A31. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.07	0.12	0.07	0.08	0.10	0.08	0.09	0.02
0.083	0.55	0.39	0.51	0.51	0.46	0.48	0.48	0.06
0.167	1.07	0.81	1.04	1.01	0.93	0.98	0.97	0.09
0.250	1.54	1.33	1.64	1.49	1.46	1.56	1.50	0.11
0.333	2.09	1.80	2.15	2.02	1.96	2.06	2.01	0.12
0.417	2.66	2.26	2.71	2.56	2.47	2.60	2.54	0.16
0.500	3.17	2.78	3.32	3.07	3.01	3.19	3.09	0.18
0.667	4.11	3.69	4.57	4.01	4.02	4.35	4.12	0.30
0.833	5.19	4.74	5.70	5.08	5.09	5.46	5.21	0.33
1.000	6.36	5.81	6.90	6.22	6.22	6.63	6.36	0.38
1.250	8.19	7.48	8.58	8.01	7.93	8.31	8.08	0.37
1.500	9.99	9.36	10.27	9.83	9.75	10.04	9.87	0.31
1.750	11.77	11.34	11.98	11.66	11.61	11.82	11.70	0.22
2.000	13.83	13.28	13.57	13.69	13.49	13.50	13.56	0.19
2.250	15.47	15.27	15.27	15.42	15.32	15.27	15.34	0.09
2.500	17.15	16.89	16.83	17.09	16.94	16.85	16.96	0.13
2.750	18.72	18.48	18.14	18.66	18.46	18.23	18.45	0.23
3.000	20.31	20.04	20.02	20.24	20.10	20.03	20.12	0.12
3.500	23.24	23.10	23.01	23.21	23.11	23.03	23.12	0.09
4.000	26.15	26.09	25.99	26.14	26.08	26.02	26.08	0.06
4.500	28.97	29.00	28.86	28.98	28.96	28.90	28.94	0.05

Table A31. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	31.78	31.91	31.77	31.81	31.84	31.81	31.82	0.05
5.500	34.58	34.65	34.51	34.60	34.60	34.55	34.58	0.05
6.000	37.32	37.30	37.19	37.32	37.28	37.22	37.27	0.05
7.000	42.44	42.14	42.24	42.37	42.24	42.22	42.27	0.11
8.000	47.33	46.55	47.00	47.14	46.86	46.89	46.96	0.27
9.000	51.83	50.63	51.34	51.53	51.11	51.16	51.27	0.41
10.000	55.92	54.35	55.41	55.53	55.01	55.15	55.23	0.53
11.000	59.94	57.62	58.94	59.36	58.53	58.61	58.83	0.79
12.000	63.37	60.72	62.22	62.71	61.76	61.85	62.10	0.90
13.000	66.26	63.47	65.00	65.56	64.55	64.62	64.91	0.95
14.000	68.91	66.11	67.48	68.21	67.15	67.14	67.50	0.97
15.000	70.95	68.28	69.42	70.28	69.23	69.14	69.55	0.94
16.000	72.42	70.20	71.11	71.87	70.98	70.88	71.24	0.78
17.000	73.97	71.85	72.35	73.44	72.51	72.23	72.72	0.81
18.000	75.16	73.19	73.79	74.67	73.83	73.64	74.05	0.73
19.000	76.24	74.31	74.56	75.76	74.86	74.50	75.04	0.78
20.000	77.24	75.36	75.43	76.77	75.85	75.41	76.01	0.80
21.000	77.99	76.26	76.13	77.56	76.66	76.16	76.79	0.79
22.000	78.67	76.83	76.77	78.21	77.28	76.79	77.42	0.82
23.000	79.51	77.53	77.26	79.02	77.96	77.33	78.10	0.95
24.000	79.98	78.26	78.00	79.55	78.63	78.07	78.75	0.83

Table A32. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.08	0.08	0.08	0.08	0.08	0.07	0.08	0.00
0.083	0.30	0.29	0.29	0.30	0.29	0.29	0.29	0.00
0.167	0.56	0.56	0.55	0.57	0.56	0.53	0.55	0.01
0.250	0.91	0.91	0.90	0.93	0.92	0.87	0.91	0.02
0.333	1.26	1.26	1.24	1.27	1.27	1.21	1.25	0.02
0.417	1.66	1.66	1.64	1.68	1.69	1.59	1.65	0.04
0.500	2.09	2.10	2.07	2.11	2.14	2.01	2.09	0.04
0.667	3.00	3.01	2.97	3.03	3.04	2.91	2.99	0.05
0.833	4.04	4.05	3.99	4.07	4.11	3.89	4.02	0.08
1.000	5.12	5.12	5.05	5.19	5.20	4.90	5.10	0.11
1.250	6.75	6.70	6.64	6.92	6.72	6.45	6.70	0.15
1.500	8.47	8.37	8.29	8.76	8.33	8.04	8.38	0.24
1.750	10.20	10.05	9.97	10.59	9.98	9.65	10.07	0.31
2.000	11.94	11.75	11.65	12.41	11.65	11.27	11.78	0.38
2.250	13.69	13.46	13.36	14.24	13.33	12.93	13.50	0.44
2.500	15.43	15.17	15.08	16.04	15.00	14.63	15.22	0.48
2.750	17.20	16.91	16.83	17.85	16.70	16.38	16.98	0.50
3.000	18.91	18.58	18.51	19.62	18.33	18.05	18.67	0.55
3.500	22.16	21.78	21.70	22.99	21.49	21.16	21.88	0.64
4.000	25.38	24.97	24.88	26.29	24.65	24.29	25.08	0.70
4.500	28.51	28.06	28.01	29.46	27.65	27.46	28.19	0.72

Table A32. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	31.53	31.08	31.05	32.47	30.65	30.53	31.22	0.71
5.500	34.46	33.97	33.96	35.44	33.50	33.44	34.13	0.74
6.000	37.13	36.59	36.62	38.19	36.03	36.12	36.78	0.80
7.000	42.10	41.55	41.61	43.15	40.95	41.16	41.75	0.79
8.000	46.61	46.06	46.15	47.62	45.41	45.79	46.27	0.77
9.000	50.75	50.22	50.32	51.70	49.58	50.00	50.43	0.73
10.000	54.26	53.85	54.00	54.93	53.29	53.89	54.04	0.54
11.000	57.46	57.20	57.39	57.80	56.75	57.50	57.35	0.35
12.000	60.29	60.14	60.42	60.29	59.72	60.84	60.28	0.37
13.000	62.76	62.72	63.11	62.44	62.30	63.84	62.86	0.56
14.000	65.15	65.20	65.69	64.55	64.75	66.73	65.34	0.79
15.000	67.14	67.29	67.85	66.29	66.89	69.10	67.43	0.96
16.000	68.97	69.14	69.86	67.91	68.59	71.47	69.32	1.23
17.000	70.57	70.85	71.58	69.29	70.40	73.31	71.00	1.35
18.000	71.90	72.29	73.08	70.33	71.89	75.05	72.42	1.57
19.000	72.76	73.17	74.06	71.04	72.70	76.24	73.33	1.73
20.000	73.64	74.14	75.05	71.72	73.74	77.37	74.28	1.87
21.000	74.41	75.01	75.89	72.32	74.72	78.26	75.10	1.95
22.000	74.94	75.65	76.56	72.62	75.44	79.09	75.72	2.11
23.000	75.50	76.30	77.22	72.97	76.18	79.86	76.34	2.25
24.000	75.96	76.78	77.72	73.39	76.65	80.41	76.82	2.29

Table A33. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00
0.083	0.25	0.25	0.25	0.25	0.24	0.26	0.25	0.01
0.167	0.49	0.49	0.50	0.49	0.48	0.51	0.49	0.01
0.250	0.78	0.77	0.78	0.81	0.74	0.78	0.78	0.02
0.333	1.14	1.11	1.13	1.18	1.06	1.14	1.13	0.04
0.417	1.56	1.52	1.55	1.60	1.47	1.56	1.54	0.05
0.500	2.00	1.96	1.99	2.06	1.89	2.00	1.98	0.06
0.667	2.98	2.90	2.94	3.09	2.79	2.95	2.94	0.10
0.833	3.98	3.87	3.92	4.16	3.69	3.92	3.92	0.15
1.000	5.07	4.91	4.96	5.33	4.70	4.91	4.98	0.21
1.250	6.79	6.59	6.65	7.12	6.33	6.58	6.68	0.26
1.500	8.57	8.33	8.39	8.98	8.04	8.26	8.43	0.32
1.750	10.39	10.13	10.18	10.86	9.82	10.02	10.23	0.36
2.000	12.20	11.92	11.96	12.72	11.60	11.77	12.03	0.39
2.250	13.99	13.70	13.74	14.54	13.36	13.53	13.81	0.42
2.500	15.83	15.52	15.56	16.42	15.15	15.34	15.64	0.45
2.750	17.67	17.32	17.39	18.29	16.91	17.18	17.46	0.48
3.000	19.53	19.16	19.25	20.19	18.70	19.05	19.31	0.51
3.500	23.14	22.73	22.85	23.85	22.20	22.67	22.91	0.56
4.000	26.62	26.22	26.38	27.26	25.66	26.30	26.41	0.53
4.500	30.07	29.69	29.90	30.64	29.09	29.93	29.89	0.51

Table A33. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 20:20 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	33.49	33.12	33.37	34.00	32.49	33.49	33.33	0.50
5.500	36.69	36.34	36.62	37.12	35.69	36.84	36.55	0.49
6.000	39.86	39.52	39.84	40.21	38.87	40.15	39.74	0.50
7.000	45.35	44.90	45.19	45.95	44.18	45.31	45.15	0.59
8.000	50.83	50.50	50.86	51.12	49.81	51.26	50.73	0.52
9.000	55.79	55.56	56.03	55.78	54.85	56.75	55.79	0.62
10.000	60.15	59.91	60.47	60.08	59.12	61.33	60.18	0.72
11.000	64.20	63.94	64.59	64.07	63.04	65.62	64.24	0.85
12.000	67.84	67.58	68.33	67.62	66.57	69.56	67.92	0.99
13.000	71.09	70.81	71.61	70.86	69.71	72.94	71.17	1.07
14.000	73.98	73.61	74.44	73.88	72.41	75.74	74.01	1.09
15.000	76.38	76.00	76.87	76.27	74.76	78.23	76.42	1.14
16.000	78.62	78.23	79.16	78.48	76.92	80.62	78.67	1.21
17.000	80.58	80.13	81.07	80.53	78.76	82.49	80.59	1.22
18.000	82.12	81.70	82.64	82.02	80.33	84.10	82.15	1.23
19.000	83.46	83.07	84.05	83.25	81.71	85.63	83.53	1.29
20.000	84.57	84.16	85.19	84.35	82.72	86.84	84.64	1.35
21.000	85.49	85.03	86.05	85.38	83.54	87.65	85.52	1.34
22.000	86.34	85.91	87.00	86.10	84.38	88.76	86.41	1.44
23.000	87.45	86.97	88.06	87.32	85.40	89.76	87.49	1.42
24.000	88.33	87.80	88.93	88.25	86.14	90.67	88.35	1.48

Table A34. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 300 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.03	0.05	0.04	0.03	0.04	0.02	0.04	0.01
0.083	0.33	0.29	0.39	0.28	0.27	0.31	0.31	0.04
0.167	0.66	0.65	0.78	0.53	0.50	0.71	0.64	0.11
0.250	0.98	0.99	1.25	0.86	0.83	1.14	1.01	0.16
0.333	1.41	1.43	1.64	1.22	1.28	1.66	1.44	0.18
0.417	1.80	1.86	2.03	1.61	1.78	2.14	1.87	0.19
0.500	2.24	2.29	2.49	2.00	2.25	2.63	2.32	0.22
0.667	3.12	3.12	3.44	2.93	3.29	3.75	3.28	0.29
0.833	4.10	3.98	4.45	3.83	4.27	4.85	4.25	0.37
1.000	5.12	4.93	5.63	4.86	5.31	5.93	5.30	0.42
1.250	6.58	6.61	7.52	6.44	6.79	7.56	6.92	0.50
1.500	8.11	8.46	9.36	8.15	8.32	9.14	8.59	0.53
1.750	9.59	10.19	11.29	9.96	9.86	10.78	10.28	0.64
2.000	11.05	11.89	12.96	11.79	11.42	12.62	11.96	0.72
2.250	12.49	13.60	14.73	13.67	12.91	14.45	13.64	0.86
2.500	14.12	15.14	16.31	15.50	14.40	16.18	15.28	0.90
2.750	15.63	16.60	17.87	17.31	15.81	17.84	16.84	0.99
3.000	16.99	18.07	19.43	19.06	17.20	19.52	18.38	1.12
3.500	19.59	20.91	22.51	22.51	19.95	22.68	21.36	1.39
4.000	22.04	23.69	25.56	25.96	22.52	25.62	24.23	1.71
4.500	24.59	26.25	28.83	29.29	25.05	28.47	27.08	2.04

Table A34. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 300 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	27.02	28.63	31.85	32.24	27.43	31.19	29.73	2.31
5.500	29.54	30.94	34.48	34.94	29.73	33.79	32.24	2.45
6.000	31.97	33.26	37.11	37.42	32.03	36.41	34.70	2.56
7.000	36.70	37.60	41.54	42.04	36.37	41.14	39.23	2.61
8.000	41.13	41.78	45.48	46.00	40.56	45.71	43.44	2.54
9.000	45.03	45.56	48.61	49.32	44.49	49.55	47.09	2.31
10.000	48.63	49.07	51.25	52.21	48.32	52.86	50.39	1.96
11.000	51.95	52.41	53.57	54.66	51.82	55.79	53.37	1.61
12.000	54.99	55.55	55.74	56.93	54.98	58.39	56.10	1.33
13.000	57.64	58.49	58.02	59.08	58.04	60.83	58.68	1.16
14.000	60.01	60.89	59.63	60.69	60.72	62.89	60.81	1.13
15.000	62.00	62.94	61.20	62.29	63.20	64.95	62.76	1.28
16.000	63.87	64.69	62.82	63.66	65.45	66.53	64.50	1.34
17.000	65.47	65.89	63.91	64.72	67.22	67.82	65.84	1.48
18.000	66.92	66.91	64.59	65.69	68.70	68.70	66.92	1.63
19.000	67.94	67.77	65.15	66.35	69.61	69.45	67.71	1.74
20.000	69.00	68.55	65.57	66.93	70.84	70.27	68.53	2.00
21.000	70.39	70.08	66.81	67.94	72.62	71.84	69.95	2.23
22.000	71.95	71.26	67.86	68.96	73.97	73.22	71.20	2.39
23.000	73.00	72.22	68.44	69.50	75.29	74.17	72.10	2.66
24.000	73.61	72.93	69.06	69.96	75.95	74.80	72.72	2.71

Table A35. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 600 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.06	0.09	0.06	0.07	0.08	0.07	0.07	0.01
0.083	0.25	0.26	0.27	0.26	0.26	0.26	0.26	0.01
0.167	0.46	0.48	0.48	0.47	0.48	0.48	0.47	0.01
0.250	0.64	0.76	0.78	0.71	0.74	0.74	0.73	0.05
0.333	0.94	1.07	1.11	1.02	1.05	1.06	1.04	0.06
0.417	1.22	1.40	1.49	1.33	1.38	1.40	1.37	0.09
0.500	1.57	1.78	1.90	1.71	1.76	1.79	1.75	0.11
0.667	2.17	2.62	2.80	2.44	2.55	2.60	2.53	0.21
0.833	2.97	3.54	3.71	3.30	3.44	3.48	3.41	0.25
1.000	3.75	4.43	4.71	4.16	4.33	4.40	4.30	0.32
1.250	5.01	5.89	6.33	5.56	5.78	5.89	5.74	0.44
1.500	6.33	7.30	7.91	6.97	7.21	7.36	7.18	0.52
1.750	7.71	8.79	9.48	8.42	8.69	8.87	8.66	0.58
2.000	9.12	10.23	10.98	9.86	10.14	10.33	10.11	0.61
2.250	10.50	11.69	12.48	11.29	11.59	11.79	11.56	0.65
2.500	12.09	13.17	13.95	12.83	13.10	13.29	13.07	0.61
2.750	13.77	14.66	15.37	14.39	14.62	14.79	14.60	0.52
3.000	15.31	16.15	16.85	15.91	16.12	16.29	16.10	0.50
3.500	18.36	19.12	19.71	18.89	19.08	19.23	19.06	0.44
4.000	21.31	22.10	22.54	21.82	22.01	22.12	21.98	0.41
4.500	24.03	25.04	25.53	24.66	24.91	25.03	24.87	0.50

Table A35. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 600 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	26.77	27.97	28.54	27.51	27.81	27.96	27.76	0.59
5.500	29.36	30.70	31.00	30.11	30.44	30.52	30.35	0.57
6.000	32.01	33.47	33.89	32.85	33.21	33.32	33.12	0.64
7.000	37.10	38.57	39.49	38.07	38.43	38.66	38.39	0.79
8.000	41.65	43.04	44.37	42.68	43.03	43.36	43.02	0.89
9.000	45.90	47.07	48.57	46.86	47.15	47.53	47.18	0.87
10.000	49.79	50.83	52.43	50.71	50.97	51.37	51.02	0.87
11.000	53.19	54.17	55.63	54.05	54.29	54.66	54.33	0.80
12.000	56.41	57.16	58.63	57.15	57.34	57.71	57.40	0.74
13.000	59.37	60.05	61.54	60.08	60.25	60.63	60.32	0.72
14.000	61.99	62.76	63.74	62.62	62.81	63.06	62.83	0.57
15.000	64.35	65.18	65.72	64.90	65.11	65.24	65.08	0.45
16.000	66.74	67.64	67.85	67.24	67.47	67.52	67.41	0.38
17.000	68.80	69.87	69.92	69.35	69.62	69.63	69.53	0.41
18.000	70.38	71.39	71.17	70.83	71.08	71.03	70.98	0.35
19.000	71.53	72.70	72.43	72.05	72.34	72.27	72.22	0.40
20.000	72.73	73.75	73.55	73.19	73.45	73.40	73.34	0.35
21.000	73.43	74.74	74.21	73.95	74.28	74.15	74.13	0.43
22.000	74.04	75.45	74.84	74.59	74.95	74.79	74.78	0.46
23.000	74.29	75.78	74.90	74.82	75.19	74.97	74.99	0.49
24.000	75.05	76.79	75.41	75.58	76.01	75.67	75.75	0.60

Table A36. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 900 kg.

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
0.000	0.05	0.06	0.06	0.04	0.06	0.07	0.06	0.01
0.083	0.20	0.21	0.20	0.17	0.20	0.24	0.20	0.02
0.167	0.36	0.38	0.36	0.34	0.35	0.41	0.37	0.02
0.250	0.57	0.59	0.57	0.54	0.54	0.64	0.57	0.04
0.333	0.82	0.85	0.81	0.79	0.75	0.93	0.82	0.06
0.417	1.10	1.14	1.09	1.07	1.02	1.23	1.11	0.07
0.500	1.43	1.48	1.41	1.39	1.31	1.61	1.44	0.10
0.667	2.18	2.26	2.13	2.14	1.95	2.48	2.19	0.18
0.833	2.99	3.07	2.90	2.98	2.65	3.33	2.99	0.22
1.000	3.85	3.94	3.73	3.89	3.40	4.23	3.84	0.27
1.250	5.23	5.31	5.05	5.33	4.60	5.66	5.20	0.35
1.500	6.65	6.72	6.40	6.83	5.84	7.10	6.59	0.43
1.750	8.06	8.13	7.77	8.29	7.11	8.55	7.98	0.50
2.000	9.49	9.56	9.19	9.72	8.53	9.99	9.41	0.51
2.250	10.91	11.00	10.62	11.12	9.94	11.46	10.84	0.52
2.500	12.32	12.41	12.02	12.52	11.33	12.90	12.25	0.53
2.750	13.77	13.87	13.45	13.99	12.71	14.38	13.69	0.57
3.000	15.20	15.30	14.84	15.47	14.03	15.84	15.11	0.62
3.500	18.01	18.12	17.62	18.28	16.74	18.72	17.91	0.68
4.000	20.81	20.94	20.42	21.06	19.50	21.60	20.72	0.71
4.500	23.52	23.68	23.05	23.83	21.94	24.47	23.41	0.86

Table A36. %Drug dissolved of indomethacin from formulation containing HPMC 37% and lactose : microcrystalline cellulose ratio of 10:30 at compression force 900 kg. (cont.)

Time(hrs)	Tablet No.						Average	SD
	1	2	3	4	5	6		
5.000	26.19	26.37	25.62	26.59	24.28	27.31	26.06	1.03
5.500	28.81	29.01	28.12	29.30	26.54	30.10	28.65	1.22
6.000	31.53	31.69	30.66	32.25	28.76	32.87	31.29	1.44
7.000	36.58	36.77	35.51	37.46	33.19	38.21	36.29	1.77
8.000	41.13	41.41	40.08	41.89	37.70	43.02	40.87	1.83
9.000	45.55	45.76	44.37	46.50	41.81	47.37	45.23	1.95
10.000	49.58	49.75	48.26	50.74	45.44	51.41	49.20	2.13
11.000	53.26	53.37	51.80	54.61	48.77	55.05	52.81	2.29
12.000	56.73	56.78	55.13	58.29	51.88	58.47	56.21	2.45
13.000	59.90	59.87	58.22	61.60	54.89	61.49	59.33	2.51
14.000	62.74	62.68	61.05	64.50	57.72	64.25	62.16	2.51
15.000	65.41	65.29	63.66	67.27	60.29	66.80	64.79	2.54
16.000	67.97	67.78	66.23	69.91	62.93	69.13	67.32	2.49
17.000	70.31	70.11	68.59	72.22	65.36	71.43	69.67	2.45
18.000	72.30	72.11	70.74	74.06	67.81	73.28	71.72	2.22
19.000	73.86	73.58	72.41	75.57	69.80	74.48	73.28	2.00
20.000	75.24	74.95	73.81	76.95	71.24	75.80	74.66	1.97
21.000	76.36	76.06	75.03	77.98	72.68	76.79	75.82	1.81
22.000	77.19	76.94	75.86	78.78	73.44	77.77	76.66	1.85
23.000	77.56	77.29	76.24	79.15	73.88	78.06	77.03	1.81
24.000	78.43	78.17	77.23	79.89	75.08	78.85	77.94	1.65

ANOVA AND MULTIPLE COMPARISON TABLES

Table B1. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 1 hr.

Source	DF	SS	MS	F	P
Compression force	2	8.20	4.10	6.46	0.003
HPMC:lactose ratio	3	4939.46	1646.49	2591.38	0.000
Interaction	6	52.19	8.70	13.69	0.000
Error	60	38.12	0.64		
Total	71	5037.98			

Table B2. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 1 hr.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	0.3379	0.2301	1.469	0.3132
	900	0.8225	0.2301	3.574	0.0020
600	900	0.4846	0.2301	2.106	0.0972

Table B3. Multiple comparison of HPMC : lactose ratio for %Drug dissolved of indomethacin matrix tablets at 1 hr.

HPMC:lactose ratio	HPMC:lactose ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	-16.7200	0.2657	-62.94	0.0000
	57:20	-19.6300	0.2657	-73.88	0.0000
	77: 0	-20.2800	0.2657	-76.32	0.0000
37:40	57:20	-2.9060	0.2657	-10.94	0.0000
	77: 0	-3.5530	0.2657	-13.37	0.0000
57:20	77: 0	-0.6478	0.2657	-2.438	0.0808

Table B4. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 6 hrs.

Source	DF	SS	MS	F	P
Compression force	2	1.5	0.7	0.14	0.868
HPMC:lactose ratio	3	12544.0	4181.3	810.70	0.000
Interaction	6	36.7	6.1	1.19	0.326
Error	60	309.5	5.2		
Total	71	12891.6			

Table B5. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 6 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	0.2233	0.6556	0.3407	0.9381
	900	-0.1217	0.6556	-0.1856	0.9812
600	900	-0.3450	0.6556	-0.5262	0.8588

Table B6. Multiple comparison of HPMC : lactose ratio for %Drug dissolved of indomethacin matrix tablets at 6 hrs.

HPMC:lactose ratio	HPMC:lactose ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	-15.49	0.7570	-20.460	0.0000
	57:20	-28.16	0.7570	-37.200	0.0000
	77: 0	-34.52	0.7570	-45.600	0.0000
37:40	57:20	-12.67	0.7570	-16.740	0.0000
	77: 0	-19.03	0.7570	-25.140	0.0000
57:20	77: 0	-6.360	0.7570	-8.401	0.0000

Table B7. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 12 hrs.

Source	DF	SS	MS	F	P
Compression force	2	2.47	1.23	0.15	0.858
HPMC:lactose ratio	3	3425.34	1141.78	142.19	0.000
Interaction	6	100.04	16.67	2.08	0.069
Error	60	481.80	8.03		
Total	71	4009.64			

Table B8. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 12 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-0.3433	0.8180	-0.4197	0.9076
	900	0.0850	0.8180	0.1039	0.9941
600	900	0.4283	0.8180	0.5236	0.8601

Table B9. Multiple comparison of HPMC : lactose ratio for %Drug dissolved of indomethacin matrix tablets at 12 hrs.

HPMC:lactose ratio	HPMC:lactose ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	2.510	0.9446	2.65	0.0488
	57:20	-7.920	0.9446	-8.38	0.0000
	77: 0	-15.030	0.9446	-15.91	0.0000
37:40	57:20	-10.420	0.9446	-11.03	0.0000
	77: 0	-17.530	0.9446	-18.56	0.0000
57:20	77: 0	-7.108	0.9446	-7.525	0.0000

Table B10. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 24 hrs.

Source	DF	SS	MS	F	P
Compression force	2	9.62	4.81	1.01	0.369
HPMC:lactose ratio	3	1858.75	619.58	130.48	0.000
Interaction	6	238.75	39.79	8.38	0.000
Error	60	284.90	4.75		
Total	71	2392.01			

Table B11. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : lactose ratio at 24 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-0.5696	0.6290	-0.9055	0.6390
	900	0.3133	0.6290	0.4981	0.8725
600	900	0.8829	0.6290	1.4040	0.3455

Table B12. Multiple comparison of HPMC : lactose ratio for %Drug dissolved of indomethacin matrix tablets at 24 hrs.

HPMC:lactose ratio	HPMC:lactose ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	11.37000	0.7264	15.65000	0.0000
	57:20	11.42000	0.7264	15.73000	0.0000
	77: 0	12.32000	0.7264	16.96000	0.0000
37:40	57:20	0.05722	0.7264	0.07878	0.9998
	77: 0	0.94944	0.7264	1.30714	0.5621
57:20	77: 0	0.89220	0.7264	1.22800	0.6115

Table B13. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 1 hr.

Source	DF	SS	MS	F	P
Compression force	2	217.862	108.931	30.87	0.000
HPMC:MCC ratio	3	468.022	156.007	44.22	0.000
Interaction	6	367.566	61.261	17.36	0.000
Error	60	211.695	3.528		
Total	71	1265.146			

Table B14. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 1 hr.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-1.4040	0.2104	-6.670	0.0000
	900	-1.6740	0.2104	-7.955	0.0000
600	900	-0.2704	0.2104	-1.285	0.4091

Table B15. Multiple comparison of HPMC : microcrystalline cellulose (MCC) ratio for %Drug dissolved of indomethacin matrix tablets at 1 hr.

HPMC:MCC ratio	HPMC:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	-3.8190	0.2430	-15.7200	0.0000
	57:20	-5.4690	0.2430	-22.5100	0.0000
	77: 0	-5.6530	0.2430	-23.2600	0.0000
37:40	57:20	-1.6500	0.2430	-6.7900	0.0000
	77: 0	-1.8340	0.2430	-7.5490	0.0000
57:20	77: 0	-0.1844	0.2430	-0.7590	0.8724

Table B16. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 6 hrs.

Source	DF	SS	MS	F	P
Compression force	2	411.57	205.78	38.41	0.000
HPMC:MCC ratio	3	273.76	91.25	17.03	0.000
Interaction	6	936.43	156.07	29.13	0.000
Error	60	321.44	5.36		
Total	71	1943.20			

Table B17. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 6 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-5.762	0.6682	-8.624	0.0000
	900	-3.788	0.6682	-5.669	0.0000
600	900	1.975	0.6682	2.955	0.0122

Table B18. Multiple comparison of HPMC : microcrystalline cellulose (MCC) ratio for %Drug dissolved of indomethacin matrix tablets at 6 hrs.

HPMC:MCC ratio	HPMC:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	2.823	0.7715	3.659	0.0029
	57:20	-1.179	0.7715	-1.529	0.4270
	77: 0	-2.452	0.7715	-3.178	0.0122
37:40	57:20	-4.002	0.7715	-5.187	0.0000
	77: 0	-5.275	0.7715	-6.837	0.0000
57:20	77: 0	-1.273	0.7715	-1.650	0.3592

Table B19. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 12 hrs.

Source	DF	SS	MS	F	P
Compression force	2	17.302	8.651	1.77	0.180
HPMC:MCC ratio	3	440.059	146.686	29.96	0.000
Interaction	6	110.891	18.482	3.78	0.003
Error	60	293.733	4.896		
Total	71	861.985			

Table B20. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 12 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-0.7184	0.6387	-1.125	0.5027
	900	0.4740	0.6387	0.742	0.7395
600	900	1.1920	0.6387	1.867	0.1572

Table B21. Multiple comparison of HPMC : microcrystalline cellulose (MCC) ratio for %Drug dissolved of indomethacin matrix tablets at 12 hrs.

HPMC:MCC ratio	HPMC:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	-2.460	0.7375	-3.335	0.0078
	57:20	-6.308	0.7375	-8.553	0.0000
	77: 0	-5.297	0.7375	-7.182	0.0000
37:40	57:20	-3.849	0.7375	-5.218	0.0000
	77: 0	-2.837	0.7375	-3.847	0.0016
57:20	77: 0	1.011	0.7375	1.371	0.5223

Table B22. ANOVA of %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 24 hrs.

Source	DF	SS	MS	F	P
Compression force	2	191.85	95.92	36.32	0.000
HPMC:MCC ratio	3	2119.54	706.51	267.49	0.000
Interaction	6	35.41	5.90	2.23	0.052
Error	60	158.47	2.64		
Total	71	2505.27			

Table B23. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various HPMC : microcrystalline cellulose (MCC) ratio at 24 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	0.4848	0.4692	1.033	0.5590
	900	3.6796	0.4692	7.843	0.0000
600	900	3.1950	0.4692	6.810	0.0000

Table B24. Multiple comparison of HPMC : microcrystalline cellulose (MCC) ratio for %Drug dissolved of indomethacin matrix tablets at 24 hrs.

HPMC:MCC ratio	HPMC:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	1.773	0.5417	3.273	0.0093
	57:20	4.816	0.5417	8.889	0.0000
	77: 0	14.078	0.5417	25.988	0.0000
37:40	57:20	3.042	0.5417	5.616	0.0000
	77: 0	12.305	0.5417	22.715	0.0000
57:20	77: 0	9.263	0.5417	17.100	0.0000

Table B25. ANOVA of %Drug dissolved of indomethacin matrix tablets containing HPMC 37% and various lactose : microcrystalline cellulose (MCC) ratios at 1 hr.

Source	DF	SS	MS	F	P
Compression force	2	42.3036	21.1518	186.68	0.000
HPMC:MCC ratio	4	47.1228	11.7807	103.98	0.000
Interaction	8	3.4232	0.4279	3.78	0.001
Error	75	8.4977	0.1133		
Total	89	101.3473			

Table B26. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various lactose : microcrystalline cellulose (MCC) ratios at 1 hr.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-1.47900	0.08691	-17.0200	0.0000
	900	-1.42800	0.08691	-16.4300	0.0000
600	900	0.05129	0.08691	0.5902	0.8258

Table B27. Multiple comparison of lactose : microcrystalline cellulose (MCC) ratios for %Drug dissolved of indomethacin matrix tablets at 1 hr.

Lactose:MCC ratio	Lactose:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
40: 0	30:10	0.7890	0.1122	7.030	0.0000
	20:20	0.6910	0.1122	6.160	0.0000
	10:30	1.6883	0.1122	15.047	0.0000
	0:40	-2.0050	0.1122	-17.870	0.0000
30:10	20:20	-0.0980	0.1122	-0.870	0.9065
	10:30	0.8994	0.1122	8.016	0.0000
	0:40	-1.2160	0.1122	-10.840	0.0000
20:20	10:30	0.9972	0.1122	8.888	0.0000
	0:40	-1.3140	0.1122	-11.710	0.0000
10:30	0:40	-0.3167	0.1122	-2.823	0.0466

Table B28. ANOVA of %Drug dissolved of indomethacin matrix tablets containing HPMC 37% and various lactose : microcrystalline cellulose (MCC) ratios at 6 hrs.

Source	DF	SS	MS	F	P
Compression force	2	207.46	103.73	19.38	0.000
HPMC:MCC ratio	4	2532.51	633.13	118.30	0.000
Interaction	8	247.53	30.94	5.78	0.000
Error	75	401.40	5.35		
Total	89	3388.89			

Table B29. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various lactose : microcrystalline cellulose (MCC) ratios at 6 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-3.715	0.5973	-6.219	0.0000
	900	-1.708	0.5973	-2.859	0.0150
600	900	2.007	0.5973	3.360	0.0035

Table B30. Multiple comparison of lactose : microcrystalline cellulose (MCC) ratios for %Drug dissolved of indomethacin matrix tablets at 6 hrs.

Lactose:MCC ratio	Lactose:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
40: 0	30:10	7.5240	0.7711	9.757	0.0000
	20:20	8.9910	0.7711	11.659	0.0000
	10:30	13.8821	0.7711	18.002	0.0000
	0:40	-14.8000	0.7711	-19.200	0.0000
30:10	20:20	1.4670	0.7711	1.902	0.3253
	10:30	6.3578	0.7711	8.245	0.0000
	0:40	-7.2800	0.7711	-9.441	0.0000
20:20	10:30	4.8911	0.7711	6.343	0.0000
	0:40	-5.8130	0.7711	-7.539	0.0000
10:30	0:40	-0.9223	0.7711	-1.196	0.7536

Table B31. ANOVA of %Drug dissolved of indomethacin matrix tablets containing HPMC 37% and various lactose : microcrystalline cellulose (MCC) ratios at 12 hrs.

Source	DF	SS	MS	F	P
Compression force	2	273.82	136.91	37.84	0.000
HPMC:MCC ratio	4	3954.31	988.58	273.23	0.000
Interaction	8	275.12	34.39	9.50	0.000
Error	75	271.36	3.62		
Total	89	4774.61			

Table B32. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various lactose : microcrystalline cellulose (MCC) ratios at 12 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-2.318	0.4911	-4.720	0.0000
	900	1.949	0.4911	3.969	0.0005
600	900	4.267	0.4911	8.689	0.0000

Table B33. Multiple comparison of lactose : microcrystalline cellulose (MCC) ratios for %Drug dissolved of indomethacin matrix tablets at 12 hrs.

Lactose:MCC ratio	Lactose:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
40: 0	30:10	6.8300	0.6340	10.770	0.0000
	20:20	10.9720	0.6340	17.304	0.0000
	10:30	17.8349	0.6340	28.129	0.0000
	0:40	-16.9700	0.6340	-26.770	0.0000
30:10	20:20	4.1450	0.6340	6.537	0.0000
	10:30	11.0083	0.6340	17.362	0.0000
	0:40	-10.1500	0.6340	-16.010	0.0000
20:20	10:30	6.8633	0.6340	10.825	0.0000
	0:40	-6.0030	0.6340	-9.468	0.0000
10:30	0:40	0.8603	0.6340	1.357	0.6568

Table B34. ANOVA of %Drug dissolved of indomethacin matrix tablets containing HPMC 37% and various lactose : microcrystalline cellulose (MCC) ratios at 24 hrs.

Source	DF	SS	MS	F	P
Compression force	2	1309.80	654.90	168.28	0.000
HPMC:MCC ratio	4	2979.56	744.89	191.41	0.000
Interaction	8	435.86	54.48	14.00	0.000
Error	75	291.87	3.89		
Total	89	5017.09			

Table B35. Multiple comparison of compression force for %Drug dissolved of indomethacin matrix tablets containing various lactose : microcrystalline cellulose (MCC) ratios at 24 hrs.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-1.407	0.5094	-2.761	0.0196
	900	7.297	0.5094	14.326	0.0000
600	900	8.704	0.5094	17.090	0.0000

Table B36. Multiple comparison of lactose : microcrystalline cellulose (MCC) ratios for %Drug dissolved of indomethacin matrix tablets at 24 hrs.

Lactose:MCC ratio	Lactose:MCC ratio	Difference of Mean	SE of difference	T-Value	P-Value
40: 0	30:10	12.342	0.6576	18.769	0.0000
	20:20	10.888	0.6576	16.558	0.0000
	10:30	16.727	0.6576	25.437	0.0000
	0:40	-14.170	0.6576	-21.550	0.0000
30:10	20:20	-1.454	0.6576	-2.211	0.1870
	10:30	4.385	0.6576	6.668	0.0000
	0:40	-1.831	0.6576	-2.785	0.0514
20:20	10:30	5.839	0.6576	8.879	0.0000
	0:40	-3.285	0.6576	-4.996	0.0000
10:30	0:40	2.554	0.6576	3.884	0.0020

Table B37. ANOVA of the apparent rate constant (k_2) of indomethacin matrix tablets from Hixson-Crowell Cube Root Kinetics Equation.

Source	DF	SS	MS	F	P
Compression force	2	0.0000026	0.0000013	0.25	0.779
HPMC: Excipient ratio	2	0.0032227	0.0016113	308.87	0.000
Type of excipient	1	0.0059811	0.0059811	1146.48	0.000
Compression force × HPMC:MCC ratio	4	0.0000905	0.0000226	4.34	0.003
Compression force × Type of excipient	2	0.0000702	0.0000351	6.73	0.002
HPMC:Excipient ratio × Type of excipient	2	0.0024292	0.0012146	232.82	0.000
Compression force × HPMC:MCC ratio × Type of excipient	4	0.0000334	0.0000083	1.60	0.181
Error	90	0.0004695	0.0000052		
Total	107	0.0122993			

Table B38. Multiple comparison of compression forces for the apparent rate constant (k_2) of indomethacin matrix tablets.

Compression force	Compression force	Difference of Mean	SE of difference	T-Value	P-Value
300	600	-0.000366	0.000538	-0.6803	0.7756
	900	-0.000091	0.000538	-0.1685	0.9845
600	900	0.000276	0.000538	0.5118	0.8658

Table B39. Multiple comparison of HPMC : excipient ratio for the apparent rate constant (k_2) of indomethacin matrix tablets.

HPMC:Excipient ratio	HPMC:Excipient ratio	Difference of Mean	SE of difference	T-Value	P-Value
17:60	37:40	-0.008830	0.000538	-16.400	0.0000
	57:20	-0.013120	0.000538	-24.370	0.0000
37:40	57:20	-0.004294	0.000538	-7.976	0.0000

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