KINETIC RELEASE OF TRAMADOL HYDROCHLORIDE FROM HYDROPHILIC SWELLABLE MATRICES CONTAINING TWO DIFFERENT DIRECTLY COMPRESSIBLE FILLERS

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HOUSEHOLD FOOD SECURITY AND NUTRITIONAL STATUS OF 1-5 YEARS AGED CHILDREN IN DHADING DISTRICT, NEPAL

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ABSTRACT

The effects of mass fractions (mf) and types of polymer on the release kinetics of tramadol HCl (TMH) from hydrophilic swellable matrices were studied. Each formulation of the 500 mg tablet contains 200 mg TMH at a fixed mf of 0.40, polymer, i.e., hydroxypropylmethylcellulose (HPMC) K4M, K15M, xanthan gum (XG) or guar gum (GG) at an mf of 0.15, 0.30, 0.45 and 0.60, respectively, and dibasic calcium phosphate dihydrate (DCPD) or spray dried lactose (SDL) as a direct compression filler. Percentage drug release (Q_i) was carried out in an USP dissolution apparatus type II in distilled water at various times (t) from 0 – 24 h. Q_i of all formulations and the square root of time was shown to have a good linear relationship with a high regression constant that indicated that the drug release from the matrix tablets followed the Higuchi model of diffusion. The results showed that the type and mf of polymer and also the type of filler that could affect the rate constant (k), natural convection (Q_0) and the lag time of TMH from matrix tablets. For various polymers used, XG provided the best retardability for drug release at all mf. For different fillers used, insoluble DCPD showed better retardability than SDL. The kinetics of TMH release from matrix tablets, using insoluble DCPD, was described by Shah et al model of diffusion, whereas those from matrices using soluble SDL was described by Jateleela et al model. From the calculation, using proposed equations in both models, most of the observed release profiles were closely fitted the predicted release profiles. Furthermore, the mechanisms of TMH transport from matrix tablets were described by the transport equation of Korsmeyer and Peppas. Matrices using GG provided quasi-Fickian diffusion, whereas most matrices using HPMC K4M or K15M provided non-Fickian transport, except matrices containing 0.15 either HPMC provided quasi-Fickian diffusion. For matrices using XG, the mf of XG, which changed the quasi-Fickian diffusion to non-Fickian transport was 0.60 XG for matrices containing DCPD and 0.45 XG for those containing SDL, respectively.

KEY WORDS: HYDROPHILIC SWELLABLE MATRIX/ TRAMADOL HYDROCHLORIDE/ HPMC K4M/ HPMC K15M/ XANTHAN GUM

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การปลดปล่อยเชิงจลนศาสตร์ของยาทรามาดอลไฮโดรคลอไรด์จากเมทริกซ์พองตัวชอบน้ำ ซึ่งประกอบด้วยสารช่วยตอกตรงสองชนิดที่แตกต่างกัน

KINETIC RELEASE OF TRAMADOL HYDROCHLORIDE FROM HYDROPHILIC SWELLABLE MATRICES CONTAINING TWO DIFFERENT DIRECTLY COMPRESSIBLE FILLERS

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บทคัดย่อ

ศึกษาผลของเศษส่วนมวลและชนิดของพอลิเมอร์ต่อจลนศาสตร์การปลดปล่อยยาทรามาดอลไฮโดรคลอไรด์ (TMH) แต่ละสูตรตำรับหนัก 500 มิลลิกรัม ประกอบด้วยตัวยา 200 มิลลิกรัม มีเศษส่วนมวลคงที่ที่ 0.4 พอลิเมอร์ที่ใช้ คือ ไฮดรอกซีโพรพิลเมธิลเซลลูโลส เค 4 เอ็ม (HPMC K4M), เค 15 เอ็ม (HPMC K15M), แซนแธนกัม (XG) หรือ กัวกัม (GG) ที่เศษส่วนมวล 0.15, 0.30, 0.45 และ 0.60 ตามลำดับ และสารช่วยตอกตรงคือไดเบสิกแคลเซียมฟอสเฟตไดไฮเดรต (DCPD) หรือ สเปรย์ดรายด์แลกโตส (SDL) การศึกษาปริมาณการปลดปล่อยตัวยาเป็นร้อยละ (Q_i) ที่เวลาต่างๆ ได้ดำเนินการโดยเครื่องมือทดสอบการละลายของ USP แบบที่ 2 โดยใช้น้ำกลั่นเป็นตัวทำละลาย ที่เวลา t ตั้งแต่ 0 – 24 ชั่วโมง ผลการทดลองพบว่า Q_i ของทุกตำรับและรากที่สองของเวลามีความสัมพันธ์เชิงเส้นตรงที่ดีพร้อมค่าสัมประสิทธิ์การถดถอยที่สูง ซึ่งแสดงให้เห็นว่าการปลดปล่อยยาจากเมทริกซ์เป็นไปตามแม่แบบการปลดปล่อยของฮิกูชิ ค่าคงที่การปลดปล่อยยาของทุกตำรับเป็นตัวแปรในการประเมินผลโดยการวิเคราะห์ทางสถิติ พบว่าชนิดและเศษส่วนมวลของพอลิเมอร์ และชนิดสารช่วยตอกตรงมีผลต่อค่าคงที่ของอัตราการปลดปล่อยยา (k) ปริมาณปลดปล่อยยาที่เวลาศูนย์ (Q_0) และเวลาหน่วงก่อนการปลดปล่อยยา ตำรับเมทริกซ์ที่ใช้แซนแธนกัมเป็นพอลิเมอร์แสดงการหน่วงการปลดปล่อยมากที่สุดที่ทุกเศษส่วนมวล สำหรับสารช่วยตอกที่ไม่ละลายน้ำ DCPD จะแสดงการหน่วงการปลดปล่อยยาได้มากกว่า SDL การปลดปล่อยเชิงจลนศาสตร์ของ TMH อธิบายโดยใช้สมการแม่แบบของชาร์และคณะสำหรับตำรับที่ใช้ DCPD เป็นสารช่วยตอกตรง และใช้สมการแม่แบบของเจตลีลาและคณะสำหรับตำรับที่ใช้ SDL เป็นสารช่วยตอกตรง พบว่าสมการแม่แบบดังกล่าวได้ผลเป็นที่น่าพอใจในการทำนายการปลดปล่อย TMH ที่ช่วงเวลาต่างๆ จากเมทริกซ์ที่ประกอบด้วยพอลิเมอร์ต่างชนิดที่เศษส่วนมวลต่างกัน ส่วนกลไกการทรานสปอร์ตของยานั้น เมทริกซ์ที่ใช้ GG จะเป็น quasi-Fickian diffusion เมทริกซ์ที่ใช้ HPMC จะให้ non-Fickian transport ยกเว้นที่เศษส่วนมวลต่ำสุดจะให้ quasi-Fickian diffusion ส่วนเมทริกซ์ที่ใช้ XG นั้น เศษส่วนมวลที่ทำให้กลไกแบบ quasi-Fickian diffusion เป็น non-Fickian transport คือ 0.60 XG เมื่อใช้ DCPD และ 0.45 XG เมื่อใช้ SDL ตามลำดับ

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LIST OF ABBREVIATIONS

%	percent
μg/mL	microgram per milliliter
ANOVA	analysis of variance
cm	centimeter
DCPD	dibasic calcium phosphate dihydrate
e.g.	exempli gratia, for example
Eq	equation
et al.	et alii, and others
GG	guar gum
g	gram
h	hour
HPMC	hydroxypropylmethylcellulose
i.e.	id est, in other words or that is
kg	kilogram
LSD	least significant difference procedure
mf	mass fraction
mg	milligram
min	minute
mL	milliliter
mm	millimeter
nm	nanometer
°C	degree Celsius
pH	the negative logarithm of the hydrogen ion concentration
R^2	coefficient of determination
rpm	revolution per minute
SD	standard deviation
SDL	spray dried lactose

LIST OF ABBREVIATIONS (cont.)

TMH	tramadol hydrochloride
USP	The United States Pharmacopeia
UV	ultraviolet
XG	xanthan gum

CHAPTER I
INTRODUCTION

Tramadol hydrochloride (TMH), a synthetic opioid of the aminocyclohexanol group, which is used in the treatment of chronic pain, including low back pain, cancer pain, painful diabetic neuropathy, polyneuropathy and fibromalgia. It has also been effective in the treatment of osteoarthritis when NSAIDs or COX-2 inhibitors alone produce inadequate pain relief. It is a centrally acting analgesic with weak opioid agonist properties without causing serious cardiovascular or respiratory side effect at therapeutic dose (1). The drug is freely soluble in water and its half-life is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 400 mg/day. Oral route is the most common route of drug administration due to reduce in dosing frequency while maintaining the analgesic effect or improve in patient compliance (2), a sustained release formulation of TMH is required. One of the most commonly used methods of modulating the drug release is to include it in a matrix system (3). There are main obstacles which should be considered when the new dosage form of this drug is formulated.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. Controlled release formulations are usually designed to achieve similar exposure the area under the plasma drug concentration-time curve (AUC) levels as the marketed immediate release formulations (4). Drug release is dependent on polymer properties, thus the application of these properties can produce well characterized and reproducible dosage forms (5). Amongst sustain release formulations, hydrophilic matrix system is the most widely used to control the rate of drug release because of its simplicity, ease in manufacturing, high drug loading and cost effectiveness (6). A hydrophilic matrix tablet consists of mixture of drug, hydrophilic polymer and excipients prepared by common tableting equipment (7).

There are various types of the hydrophilic polymer, i.e., synthetic polymer, semisynthetic polymer and natural polymer. In the recent period, there is increased interest also in natural polymeric substances e.g., alginate, carrageenan, arabic gum, pectin and xanthan gum. Whose advantage consists in safety, easy availability, and a relatively low price (8). The drug release rate from hydrophilic matrix tablets is determined by several properties, such as the composition of a formulation, the manner of production, the properties of the drug itself and the properties of the polymer in the matrix, where molecular weight, hydrophilicity, degree of cross linking, degree of substitution, etc, are all polymer parameters known to influence the swelling and erosion of the matrices (9). The mechanism of drug release from swellable matrix tablets may be affected by many factors such as polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, drug distribution inside the matrix and drug/polymer ratio (10). Several mathematical models are used to predict drug release in matrix system. The most famous and the most often used model to describe drug release from a matrix system is the one proposed by Higuchi in 1961. Higuchi described the cumulative amount of drug released is proportional to the square root of time in the early time approximation. This model is based on the hypotheses that an initial drug concentration in the matrix is much higher than drug solubility, the diffusivity is constant, there are no swelling and erosion of the matrix and perfect sink conditions are always attained in the release environment (11, 12). Beside this equation, A hydrophilic matrix, the mechanisms which drug released are complex and involve the simultaneous absorption of water and desorption of drug. It has been reported that the mechanisms occurring in drug release include drug diffusion through the swelling gel layer and device erosion of the swollen gel layer. To account for these dual release mechanism, Peppas and Krosmeyer proposed the use of a semi-empirical model built by the sum of two different power of time, accounting for the pure diffusivity phenomenon (the so-called Fickian’s term) and for another contribution to the release kinetics, due to the relaxation of the polymer molecules (the so-called non-Fickian or case-II “relaxation” term) (11-13). Shah et al. developed a working equation to predict drug release from hydroxypropylmethylcellulose (HPMC) matrices containing different polymer concentrations and assumed that: (i) drug release can be approximately modeled using the square root of time relation; (ii) the apparent diffusion coefficient of drug in the rubbery region is related to the tortuosity of the swelling layer; (iii) the tortuosity of the swelling layer depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration in the matrix and; (iv) the porosity of the swelling layer is constant (14, 15).

Jateleela et al. recently developed the new diffusion model from Shah et al. equation to predict the drug release from HPMC containing different mass fraction and using spray dried lactose as a soluble filler. This model is based on: (i) drug release can be approximately modeled using square root of time relation; (ii) the apparent diffusivity of drug in the rubbery region is related to the porosity and the tortuosity of the swelling layer; (iii) the porosity is directly proportional to the volume fraction of water soluble solutes in matrix, which is related to (1 – polymer mass fraction)/apparent density of mixed solute compact and (iv) the tortuosity depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration (16).

The purpose of this study is to characterize the kinetic release of TMH from hydrophilic swellable matrix tablets containing four types of polymers namely hydroxypropylmethycellulose (HPMC) K4M, HPMC K15M, xanthan gum (XG) and guar gum (GG) with two different directly compressible fillers, dibasic calcium phosphate dihydrate (DCPD) and spray-dried lactose (SDL). In addition, the effect of these both fillers on the release kinetics of TMH from matrices containing such polymers was determined. Subsequently, various once-daily doses were mathematically constructed from these release kinetic models for TMH matrices containing the most suitable polymer along with each filler.

CHAPTER II
OBJECTIVES

The objectives of this study were as follows:

2.1 To investigate the effect of mass fraction, different polymers and two different fillers on tramadol hydrochloride (TMH) release from hydrophilic swellable matrices.

2.2 To describe the drug release characteristics from TMH matrices containing different polymers and two different fillers using the following diffusion models of Higuchi, Shah et al., and Jateleela et al. along with transport model of Korsmeyer-Peppas.

2.3 To mathematically construct the once-daily dose controlled release TMH matrices using appropriate hydrophilic swellable polymers and direct compression fillers.

CHAPTER III
LITERATURE REVIEW

3.1 Oral Controlled Release Systems

Oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised (19). Controlled realease system oral drug delivery system has been shown to offer advantages over conventional systems. These include reduced dosing frequency, dose reduction, improved patient compliance, constant level of drug concentration in blood plasma, reduced toxicity due to overdose, reduces the fluctuation of peak valley concentration and night time dosing can be avoided (20). Sustained release systems are considered a wiser approach for the drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration (21). Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release as follows: (i) dissolution and/or diffusion, (ii) ion exchange resin, and (iii) osmotic system (22-24).

Dissolution - controlled release can be obtained by slowing the dissolution rate of a drug in the gastrointestinal tract medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by Eq. (1).

$$dm/dt = ADS/h \qquad \text{Eq. (1)}$$

In eq. (1), S is the aqueous solubility of the drug, A is the surface area of the dissolving particle or tablet, D is the diffusivity of the drug, and h is the thickness of the boundary layer.

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. The diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution – controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion-controlled device, the rate of drug released (dm/dt) can be calculated uing Eq. (2).

$$dm/dt = ADK(\Delta C)/l \qquad \text{Eq. (2)}$$

In Eq. (2), A is the area, D is the diffusion coefficient, K is the partition coefficient of the drug between the drug core and the membrane, l is the diffusional path length, and ΔC is the concentration difference across the membrane. In order to achieve a constant release rate, all of the terms on the right side of Eq. (2) must be held constant. It is very common for diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug-resin complex is formed by prolonged exposure of drug to the resin

The last release mechanism is osmotic system, to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser-drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Therefore, the rate of drug delivered from the system is dependent on the osmotic pressure of the formulation (π_s) as shown in Eq. 3.

$$dm/dt = A(k\pi_s S)/h \qquad \text{Eq. (3)}$$

where A is the membrane area, k is the membrane permeability, and h is the membrane thickness (23).

3.2 Matrix system

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms. In actual practice direct compression of drug, retardant material, additives is done to form a tablet in which drug particles are embedded in the matrix core of the retardant. Among the different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity now a days because it has the advantage of simple processing and a low cost of fabrication. The loading dose is most convenient to include in separate layer or in a coating applied to the tablet. Sustained release matrix tablet can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives, and another one involves granulation prior to compression (25). Release of a freely soluble drug can be retarded using an appropriate combinations of hydrophilic and hydrophobic polymers matrices (26-27).

Hydrophilic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug releases by dissolution, diffusion and/or erosion.

Hydrophobic matrix systems are founded by waxes mainly and can be suitable for drugs which have a high solubility (19).

3.3 Release Mechanism of Hydrophilic Matrix

The mechanism of drug release from hydrophilic matrix tablets may be affected by many factors such as polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, drug distribution inside the matrix and drug/polymer ratio (10). After oral administration, on contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer via diffusion or erosion of the gel eventually allowing drug to be released (19). This hydration, due to the increase in size of the polymer molecules as a consequence of the entry of solvent (a relaxation of the polymer chains), leads to the formation of a zone in which the polymer passes from the crystalline state to a “rubbery” state known a gel layer. Several transport phenomena take place through this gel layer: the entry of the aqueous medium and the exit of the drug to the outside of the system, and phenomena of matrix erosion (7, 10-12, 28).

The initial hydration of the polymeric molecule is a viscous gel layer formation, causing an increased in the volume of the matrix, referred as swelling, As time progresses and more and more water enters the system, polymeric molecular chain gets uncoiled due to hydration, weaker the gel becomes on the outer region of the gel structure. When the entire polymeric molecule is uncoiled, referred as relaxation, it finally disentangles from the surface of the matrix, referred as erosion or dissolution (7).

Three main fronts appear during the drug release process are represented of polymer swelling/erosion and drug delivery from matrix systems (7, 10-12, 28)

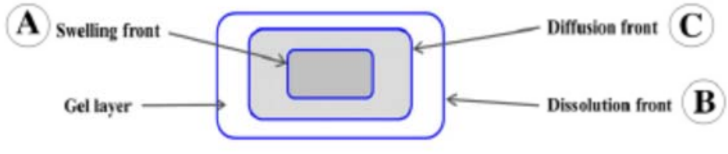


Figure 3.1 Schematic of the hydrophilic matrix after entry of the dissolution medium (7)

A. The swelling front: When contact with water, the polymer passes from the glassy state to a rubbery state.

B. The erosion front or dissolution front: This front separates the release environment from the matrix.

C. The diffusion front: This is located between the swelling front and erosion front and it separates the zone of the gelified matrix containing dissolved drug from the zone of the matrix containing dispersed drug.

The complex gelatinous layer controls the release of drugs by two mechanism

1. Water-soluble drugs released by diffusion out of the gel layer.
2. Drugs released by erosion of the gel regardless of drug solubility in the dissolution media. A water insoluble drug is exposed through erosion

3.4 Kinetic Modeling

Several mathematical models are used to predict drug release in matrix system, including Higuchi equation, Krosmeyer-Peppas model, Shah et al model and Jateleela et al model.

3.4.1 Higuchi's model (13-14)

The most famous and the most often used model to describe drug release from a matrix system is the one propoled by Higuchi in 1961. Higuchi described the cumulative amount of drug released is proportional to the square root of time in the early time approximation. This model is based on the hypothesis that:

(i) initial drug concentration in the matrix is much higher than drug solubility

(ii) drug diffusion takes place only in one dimension

(iii) drug particles are much smaller than system thickness

(iv) matrix swelling and dissolution are negligible

(v) drug diffusivity is constant and

(vi) perfect sink conditions are always attained in the release environment.

$$Q = K\sqrt{t} \qquad \text{Eq. (4)}$$

where Q is the amount of drug released in time, t and K is kinetic constant.

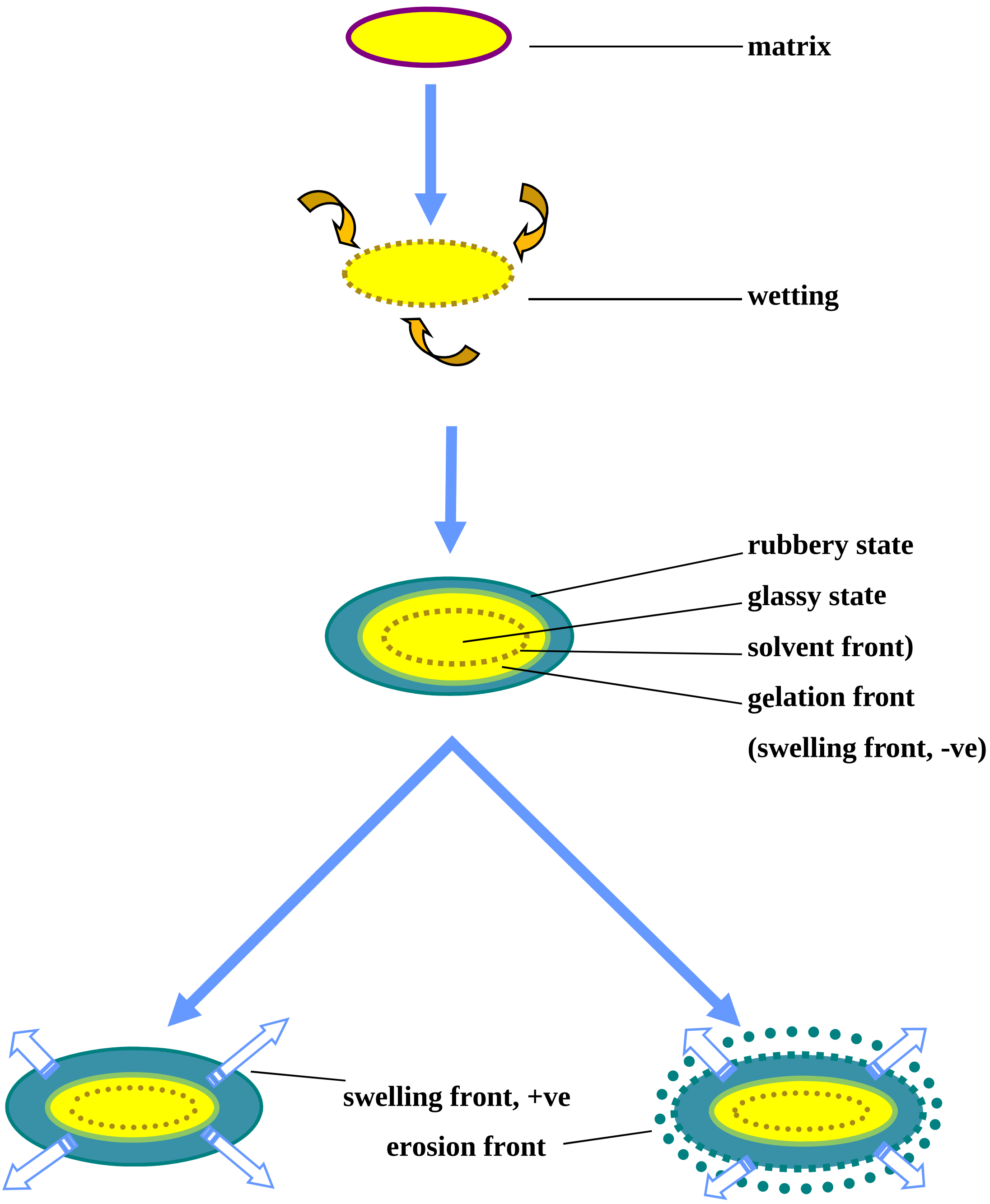


Figure 3.2 Schematic of the hydrophilic matrix after entry of the dissolution medium (29).

3.4.2 Korsmeyer-Peppas model (30-32)

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% release data was fitted in Kormeyer-Peppas model:

$$M_t/M_\alpha = Kt^n \qquad \text{Eq. (5)}$$

where M_t/M_α is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 3.1 for cylindrical shaped matrices. Taking logarithm both sides, we obtain:

$$\log M_t/M_\alpha = \log K + n\log t \qquad \text{Eq. (6)}$$

Table 3.1 Characterization of the order of release mechanism by the value of *n*

Release exponent (*n*)	**Drug transport mechanism**
n < 0.45	Quasi-Fickian diffusion
0.45	Fickian diffusion
0.45 < *n* <0.89	Non-Fickian transport
0.89	Zero-order transport
n > 0.89	Super case II transport

There are several simultaneous processes considered in this model:

- Diffusion of water into the tablet
- Swelling of the tablet as water enters
- Formation of gel
- Diffusion of drug and filler out of the tablet
- Dissolution of the polymer matrix

Key attributes of the model include:

- Tablet geometry is cylindrical
- Water and drug diffusion coefficients vary as functions of water concentration

- Polymer dissolution is incorporated
- Change in tablet volume is considered By incorporating the first 60% of release data, mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.

3.4.3 Shah et al. Model (14-15)

Shah et al. developed a working equation to predict drug release from hydroxypropylmethylcellulose (HPMC) matrices containing different polymer concentrations and assumed that: (i) drug release can be approximately modeled using the square root of time relation as in Eq. (4); (ii) the apparent diffusion coefficient of drug in the rubbery region is related to the tortuosity of the swelling layer as in Eq. (7); (iii) the tortuosity of the swelling layer depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration in the matrix as in Eq. (8); (iv) the porosity of the swelling layer is constant as in Eq. (8).

$$\varepsilon = \delta f / \rho_a = \text{constant} \qquad \text{Eq. (7)}$$

$$\tau = \psi C_p \qquad \text{Eq. (8)}$$

$$D_a = \gamma / C_p \qquad \text{Eq. (9)}$$

Substitute these parameters in Eq. (4)

$$Q = \frac{\sigma\sqrt{t}}{\sqrt{C_p}} \qquad \text{Eq. (10)}$$

where δ, ψ, γ and σ are kinetic constants.

From Eq (10) Q is the function of C_p and can be expressed as

$$Q = \alpha + \beta \sqrt{1/(C_p} \qquad \text{Eq. (11)}$$

where α and β are kinetic constants.

The regression equations for the amount of drug released at1, 2, 3, ….i h (Q_1, Q_2, Q_3, …Q_i) in relation of polymer concentration are as follows:

$$Q_i = a_i + b_i \sqrt{(1/C_p}$$ Eq. (12)

A plot of the amount, Q_i versus $\sqrt{(1/C_p}$ will give a_i and b_i. It is possible that both a_i and b_i are a function of the square root of time, therefore

$$a_i = c + K_a\sqrt{t}$$ Eq. (13)

$$b_i = d + K_b\sqrt{t}$$ Eq. (14)

where c, d, K_a and K_b are the regression constants.

Eq (10) is further derived to obtain the working equation for prediction drug release from a hydrophilic swellable matrix:

$$Q_i = (c + K_a\sqrt{t}\,) + (d + K_b\sqrt{t}\,)\sqrt{(1/C_p)}$$ Eq (15)

$$Q_i = (c + d\sqrt{(1/C_p)}) + (K_a + K_b\sqrt{(1/C_p)})\sqrt{t}$$ Eq (16)

3.4.4 Jateleela et al. model (16)

Jateleela et al. recently developed the new diffusion model from Shah et al. equation to predict the drug release from HPMC containing different mass fraction and using Spray dried lactose as a soluble filler. This model is based on: (i) drug release can be approximately modeled using square root of time relation as in Eq. (4); (ii) the apparent diffusivity of drug in the rubbery region is related to the porosity and the tortuosity of the swelling layer in Eq. (17); (iii) the porosity is directly proportional to the volume fraction of water soluble solutes in matrix, which is related to (1 – polymer mass fraction)/apparent density of mixed solute compact (ρ_a) as in Eq. (18) and (iv) the tortuosity depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration as in Eq. (19).

$$D_a = \varepsilon/\tau$$ Eq. (17)

$$\varepsilon = \delta\,(1 - C_p)/\rho_a$$ Eq. (18)

$$\tau = \psi C_p$$ Eq. (19)

$$D_a = \gamma\,(1 - C_p)/C_p$$ Eq. (20)

Substitute these parameters in Eq (4)

$$Q = \frac{\sigma\sqrt{(1-C_p)t}}{\sqrt{C_p}} \qquad \text{Eq. (21)}$$

where δ, ψ, γ and σ are kinetic constants.

From Eq (21) Q is the function of C_p and can be expressed as

$$Q = \alpha + \beta\sqrt{(1-C_p)/C_p} \qquad \text{Eq. (22)}$$

where α and β are kinetic constants.

The regression equations for the amount of drug released at 1, 2, 3, ….i h (Q_1, Q_2, Q_3, ...Q_i) in relation of polymer concentration are as follows:

$$Q_i = a_i + b_i\sqrt{(1-C_p)/C_p} \qquad \text{Eq. (23)}$$

A plot of the amount, Q_i versus $\sqrt{(1-C_p)/C_p}$ will give a_i and b_i. It is possible that both a_i and b_i are a function of the square root of time, therefore

$$a_i = c + K_a\sqrt{t} \qquad \text{Eq. (24)}$$

$$b_i = d + K_b\sqrt{t} \qquad \text{Eq. (25)}$$

where c, d, K_a and K_b are the regression constants.

Equation (23) is further derived to obtain the working equation for prediction drug release from a hydrophilic swellable matrix.

$$Q_i = (c + K_a\sqrt{t}\,) + (d + K_b\sqrt{t}\,)\sqrt{(1-C_p)/C_p}) \qquad \text{Eq. (26)}$$

$$Q_i = (c + d\sqrt{(1-C_p)/C_p}) + (K_a + K_b\sqrt{(1-C_p)/C_p})\sqrt{t} \qquad \text{Eq. (27)}$$

3.5 Factors Affecting Drug Released from Matrix Tablet

Many factors affecting the release of drugs from matrix tablet have been investigated. These factors are the type of polymer, drug:polymer ratio, solubility of drug and fillers and compression force relate to the release of drug from hydrophilic swellable matrices (7,27).

3.5.1 Drug-related factors

Among various factors, drug solubility plays a very important role in modifying the rate and extent of drug release. For highly water-soluble drug candidates, dissolution from a hydrophilic polymeric matrix is primarily controlled by the diffusion of the drug molecules through the hydrogel layer; a high drug concentration gradient within the gel layer facilitates drug delivery. For drug candidates with lower aqueous solubility, however, drug release rate is mainly dependent upon the erosion of the polymeric matrix. As result, the swelling characteristics of the hydrophilic polymer may significantly influence drug release profiles. In addition, hydration and erosion of the polymer matrix lead to further water intake and penetration; this will subsequently impact drug diffusion and dissolution . Li HT investigated the effect of drug solubility on polymer hydration and drug dissolution from modified release matrix tablets of polyethylene oxide (PEO), using acetaminophen (ACE) and ibuprofen (IBU). The results found that both drug solubility and polymer hydration play important roles in drug dissolution of modified release matrix tablet. These two parameters are closely related to each other and equally contribute to drug release modifications. High drug solubility is able to facilitate faster water penetration into the polymer matrix and diffusion of soluble drug molecules across the hydrogel layer. On the other hand, polymer hydration enables the swelling of the hydrophilic PEO, subsequently leading to more water penetration and drug dissolutiom (33). Prasanthi et al. studied the effect of drug solubility on the release kinetic of water soluble tramadol hydrochloride and insoluble aceclofenac from hydrophilic polymer (HPMC). Mechanism of drug release from the tablets having soluble drug was found that anomalous non-Fickian diffusion transport where as insoluble drug showed zero-order release (34).

3.5.2 Polymer-related

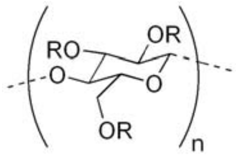
The retardability of matrix system depended on the type, amount and the property of polymer. Several studied investigated that which polymer and its ratio were appropriate to provide the desirable kinetic release. Goyal A et al. investigated the factors influencing the release characteristics of drug substances from hydrophilic polymer matrix tablet using various hydrophilic polymer such as Polyethylene oxide (PEO), Hydroxyethyl cellulose (HEO) and Xanthan gum (XG), and the effect of addition of diluent. From a comparison of various polymers, it was found that one important polymer property should be that the polymer must hydrate quickly to form a gel layer before the contents of the tablet can dissolve prematurely. It was evident that the best sustained release tablet could be produced using PEO along with HEC as hydrophilic controlling polymer. Also it was found that amongst diluents, MCC swelled more in comparison with DCP and played an important role in retardation of drug release (35). Talukdar et al. also compared XG and HPMC used as matrices forming agent for controlled-release drug delivery and the result showed that XG has higher drug-retarding ability than HPMC because drug diffusion in hydrated HPMC matrices is higher than in hydrated XG matrices. The release of a drug from XG matrices followed almost time-independent kinetics while the release from HPMC matrices followed time-dependent kinetics (36, 37).

3.5.3 Other factors

Besides, the effect of drug and polymer, the other factors such as pH of dissolution medium, the additives in formulation, characteristics of tablet and the manufacturing process can also affect the behavior of drug release. Talukdar et al. investigated the swelling and drug release behavior of XG matrix tablets using three drugs having different properties. The former of drug release is mainly influenced by the ionic strength and buffer concentration. The latter is affected by the solubility of the drug. The mechanism of matrix swelling follows Case I diffusion, whereas drug release from this polymer matrix conforms to Case II diffusion (38). Tajarobi et al. investigated the impact of the solubility of additives on the progression of the swelling and erosion fronts of sustained release HPMC matrix tablets by using MRI to determine front movement. The dissolution rate of the tablets was highest for the HPMC/mannitol formulation, followed by HPMC/dicalcium phosphate (DCP) and plain HPMC tablet. The release of the highly soluble mannitol was governed by diffusion, whereas the poorly soluble DCP was released at the same rate as the matrix erosion (39). Lotfipour et al. also investigated the effect of fillers on the release rate of atenolol from HPMC matrices, lactose (a water-soluble filler) and DCP (a water-insoluble filler) were used. The results showed that an increase in the concentration of fillers resulted in an increase in the release rate of the drug from matrices and hydrophilicity or hydrophobicity of fillers had no significant effect on the release profile which that release was controlled by both diffusion and erosion (40). In contrast the recently study, Vaidya et al. studied the effect of insoluble diluents such as microcrystalline cellulose (MCC) and DCP on the release profile of sustained release tablets containing HPMC matrices. The results showed a decrease in the drug release as the concentration of these insoluble diluents is increased. This might be due to the insoluble nature of MCC and DCP which may retard the penetration in the drug release (41). Velasco et al. evaluated the relationship and influence of formulation and technological factors such as drug:HPMC ratio, particle size of the drug, particle size of HPMC and compression force on drug release from matrices containing HPMC and diclofenac sodium as a model drug. The results of study showed the rate and mechanism of diclofenac sodium release from HPMC K15M matrices are mainly controlled by the drug:HPMC ratio. The lag time was statistically higher for those tablets containing the higher polymer ratio, may be due to a greater time being required for the formation of a stable diffusional pathlength. The drug and HPMC particle size also influence the drug release parameters, although to a lesser extent (42).

3.6 Hydrophilic Polymers

Hydroxypropylmethylcellulose (HPMC), a semi-synthetic cellulose derivative, is widely used as a matrix former in oral controlled release tablet formulations. Its widespread use is mainly due to its generally regarded as safe status and biodegradable nature. Furthermore, it is compatible with numerous drug, accommodates high levels of drug loading and can be easily incorporated to form matrix tablets by direct blending or granulation. The availability of a wide range of viscosity grades also allows the formulator to modify the release of drugs from HPMC matrix tablets according to therapeutic need. Drug release from HPMC matrix tablet involves complex mechanisms. In contact with water, HPMC swells to form a gel, which serves as a barrier to drug diffusion. Drug release from the HPMC-drug matrix involves solvent penetration into the dry matrix, gelatinization of the polymer, dissolution of the drug and diffusion of the solubilized drug through the gel layer. Concomitantly, outer layers of the tablet become fully hydrated and dissolved, a process generally referred to as erosion. Increasing the HPMC concentration in the tablet or using higher viscosity grades increases the strength of the gel layer and retards the penetration of water into the dry glassy core. This results in a decrease in release of both water-soluble and water-insoluble drugs. Modification of drug release from HPMC matrix tablets has been achieved by adjusting the polymer concentration and by using different viscosity grades of HPMC (43).



R = H or CH_3 or $CH_2CH(OH)CH_3$

Figure 3.3 Structure of HPMC (44)

In recent years there have been important developments in different dosage form for existing and newly designed drugs and natural products, and semi-synthetic as well as synthetic excipients often need to be used for a variety of purposes. Gums and mucilages are widely used natural materials for conventional and novel dosage forms. These natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available. They can be modified in different ways to obtain tailor-made materials for drug delivery systems (45).

Xanthan gum is a high molecular weight extracellular polysaccharide, produced on commercial scale by the viscous fermentation of gram negative bacterium *Xanthomonas campesteris.* The molecule consists of a backbone indentical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymers, which until recently had been limited for use in thickening, suspending and emulsifying water based systems (46).

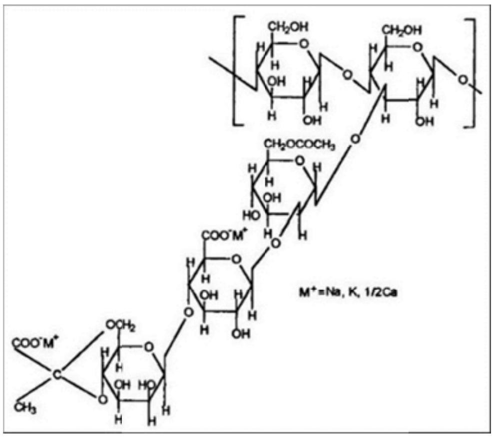


Figure 3.4 Structure of xanthan gum (47)

Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches. Guar gum is more soluble than locust bean gum and is a better emulsifier as it has more galactose branch points. It degrades at extremes of pH and temperature (e.g. pH 3 at 50°C) It remains stable in solution over pH range 5-7. Strong acids cause hydrolysis and loss of viscosity, and alkalies in strong concentration also tend to reduce viscosity. It is insoluble in most hydrocarbon solvents. Guar gum is used and investigated as a thickener in cosmetics and binder or disintegrator in tablets (45).

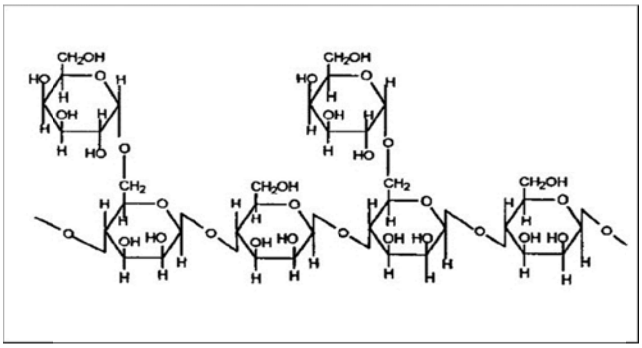


Figure 3.5 Structure of guar gum (47)

Sourabh J et al. evaluated the matrix tablets using pectin, guar gum and xanthan gum. It was showed the dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approximately 15 hrs (46).

Table 3.2 A list of commonly studied hydrophilic polymers for controlled release (7).

Type	Swelling characteristics	Source	Comments
Cellulosics			
Hypromellose (HPMC)	pH independent	Semi-synthetic	Different chemistries and different viscosity grades are available. Polymer of choice for sustained release tablets.
Hydroxypropyl cellulose (HPC)	pH independent	Semi-synthetic	Available in different viscosities. Higher viscosities grades have shown to work synergistically with HPMC
Hydroxyethyl cellulose (HEC)	pH independent	Semi-synthetic	Available in different viscosities.
Sodium carboxymethyl cellulose (CMC)	pH dependent	Semi-synthetic	It is ionic in nature, and pH dependent swellable. It may be used in combination with HPMC

Table 3.2 A list of commonly studied hydrophilic polymers for controlled release (cont.)

Non-cellulosic-gums/polysaccharide			
Sodium alginate	pH dependent	Natural	It forms insoluble complex with calcium salt. It may be used in combination with HPMC
Xanthan gum	pH dependent	Natural	Available in different grade. Acts synergistically with other hydrophilic polymer.
Carrageenan	pH dependent	Natural	Available in different chemistries. Acts synergistically with other hydrophilic matrix polymers.
Guar gum	pH independent	Natural	It has been used synergistically along with other hydrophilic polymer in matrix tablets.
Non-cellulosics-others			
Polyethylene oxide	pH independent	Synthetic	It is a linear polymer, non-ionic, pH-independent, highly swellable and fastest hydrating polymer.

3.7 Direct Compressible Fillers used in Matrix Tablet

Direct compression (DC) is the tableting of a blend of ingredient without preliminary granulation or agglomeration process. Diluets are incorporated into matrix tablet dosage forms to increase dosage form volume or weight, and as such they can also be as fillers.

3.7.1 Dibasic Calcium Phosphate

Dibasic calcium phosphate (DCP), also known as calcium monohydrogen phosphate, is a dicalcium phosphate. It is usually found as the dihydrate, with the chemical formula of $CaHPO_4$. $2H_2O$, but it can be thermally converted to the anhydrous form. It is practically insoluble in water, with a solubility of 0.02 g per 100 mL at 25°C. It contains about 29.5 percent calcium in its anhydrous form (48).

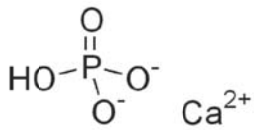


Figure 3.6 Structure of Dibasic calcium phosphate anhydrous (49)

3.7.2 Spray Dried Lactose

Spray dried lactose (SDL), it is the soluble type of filler that is one of the most widely used as direct compression. It is a disaccharide of galactose and glucose, is prepared by spray-drying a suspension of fine α-lactose monohydrate particles in a saturated aqueous solution of lactose. As show in figure 3.8, it is the mixture of amorphous lactose, which is a 1:1 mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(1⟶4)-D-glucopyranose monohydrate form is 360.31. The physical properties of SDL is white, odourless, free flowing powder slightly sweet is taste. It is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety (50).

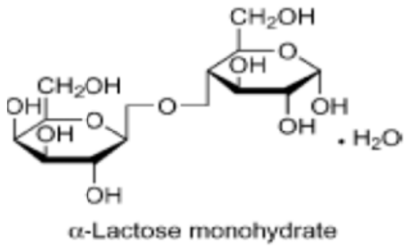


Figure 3.7 Structure of lactose monohydrate (51)

3.8 Model Drug

Tramadol hydrochloride, a synthetic opioid of the aminocyclohexanol group, which is used in the treatment of chronic pain, including low back pain, cancer pain, painful diabetic neuropathy, polyneuropathy and fibromalgia. The drug is freely soluble in water. The half-life of a drug is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 400 mg/day (1, 2).

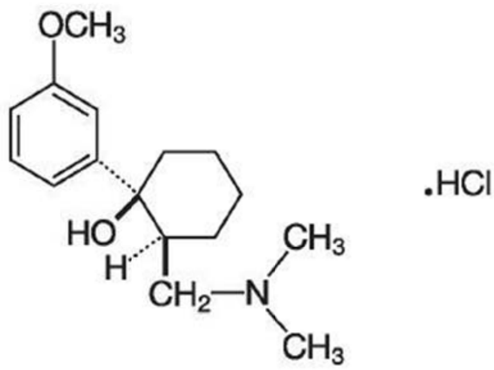


Figure 3.8 Structure of tramadol hydrochloride (52)

CHAPTER IV
MATERIALS AND METHODS

4.1 Materials

4.1.1 Chemicals

4.1.1.1 Tramadol hydrochloride (Yag-mag Labs Pvt., Andhra Pradesh, India)

4.1.1.2 Hydroxypropylmethylcellulose K4M (Methocel® K4M Premium, Dow Chemical, USA)

4.1.2.3 Hydroxypropylmethylcellulose K15M (Methocel® K15M Premium, Dow Chemical, USA)

4.1.2.4 Xanthan gum (Pernhofen Factory, Wulzeshofen, Austria)

4.1.2.5 Guar gum (Chemipan, Bangkok, Thailand)

4.1.2.6 Dibasic calcium phosphate dihydrate (Emcompress®, Sudeep Pharma, India)

4.1.2.7 Spray dried lactose (FlowLac® 90, Maggle Pharma, Germany)

4.1.2.8 Distilled water

4.1.2 Equipments

4.1.2.1 Dissolution apparatus II (Model VK700, Vankel, USA)

4.1.2.2 UV-Spectrophotometer (Model UV1601, Shimadzu, Japan)

4.1.2.3 Electrical analytical balance (Model A2005, Satorius AG, Göttingen, Germany)

4.1.2.4 Hydraulic press (Model C, Fred S, Carver Inc., USA)

4.1.2.5 Hardness tester (Model PTB 311, D6452, Pharma Test, Hamburg, Germany)

4.2 Methods

4.2.1 Preparation of Matrix Tablets Formulations

4.2.1.1 Preparation of Blends

The tablets from all formulations as depicted in Tables 4.1 and 4.2, were prepared by a direct compression method. The batch size of each formulation was 20 tablets and the tablet weight for each formulation was 500 mg. A 200 mg tramadol hydrochloride (TMH) was used as a model drug. Different polymer, hydroxypropylmethylcellulose K4M (HPMC K4M), HPMC K15M, xanthan gum (XG) or guar gum (GG) was used as a hydrophilic polymer at the mass fraction (mf) of 0, 0.15, 0.30, 0.45 or 0.60 of formulation. Different filler, DCPD or SDL was used as a filler to make a tablet weight of 500 mg. All materials were passed manually through a 40-mesh screen. The mixture was well blended in mortar and pestle for 15 min.

4.2.1.2 Preparation of matrix tablets

Each matrix tablet was manually prepared by direct compression of the 500 mg mixture at a force of 1000 kg in a hydraulic press equipped with 12.5-mm round flat-face punch and die. After compaction, the tablets were stored at room temperature for a few days before testing the drug release in order to complete the tablet relaxation. The prepared matrix tablets was evaluated for the weight variation, hardness, drug content and drug release within one week after tablet compression.

4.2.2 Evaluation of Matrix Tablets

4.2.2.1 Weight variation of tablets

Weight variation of 10 tablets was determined by weighing each tablet individually. The average and their standard deviation were then calculated.

Table 4.1 TMH formulations prepared with different polymers in 500 mg matrix tablets containing dibasic calcium phosphate (DCPD) as shown in formulation 1 – 17.

Formulation	TMH (mg)	DCPD (mg)	Polymer	Mass fraction
F1	200	300	-	-
F2	200	225	75 mg HPMC K4M	0.15
F3	200	150	150 mg HPMC K4M	0.30
F4	200	75	225 mg HPMC K4M	0.45
F5	200	-	300 mg HPMC K4M	0.60
F6	200	225	75 mg HPMC K15M	0.15
F7	200	150	150 mg HPMC K15M	0.30
F8	200	75	225 mg HPMC K15M	0.45
F9	200	-	300 mg HPMC K15M	0.60
F10	200	225	75 mg XG	0.15
F11	200	150	150 mg XG	0.30
F12	200	75	225 mg XG	0.45
F13	200	-	300 mg XG	0.60
F14	200	225	75 mg GG	0.15
F15	200	150	150 mg GG	0.30
F16	200	-	225 mg GG	0.45
F17	200	-	300 mg GG	0.60

Table 4.2 TMH formulations prepared with different polymers in 500 mg matrix tabletscontaining spray dried lactose (SDL) as shown in formulation 18–30.

Formulation	TMH (mg)	SDL (mg)	Polymers	Mass fraction
F18	200	300	-	-
F19	200	225	75 mg HPMC K4M	0.15
F20	200	150	150 mg HPMC K4M	0.30
F21	200	75	225 mg HPMC K4M	0.45
F22	200	225	75 mg HPMC K15M	0.15
F23	200	150	150 mg HPMC K15M	0.30
F24	200	75	225 mg HPMC K15M	0.45
F25	200	225	75 mg XG	0.15
F26	200	150	150 mg XG	0.30
F27	200	75	225 mg XG	0.45
F28	200	225	75 mg GG	0.15
F29	200	150	150 mg GG	0.30
F30	200	-	225 mg GG	0.45

4.2.2.2 Hardness determination

Three tablets were sampled and individually measured the hardness by using a hardness tester.

4.2.2.3 Content uniformity

Four tablets were pulverized, and three samples of 500 mg each was transferred to a 500-ml volumetric flask and brought to volume with distilled water. Samples will be stirred for 3 h with a magnetic stirrer. Transfer 10 mL of the clearly filtered solution into 50-mL volumetric flask. Then the volume was adjusted with the distilled water. An aliquot was filtered and analyzed for drug content by measuring its absorbance at a wavelength of 272.0 nm by a UV spectrophotometer.

4.2.3 Determination of Drug Release from Hydrophilic Matrix Tablets

4.2.3.1 Preparation of Standard Curve

250 mg of TMH was accurately weighed, dissolved in distilled water and precisely diluted to volume in a 250-ml volumetric flask, various dilutions were made to obtain standard solutions of 40, 60, 80, 100, 120 µg/ml. The absorbance of these solutions were measured at a wavelength of 272.0 nm by the UV spectrophotometer.

4.2.3.2 *In vitro* Release Method

The release of TMH from the matrices (n = 5) will be measured in a 900 ml of distilled water at 37°C ± 0.5 using paddle apparatus at a speed of 50 rpm. The samples will be withdrawn at 1, 2, 4, 6, 8, 12 and 24 h time intervals. Samples will be replaced by its equivalent distilled water. The samples will be filtered and analyzed at 272 nm by the UV spectrophotometer. Cumulative percentage of drug release will be calculated.

4.2.3.3 Kinetics of Drug Release

Equations for predicting the 60% of drug release for matrix tablets containing hydrophilic polymer, Higuchi's model of diffusion was applied to each formulation in order to investigate whether drug release from matrix tablets obeyed such model or not, as previously described in Eq. (4).

Due to different water solubility of filler type and its effect on the porosity and tortuosity formation in the matrix tablets immersing in aqueous medium, model of diffusion of Shah et al. was used to obtain the working equations for predicting the drug release for matric tablets containing insoluble filler, i.e., DCPD, whereas that of Jateleela et al. was used to obtain the working, i.e. SDL, as previously described in Eq. (16) and Eq. (27), respectively

In addition, the transport model of Korsmeyer and Peppas was used to describe the mechanism of drug release, as previously described in Eq (5).

4.2.4 Statistical Analysis

The relationship between 2 variables, i.e., mass fraction ratio and percentage drug release was determined by an analysis of linear regression. The criteria was established for evaluation the correlation of 2 variables as follows: (i) R^2

of 0.9900 – 1.000 = excellent, (ii) R^2 of 0.9800 – 0.9899 = good, and (iii) R^2 of 0.9700 – 0.9799 = fair. The drug release data of different formulations of TMH matrices are subjected to analysis of variance (ANOVA, α = 0.01) and multiple comparison test using least significant difference procedure (LSD, α = 0.01, 2-tailed) for comparing the release data namely rate constant, natural convection and lag time. Then 1% allowance was calculated as follow: (47).

$$1\%\ allowance\ (\%A) = \quad t\sqrt{s^2\left(\frac{1}{n_i}+\frac{1}{n_j}\right)} \qquad \text{Eq. (29)}$$

where S_2 = pooled variance from the analysis of variance, *DF* = degree of freedom for the pooled variance from the analysis of variance, n_i, n_j = the number of observation from which the means were determined, and t = a critical value at α = 0.01, which depends upon the *DF*.

4.2.5 Determination of Swelling Property (47)

The swelling property of different polymers and polymer matrix formulations powder were studied by measuring the change in volume of solid mixture in water. Certain amounts of each formulation (n = 3) were placed in 10-ml graduated cylinders (48). Subsequently, water was added to a volume of 10 ml. The swelling property of the formulations observed within 24 h was expressed as the swelling ratio. The swelling ratio (Q_d) for each formulation was calculated from the following equation

$$Q_d = \frac{V_s - V_d}{V_d} \qquad \text{Eq. (28)}$$

where V_d and V_s represented the volume of the initial dried polymer and the final volume of swollen formulation, respectively. The experiments were done in triplicate.

CHAPTER V
RESULTS AND DISCUSSION

5.1 Preparation of Matrix Tablets

The formulations as depicted in Tables 4.1 and 4.2 were prepared by a direct compression method using hydraulic press. Most formulations could be prepared appropriate tablets with good physical properties, whereas the formulations without polymers, the tablets were friable.

5.2 Evaluation of Matrix Tablets

5.2.1 Weight Variation

The amount of 6 tablets were weighed individually for weight variation test. The average weight and their standard deviation (SD) were calculated. The data were depicted in Tables 5.1 – 5.2. Each SD of tablet weight was less than 1.5. The tablet weight variation and SD were so low for all the formulations.

5.2.2 Hardness

The hardness values of TMH matrix tablets compressed at 1000 kg compression forces were given in Table 5.1 – 5.2. HPMC K4M and HPMC K15M provided tablets with higher hardness than matrices using XG and GG matrices. Both HPMC and XG have plastic deformation and therefore more bonding will occur, resulting in tablets with high hardness. Addition of non-polymeric material would decrease plastic behavior, resulting in lower hardness tablet. These indicated that increasing the amount of filler decreased the hardness in matrices using HPMC and XG. GG matrices showed the lowest hardness. This might be due to its lowest binding property. It was observed that tablet hardness was influenced by the type and content of filler.

Table 5.1 Weight variation, hardness and drug content of TMH matrix tablets containing DCPD with different polymers.

Formulation	Weight, mg (SD)	Hardness, kg (SD)	% Drug content (SD)
F1	492.72 (0.74)	3.80 (0.46)	100.76 (0.18)
F2	500.22 (0.39)	11.23 (0.50)	99.89 (0.50)
F3	501.08 (1.17)	17.07 (0.40)	97.55 (0.14)
F4	499.48 (0.82)	23.13 (0.65)	97.78 (0.22)
F5	501.9 (0.67)	27.57 (0.91)	97.51 (0.96)
F6	495.98 (0.30)	11.37 (0.55)	99.06 (0.12)
F7	499.40 (0.86)	16.80 (0.75)	98.35 (1.82)
F8	500.00 (0.81)	23.60 (0.87)	97.79 (0.16)
F9	500.08 (0.87)	28.27 (0.96)	97.65 (0.34)
F10	499.30 (0.77)	10.70 (1.40)	99.46 (0.29)
F11	499.78 (0.66)	15.23 (0.60)	97.27 (0.56)
F12	498.98 (0.48)	18.80 (0.87)	99.35 (0.16)
F13	499.27 (0.31)	19.20 (1.28)	97.61 (0.29)
F14	497.35 (0.52)	4.43 (0.15)	99.93 (0.36)
F15	496.80 (0.49)	8.23 (0.15)	99.36 (0.32)
F16	497.83 (0.80)	6.40 (0.30)	99.22 (0.13)
F17	498.98 (0.58)	4.60 (0.26)	99.00 (0.68)

Table 5.2 Weight variation, hardness and drug content of TMH matrix tablets containing SDL with different polymers.

Formulation	Weight, mg (SD)	Hardness, kg (SD)	% Drug Content (SD)
F18	492.47 (0.82)	4.50 (0.36)	99.17 (0.25)
F19	497.68 (0.75)	11.27 (0.61)	97.97 (0.86)
F20	498.70 (0.38)	17.17 (0.15)	98.38 (1.07)
F21	499.52 (0.28)	24.43 (0.67)	99.70 (0.44)
F22	497.62 (0.69)	11.93 (0.35)	98.86 (0.18)
F23	500.05 (0.38)	17.07 (1.04)	98.50 (0.22)
F24	499.05 (0.58)	23.57 (0.15)	97.53 (1.27)
F25	493.05 (1.21)	10.97 (0.59)	97.39 (0.61)
F26	497.35 (0.67)	15.40 (0.70)	99.20 (0.60)
F27	498.25 (0.57)	19.03 (0.84)	98.21 (0.27)
F28	493.52 (0.74)	4.57 (0.31)	99.30 (0.15)
F29	496.42 (0.58)	6.77 (0.70)	99.58 (0.29)
F30	497.47 (0.79)	5.33 (0.31)	99.36 (0.19)

5.2.3 Content Uniformity

The content of TMH in hydrophilic swellable matrix tablets was analyzed by using the UV-spectrophotometer at the wavelength of 272.0 nm. The amount of the active ingredient in each of 3 units tested were within the range of 97.27 – 100.76% and SD of 0.12 – 1.27 indicated the uniformity of drug content in each tablet batch prepared with low weight variation.

5.3 Preparation of Standard Curve

Standard curve of TMH in distilled water was obtained from the standard solutions in the concentration of 40 – 120 µg/mL. Data for a calibration curve of TMH were listed in Table 5.3 and a calibration curve of absorbance at the wavelength 272.0 nm *vs.* concentration is presented in Figure 5.10. The linear regression line was obtained with a good coefficient of determination (R^2) of 0.9999. This indicated that this plot followed Beer's law and was presented as follows:

$$A = 0.0059C - 0.0032 \qquad \text{Eq. (30)}$$

Where A is an absorbance at wavelength 272.0 nm, and C is TMH concentration in distilled water (µg/mL).

Table 5.3 UV absorbance of TMH in distilled water at wavelength of 272.0 nm.

Concentration (µg/mL)	Absorbance			
	1	2	3	Mean ± SD
40	0.2313	0.2318	0.2401	0.2344 ± 0.0049
60	0.3445	0.3433	0.3539	0.3472 ± 0.0058
80	0.4656	0.4664	0.4736	0.4685 ± 0.0044
100	0.5823	0.5819	0.5890	0.5844 ± 0.0040
120	0.7006	0.7031	0.7102	0.7046 ± 0.0050

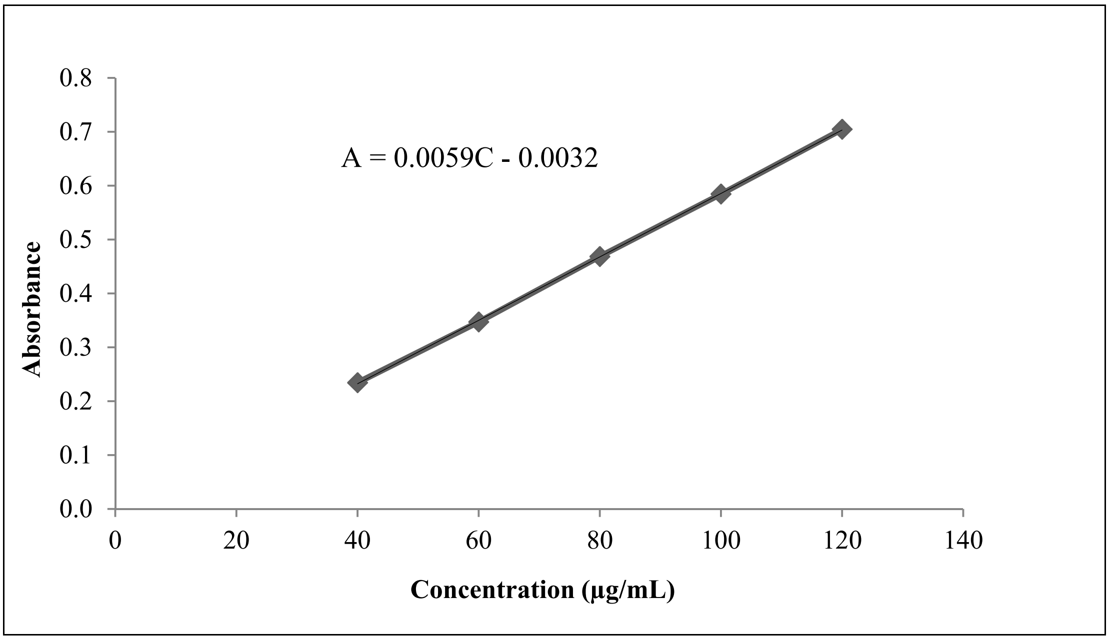


Figure 5.1 Standard curve of TMH in distilled water at 272.0 nm.

5.4 Drug Release Kinetics

Kinetic drug releases obtained for all formulations were plotted in mode of data treatments as follows:

(i) Higuchi's model of diffusion: cumulative percentage drug released versus square root of time,

(ii) Shah et al. model of diffusion, and working equation to predict drug release from matrix containing an insoluble filler,

(iii) Jateleela et al. model of diffusion and working equation to predict drug release from matrix containing a soluble filler,

(iv) Korsmeyer and Peppas model of drug transport: logarithm of percentage drug released from matrix versus logarithm of time, and

(v) an analysis of variance (ANOVA, $\alpha = 0.01$) and a multiple comparison test using least significant difference procedure (LSD, $\alpha = 0.01$, 2-tailed) for comparing TMH release data of different formulations, *i.e.*, kinetic constant (k), natural convection in percentage drug released at time zero (Q_0), and lag time in min.

5.4.1 Higuchi model, the Release of TMH from Matrices Using DCPD at Various mf of HPMC K4M.

Table 5.4 The percent drug released of TMH from matrices using DCPD at HPMC K4M mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	36.80	37.41	37.30	37.71	37.09	37.26 ± 0.34
2	1.41	51.64	52.30	53.40	53.68	52.28	52.66 ± 0.85
4	2.00	72.14	73.13	73.19	74.42	72.66	73.11 ± 0.85
6	2.45	86.47	87.01	87.40	87.84	86.58	87.06 ± 0.57
8	2.83	94.58	96.57	96.59	97.66	95.17	96.11 ± 1.23
12	3.46	102.94	102.92	103.98	102.82	103.04	103.14±0.48
24	4.9	104.86	103.68	104.75	103.61	104.37	104.26 ± 0.59

Table 5.5 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K4M mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	32.18	32.72	32.61	32.93	32.19	32.53	0.33
Q_0, %	5.95	5.86	6.37	6.43	6.36	6.19	0.27
Lag time, min	-11.09	-10.75	-11.72	-11.72	-11.85	-11.43	0.48
R^2	0.9940	0.9962	0.9951	0.9951	0.9944	0.9950	0.0008

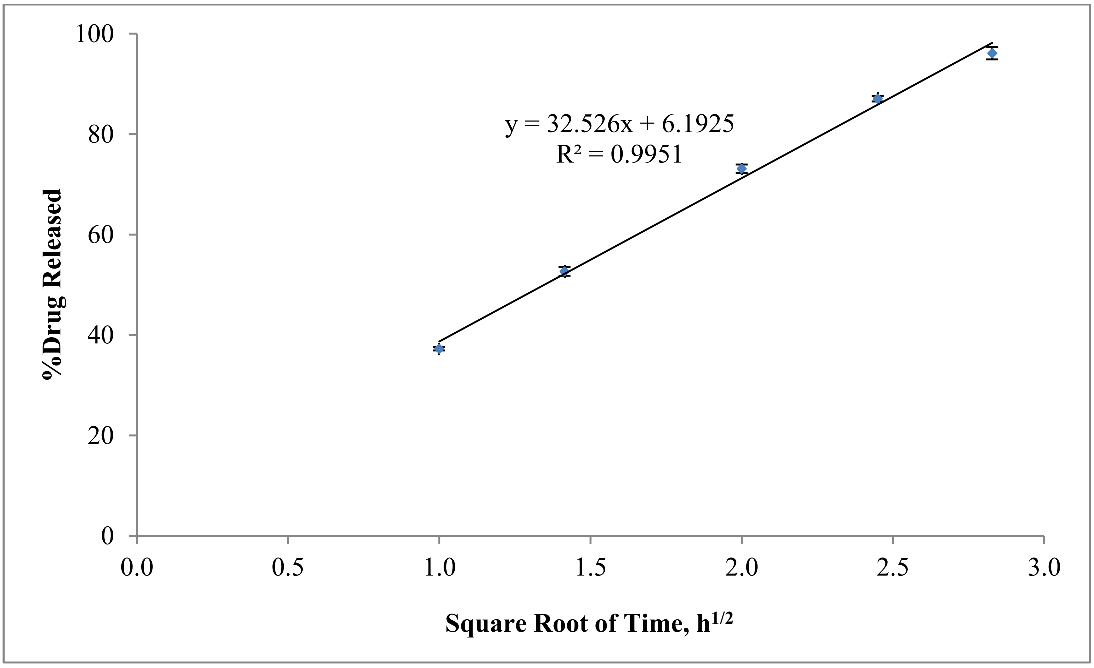


Figure 5.2 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K4M mf of 0.15.

Table 5.6 The percent drug released of TMH from matrices using DCPD at HPMC K4M mf of 0.30.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	28.24	28.33	29.27	28.98	28.70	28.70± 0.43
2	1.41	41.73	42.24	43.36	42.98	41.45	42.35± 0.81
4	2.00	61.01	60.98	60.92	61.58	60.93	61.09± 0.28
6	2.45	73.67	74.08	75.30	75.47	73.94	74.49± 0.83
8	2.83	82.10	82.53	83.37	82.93	81.57	82.50±0.70
12	3.46	97.31	97.90	97.98	99.35	97.29	103.14 ± 0.48
24	4.90	104.88	107.34	107.19	106.12	105.75	106.2 ± 1.03

Table 5.7 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K4M mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	29.88	29.98	29.94	30.03	29.60	29.89	0.17
Q_0, %	-0.56	-0.48	0.41	0.18	0.051	-0.08	0.42
Lag time, min	1.12	0.96	-0.82	-0.36	0.1	0.2	0.83
R^2	0.9955	0.9959	0.9963	0.9944	0.9945	0.9953	0.0008

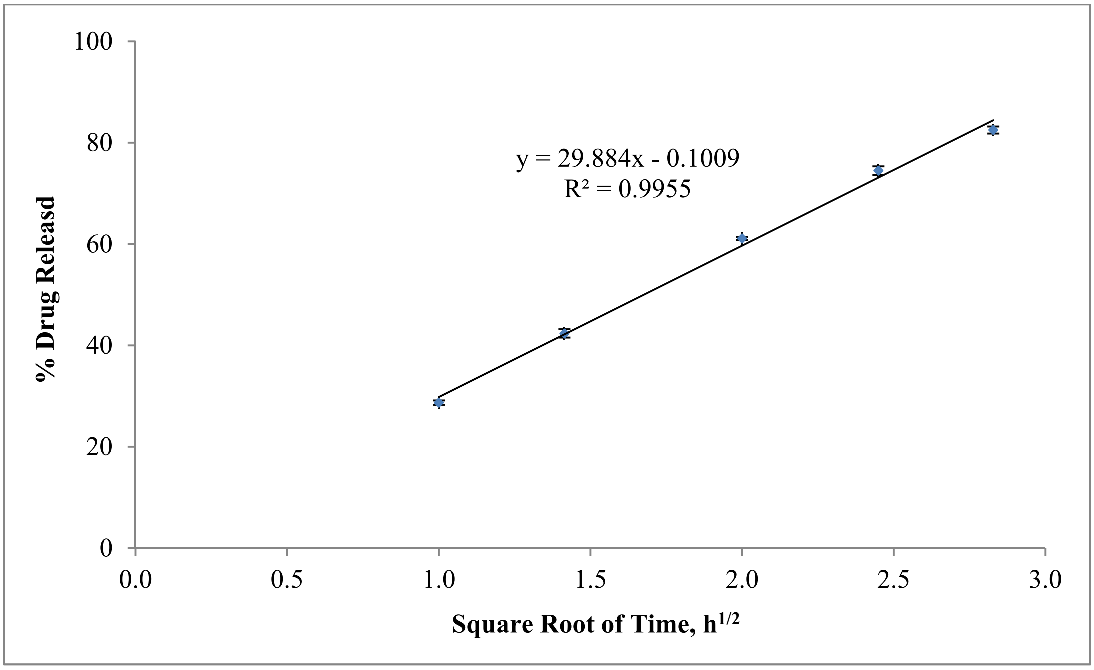


Figure 5.3 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K4M mf of 0.30.

Table 5.8 The percent drug released of TMH from matrices using DCPD at HPMC K4M mf of 0.45.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	25.07	23.51	23.89	24.16	24.77	24.28 ± 0.64
2	1.41	36.98	35.69	35.83	36.10	37.63	36.45 ± 0.83
4	2.00	52.74	50.44	50.66	52.09	53.22	51.83 ± 1.24
6	2.45	64.17	64.15	64.08	65.88	66.98	65.05±1.32
8	2.83	76.86	74.75	74.26	75.20	76.56	75.52±1.14
12	3.46	90.79	89.28	89.04	89.76	90.68	89.91±0.80
24	4.90	106.38	106.21	104.51	105.94	105.10	105.63 ± 0.80

Table 5.9 Kinetic constant k , natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K4M mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	27.81	27.86	27.46	28.12	28.33	27.92	0.33
Q_0, %	-2.74	-4.30	-3.49	-3.81	-3.08	-3.49	0.61
Lag time, min	5.91	9.26	7.63	8.15	6.52	7.49	1.33
R^2	0.9985	0.9992	0.9994	0.9994	0.9992	0.9991	0.0003

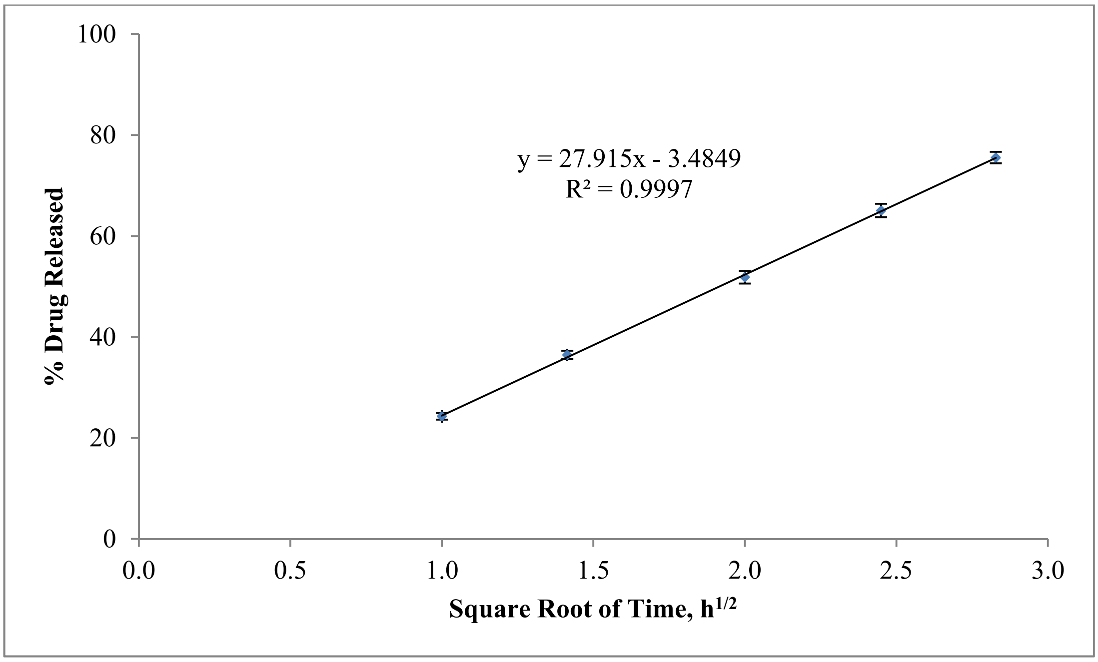


Figure 5.4 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K4M mf of 0.45.

Table 5.10 The percent drug released of TMH from matrices using DCPD at HPMC K4M mf of 0.60.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	22.46	22.35	22.69	22.19	23.28	22.60 ± 0.42
2	1.41	32.36	32.59	32.57	32.47	33.08	32.61 ± 0.28
4	2.00	47.59	47.73	47.65	48.09	48.63	47.94 ± 0.43
6	2.45	60.53	60.34	60.11	60.74	60.68	60.48 ± 0.26
8	2.83	70.06	70.57	70.91	71.33	71.15	70.80 ± 10.50
12	3.46	86.23	85.95	87.30	86.95	86.58	86.60 ±0.54
24	4.90	102.81	103.81	103.65	103.03	103.46	103.35±0.42

Table 5.11 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K4M mf of 0.60 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	26.29	26.46	26.40	26.95	26.28	26.48	0.28
Q_0, %	-4.37	-4.57	-4.38	-5.28	-3.57	-4.44	0.61
Lag time, min	9.97	10.36	9.95	11.76	8.15	10.04	1.29
R^2	0.9993	0.9995	0.9990	0.9995	0.9994	0.9993	0.0002

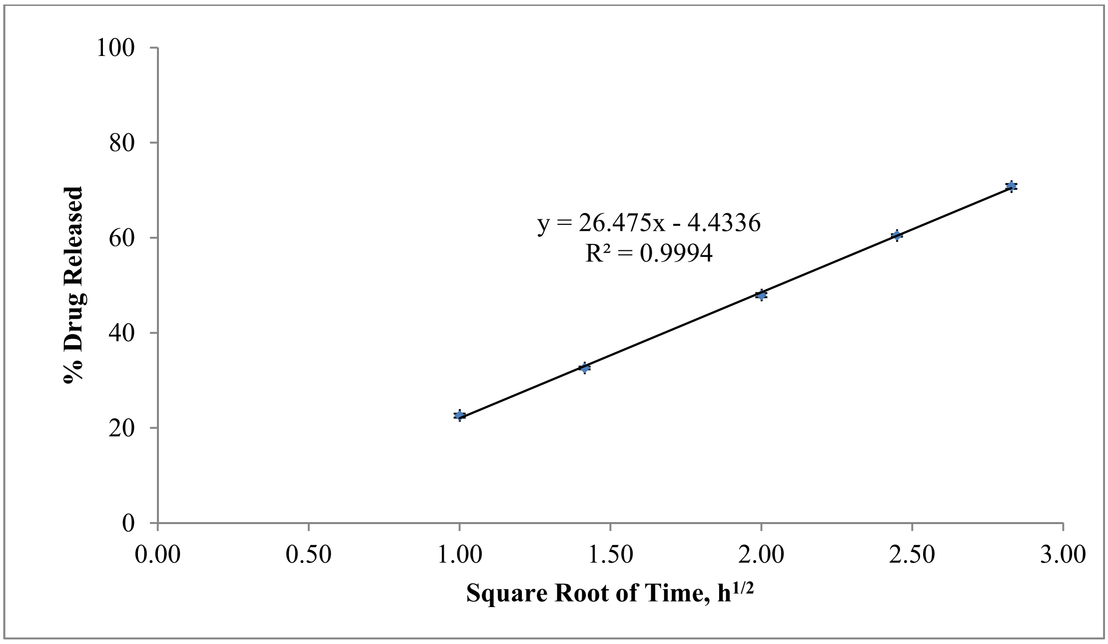


Figure 5.5 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K4M mf of 0.60.

5.4.2 Shah *et al.* Model of Diffusion for Matrices Using DCPD at Various mf of HPMC K4M.

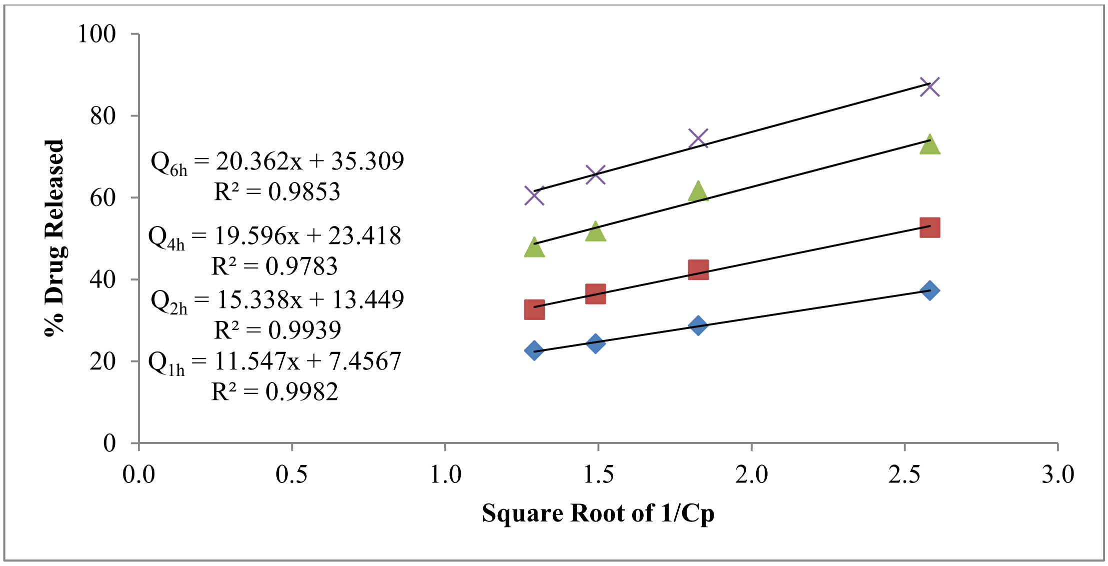


Figure 5.6 Regression analysis of percentage TMH released (Q) from matrices using DCPD and square root of $1/C_p$ of HPMC K4M at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; and ✕, 6 h.

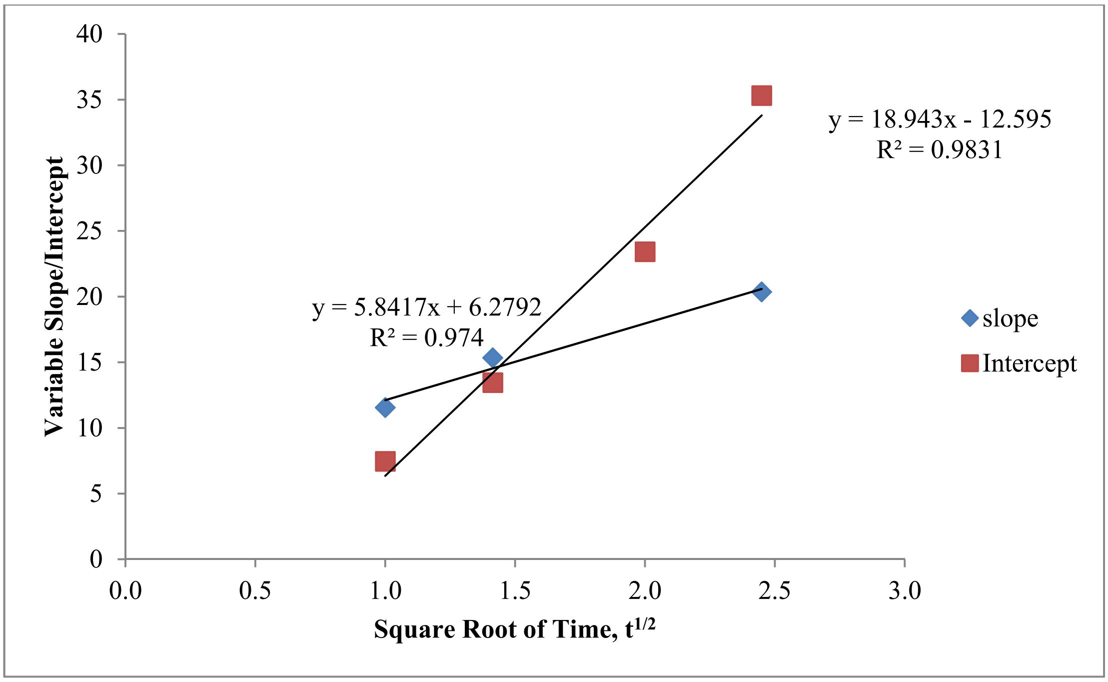


Figure 5.7 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using DCPD at various mf of HPMC K4M. Keys: ♦, slope; and ■, intercept.

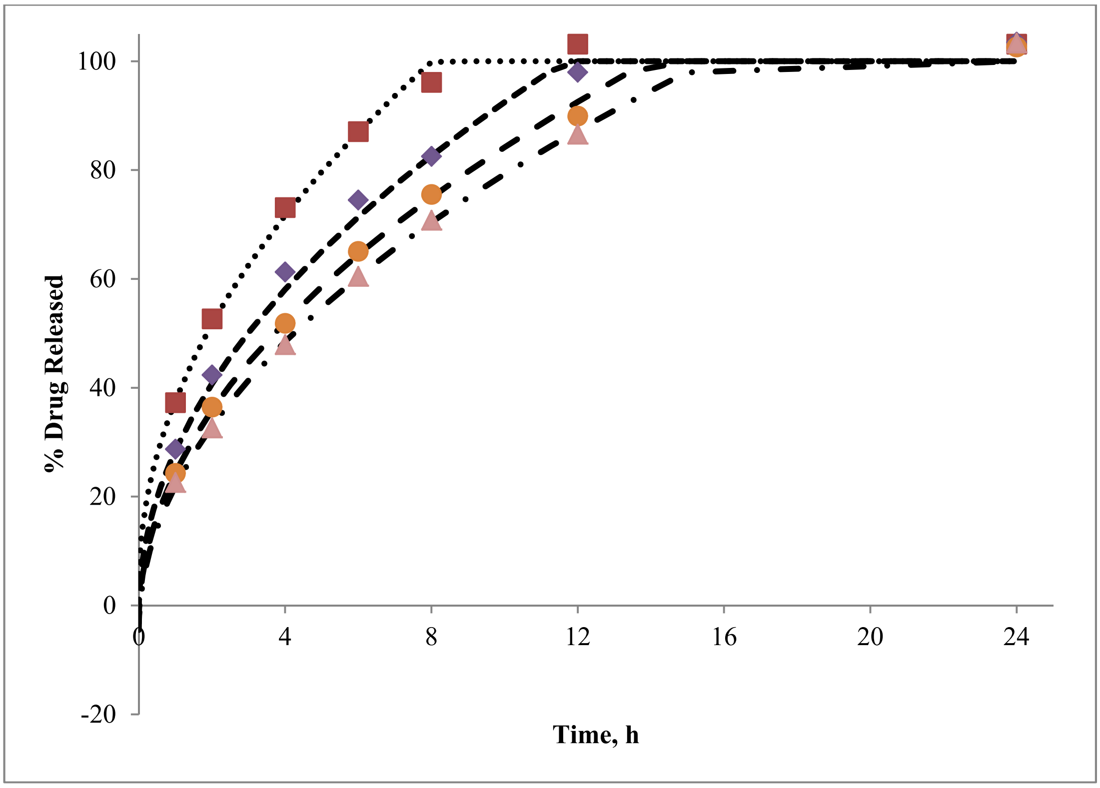


Figure 5.8 Predicted release profiles proposed by Shah et al. model versus experimental data for matrices using DCPD at various mf of HPMC K4M. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - · -, 0.60. Experimental: ■, 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.3 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released *versus* Logarithm of Time for Matrices Using DCPD at Various mf of HPMC K4M.

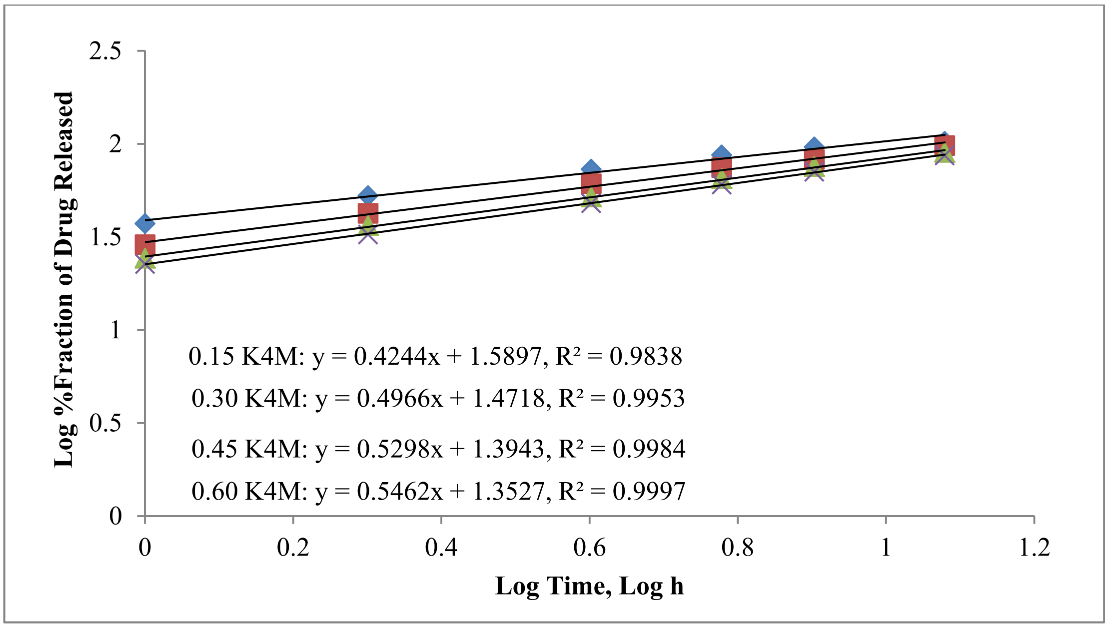


Figure 5.9 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using DCPD at various mf of HPMC K4M. Keys: ♦, 0.15 K4M; ■, 0.30 K4M; ▲, 0.45 K4M; and ✕, 0.60 K4M.

Table 5.12 Characterization of the order of release mechanism by the value of n for matrices using DCPD at various mf of HPMC K4M.

Filler	**Polymer**	**mf**	**Release exponent (*n*)**	**Drug transport mechanism**
DCP	HPMC K4M	0.15	0.42	quasi-Fickian diffusion
		0.30	0.50	non-Fickian transport
		0.45	0.53	non-Fickian transport
		0.60	0.55	non-Fickian transport

5.4.4 Higuchi model, the release of TMH from matrices using DCPD at various mf of HPMC K15M.

Table 5.13 The percent drug released of TMH from matrices using DCPD at HPMC K15M mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	35.41	34.95	34.25	33.75	35.45	34.76 ± 0.74
2	1.41	50.33	50.06	49.59	49.99	51.61	50.32 ± 0.77
4	2.00	71.71	70.80	70.60	71.06	72.96	71.43 ± 0.95
6	2.45	83.59	83.12	82.76	82.36	84.12	83.19 ±0.69
8	2.83	92.24	93.54	92.74	92.26	94.11	92.98 ± 0.82
12	3.46	99.89	100.74	100.64	100.48	101.76	100.70±0.68

Table 5.14 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K15M mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	33.67	33.51	33.77	33.83	33.94	33.74	0.16
Q_0, %	2.49	2.24	1.35	1.23	2.80	2.02	0.70
Lag time, min	-4.44	-4.01	-2.4	-2.18	-4.9	-3.59	1.23
R^2	0.9957	0.9966	0.9960	0.9927	0.9924	0.9947	0.0020

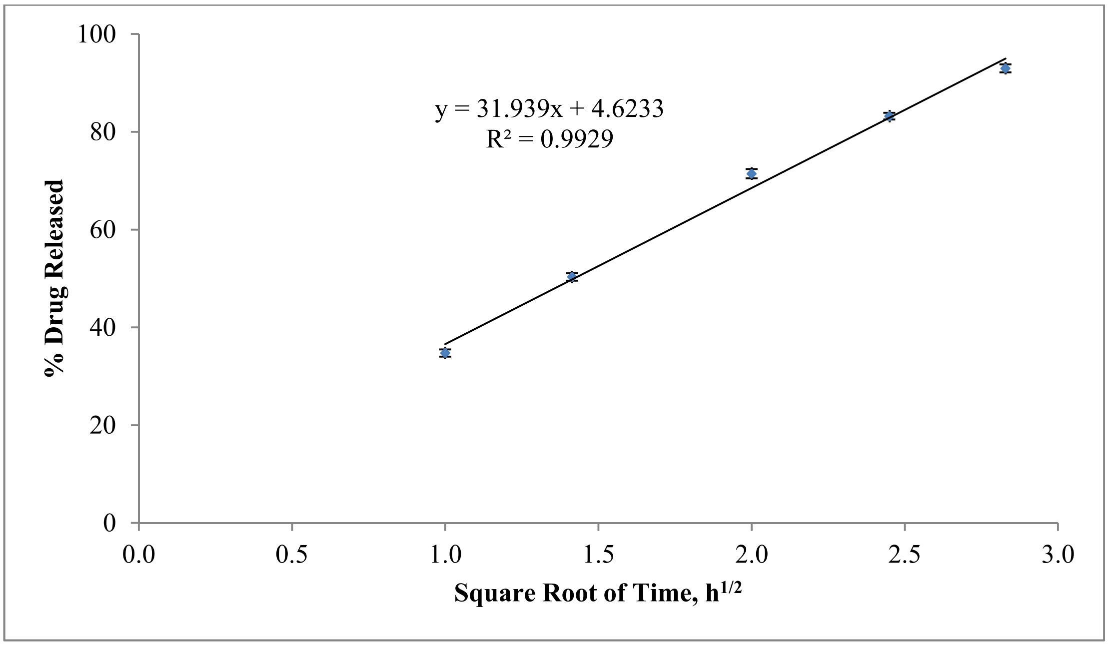


Figure 5.10 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K15M mf of 0.15.

Table 5.15 The percent drug released of TMH from matrices using DCPD at HPMC K15M mf of 0.30.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	27.69	27.57	27.82	27.50	27.72	27.66 ± 0.13
2	1.41	40.85	41.70	41.72	41.45	42.91	41.73 ± 0.75
4	2.00	59.75	60.11	60.64	58.00	60.48	59.80±1.06
6	2.45	72.73	73.22	73.21	72.16	73.67	73.00±0.58
8	2.83	82.90	83.13	83.77	83.39	83.61	83.36±0.35
12	3.46	96.52	97.03	97.49	96.92	98.28	97.25±0.67
24	4.90	106.06	104.37	106.90	105.95	107.21	106.10±1.11

Table 5.16 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at K15M mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	30.39	30.45	30.61	30.34	30.41	30.44	0.10
Q_0, %	-2.12	-1.88	-1.9	-2.32	-1.27	-1.90	0.35
Lag time, min	4.19	3.7	3.72	4.59	2.51	3.74	0.78
R^2	0.9987	0.9981	0.9983	0.9994	0.9972	0.9983	0.0008

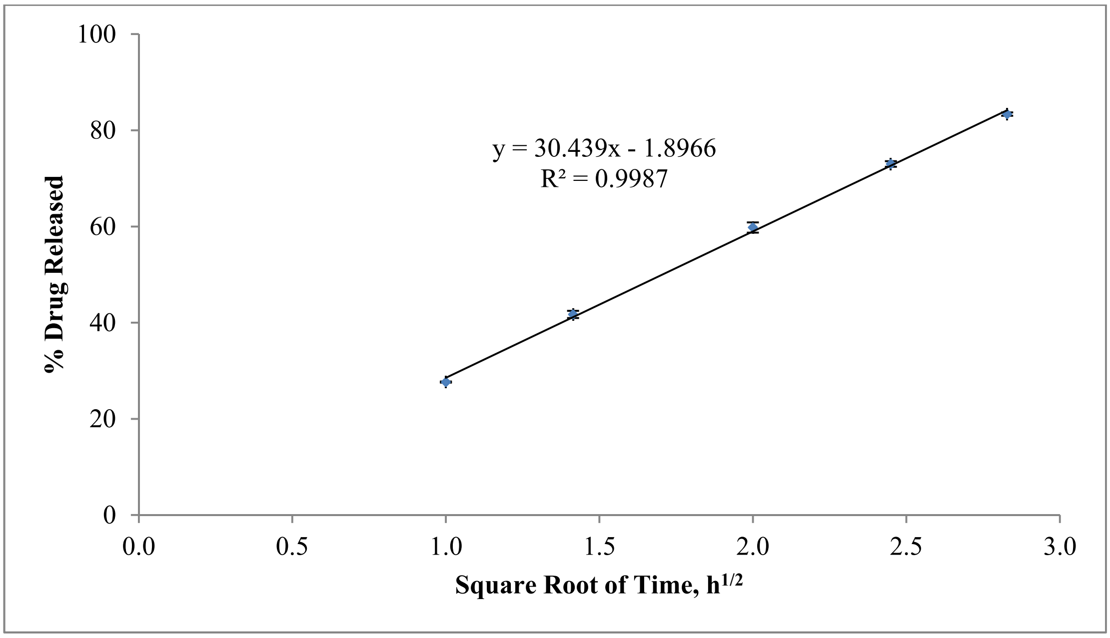


Figure 5.11 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K15M mf of 0.30.

Table 5.17 The percent drug released of TMH from matrices using DCPD at HPMC K15M mf of 0.45.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	23.32	24.33	23.51	23.24	23.70	23.62±0.43
2	1.41	35.76	36.77	35.21	34.87	35.75	35.67±0.50
4	2.00	52.08	54.22	52.69	51.44	53.23	52.73±1.07
6	2.45	64.17	66.52	64.82	64.11	65.75	65.07±1.04
8	2.83	75.37	77.60	75.75	74.78	76.28	75.96±1.07
12	3.46	88.89	91.06	89.88	89.26	90.65	89.95 ± 0.91
24	4.90	105.33	105.52	106.63	105.35	104.80	105.53±0.67

Table 5.18 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K15M mf of 0.45 from linear regression analysis of percentage K15M released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	28.23	29.06	28.59	28.20	28.83	28.58	0.37
Q_0, %	-4.57	-4.44	-5.03	-4.98	-4.95	-4.79	0.27
Lag time, min	9.71	9.17	10.56	10.60	10.30	10.07	0.62
R^2	0.9997	0.9998	0.9998	1.000	0.9998	0.9998	0.0001

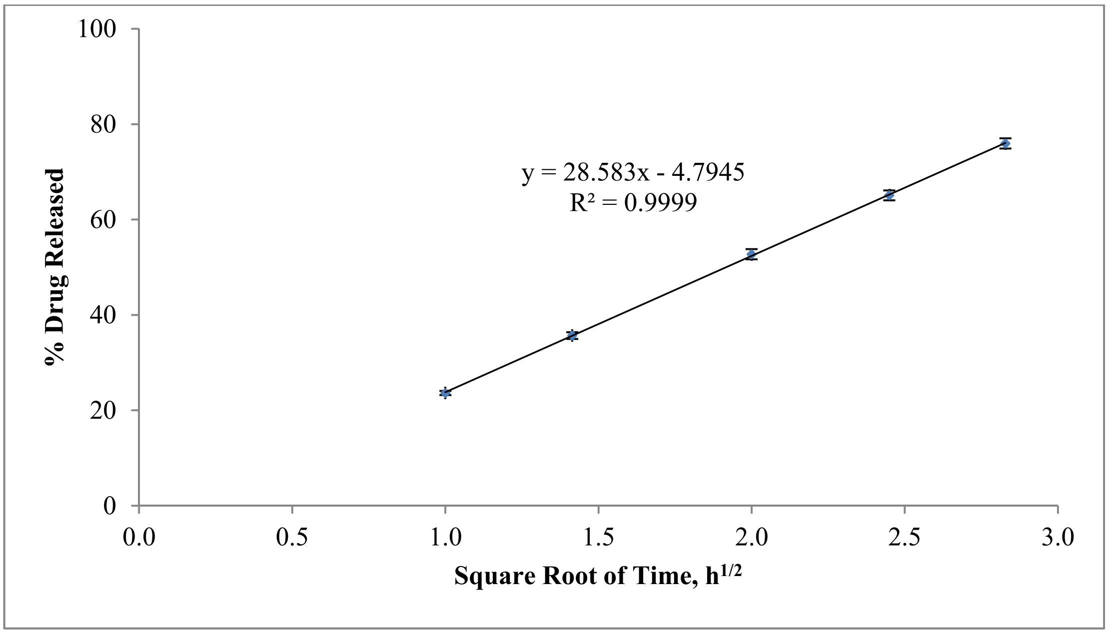


Figure 5.12 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K15M mf of 0.45.

Table 5.19 The percent drug released of TMH from matrices using DCPD at HPMC K15M mf of 0.60.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	20.88	20.94	20.99	20.90	20.33	20.81±0.27
2	1.41	32.51	32.69	33.18	32.76	32.39	32.71±0.30
4	2.00	48.87	49.64	48.35	49.43	48.90	49.04±0.51
6	2.45	60.87	60.10	58.77	60.40	60.08	60.04±0.78
8	2.83	72.40	72.02	69.90	71.51	72.29	71.62±1.02
12	3.46	86.09	85.27	84.18	85.55	86.08	85.43±0.79
24	4.90	101.21	101.01	101.77	100.93	102.39	101.46±0.62

Table 5.20 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at HPMC K15M mf of 0.60 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet No.						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	27.98	27.61	26.27	27.47	28.02	27.47	0.71
Q_0, %	-7.14	-6.44	-4.69	-6.24	-7.52	-6.41	1.09
Lag time, min	15.31	13.99	10.71	13.63	16.1	13.95	2.07
R^2	0.9997	0.9987	0.9987	0.9994	0.9991	0.9991	0.0004

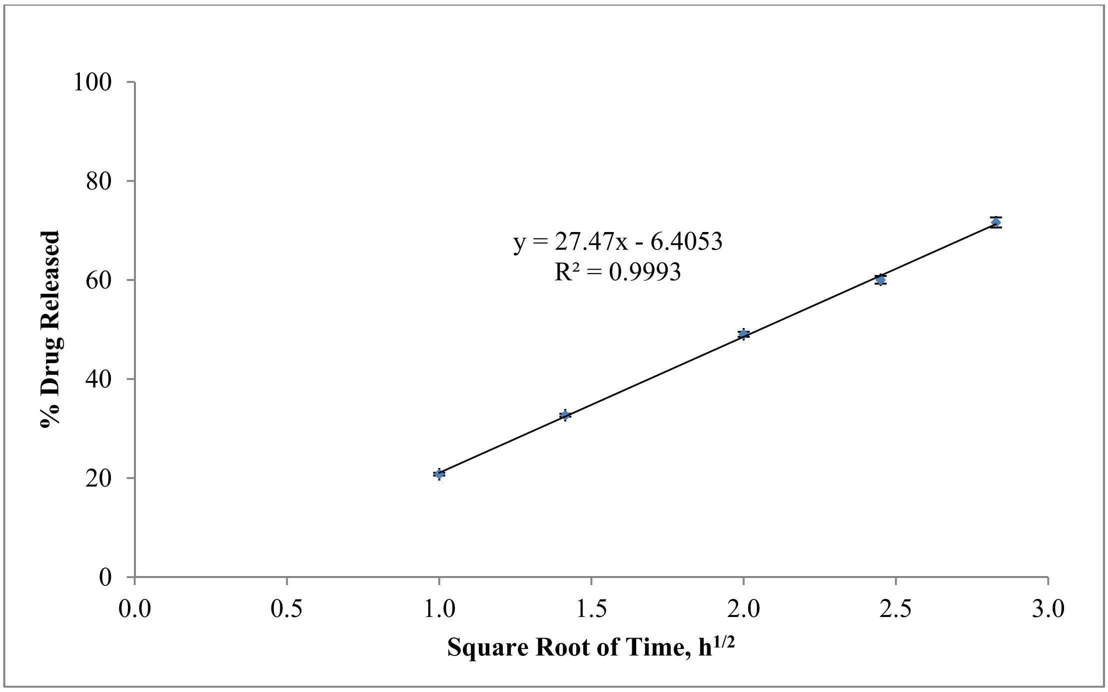


Figure 5.13 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at HPMC K15M mf of 0.60.

5.4.5 Shah *et al.* Model of Diffusion for Matrices Using DCPD at Various mf of HPMC K15M.

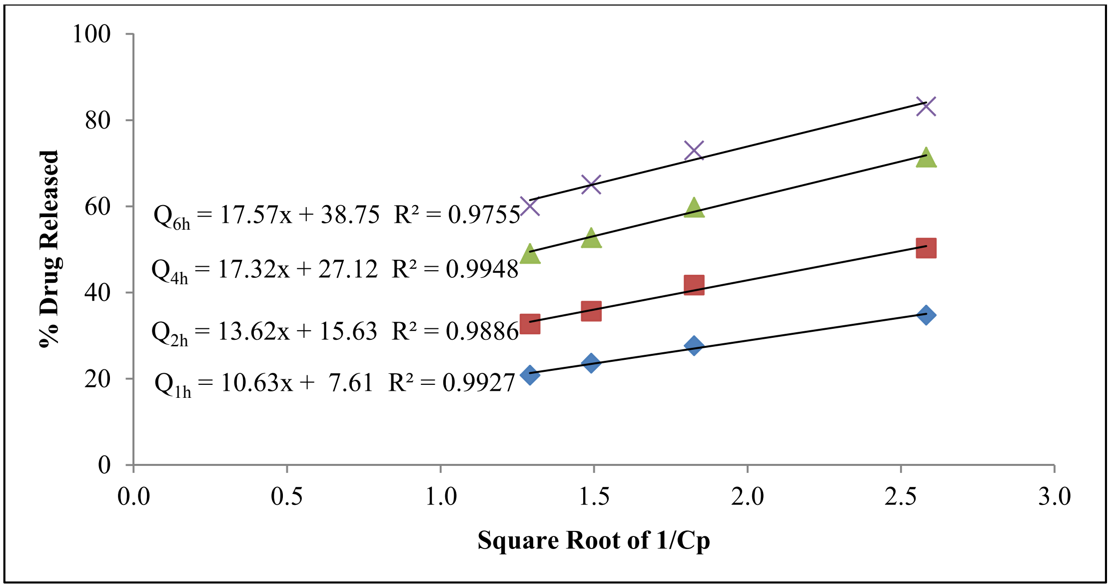


Figure 5.14 Regression analysis of percentage TMH released (Q) from matrices using DCPD and square root of $1/C_p$ of HPMC K15M at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; and ✕, 6 h.

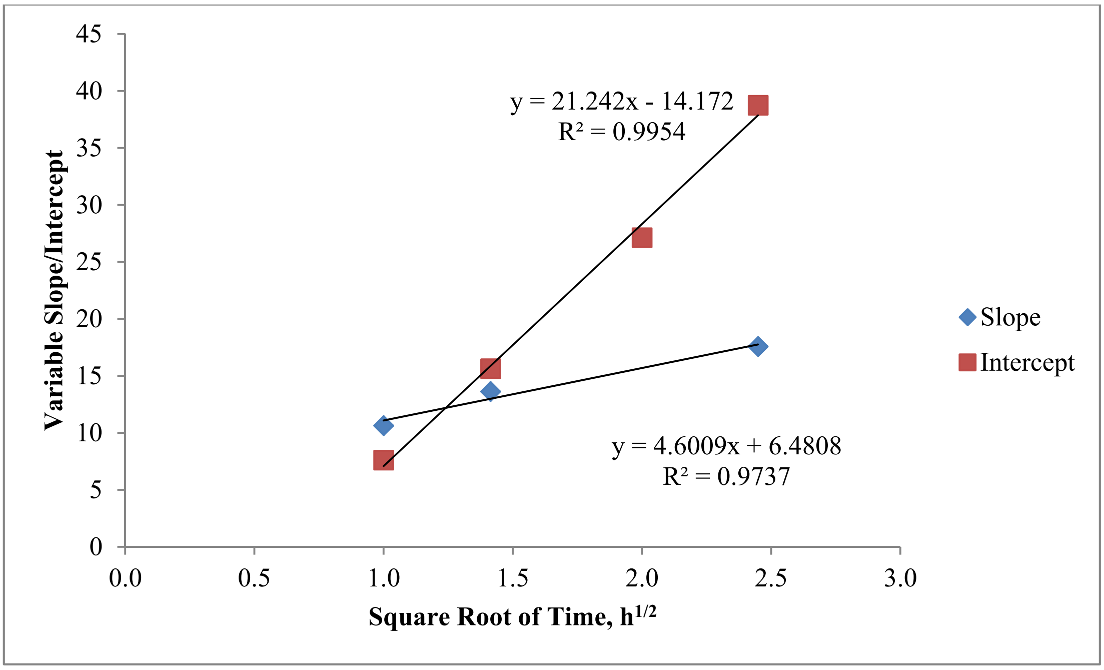


Figure 5.15 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using DCPD at various mf of HPMC K15M. Keys: ♦, slope; and ■, intercept.

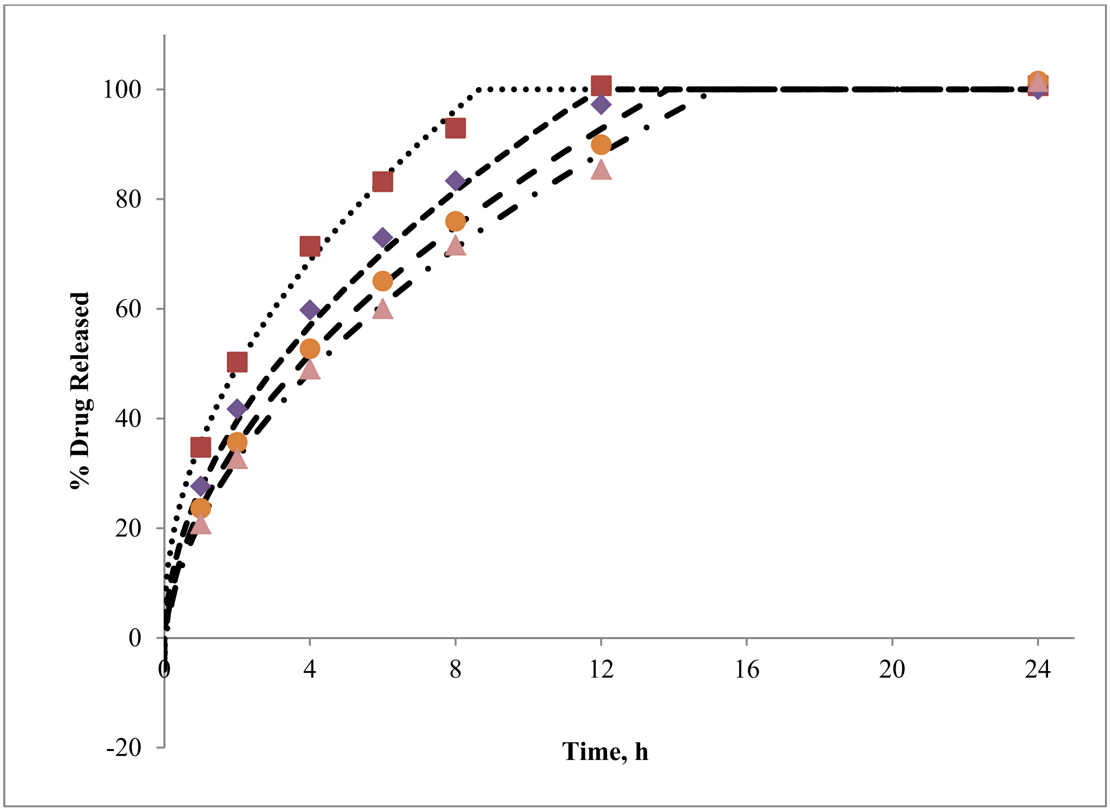


Figure 5.16 Predicted release profiles proposed by Shah et al. model versus experimental data for matrices using DCPD at various mf of K15M. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■ 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.6 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrices Using DCPD at Various mf of HPMC K15M.

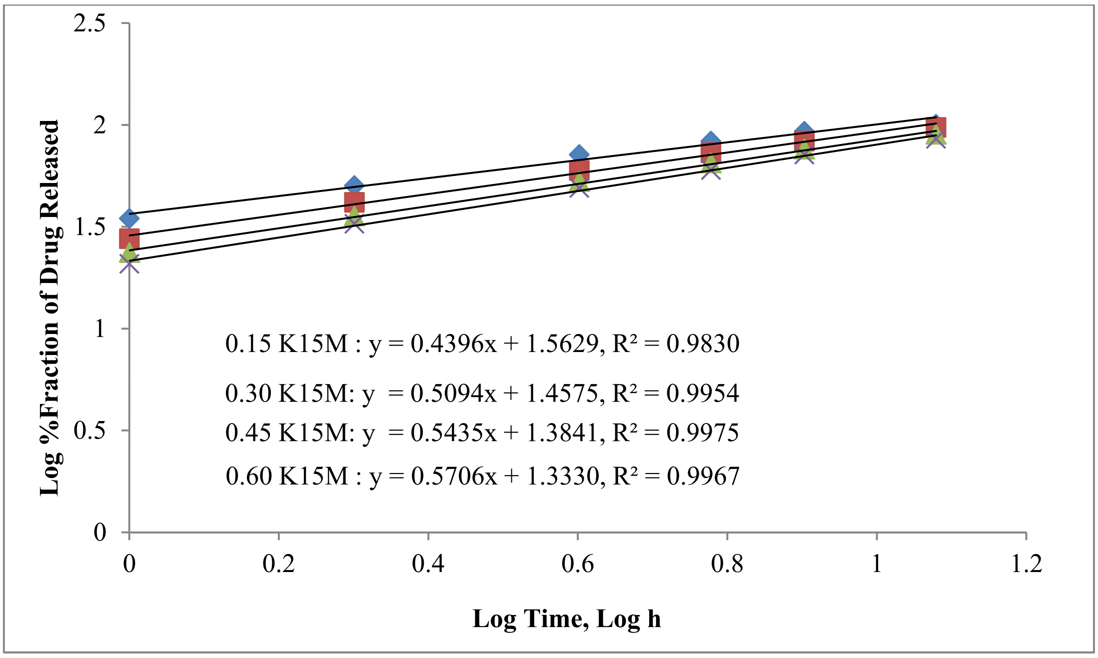


Figure 5.17 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using DCPD at various mf of HPMC K15M. Keys: ♦, 0.15 K15M; ■, 0.30 K15M; ▲, 0.45 K15M; and ✕, 0.60 K15M.

Table 5.21 Characterization of the order of release mechanism by the value of n for matrices using DCPD at various mf of K15M.

Filler	Polymer	mf	Release Exponent (*n*)	Drug Transport Mechanism
DCPD	HPMC K15M	0.15	0.44	quasi-Fickian diffusion
		0.30	0.51	non-Fickian transport
		0.45	0.54	non-Fickian transport
		0.60	0.57	non-Fickian transport

5.4.7 Higuchi model, the Release of TMH from Matrices Using DCPD at Various mf of XG.

Table 5.22 The percent drug released of TMH from matrices using DCPD at XG mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	35.90	36.23	36.23	35.62	35.69	35.94±0.29
2	1.41	48.81	49.33	49.18	49.27	49.19	49.16±0.20
4	2.00	65.96	65.47	65.47	65.54	65.54	65.60±0.21
6	2.45	75.81	74.83	75.57	75.56	75.56	75.47±0.37
8	2.83	83.77	83.02	87.54	82.90	82.52	83.96±2.06
12	3.46	89.59	89.63	90.01	89.33	89.90	89.69±0.27
24	4.90	99.15	100.51	100.05	98.69	99.00	99.48±0.77

Table 5.23 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at XG mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	26.25	25.45	27.48	25.86	25.68	26.14	0.72
Q_0, %	11.17	12.45	9.54	11.67	11.93	11.35	1.00
Lag time, min	-25.53	-29.35	-20.83	-27.08	-27.87	-26.13	2.92
R^2	0.9931	0.9930	0.9977	0.9912	0.9903	0.9931	0.0026

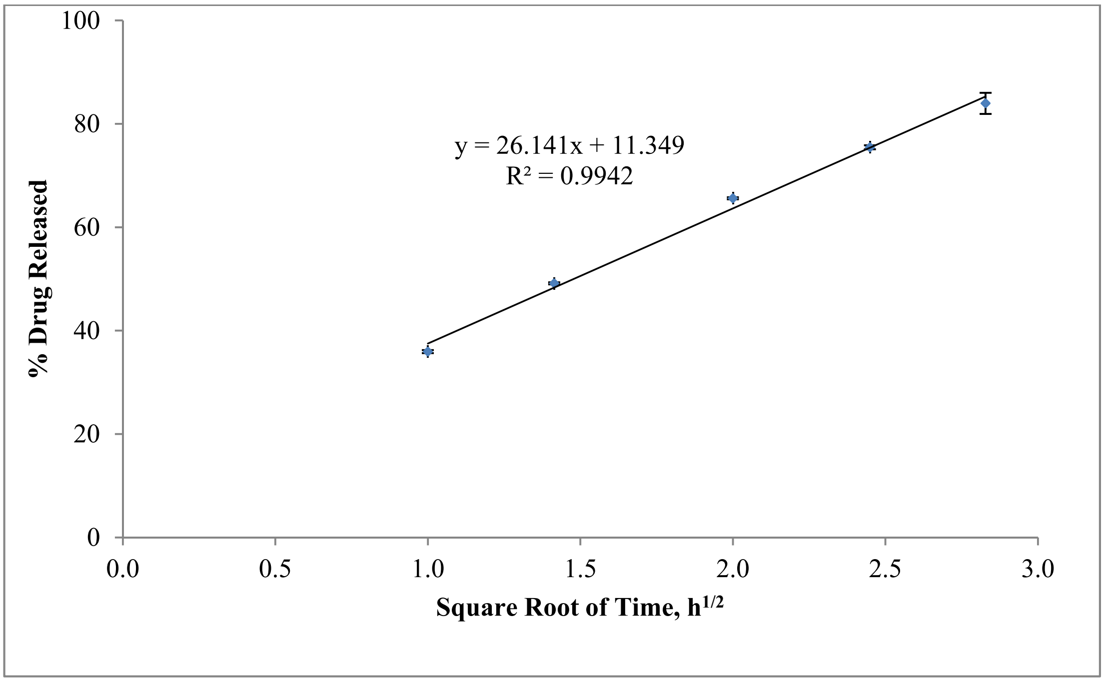


Figure 5.18 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at XG mf of 0.15.

Table 5.24 The percent drug released of TMH from matrices using DCPD at XG mf of 0.30.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	26.41	26.47	26.16	26.33	26.22	26.32 ± 0.13
2	1.41	37.57	37.19	36.42	36.67	36.88	36.95 ± 0.45
4	2.00	50.91	51.37	50.69	51.19	51.27	51.08 ± 0.28
6	2.45	60.70	60.82	59.67	59.80	60.37	60.27 ± 0.52
8	2.83	67.50	68.17	68.06	68.51	68.31	68.11± 0.38
12	3.46	75.82	76.38	76.62	75.28	74.86	75.79±0.73
24	4.90	87.08	88.47	89.41	86.65	87.35	87.79±1.13

Table 5.25 Kinetic constant *k*, natural convection (Q_0), lag time and R^2 for matrices using DCPD at XG mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	22.64	22.86	22.85	22.65	22.99	22.80	0.13
Q_0, %	4.81	4.49	3.92	4.46	4.04	-4.53	1.89
Lag time, min	-12.75	-11.78	-10.29	-11.81	-10.54	-11.44	0.90
R^2	0.9970	0.9971	0.9984	0.9972	0.9975	0.9974	0.0005

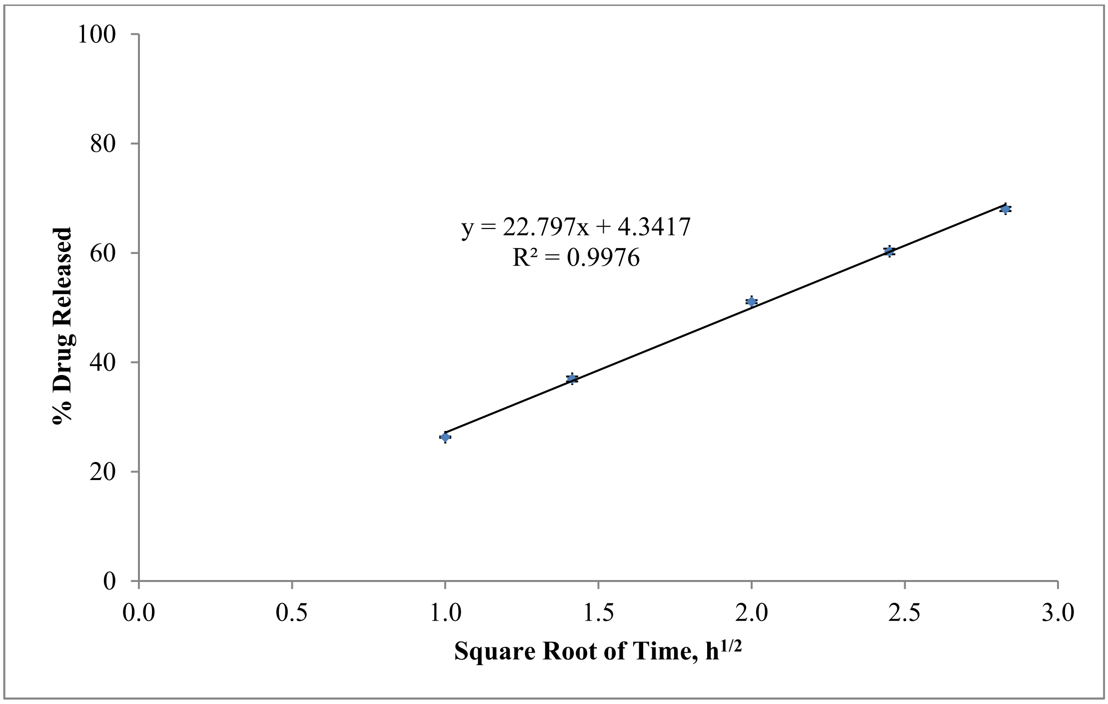


Figure 5.19 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at XG mf of 0.30.

Table 5.26 The percent drug released of TMH from matrices using DCPD at XG mf of 0.45.

Time		Tablet Number					
h	$h^{1/2}$	1	2	3	4	5	Mean ± SD
1	1.00	20.76	20.19	20.96	20.23	21.49	20.73±0.54
2	1.41	29.63	29.13	30.40	29.32	30.29	29.75±0.57
4	2.00	41.42	40.38	41.56	41.35	41.93	41.33±0.58
6	2.45	49.63	48.62	48.77	49.15	48.99	49.03±0.39
8	2.83	56.16	55.00	55.59	54.77	55.89	55.48±0.59
12	3.46	64.45	63.19	64.45	62.34	62.98	63.48±0.94
24	4.90	79.58	80.28	79.96	81.34	83.27	80.89±1.49

Table 5.27 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD containing XG at mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	19.38	19.01	18.69	19.01	18.67	18.95	0.26
Q_0, %	1.95	1.81	3.22	2.12	3.52	2.52	0.70
Lag time, min	-6.04	-5.71	-10.34	-6.69	-11.31	-8.02	2.33
R^2	0.9984	0.9984	0.9965	0.9952	0.9974	0.9972	0.0012

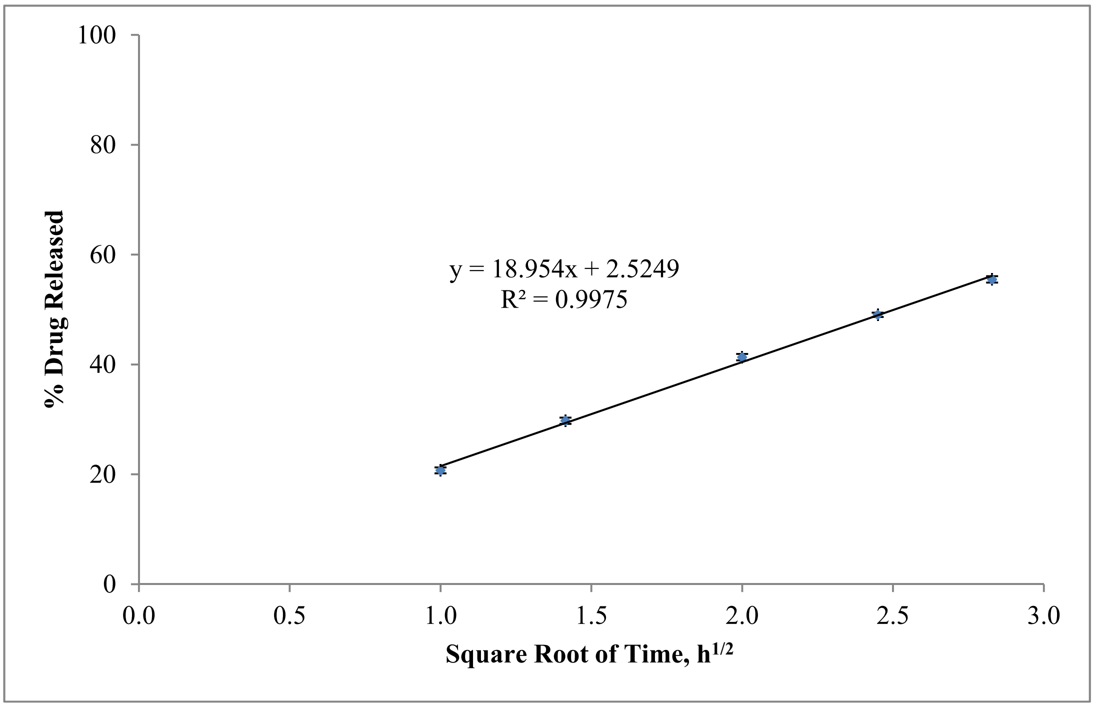


Figure 5.20 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at XG mf of 0.45.

Table 5.28 The percent drug released of TMH from matrices using DCPD at XG mf of 0.60.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	16.11	15.86	15.65	15.67	15.79	15.82 ± 0.19
2	1.41	24.62	23.29	23.42	23.57	23.15	23.61 ± 0.59
4	2.00	33.44	33.40	31.97	32.14	32.75	32.74±0.68
6	2.45	41.16	41.62	40.96	40.91	40.22	40.97±0.51
8	2.83	47.09	47.32	46.17	47.30	46.57	46.89±0.50
12	3.46	58.10	58.05	57.06	57.42	58.10	57.75±0.48
24	4.90	82.45	82.17	78.56	79.57	76.36	79.82±2.55

Table 5.29 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at XG mf of 0.60 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	2	3	4	5	Mean	SD
k, % $h^{-1/2}$	16.71	17.33	16.74	17.14	16.75	16.93	0.25
Q_0, %	0.09	-1.30	-0.81	-1.30	-0.78	-0.82	0.51
Lag time, min	-0.32	-4.50	-2.90	-4.55	-2.79	-3.01	1.54
R^2	0.9978	0.9994	0.9974	0.9982	0.9998	0.9985	0.0009

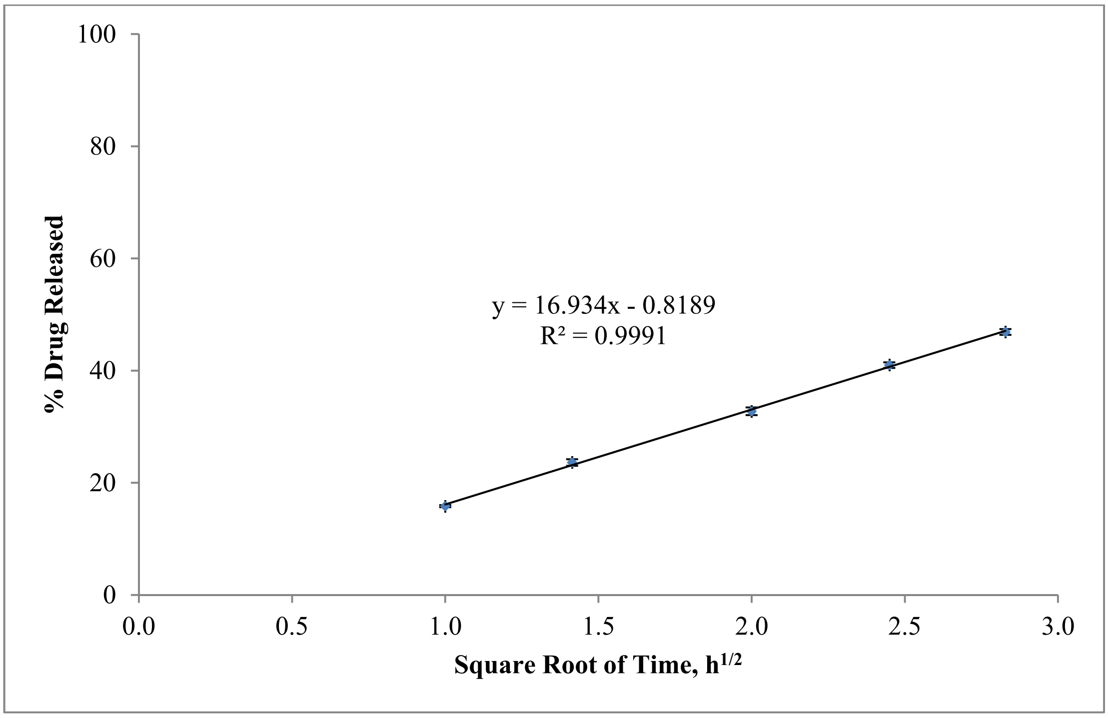


Figure 5.21 The linear regression of mean percentage TMH released and $\sqrt{t}$ at for matrices using DCPD at XG mf of 0.60.

5.4.8 Shah *et al.* Model of Diffusion for Matrix Using DCPD at Various mf of XG.

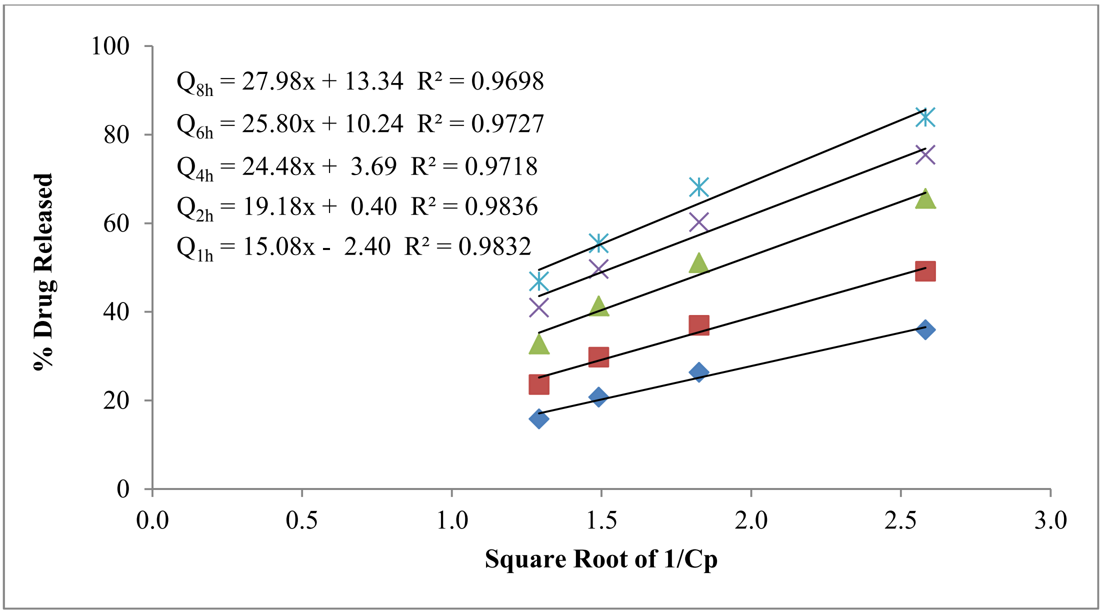


Figure 5.22 Regression analysis of percentage TMH released (Q) from matrices using DCPD and square root of $1/C_p$ of XG at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; ✕, 6 h; and ✱, 8 h.

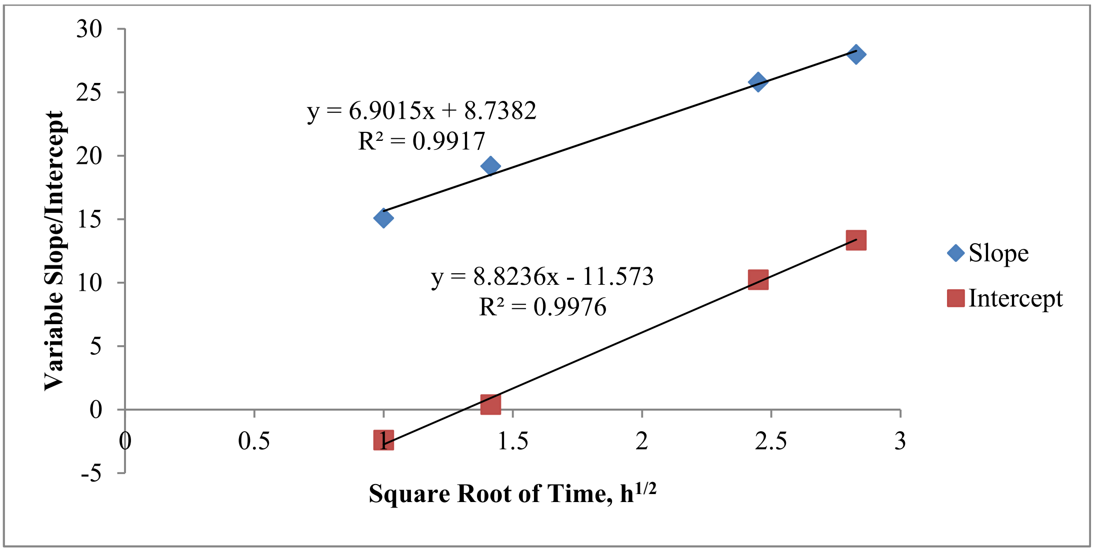


Figure 5.23 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using DCPD at various mf of XG. Keys: ♦, slope; and ■, intercept.

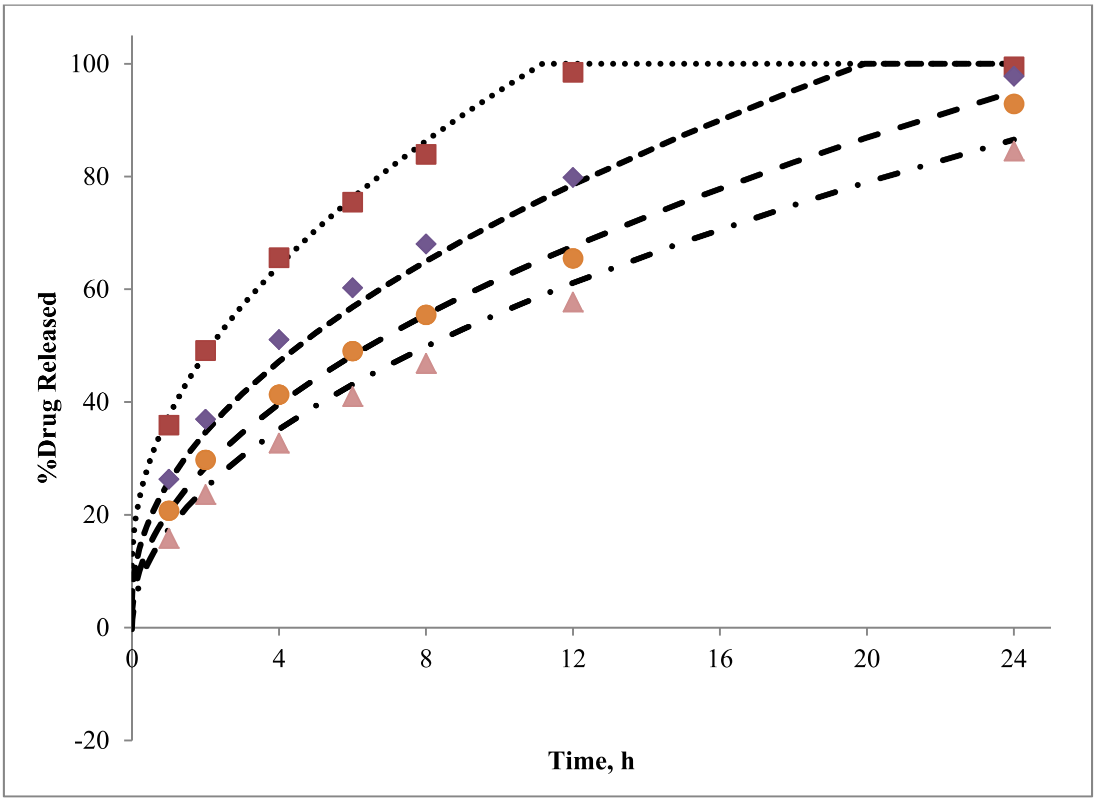


Figure 5.24 Predicted release profiles proposed by Shah *et al.* model versus experimental data for matrices using DCPD at various mf of XG. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■ 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.9 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrices Using DCPD at Various mf of XG.

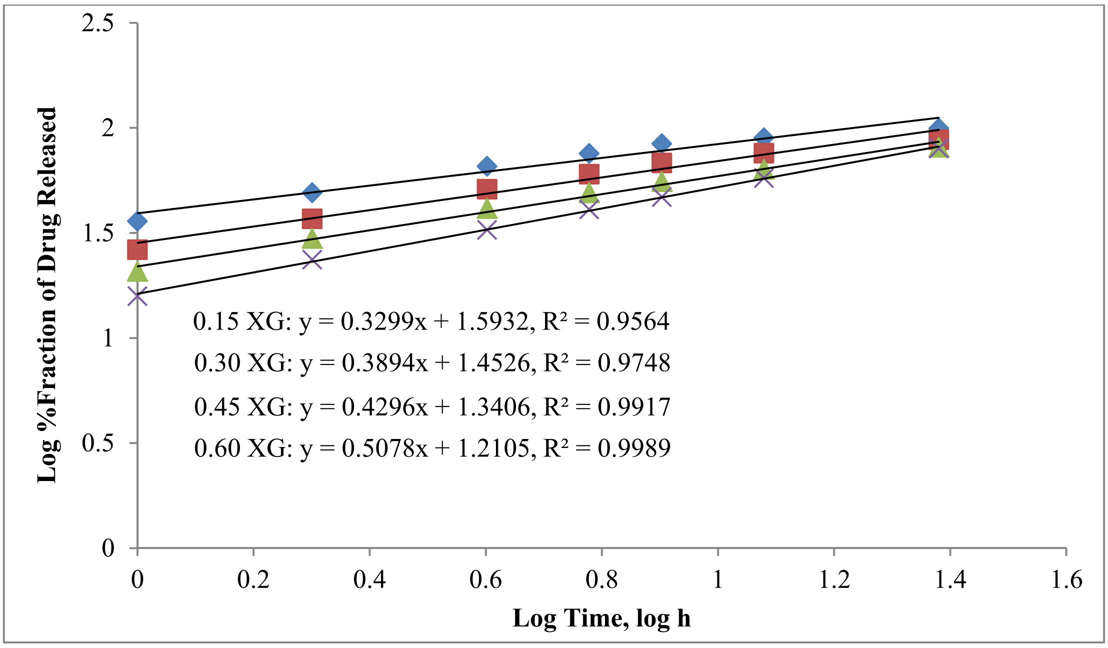


Figure 5.25 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using DCPD at various mf of XG. Keys: ♦, 0.15 XG; ■, 0.30 XG; ▲, 0.45 XG; and ✕, 0.60 XG.

Table 5.30 Characterization of the order of release mechanism by the value of n for matrices using DCP at various mf of XG

Filler	**Polymer**	**MF**	**Release Exponent (*n*)**	**Drug Transport Mechanism**
DCPD	XG	0.15	0.33	quasi-Fickian diffusion
		0.30	0.39	quasi-Fickian diffusion
		0.45	0.43	quasi-Fickian diffusion
		0.60	0.51	non-Fickian transport

5.4.10 Higuchi model, the Release of TMH from Matrices Using DCPD at Various mf of GG.

Table 5.31 The percent drug released of TMH from matrices using DCPD at GG mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	45.61	46.47	43.63	44.18	41.49	44.28±1.92
2	1.41	63.13	64.07	60.61	61.98	59.49	61.86±1.85
4	2.00	83.21	82.85	79.46	83.28	81.39	82.04±1.63
6	2.45	92.48	93.41	90.14	90.66	89.72	91.28±1.59
8	2.83	97.56	97.82	96.95	97.04	97.77	97.43±0.41
12	3.46	99.94	100.28	99.02	99.13	99.70	99.61± 0.53
24	4.90	101.2	101.44	100.84	100.99	100.99	101.09± 0.23

Table 5.32 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at GG mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	32.54	32.28	32.05	32.58	33.77	32.64	0.59
Q_0, %	15.27	16.31	13.47	14.12	10.08	13.85	2.12
Lag time, min	-28.16	-30.32	-25.22	-26.00	-17.91	-25.52	4.20
R^2	0.9828	0.9870	0.9891	0.9728	0.9776	0.9819	0.0060

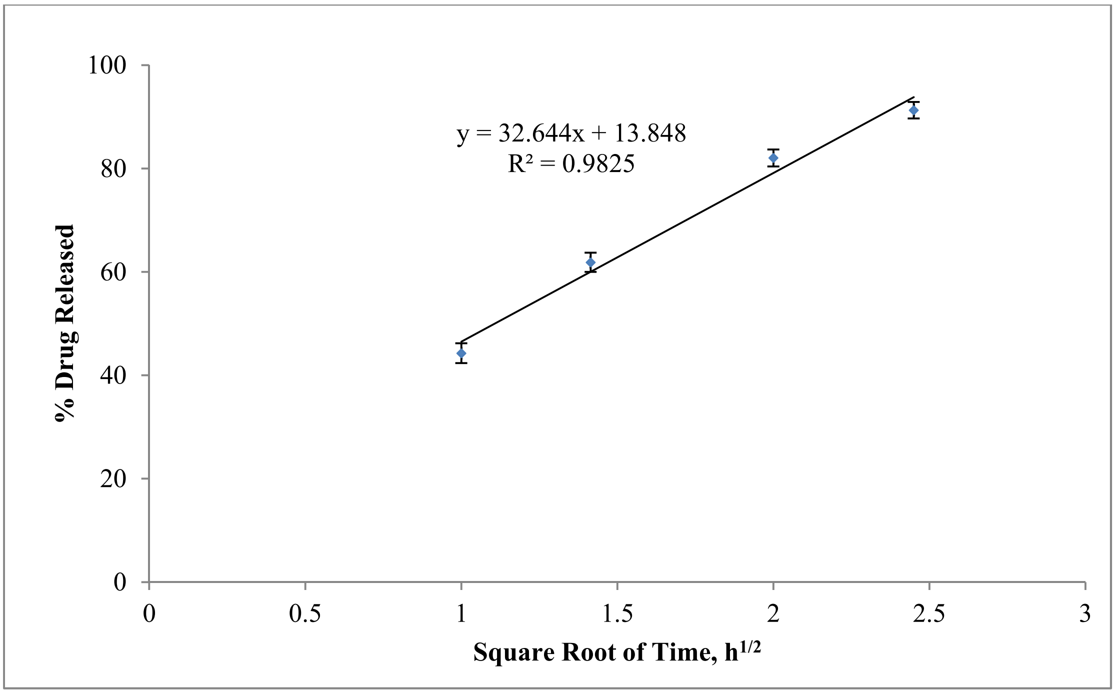


Figure 5.26 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at GG mf of 0.15.

Table 5.33 The percent drug released of TMH from matrices using DCPD at GG mf of 0.30.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	41.00	39.76	38.80	39.54	41.22	40.07± 1.02
2	1.41	57.60	56.31	54.87	56.35	56.98	56.42± 1.02
4	2.00	77.19	75.35	75.02	76.72	77.05	76.27± 1.01
6	2.45	87.57	85.61	85.60	87.06	87.51	86.67± 0.99
8	2.83	94.74	92.67	92.85	93.86	93.53	93.53± 0.83
12	3.46	99.65	97.97	99.40	99.16	99.42	99.12± 0.66
24	4.90	102.33	100.57	101.96	102.18	102.18	101.86± 0.76

Table 5.34 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at GG mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	32.26	31.71	32.54	33.00	32.21	33.34	0.47
Q_0, %	10.48	9.85	7.74	8.28	10.42	9.35	1.27
Lag time, min	-19.49	-18.64	-14.27	-15.05	-19.41	-17.37	2.51
R^2	0.9863	0.9889	0.9911	0.9888	0.9913	0.9893	0.0020

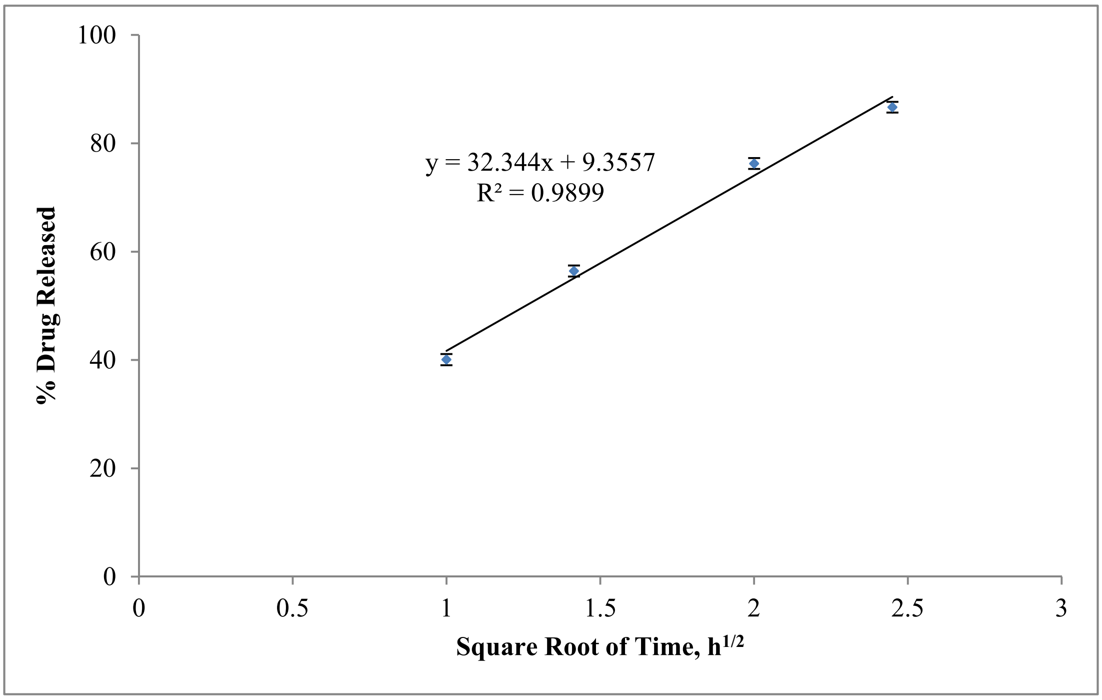


Figure 5.27 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at GG mf of 0.30.

Table 5.35 The percent drug released of TMH from matrices using DCPD at GG mf of 0.45.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	38.25	39.07	37.83	39.22	38.80	38.64± 0.58
2	1.41	54.29	54.38	52.36	54.11	53.82	53.79± 0.83
4	2.00	71.96	74.90	73.57	75.24	74.45	74.03± 1.32
6	2.45	82.81	86.00	85.07	86.10	87.34	85.46± 1.69
8	2.83	90.25	92.01	91.76	92.01	92.62	91.73± 0.88
12	3.46	97.33	97.77	97.11	98.19	98.02	97.68± 0.46
24	4.90	101.95	101.29	101.01	101.38	101.48	101.48±0.38

Table 5.36 Kinetic constant k, natural convection (Q_0), lag time and R^2 for DCPD matrices containing GG at mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	30.62	32.71	33.07	32.25	33.71	32.47	1.16
Q_0, %	9.29	7.46	5.46	7.21	5.77	7.04	1.53
Lag time, min	-18.20	-13.68	-9.91	-13.41	-10.27	-13.10	3.34
R^2	0.9915	0.9937	0.9953	0.9961	0.9977	0.9949	0.0002

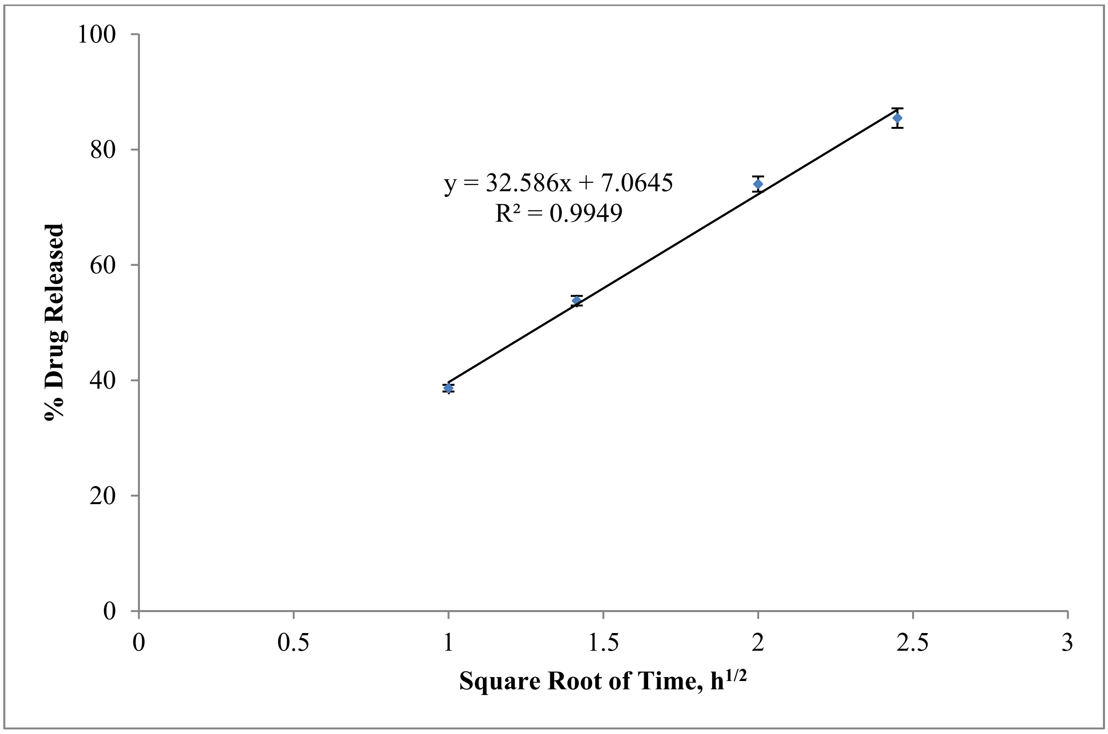


Figure 5.28 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at GG mf of 0.45.

Table 5.37 The percent drug released of TMH from matrices using DCPD at GG mf of 0.60.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	33.41	33.60	33.09	34.84	35.17	34.02± 0.92
2	1.41	46.91	47.01	46.39	48.18	48.95	47.49± 1.05
4	2.00	64.36	64.99	64.01	65.36	65.59	64.86± 0.67
6	2.45	76.17	75.28	74.84	75.48	75.71	75.50± 0.49
8	2.83	81.82	81.40	79.74	82.16	81.97	81.42± 0.98
12	3.46	95.31	96.01	95.39	95.48	96.90	95.82± 0.67
24	4.90	101.57	101.53	100.53	101.02	102.32	101.39± 0.67

Table 5.38 Kinetic constant k, natural convection (Q_0), lag time and R^2 for matrices using DCPD at GG mf of 0.60 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	29.48	28.96	28.92	28.15	27.95	28.69	0.63
Q_0, %	4.66	5.56	4.99	7.69	8.41	6.26	1.68
Lag time, min	-9.48	-11.52	-10.01	-16.39	-18.05	-13.09	3.89
R^2	0.9981	0.9951	0.9966	0.9950	0.9941	0.9958	0.0016

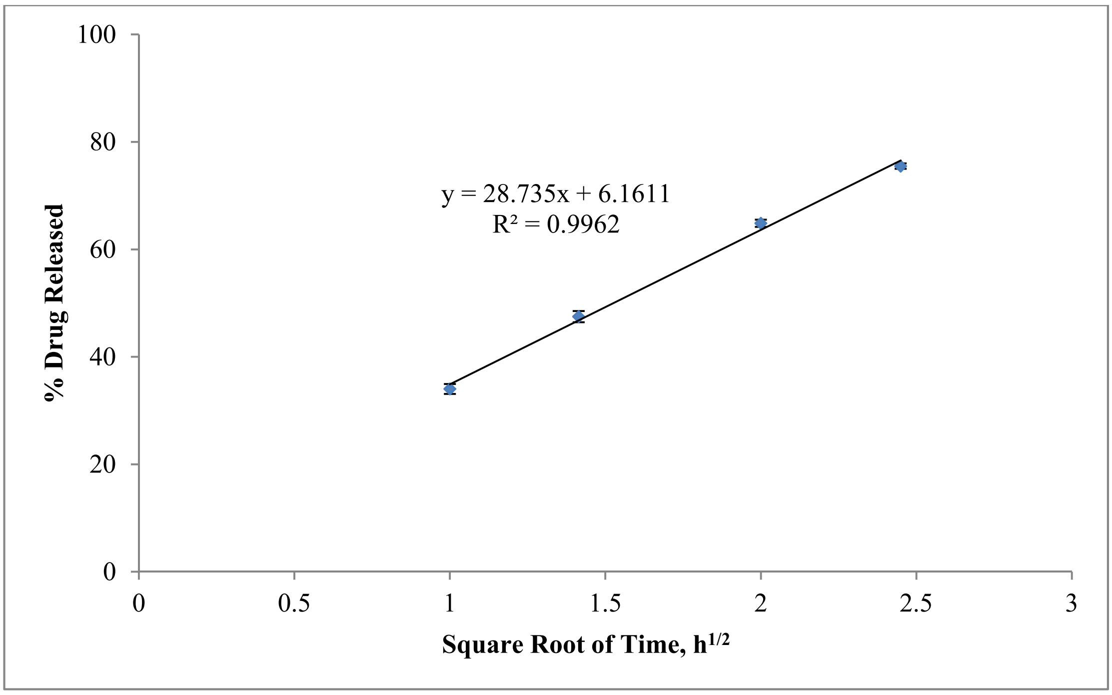


Figure 5.29 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using DCPD at GG mf of 0.60.

5.4.11 Shah *et al.* Model of Diffusion for Matrices Using DCPD at Various mf of GG.

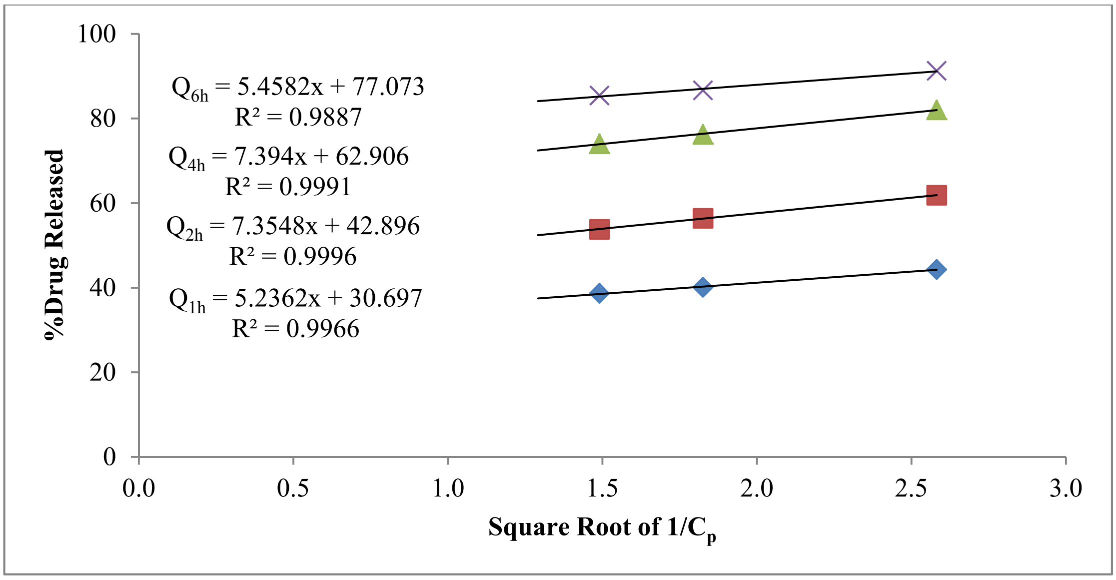


Figure 5.30 Regression analysis of percentage TMH released (Q) from matrices using DCPD and square root of $1/C_p$ of GG at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; and ✕, 6 h.

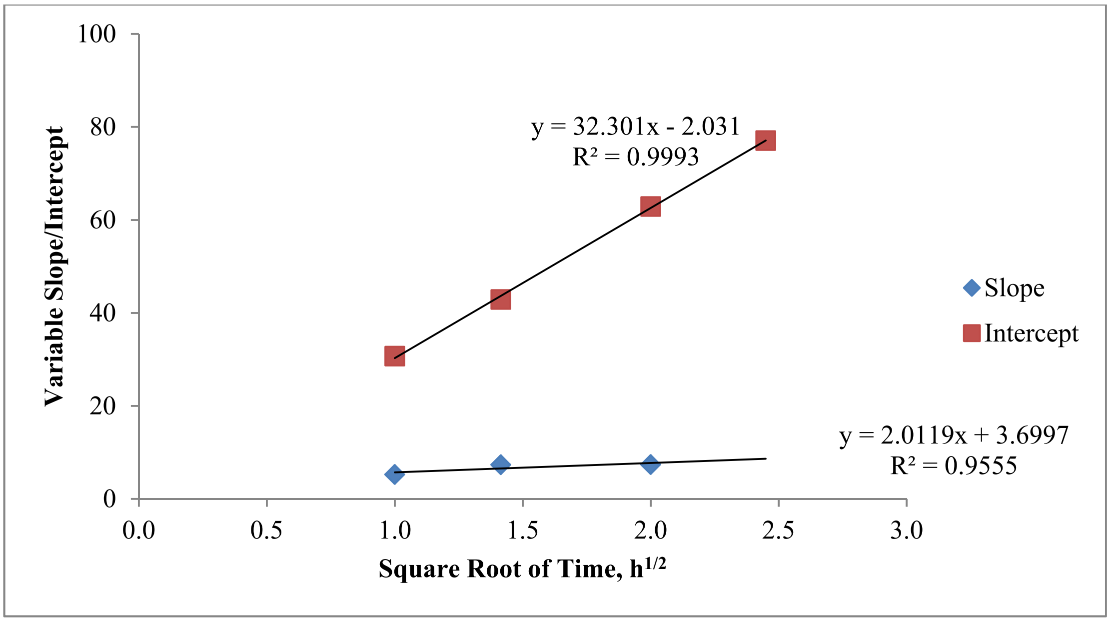


Figure 5.31 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using DCPD at various mf of GG. Keys: ♦, slope; and ■, intercept.

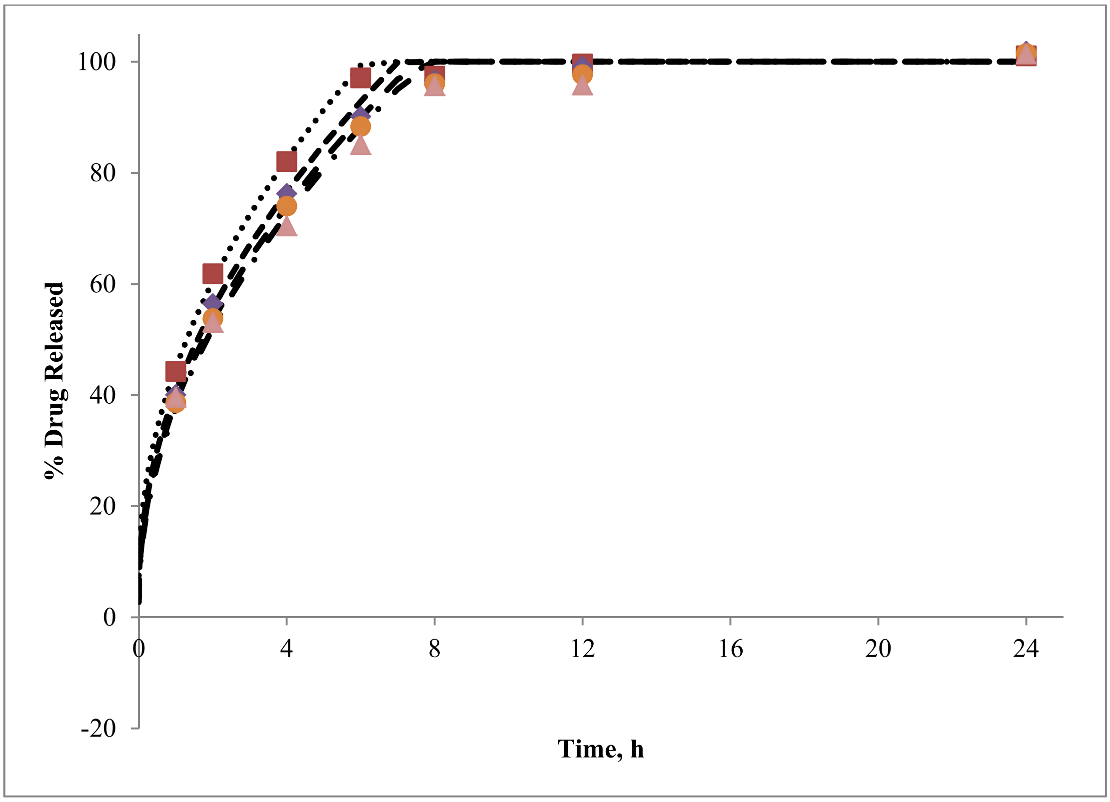


Figure 5.32 Predicted release profiles proposed by Shah *et al.* model versus experimental data for matrices using DCPD at various mf of GG. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■ 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.12 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrix Using DCPD at Various mf of GG.

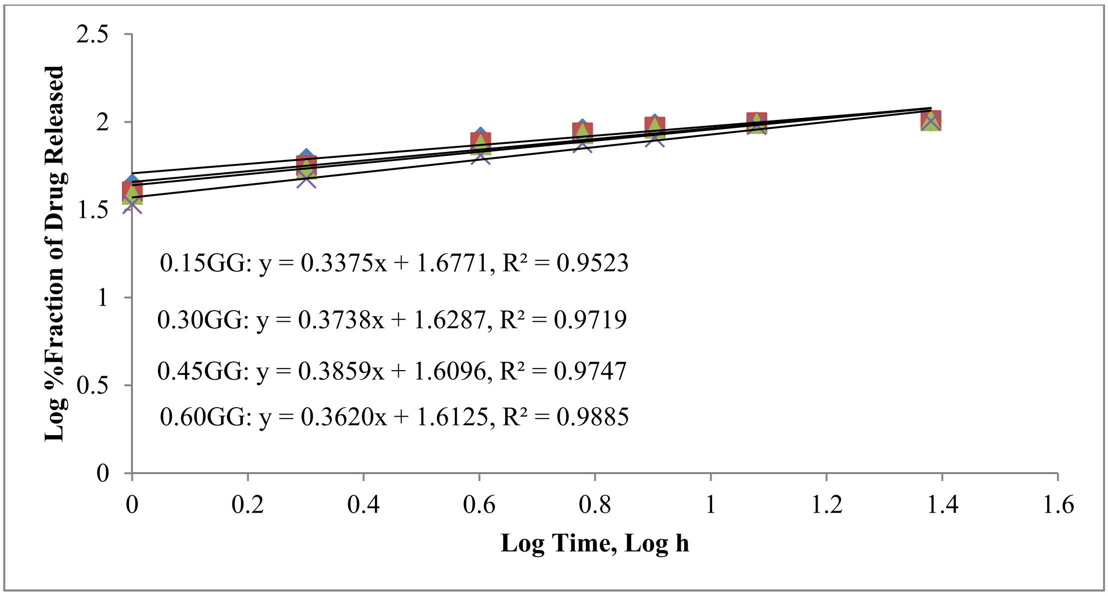


Figure 5.33 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using DCPD at various mf of GG. Keys: ♦, 0.15 GG; ■, 0.30 GG; ▲, 0.45 GG; and ×, 0.60 GG.

Table 5.39 Characterization of the order of release mechanism by the value of n for matrices using DCPD at various mf of GG.

Filler	**Polymer**	**MF**	**Release exponent (*n*)**	**Drug transport mechanism**
DCPD	GG	0.15	0.34	quasi-Fickian Diffusion
		0.30	0.37	quasi-Fickian Diffusion
		0.45	0.39	quasi-Fickian Diffusion
		0.60	0.36	quasi-Fickian Diffusion

Table 5.40 Rate constant, *k* and ANOVA test of matrices using DCPD at various mf of different polymers.

Polymer	MF	Release rate, % $h^{-1/2}$				
		1	2	3	4	5
HPMC K4M	0.15	32.18	32.72	32.61	32.93	32.19
	0.30	29.88	29.98	29.94	30.03	29.60
	0.45	27.81	27.86	27.46	28.12	28.33
	0.60	26.29	26.46	26.40	26.95	26.28
HPMC K15M	0.15	33.67	33.51	33.77	33.83	33.94
	0.30	30.39	30.45	30.61	30.34	30.41
	0.45	28.23	29.06	28.59	28.20	28.83
	0.60	27.98	27.61	26.27	27.47	28.02
XG	0.15	26.25	25.45	27.48	25.86	25.68
	0.30	22.64	22.86	22.85	22.65	22.99
	0.45	19.38	19.01	18.69	19.01	18.67
	0.60	16.71	17.33	16.74	17.14	16.75
GG	0.15	32.54	32.28	32.05	32.58	33.77
	0.30	32.26	31.71	32.54	33.00	32.21
	0.45	30.62	32.71	33.07	32.25	33.71
	0.60	29.48	28.96	29.92	28.15	27.95

Source of Variation	Sum of Square (SS)	Degree of Freedom (DF)	Mean of Square (MS)	F-Ratio	p-value
Between Groups	1809.97	15	120.66	422.39	6.21×10^{-58}*
Within Groups	18.28	64	0.29		
Total	**1828.26**	**79**			

*highly significant difference (p << 0.01)

Table 5.41 Rate constant (*k*) of matrices using DCP at various mf of each polymers, LSD 1% allowance (α = 0.01, 2-tailed).

t = 2.655 at *DF* of 64	LSD: 1% allowance = $t\sqrt{s^2(\frac{1}{n_i}+\frac{1}{n_j})}$ = 0.90															
R_x	0.15 K15M	0.15 GG	0.15 K4M	0.45 GG	0.30 GG	0.30 K15M	0.30 K4M	0.60 GG	0.45 K15M	0.45 K4M	0.60 K15M	0.60 K4M	0.15 XG	0.30 XG	0.45 XG	0.60 XG
1	33.67	32.54	32.18	30.62	32.26	30.39	29.88	29.48	28.23	27.81	27.98	26.29	26.25	22.64	19.38	16.71
2	33.51	32.28	32.72	32.71	31.71	30.45	29.98	28.96	29.06	27.86	27.61	26.46	25.45	22.86	19.01	17.33
3	33.77	32.05	32.61	33.07	32.54	30.61	29.94	29.92	28.59	27.46	26.27	26.40	27.48	22.85	18.69	16.74
4	33.83	32.58	32.93	32.25	33.00	30.34	30.03	28.15	28.20	28.12	27.47	26.95	25.86	22.65	19.01	17.14
5	33.94	33.77	32.19	33.71	32.21	30.41	29.60	27.95	28.83	28.33	28.02	26.28	25.68	22.99	18.67	16.75
Mean($\bar{X}$)	33.74	32.64	32.53	32.47	32.34	30.44	29.89	28.89	28.58	27.92	27.47	26.48	26.14	22.80	18.95	16.93
$\bar{X}$– (%A)	32.84	31.74	31.63	31.57	31.44	29.54	28.99	27.99	27.68	27.02	26.57	25.58	25.24	21.90	18.05	16.03

Table 5.41 Rate constant (*k*) of matrices using DCPD at various mf of each polymer, LSD 1% allowance (α = 0.01, 2-tailed)(cont.).

For each mf of polymers:

K4M: 0.15 > 0.30 > 0.45 > 0.60

K15M: 0.15 > 0.30 > 0.45 > 0.60

XG: 0.15 > 0.30 > 0.45 > 0.60

GG: 0.15 ≈ 0.30 ≈ 0.45 > 0.60

For each polymer:

At 0.15: K15M ≈ GG ≈ K4M > XG

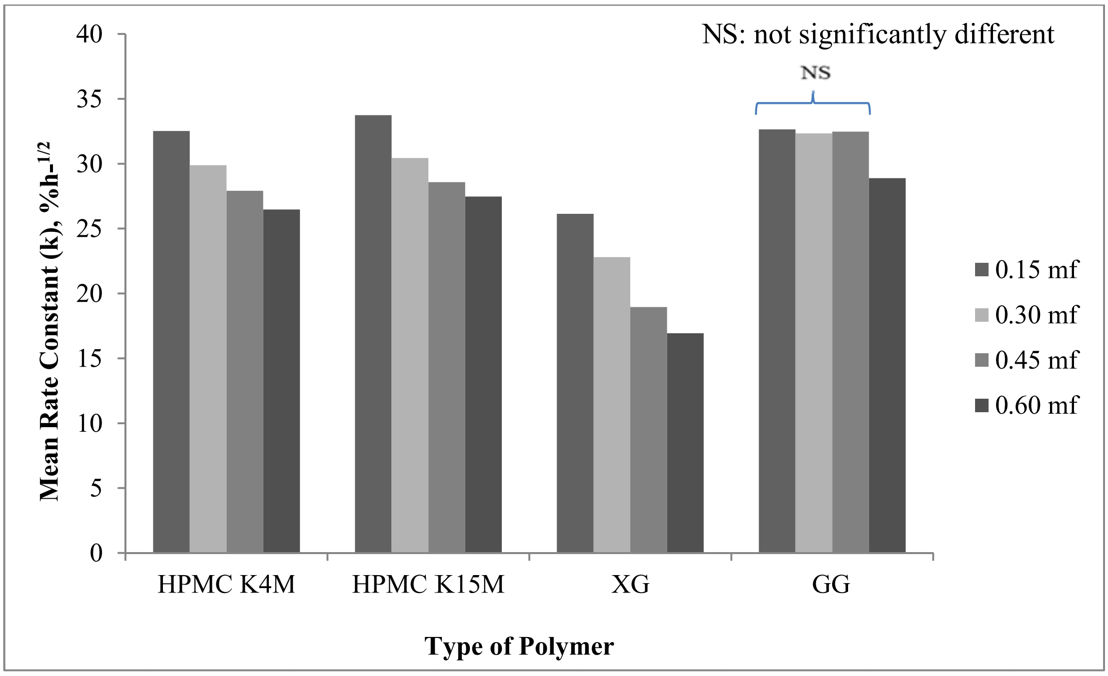
At 0.30: GG > K15M ≈ K4M > XG

At 0.45: GG > K15M ≈ K4M > XG

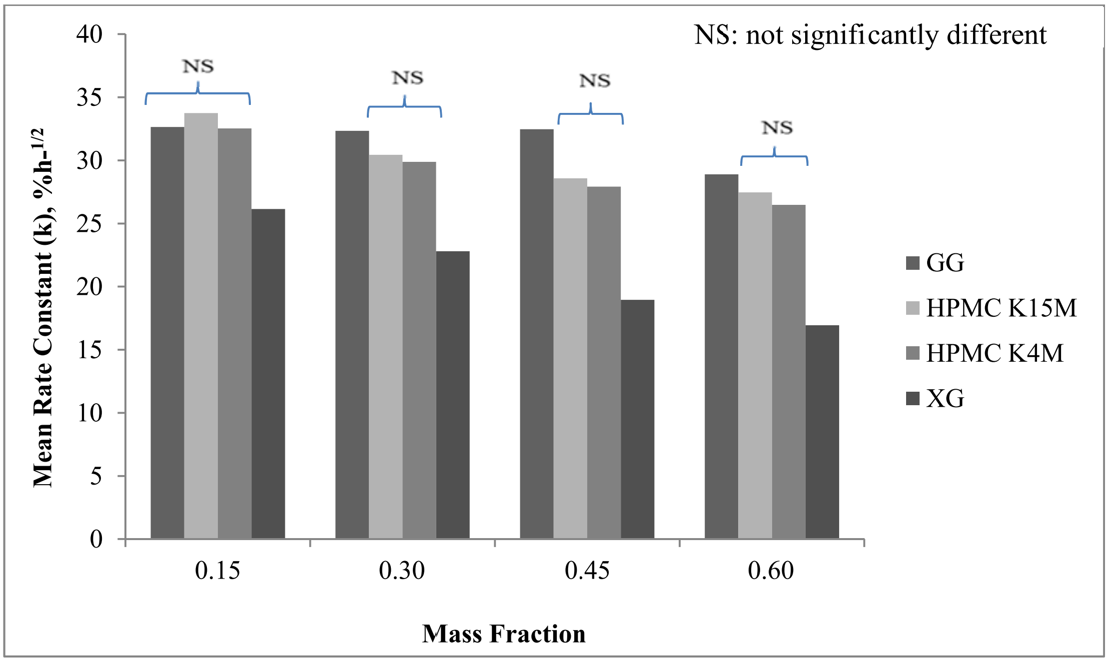
At 0.60: GG > K15M ≈ K4M > XG

The composition of TMH formulations prepared with DCPD containing various polymers are shown in Table 4.1. As depicted in Fig. 5.2- 5.5 for HPMC K4M matrices, Fig. 5.11 – 5.14 for HPMC K15M matrices, Fig. 5.18– 5.21 for XG matrices, and Fig. 5.27 – 5.30 for GG matrices plots of mean percentage of drug released from each matrix containing DCPD at various mass fractions of different polymers versus square root of time provided a linear relationship. These showed that release of TMH from all matrices obeyed Higuchi's model of diffusion with high regression coefficient (R^2).

From equation (4), the kinetics constants, *k* were received by linear regression analysis between percentage drug release from various matrices and square root of time. From such regression analysis, the data of kinetics constants *k*, natural convection (Q_o), lag time and R^2 were received as shown in Table 5.5, 5.7, 5.9 and 5.11 for HPMC K4M; Table 5.14, 5.16, 5.18 and 5.20 for HPMC K15M; Table 5.23, 5.25, 5.27 and 5.29 for XG and Table 5.32, 5.34, 5.36 and 5.38 for GG respectively. For each polymer, the concentration of polymer, K4M, K15M and XG increased from the mass fraction of 0.15 to 0.30, 0.45 or 0.60, the release kinetic constant, k decreased.



(a)



(b)

Figrure 5.34 (a) The bar chart of mean rate constant (*k*) and type of polymers of matrix tablets using DCPD at mf of polymer.

(b) The bar chart of mean rate constant (*k*) and mf of matrix tablets using DCPD as a filler.

Analysis of variance ((ANOVA), α = 0.01) of these release data showed a significant difference in k of different formulations. Furthermore, from a multiple-comparison of these kinetics constants, the TMH release rate from matrices containing various polymer were ranked as follows: (i) for HPMC K4M, HPMC K15M and XG: 0.15 > 0.30 > 0.45 > 0.60 respectively; (ii) for GG: 0.15 ≈ 0.30 ≈ 0.45 > 0.60. For each mass fraction of polymers, k of matrices using different polymers might be ranked as (i) at mf of 0.15: GG ≈ K4M ≈ K15M > XG, and (ii) at mf of 0.30 to 0.60: GG > K15M ≈ K4M > XG.

As depicted in Fig. 5.6 for HPMC K4M, Fig. 5.14 for HPMC K15M, and Fig. 5.22 for XG, plots of mean percentage of drug released at different given times (1-6 h) for HPMC K4M and HPMC K15M) and 1-8 h for XG from each matrix versus square root of $1/C_p$, showed good linearity. From linear regression analysis from these plots in each Figure, the intercept (a_i) and slope (b_i) for each polymer were obtained with high regression coefficients.

Using Eq. (16), the working equations to predict drug release from matrices containing DCPD are as follows:

Q = (-12.60 + 6.28x) + (18.94 + 5.84x)$\sqrt{t}$ for HPMC K4M Eq. (31)

Q = (-14.17 + 6.48x) + (21.24 + 4.6x)$\sqrt{t}$ for HPMC K15M Eq. (32)

Q = (-11.57 + 8.74x) + (8.82 + 6.90x)$\sqrt{t}$ for XG Eq. (33)

Q = (-2.03 + 3.70x) + (32.30 + 2.01x)$\sqrt{t}$ for GG Eq. (34)

where x = $\sqrt{(1/C_p)}$

Fig. 5.8, Fig. 5.16, Fig. 5.24 and Fig. 5.32 showed the predicted TMH release profiles proposed by Shah et al. model versus experimental data for DCPD matrices using HPMC K4M, K15M, XG and GG, respectively. Almost experimental data from release testing are closely matched the predicted release profiles. This implies that the release profiles of TMH from various matrices can be predicted mainly by the diffusion model of Shah et al for insoluble filler, DCPD whereas experimental data of XG at low mass fraction showed overestimation due to concentration of polymer and structural strength too low to maintain matrix and caused easily matrix erosion resulting in higher drug releasing while some lines of XG experimental data showed underestimation because of highly water uptake to XG matrix caused high hydration rate and high tortuosity resulting in low porosity and low drug releasing.

The Korsmeyer-Peppas equation ($M_t /M_\alpha = Kt^n$) is the best equation to study the *in-vitro* drug release profile in such matrix formulations. The main parameters for Korsmeyer-Peppas equation (*n* values) were obtained from linear regression analysis. The n values indicate that which mechanism is prominent in drug release from matrices.

DCPD matrices containing HPMC K4M and HPMC K15M at mf of 0.15 followed quasi-Fickian diffusion (n < 0.45), and those matrices containing HPMC K4M and HPMC K15M at mf of 0.30, 0.45 and 0.60 followed non-Fickian transport (0.45 < n = 0.89) as shown in Table 5.12 and 5.21 respectively. DCPD matrices containing XG at mf of 0.15, 0.30 and 0.45 followed quasi-Fickian diffusion mechanism (0 < n < 0.45) those matrices containing XG at mf of 0.60 followed non-Fickian transport (0.45 < n = 0.89) as shown in Table 5.30. DCPD matrices containing GG at mf of 0.15, 0.30, 0.45 and 0.60 followed quasi-Fickian diffusion mechanism (n < 0.45) as shown in Table 5.39.

Table 5.42 Natural convection, % and ANOVA test of matrices using DCPD at various mf of different polymers.

Polymer	mf	Natural Convection, %				
		1	2	3	4	5
HPMC K4M	0.15	5.95	5.86	6.37	6.43	6.36
	0.30	-0.56	-0.48	0.41	0.18	0.05
	0.45	-2.74	-4.30	-3.49	-3.82	-3.08
	0.60	-4.37	-4.57	-4.38	-5.28	-3.57
HPMC K15M	0.15	2.49	2.24	1.35	1.23	2.80
	0.30	-2.12	-1.88	-1.90	-2.32	-1.27
	0.45	-4.57	-4.44	-5.03	-4.98	-4.95
	0.60	-7.14	-6.44	-4.69	-6.24	-7.52
XG	0.15	11.17	12.45	9.54	11.67	11.93
	0.30	4.81	4.49	3.92	4.46	4.04
	0.45	1.95	1.81	3.22	2.12	3.52
	0.60	0.09	-1.30	-0.81	-1.30	-0.78
GG	0.15	15.27	16.31	13.47	14.12	10.08
	0.30	10.48	9.85	7.74	8.28	10.42
	0.45	9.29	7.46	5.46	7.21	5.77
	0.60	4.66	5.56	4.99	7.69	8.41

Source of Variation	Sum of Square (SS)	Degree of Freedom (DF)	Mean of Square (MS)	F-Ratio	p-value
Between Groups	2797.83	15	186.52	169.41	1.75×10^{-45}
Within Groups	70.46	64	1.10		
Total	**2868.30**	**79**			

*highly significantly difference (p << 0.01)

Table 5.43 Natural convection (Q_0), % of matrices using DCPD at various mf of different polymers, LSD 1% allowance (α = 0.01, 2-tailed).

t = 2.655 at *DF* of 64	LSD 1% allowance = $t\sqrt{s^2(\frac{1}{n_i}+\frac{1}{n_j})}$ = 1.76															
R_x	0.15 GG	0.15 XG	0.30 GG	0.45 GG	0.60 GG	015 K4M	0.30 XG	0.45 XG	0.15 K15M	0.30 K4M	0.60 XG	0.30 K15M	0.45 K4M	0.60 K4M	0.45 K15M	0.60 K15M
1	15.27	11.17	10.48	9.29	4.66	5.95	4.81	1.95	2.49	-0.56	0.09	-2.12	-2.74	-4.37	-4.57	-7.14
2	16.31	12.45	9.85	7.46	5.56	5.86	4.49	1.81	2.24	-0.48	-1.3	-1.88	-4.30	-4.57	-4.44	-6.44
3	13.47	9.54	7.74	5.46	4.99	6.37	3.92	3.22	1.35	0.41	-0.81	-1.90	-3.49	-4.38	-5.03	-4.69
4	14.12	11.67	8.28	7.21	7.69	6.43	4.46	2.12	1.23	0.18	-1.3	-2.32	-3.82	-5.28	-4.98	-6.24
5	10.08	11.93	10.42	5.77	8.41	6.36	4.04	3.52	2.80	0.05	-0.78	-1.27	-3.08	-3.57	-4.95	-7.52
Mean($\bar{X}$)	13.85	11.35	9.35	7.04	6.26	6.19	4.34	2.52	2.02	-0.08	-0.82	-1.90	-3.49	-4.43	-4.79	-6.41
$\bar{X}$–(% A)	12.09	9.59	7.59	5.28	4.50	4.43	2.58	0.76	0.26	-1.84	-2.58	-3.66	-5.25	-6.19	-6.55	-8.17

Table 5.43 Natural convection, % of matrices using DCPD at various mf of different polymers, LSD 1% allowance ($\alpha = 0.01$, 2-tailed) (cont.).

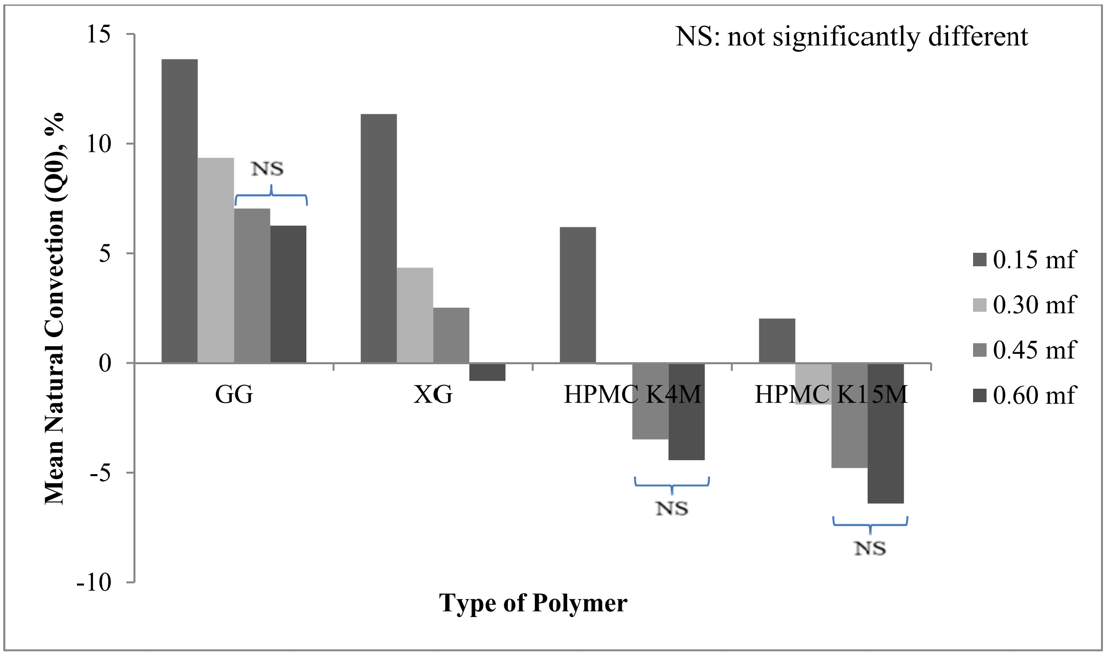
For each mf of polymers:

K4M: 0.15 > 0.30 > 0.45 ≈ 0.60
K15M: 0.15 > 0.30 > 0.45 ≈ 0.60
XG: 0.15 > 0.30 > 0.45 > 0.60
GG: 0.15 > 0.30 > 0.45 ≈ 0.60

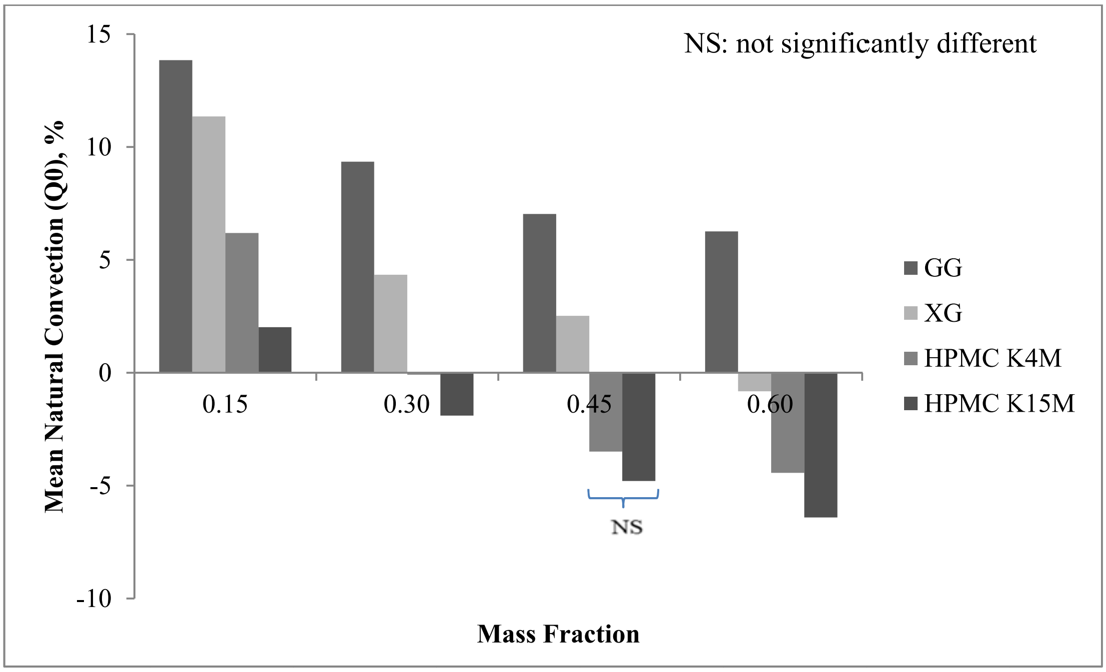
For each polymer:

At 0.15: GG > XG > K4M > K15M
At 0.30: GG > XG > K4M > K15M
At 0.45: GG > XG > K4M ≈ K15M
At 0.60: GG > XG > K4M > K15M

From multiple comparison with LSD procedure, it was found that Q_0 from matrices containing various polymer were ranked as follows: (i) for HPMC K4M, HPMC K15M and GG: 0.15 > 0.30 > 0.45 ≈ 0.60 respectively; (ii) for XG: 0.15 > 0.30 > 0.45 > 0.60. These indicated that high mf of polymer could lower natural convection of matrices, resulting in lower TMH release. At each mf of polymers, Q_0 of different polymers might be ranked as follows: (i) at mf of 0.15, 0.30 and 0.60: GG > XG > K4M > K15M respectively; (ii) at mf of 0.45: GG > XG > K4M ≈ K15M. For various polymers, GG showed highest natural convection and highest TMH release in the initial time. According to nature of matrices using GG with high natural convection might cause no diffusion front resulting in high releasing of drug.



(a)



(b)

Figrure 5.35 (a) The bar chart of mean natural convection (Q_0) and type of polymers of matrix tablets using DCPD at various mf of polymer.

(b) The bar chart of mean natural convection (Q_0) and mf of matrix tablets using DCPD as a filler.

Table 5.44 Lag time, min and ANOVA test of matrices using DCPD at various mf of different polymers.

Polymer	mf	Lag Time, min				
		1	2	3	4	5
HPMC K4M	0.15	-2.05	-1.92	-2.29	-2.29	-2.34
	0.30	0.02	0.02	-0.01	0.00	0.00
	0.45	0.58	1.43	0.97	1.11	0.71
	0.60	1.66	1.79	1.65	2.30	1.11
HPMC K15M	0.15	-0.33	-0.27	-0.10	-0.08	-0.41
	0.30	0.29	0.23	0.23	0.35	0.10
	0.45	1.57	1.40	1.86	1.87	1.77
	0.60	3.91	3.26	1.91	3.10	4.32
XG	0.15	-10.86	-14.36	-7.23	-12.22	-12.95
	0.30	-2.71	-2.31	-1.77	-2.33	-1.85
	0.45	-0.61	-0.54	-1.78	-0.75	-2.13
	0.60	0.00	-0.34	-0.14	-0.35	-0.13
GG	0.15	-13.21	-15.32	-10.60	-11.27	-5.35
	0.30	-6.33	-5.79	-3.39	-3.78	-6.28
	0.45	-5.52	-3.12	-1.64	-3.00	-1.76
	0.60	-1.50	-2.21	-1.67	-4.48	-5.43

Source of Variation	Sum of Square (SS)	Degree of Freedom (DF)	Mean of Square (MS)	F-Ratio	p-value
Between Groups	1333.25	15	88.88	46.08	1.89×10^{-28}
Within Groups	123.44	64	1.93		
Total	**1456.69**	**79**			

*highly significant difference (p << 0.01)

Table 5.45 Lag time in min of matrices using DCPD at various mf of different polymers, LSD 1% allowance (α = 0.01, 2-tailed).

t = 2.655 at DF of 64	LSD 1% allowance $t\sqrt{s^2(\frac{1}{n_i}+\frac{1}{n_j})}$ =2.33															
R_x	0.60 K15M	0.60 K4M	0.45 K15M	0.45 K4M	0.30 K15M	0.30 K4M	0.60 XG	0.15 K15M	0.45 XG	0.15 K4M	0.30 XG	0.45 GG	0.60 GG	0.30 GG	0.15 GG	0.15 XG
1	3.91	1.66	1.57	0.58	0.29	0.02	0.00	-0.33	-0.61	-2.05	-2.71	-5.52	-1.50	-6.33	-13.21	-10.86
2	3.26	1.79	1.40	1.43	0.23	0.02	-0.34	-0.27	-0.54	-1.92	-2.31	-3.12	-2.21	-5.79	-15.32	-14.36
3	1.91	1.65	1.86	0.97	0.23	-0.01	-0.14	-0.10	-1.78	-2.29	-1.77	-1.64	-1.67	-3.39	-10.60	-7.23
4	3.10	2.30	1.87	1.11	0.35	0.00	-0.35	-0.08	-0.75	-2.29	-2.33	-3.00	-4.48	-3.78	-11.27	-12.22
5	4.32	1.11	1.77	0.71	0.10	0.00	-0.13	-0.41	-2.13	-2.34	-1.85	-1.76	-5.43	-6.28	-5.35	-12.95
Mean($\bar{X}$)	3.30	1.70	1.69	0.96	0.24	0.00	-0.19	-0.24	-1.16	-2.18	-2.19	-3.01	-3.06	-5.11	-11.15	-11.52
$\bar{X}$–(%A)	0.97	-0.63	-0.64	-1.37	-2.09	-2.33	-2.52	-2.57	-3.49	-4.51	-4.52	-5.34	-5.39	-7.44	-13.48	-13.85

Table 5.45 Lag time in min of matrices using DCPD at various mf of different polymers, LSD 1% allowance ($\alpha = 0.01$, 2-tailed) (cont.).

For each mf of polymers:

K4M: 0.60 ≈ 0.45 ≈ 0.30

K15M: 0.60 ≈ 0.45 ≈ 0.30

XG: N/A

GG: N/A

For each polymer:

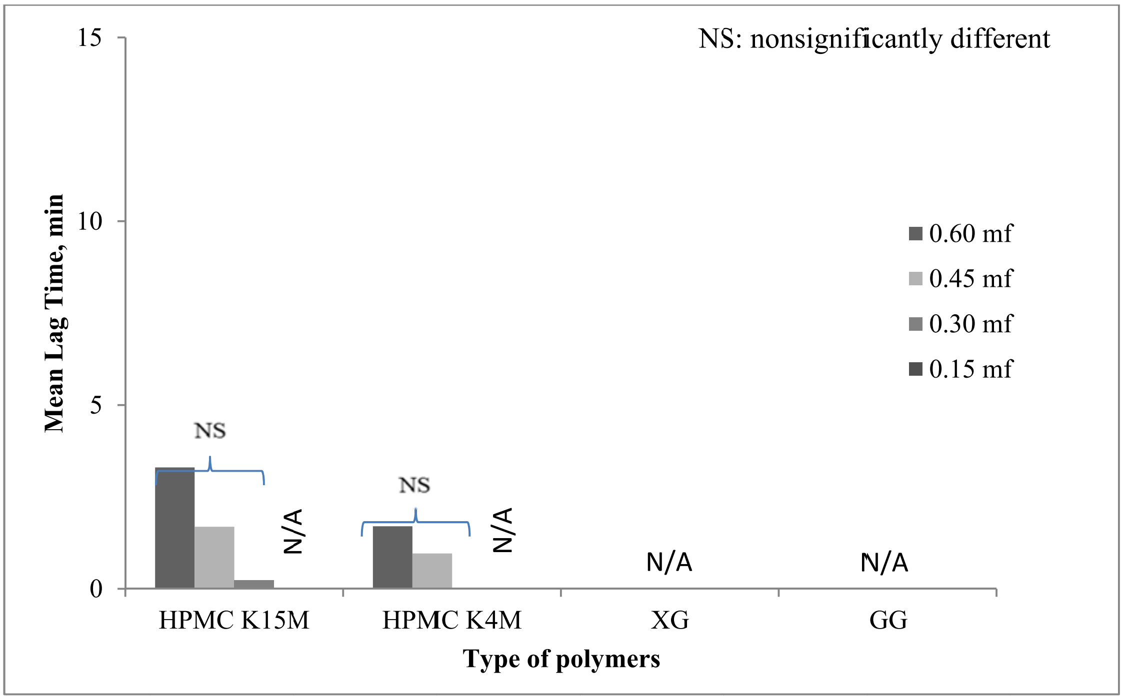
At 0.15: N/A

At 0.30: K15M ≈ K4M

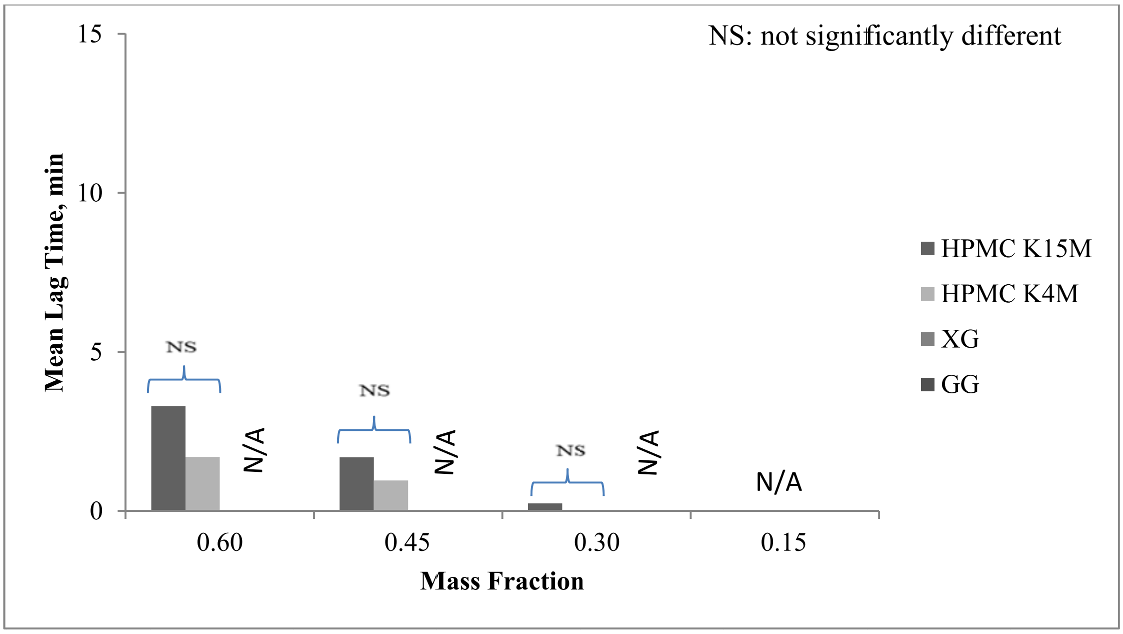
At 0.45: K15M ≈ K4M

At 0.60: K15M ≈ K4M

From multiple comparison with LSD procedure, it was found that lag time from matrices containing various polymers were ranked as follows: (i) for HPMC K4M and HPMC K15M: 0.60 ≈ 0.45 ≈ 0.30 and (ii) for XG and GG: not applicable, At each mf of polymers, lag time of matrices using different polymers might be ranked as follows: (i) at mf of 0.15: not applicable; (ii) at mf of 0.30 to 0.60: HPMC K15M ≈ HPMC K4M.



(a)



(b)

Figrure 5.36 (a) The bar chart of mean lag time and type of polymers of matrix tablets using DCPD at various mf of polymer.

(b) The bar chart of mean lag time and mf of matrix tablets using DCPD as a filler.

5.4.13 Higuchi model, the Release of TMH from Matrices Using SDL at Various mf of HPMC K4M.

Table 5.46 The percent drug released of TMH from matrices using SDL at HPMC K4M mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	35.10	35.43	34.15	36.19	36.02	35.38 ± 0.81
2	1.41	52.58	52.22	51.23	52.91	53.33	52.46 ±0.80
4	2.00	75.09	75.91	73.50	76.70	78.50	75.94 ±1.86
6	2.45	89.72	90.83	87.46	90.68	92.52	90.24 ± 1.85
8	2.83	98.74	99.18	96.84	99.53	100.98	99.05±1.50
12	3.46	100..02	100.29	99.70	100.24	102.17	100.48±0.97

Table 5.47 Kinetic constant k, natural convection (Q_0) and R^2 for matrices using SDL at HPMC K4M mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	37.75	38.51	36.92	37.99	39.50	38.13	0.96
Q_0, %	-1.66	-2.48	-1.77	-1.06	-2.69	-1.93	0.66
Lag time, min	2.64	3.86	2.88	1.67	4.09	3.03	0.98
R^2	0.9975	0.9982	0.9969	0.9959	0.9989	0.9971	0.0008

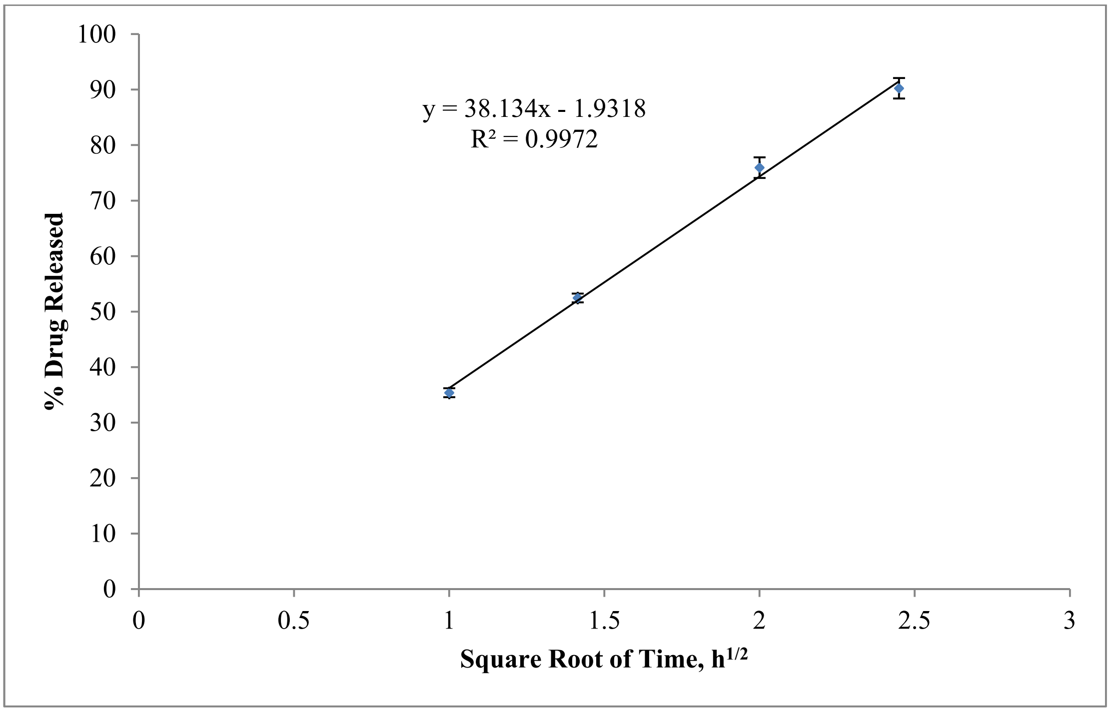


Figure 5.37 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at HPMC K4M mf of 0.15.

Table 5.48 The percent drug released of TMH from matrices using SDL at HPMC K4M mf of 0.30.

Time		Tablet Number					
h	**$h^{1/2}$**	1	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	28.58	28.94	28.54	28.70	29.10	28.77±0.24
2	1.41	41.77	41.95	41.68	42.15	42.94	42.10±0.51
4	2.00	61.07	61.21	60.73	62.16	62.48	61.53±0.75
6	2.45	73.96	74.03	73.73	74.91	74.72	74.27±0.52
8	2.83	84.93	83.95	84.10	85.07	85.57	84.72±0.68
12	3.46	96.45	95.19	95.41	95.70	95.49	95.65±0.49
24	4.90	103.13	102.64	101.46	101.80	100.33	101.83 ±1.09

Table 5.49 Kinetic constant *k*, natural convection (Q_0) and R^2 for matrices using SDL at HPMC K4M mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	30.93	30.36	30.57	31.10	30.9	30.77	0.30
Q_0, %	-1.89	-0.83	-1.50	-1.68	-0.94	-1.37	0.46
Lag time, min	3.67	1.64	2.94	3.24	1.83	2.66	0.89
R^2	0.9991	0.9983	0.9989	0.9977	0.9980	0.9984	0.0006

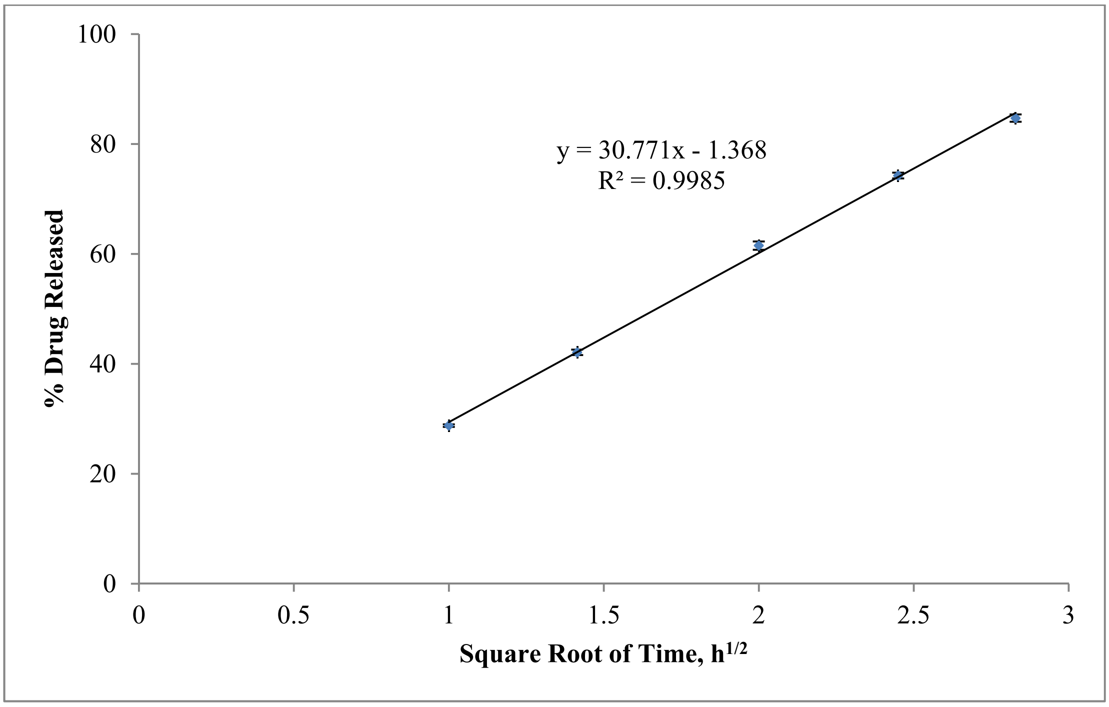


Figure 5.38 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at HPMC K4M mf of 0.30.

Table 5.50 The percent drug released of TMH from matrices using SDL at HPMC K4M mf of 0.45.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	25.09	25.32	24.46	25.11	25.17	25.03 ± 0.33
2	1.41	36.47	37.60	35.26	36.81	37.18	36.66 ± 0.89
4	2.00	53.54	53.02	51.59	53.81	53.68	53.13 ± 0.91
6	2.45	65.98	67.10	64.59	66.74	66.87	66.26±1.02
8	2.83	75.82	76.53	74.69	76.63	75.93	75.92± 0.77
12	3.46	89.72	90.03	88.12	90.22	89.80	89.58± 0.84
24	4.90	101.06	99.96	99.47	99.45	100.68	100.12±0.72

Table 5.51 Kinetic constant *k*, natural convection (Q_0) and R^2 for matrices using SDL at HPMC K4M mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	2	3	4	5	Mean	SD
k, % $h^{-1/2}$	27.95	28.11	27.67	28.37	28.00	28.02	0.25
Q_0, %	-2.79	-2.58	-3.52	-3.16	-2.51	-2.9	0.42
Lag time, min	6.00	5.51	7.63	6.68	5.38	6.24	0.93
R^2	0.9997	0.9992	0.9998	0.9997	0.9992	0.9995	0.0002

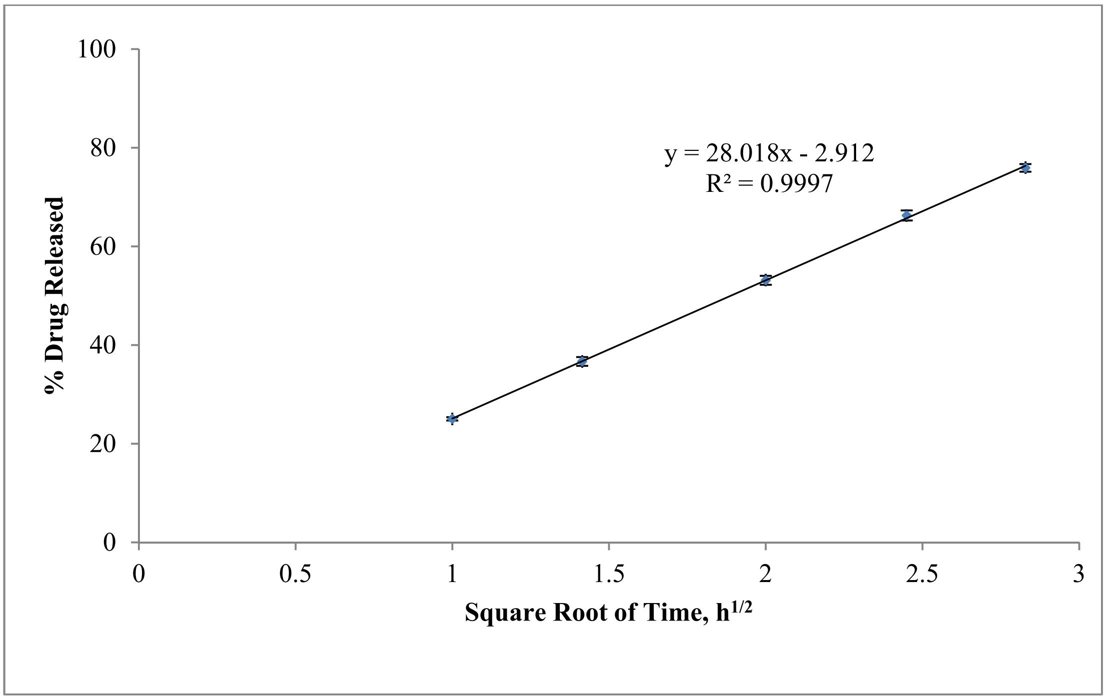


Figure 5.39 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at HPMC K4M mf of 0.45.

5.4.14 Jateleela *et al.* Model of Diffusion for Matrices Using SDL at Various mf of HPMC K4M.

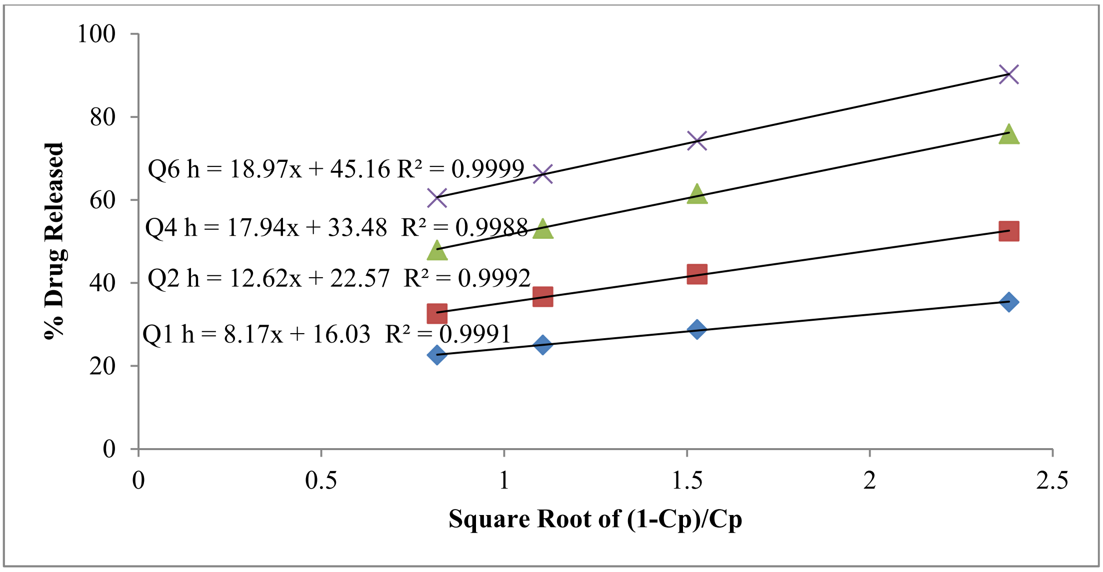


Figure 5.40 Regression analysis of percentage TMH released (*Q*) from SDL matrices and square root of $(1\text{-}C_p)/C_p$ of HPMC K4M at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h and ✕, 6 h.

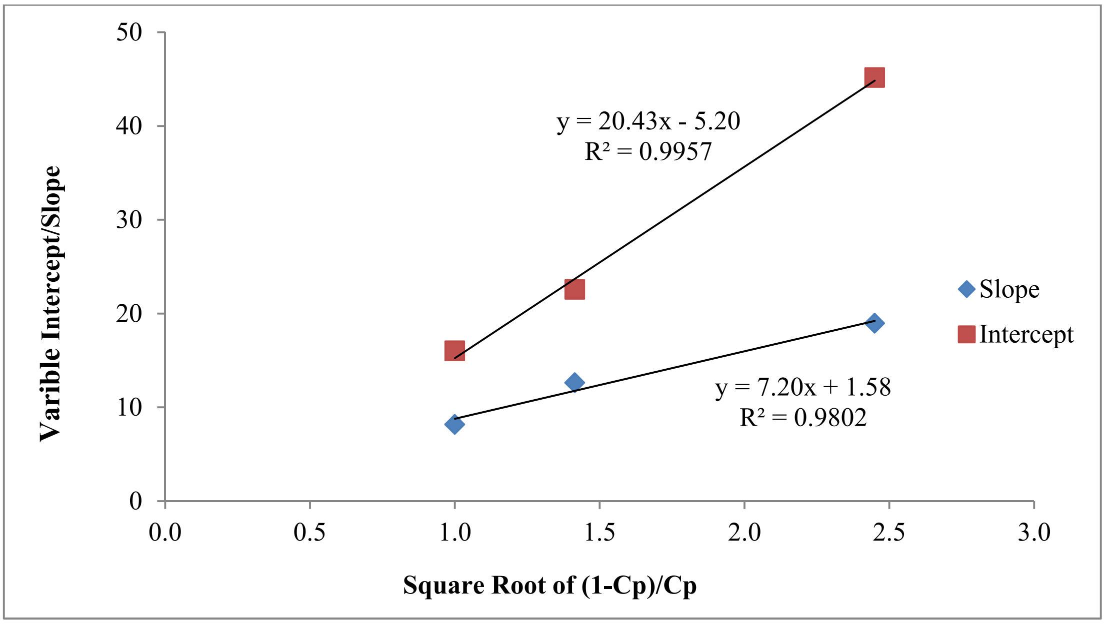


Figure 5.41 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using SDL at various mf of HPMC K4M. Keys: ♦, slope; and ■, intercept.

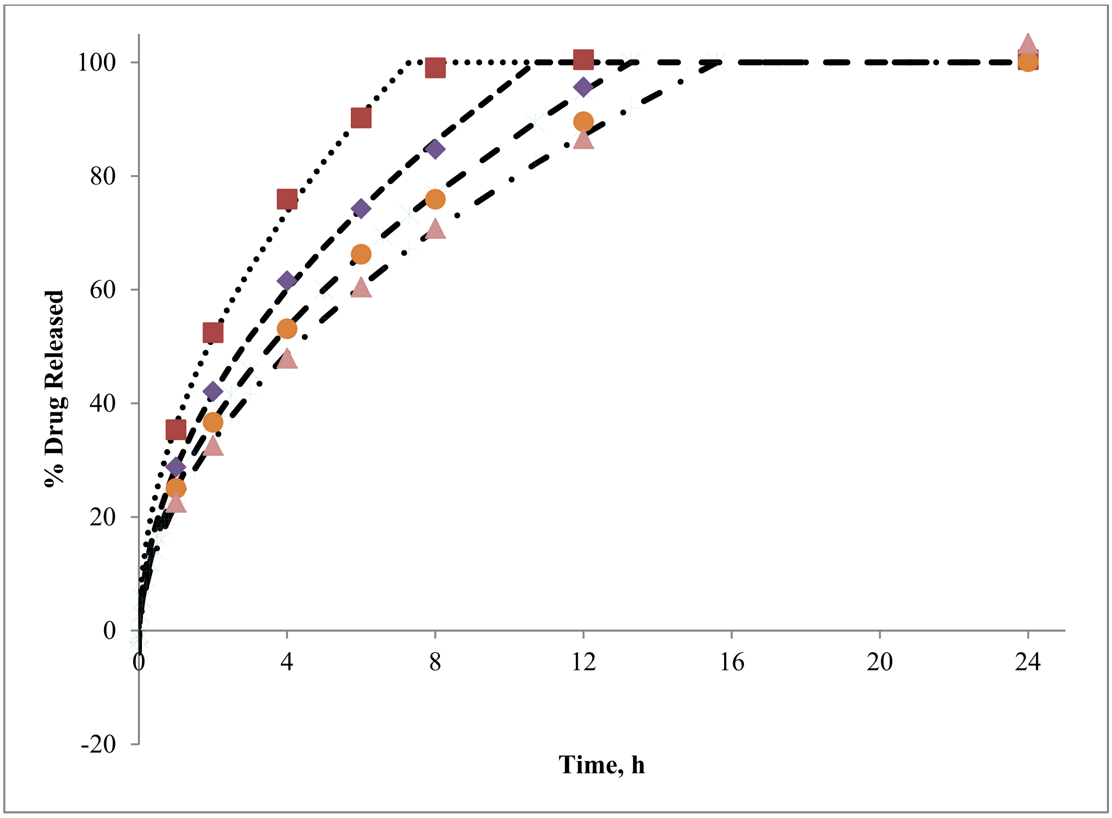


Figure 5.42 Predicted release profiles proposed by Jateleela *et al.* model versus experimental data for matrices using SDL at various mf of HPMC K4M. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■, 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.15 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrices Using SDL at Various mf of HPMC K4M.

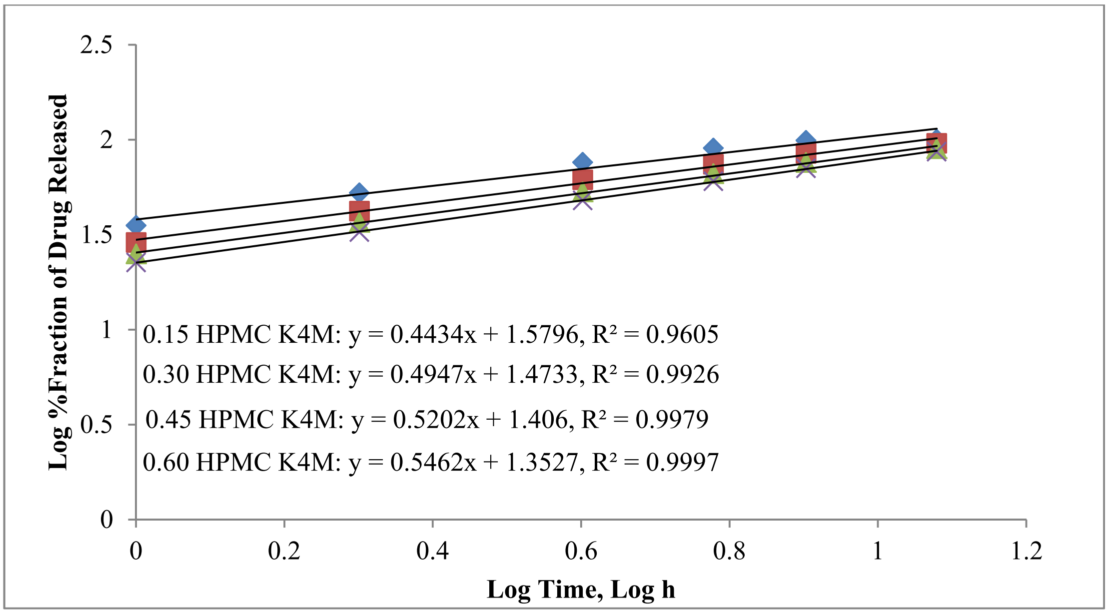


Figure 5.43 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using SDL at various mf of HPMC K4M. Keys: ♦, 0.15 K4M; ■, 0.30 K4M; ▲, 0.45 K4M and ✕, 0.60 K4M.

Table 5.52 Characterization of the order of release mechanism by the value of n for matrices using SDL at various mf of HPMC K4M.

Filler	Polymer	mf	Release Exponent (*n*)	Drug Transport Mechanism
SDL	HPMC K4M	0.15	0.44	quasi-Fickian diffusion
		0.30	0.49	non-Fickian transport
		0.45	0.52	non-Fickian transport
		0.60	0.55	non-Fickian transport

5.4.16 Higuchi model, the Release of TMH from Matrices Using SDL at Various mf of HPMC K15M.

Table 5.53 The percent drug released of TMH from matrices using SDL at HPMC K15M mf of 0.15.

Time		Tablet Number					
h	$h^{1/2}$	1	2	3	4	5	Mean ± SD
1	1.00	33.03	34.02	34.40	33.33	32.66	33.49 ± 0.71
2	1.41	48.97	49.04	48.95	47.94	47.69	48.52 ±0.65
4	2.00	70.16	70.61	70.08	69.47	69.88	70.04 ± 0.42
6	2.45	85.40	84.87	85.00	83.35	83.61	84.44 ± 0.91
8	2.83	96.15	95.63	94.33	94.28	94.32	94.94±0.88
12	3.46	100.57	98.72	97.96	97.15	97.64	98.41±1.33
24	4.90	101.72	100.85	100.38	100.44	100.48	100.78±0.56

Table 5.54 Kinetic constant *k*, natural convection (Q_0) and R^2 for matrices using SDL at HPMC K15M mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	36.13	35.31	35.07	34.81	35.51	35.37	0.50
Q_0, %	-2.6	-0.96	-0.56	-1.2	-2.48	-1.56	0.92
Lag time, min	4.32	1.63	0.96	2.07	4.19	2.63	1.53
R^2	0.9994	0.9990	0.9997	0.9989	0.9982	0.9990	0.0005

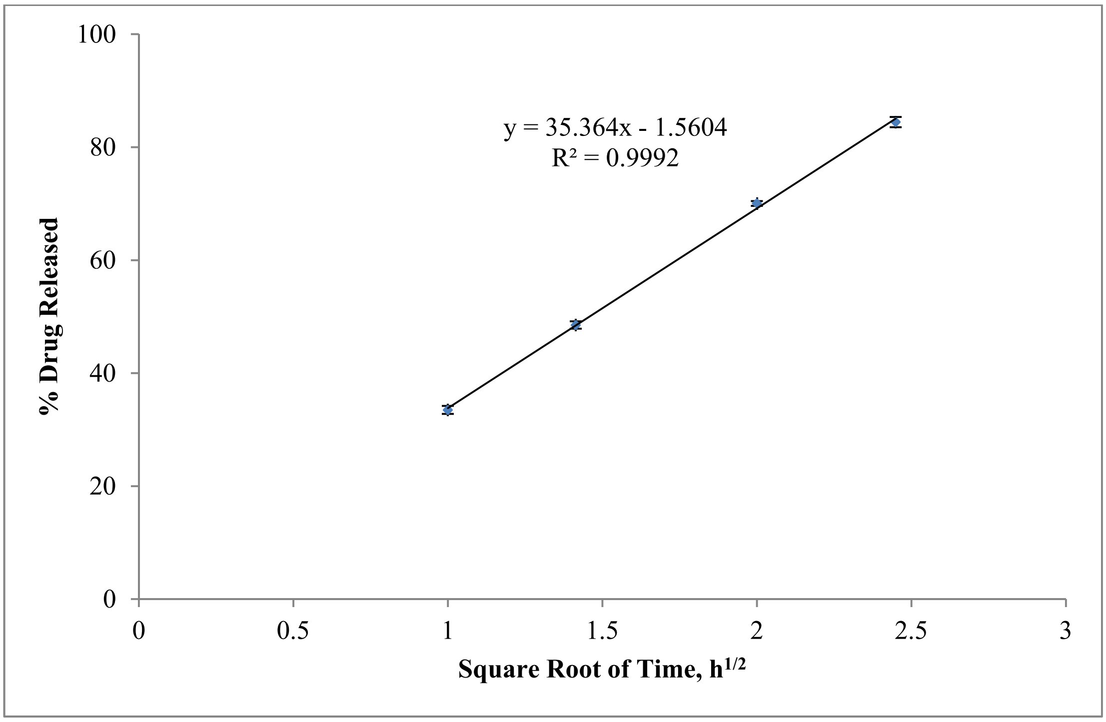


Figure 5.44 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at HPMC K15M mf of 0.15.

Table 5.55 The percent drug released of TMH from matrices using SDL at HPMC K15M mf of 0.30.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	26.64	27.86	27.23	26.77	26.94	27.09±0.48
2	1.41	40.01	40.60	40.80	39.75	41.50	40.53 ± 0.69
4	2.00	57.48	58.97	57.86	57.16	59.09	58.11 ± 0.87
6	2.45	70.36	71.21	71.52	70.60	72.76	71.29±0.94
8	2.83	80.98	81.92	81.24	80.92	82.51	81.51±0.68
12	3.46	94.55	94.17	94.38	94.23	94.73	94.41±0.23
24	4.90	101.64	102.22	101.55	102.95	101.41	101.95±0.63

Table 5.56 Kinetic constant k, natural convection (Q_0) and R^2 for SDL matrices containing HPMC K15M at mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	29.65	29.61	29.59	29.68	30.38	29.78	0.34
Q_0, %	-2.37	-1.28	-1.63	-2.49	-2.33	-2.02	0.53
Lag time, min	4.80	2.59	3.31	5.03	4.60	4.07	1.06
R^2	0.9994	0.9992	0.9989	0.9996	0.9980	0.9990	0.0006

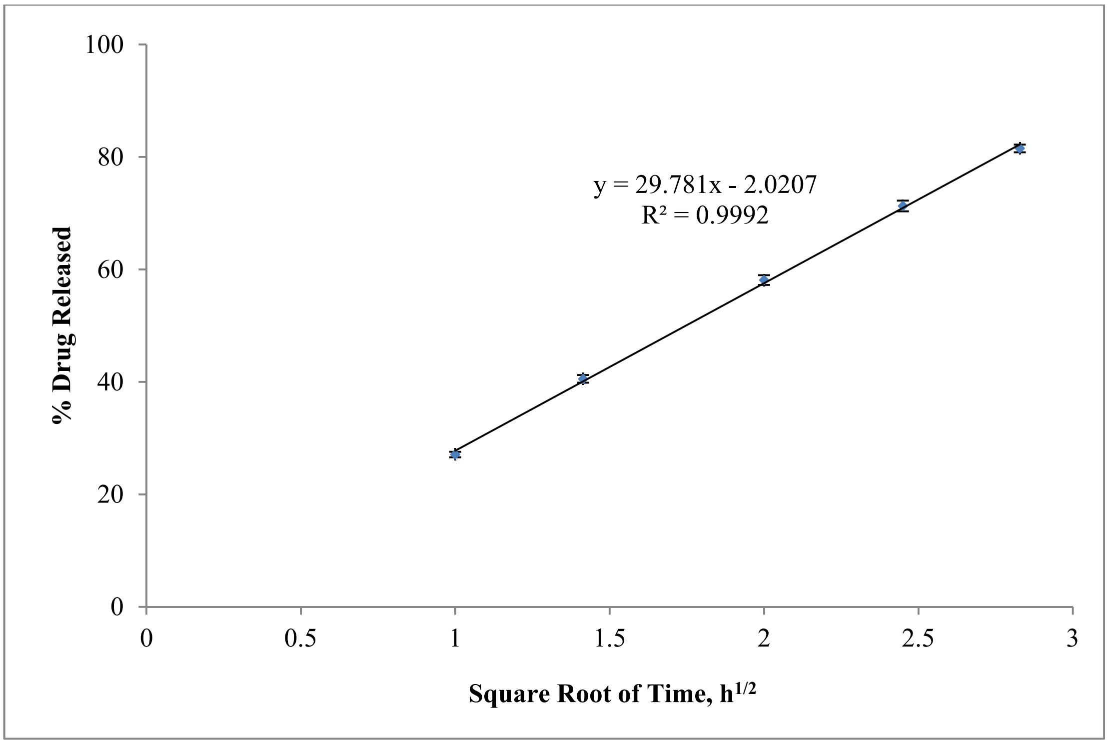


Figure 5.45 The linear regression of mean percentage TMH released and $\sqrt{t}$ for SDL matrices containing HPMC K15M at mf of 0.30.

Table 5.57 The percent drug released of TMH from matrices using SDL at HPMC K15M mf of 0.45.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	24.58	23.99	24.31	24.56	24.56	24.40±0.26
2	1.41	36.18	35.66	35.16	36.22	36.29	35.90±0.48
4	2.00	52.56	52.01	52.50	53.53	53.78	52.87±0.75
6	2.45	65.13	63.72	64.10	65.23	65.58	64.75±0.80
8	2.83	75.31	74.63	74.98	75.29	75.27	75.10±0.29
12	3.46	89.44	87.57	88.02	88.65	89.25	88.58±0.80
24	4.90	101.38	101.21	101.01	101.35	101.59	101.31±0.21

Table 5.58 Kinetic constant *k*, natural convection (Q_0) and R^2 for SDL matrices containing HPMC K15M at mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	36.13	35.31	35.07	34.81	35.51	35.37	0.50
Q_0, %	-3.15	-3.43	-3.65	-3.01	-3.00	-3.25	0.28
Lag time, min	6.80	7.47	7.88	6.49	6.45	7.02	0.63
R^2	1.0000	0.9998	0.9996	0.9994	0.9991	0.9996	0.0003

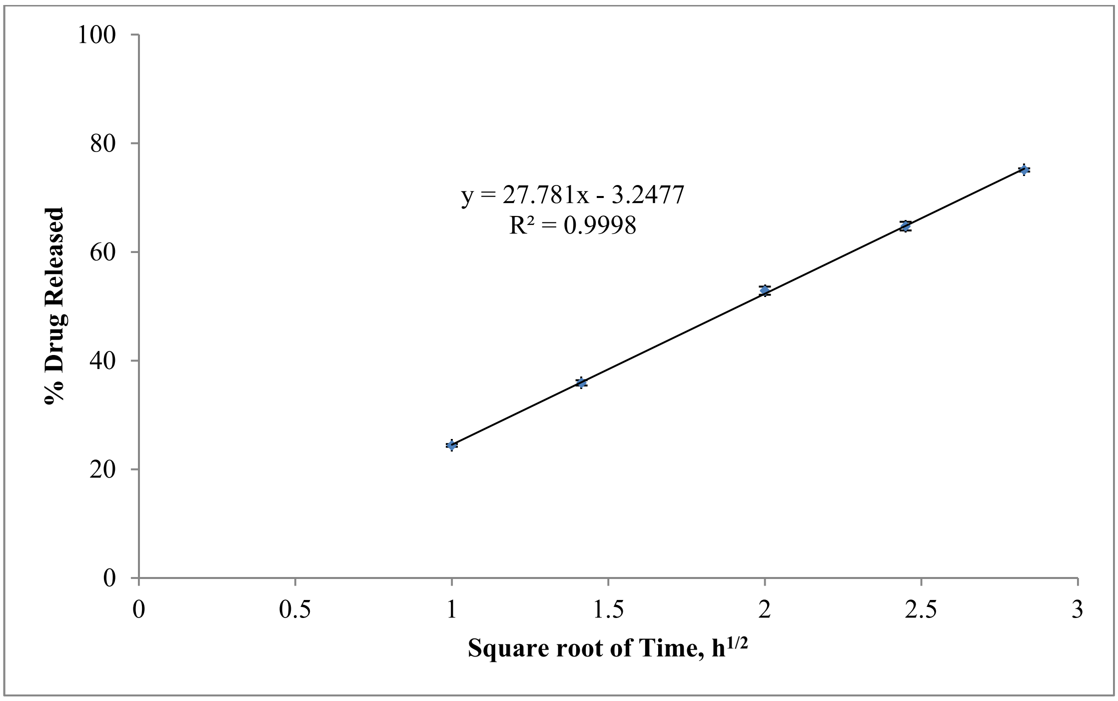


Figure 5.46 The linear regression of mean percentage TMH released and $\sqrt{t}$ for SDL matrices containing HPMC K15M at mf of 0.45.

5.4.17 Jateleela *et al.* Model of Diffusion for Matrices Using SDL at Various mf of HPMC K15M.

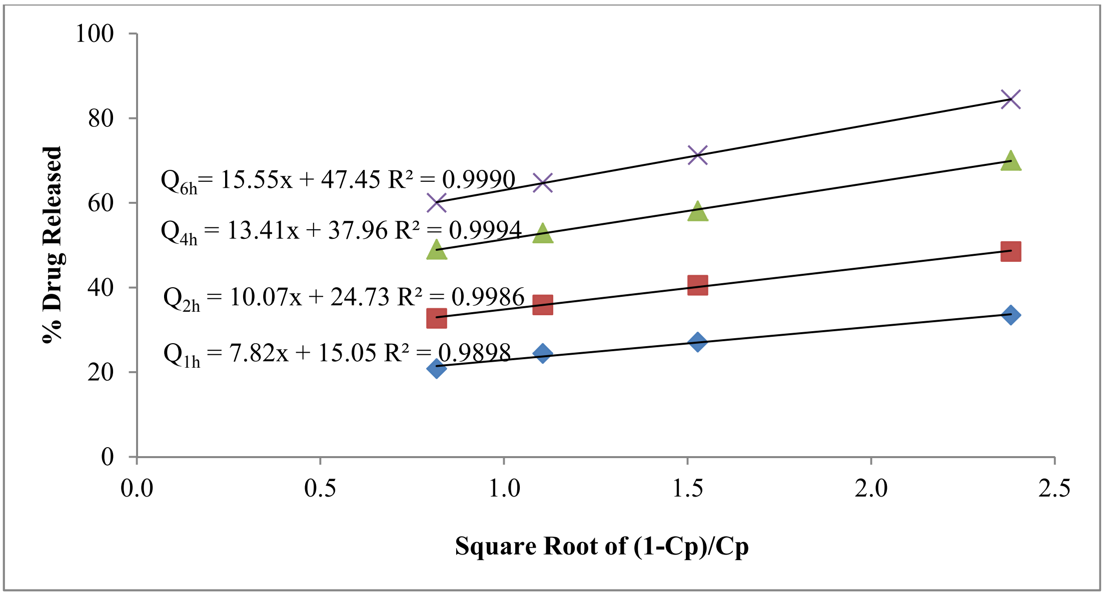


Figure 5.47 Regression analysis of percentage TMH released (Q) from SDL matrices and square root of $(1-C_p)/C_p$ of HPMC K15M at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; and ✕, 6 h.

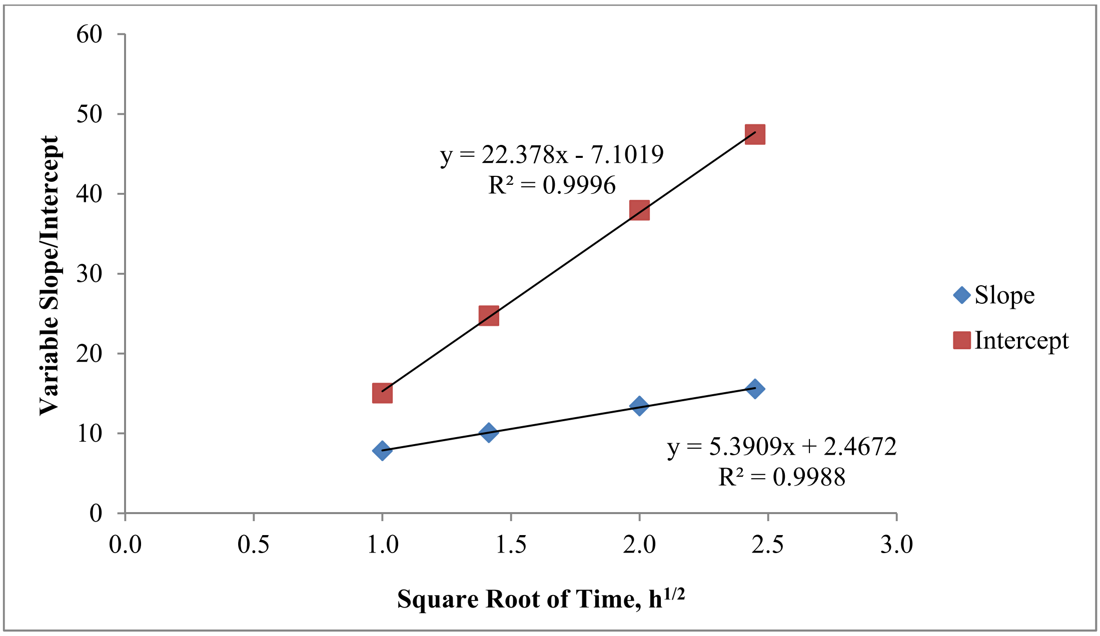


Figure 5.48 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrix using SDL at various mf of HPMC K15M. Keys: ♦, slope; and ■, intercept.

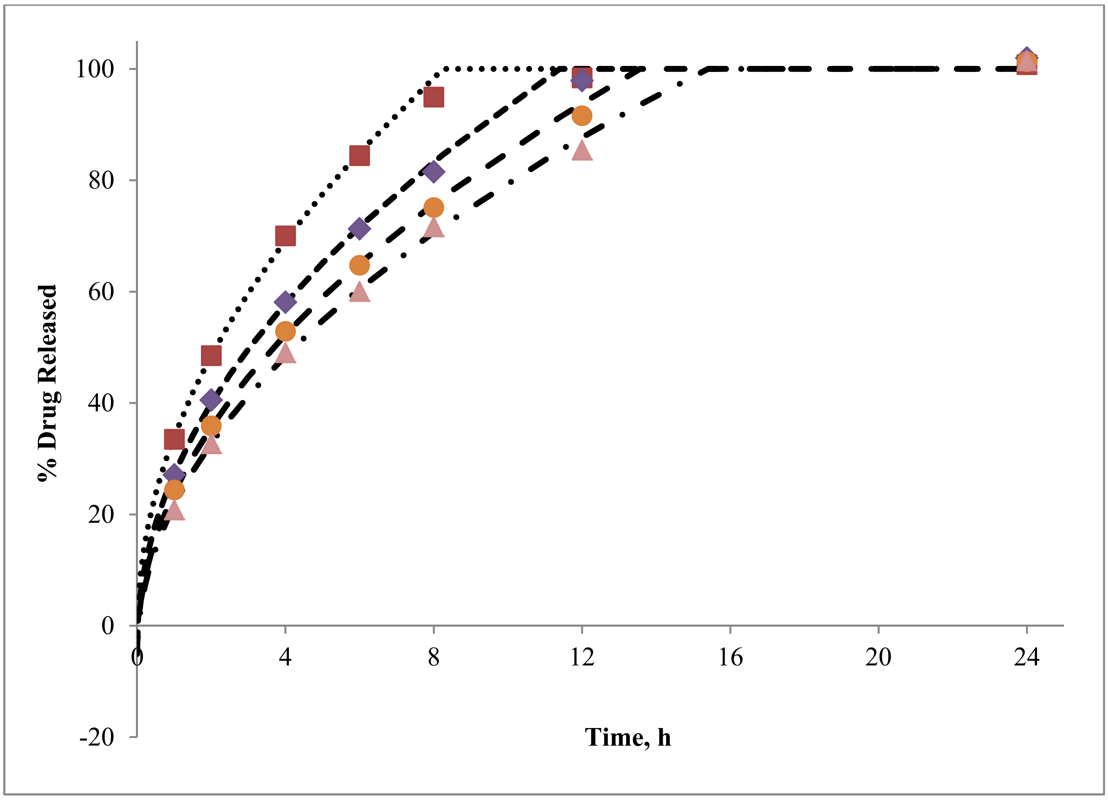


Figure 5.49 Predicted release profiles proposed by Jateleela et al. model versus experimental data for matrices using SDL at various mf of HPMC K15M. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■, 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.18 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrices Using SDL at Various mf of HPMC K15M.

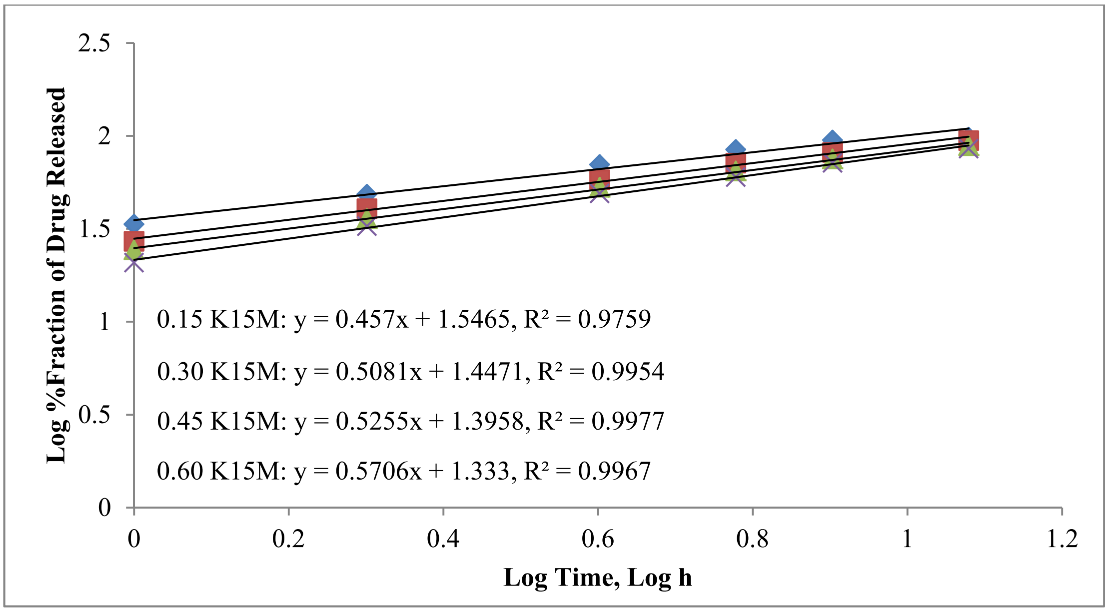


Figure 5.50 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using SDL at various mf of HPMC K15M. Keys: ♦, 0.15 K15M; ■, 0.30 K15M; ▲, 0.45 K15M. and ✕, 0.60 K15M.

Table 5.59 Characterization of the order of release mechanism by the value of n for SDL matrices at various mf of HPMC K15M.

Filler	**Polymer**	**mf**	**Release Exponent (*n*)**	**Drug Transport Mechanism**
SDL	HPMC K15M	0.15	0.46	non-Fickian diffusion
		0.30	0.51	non-Fickian transport
		0.45	0.53	non-Fickian transport
		0.60	0.57	non-Fickian transport

5.4.19 Higuchi model, the release of TMH from Matrices Using SDL at Various mf of XG

Table 5.60 The percent drug released of TMH from matrices using SDL at XG mf of 0.15.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	36.65	36.29	36.50	36.88	36.97	36.66±0.28
2	1.41	50.52	50.40	50.97	50.39	51.00	50.65±0.31
4	2.00	67.36	66.76	67.13	66.86	67.20	67.06±0.24
6	2.45	76.70	76.09	76.73	77.40	76.70	76.72±0.46
8	2.83	82.87	82.73	81.71	82.20	82.25	82.35±0.46
12	3.46	88.26	88.51	88.48	88.31	88.79	88.47±0.21
24	4.90	99.71	98.95	101.15	100.30	100.21	100.06±0.81

Table 5.61 Kinetic constant k, natural convection (Q_0) and R^2 for matrices using SDL at XG mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	25.41	25.38	24.90	25.23	24.91	25.17	0.25
Q_0, %	13.56	13.25	14.34	13.85	14.54	13.91	0.53
Lag time, min	-32.02	-31.32	-34.55	-32.94	-35.02	-33.17	1.59
R^2	0.9844	0.9859	0.9787	0.9831	0.9824	0.9829	0.0024

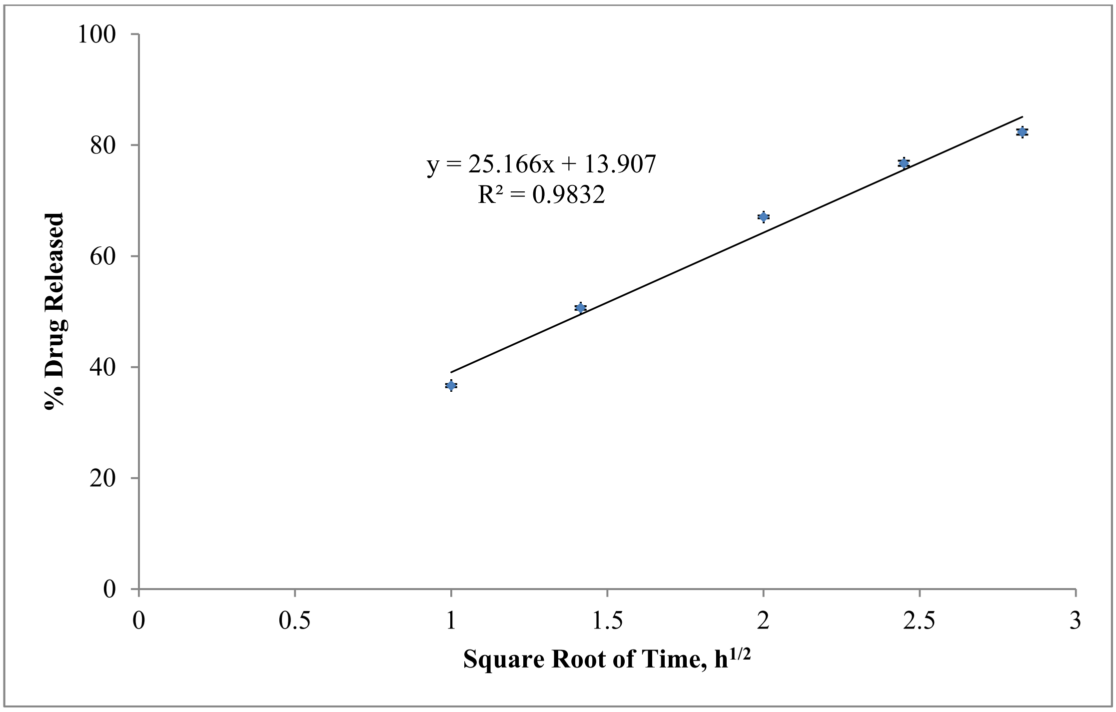


Figure 5.51 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at XG mf of 0.15.

Table 5.62 The percent drug released of TMH from matrices using SDL at XG mf of 0.30.

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	27.11	27.02	26.43	26.64	26.79	26.80±0.28
2	1.41	37.66	38.53	37.84	38.45	38.13	38.12±0.38
4	2.00	51.93	52.49	51.98	52.58	52.60	52.32±0.33
6	2.45	61.56	61.04	60.98	61.57	62.04	61.44±0.44
8	2.83	68.18	68.19	68.26	68.36	28.21	68.24±0.07
12	3.46	77.13	76.32	77.08	77.87	79.32	77.54±1.13
24	4.90	96.07	96.70	95.97	98.13	96.84	96.74±0.87

Table 5.63 Kinetic constant k, natural convection (Q_0) and R^2 for matrices using SDL at XG mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	22.67	22.40	22.82	22.78	22.84	22.70	0.18
Q_0, %	5.35	6.03	4.87	5.37	5.29	5.38	0.42
Lag time, min	-14.16	-16.15	-12.80	-14.14	-13.90	-14.23	1.21
R^2	0.9960	0.9938	0.9951	0.9931	0.9929	0.9944	0.0013

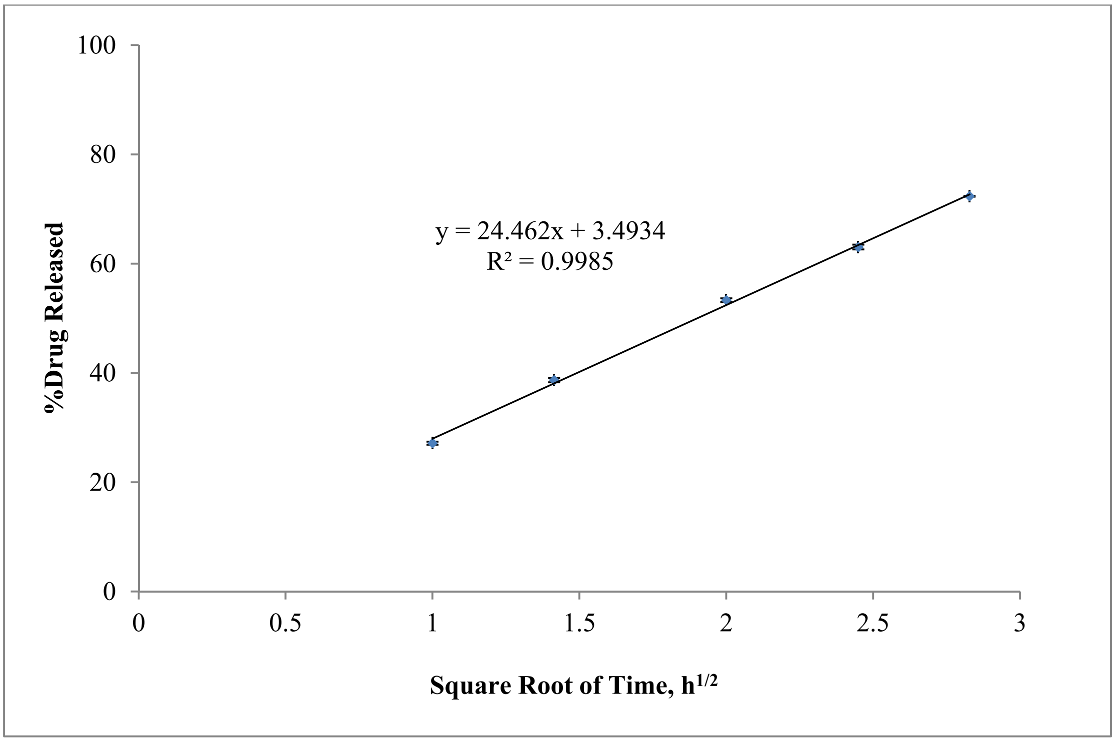


Figure 5.52 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at XG mf of 0.30.

Table 5.64 The percent drug released of TMH from matrices containing SDL at XG mf of 0.45.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	21.03	20.76	21.24	20.75	20.67	20.89±0.24
2	1.41	30.09	29.46	30.36	29.65	30.03	29.92±0.36
4	2.00	42.42	41.70	43.44	42.05	42.30	42.38±0.65
6	2.45	50.97	50.38	51.35	50.25	51.21	50.83±0.49
8	2.83	58.83	57.09	58.54	57.00	57.87	57.86±0.83
12	3.46	67.26	65.14	66.86	65.26	67.50	66.40±1.12
24	4.90	89.65	86.83	88.49	86.11	87.50	87.72 ± 1.39

Table 5.65 Kinetic constant k, natural convection (Q_0) and R^2 for matrices using SDL at XG mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	20.57	19.97	20.42	19.88	20.40	20.25	0.30
Q_0, %	0.8	1.16	1.41	1.4	0.87	1.13	0.29
Lag time, min	-2.33	-3.49	-4.14	-4.23	-2.56	-3.35	0.88
R^2	0.9995	0.9990	0.9977	0.9983	0.9984	0.9986	0.0007

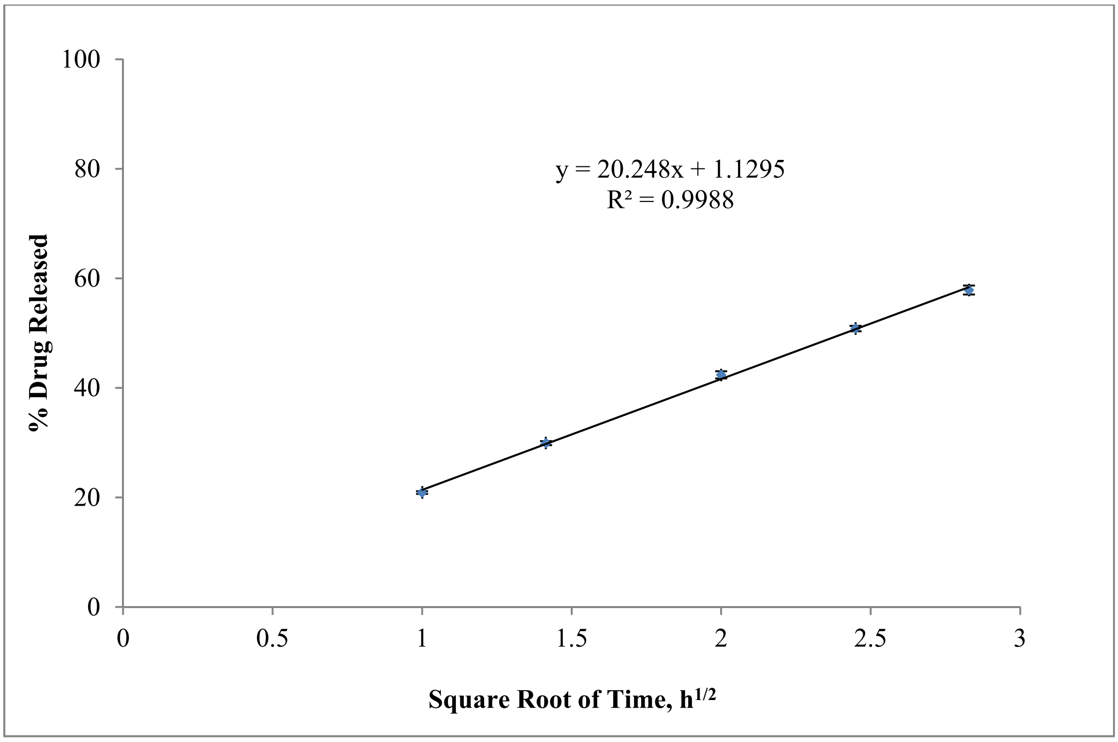


Figure 5.53 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at XG mf of 0.45.

5.4.20 Jateleela *et al.* Model of Diffusion for Matrices Using SDL at Various mf of XG.

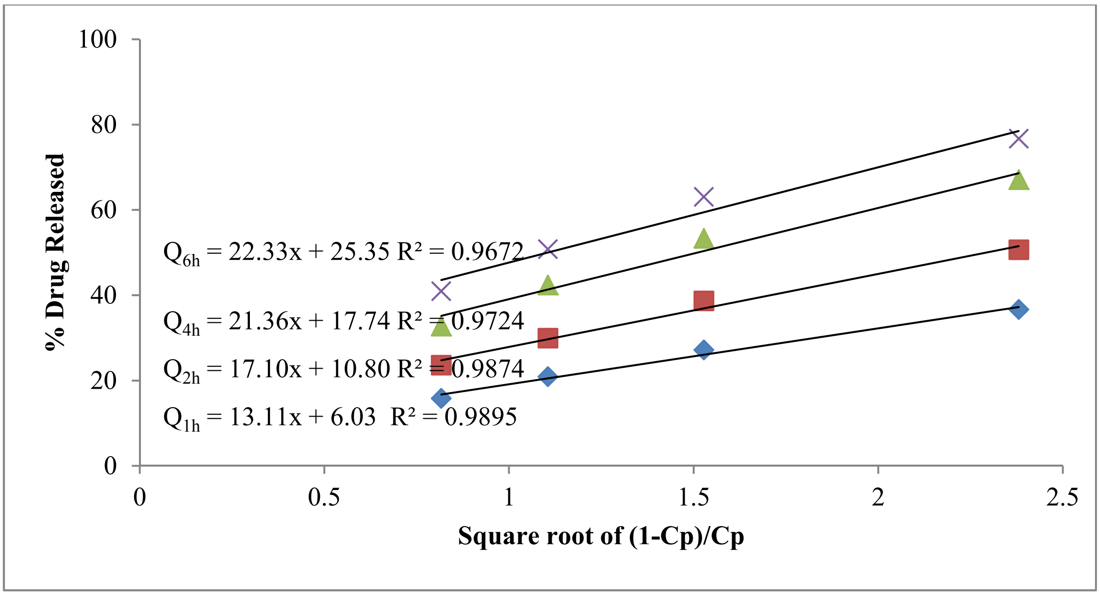


Figure 5.54 Regression analysis of percentage TMH released (Q) from SDL matrices and square root of $(1\text{-}C_p)/C_p$ of XG at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4h; and ✕, 6 h.

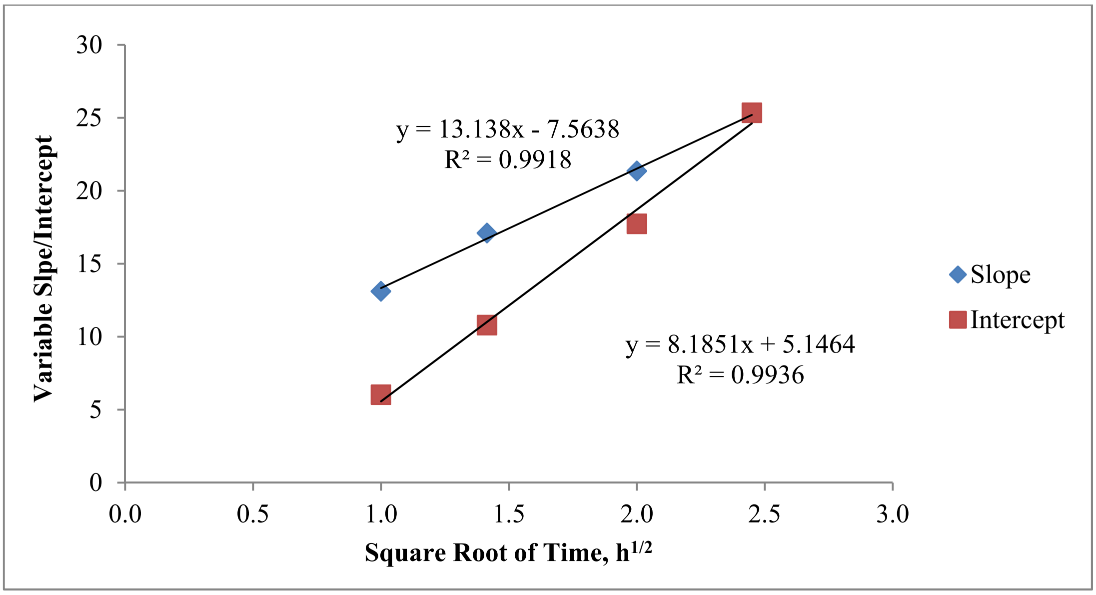


Figure 5.55 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using SDL at various mf of XG. Keys: ♦, slope; and ■, intercept.

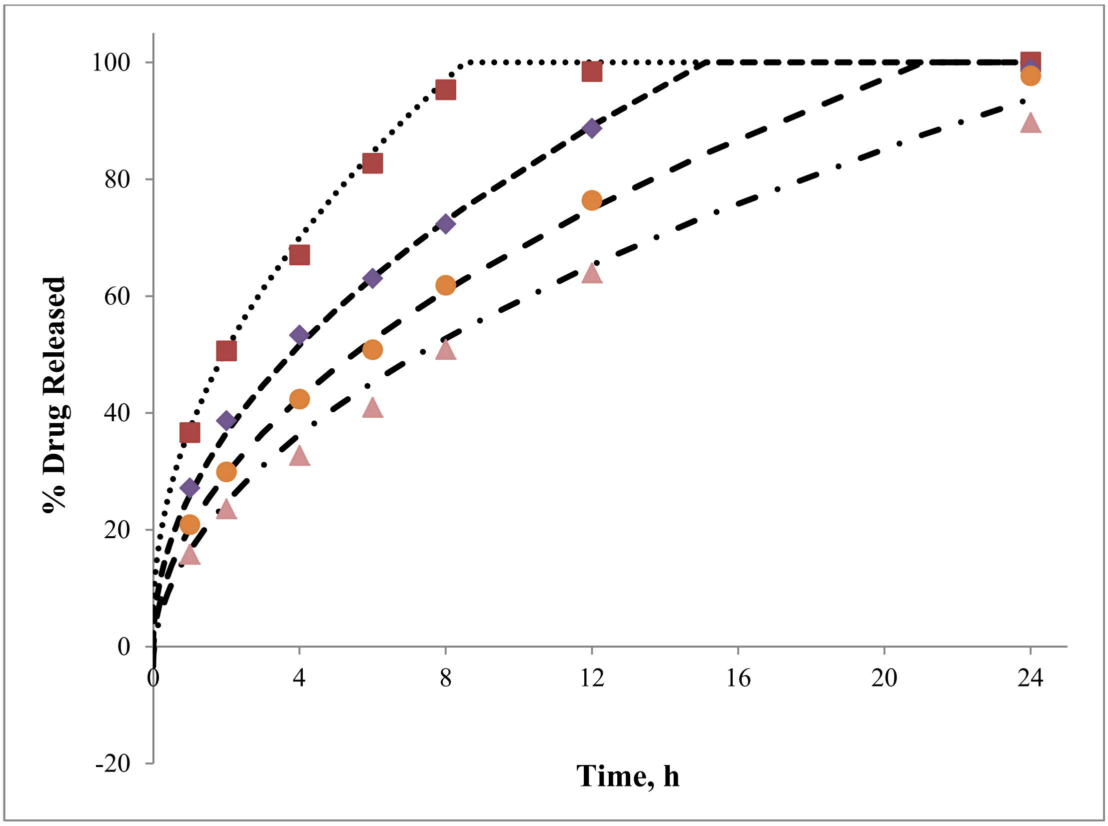


Figure 5.56 Predicted release profiles proposed by Jateleela et al. model versus experimental data for matrices using SDL at various mf of XG. Key: Predictional: ...., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■, 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.21 Korsmeyer and Peppas Model of Diffusion: Logarithm of Percentage Drug Released versus Logarithm of Time for Matrices Using SDL at Various mf of XG.

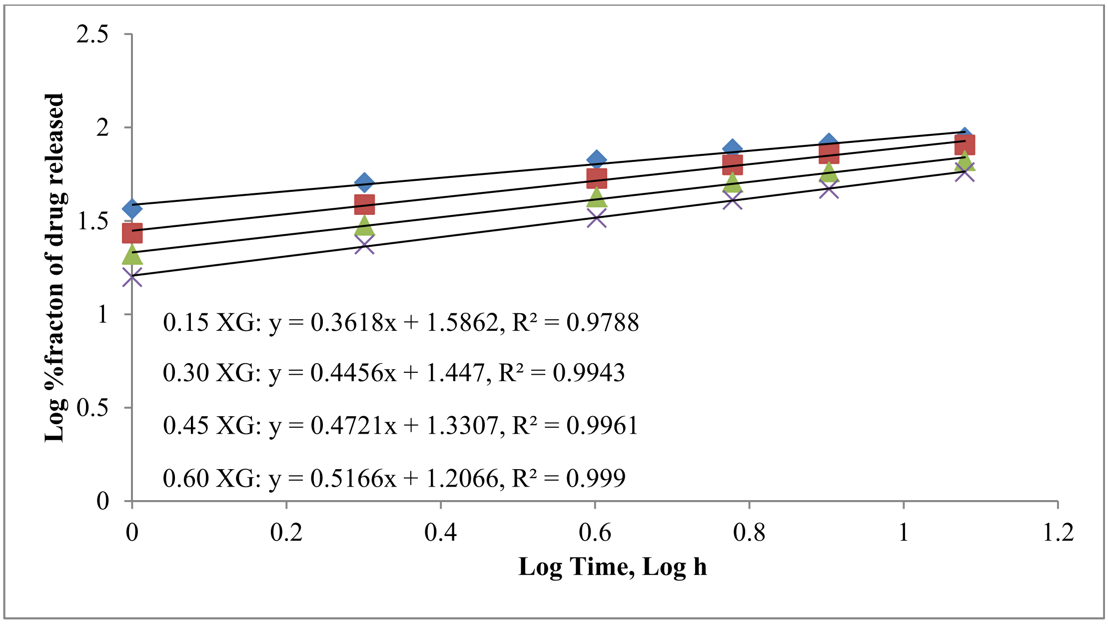


Figure 5.57 The linear relationship between logarithm of percentage drug released and logarithm of time for matrices using SDL at various mf of XG. Keys: ♦, 0.15 XG; ■, 0.30 XG; ▲, 0.45 XG and ✕, 0.60 XG.

Table 5.66 Characterization of the order of release mechanism by the value of n for matrices using SDL at various mf of XG

Filler	**Polymer**	**MF**	**Release Exponent (*n*)**	**Drug Transport Mechanism**
SDL	XG	0.15	0.36	quasi-Fickian diffusion
		0.30	0.45	Fickian diffusion
		0.45	0.47	non-Fickian transport
		0.60	0.52	non-Fickian transport

5.4.22 Higuchi Model, the Release of TMH from Matrices Using SDL at Various mf of GG

Table 5.67 The percent drug released of TMH from matrices using SDL at GG mf of 0.15.

Time		Tablet Number					
h	$h^{1/2}$	1	2	3	4	5	Mean ± SD
1	1.00	59.21	57.60	61.89	62.08	60.92	60.34±1.91
2	1.41	72.54	72.91	75.24	75.87	74.49	74.21±1.45
4	2.00	86.82	87.02	89.63	88.99	86.92	87.88±1.33
6	2.45	94.03	95.25	97.41	97.57	95.40	95.93±1.52
8	2.83	97.71	98.04	100.89	100.11	99.98	99.35±1.39
12	3.46	100.40	100.22	101.93	101.36	101.49	101.08±0.74

Table 5.68 Kinetic constant *k*, natural convection (Q_0) and R^2 for SDL matrices containing GG at mf of 0.15 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	24.02	25.65	24.47	24.14	23.39	24.33	0.83
Q_0, %	36.93	34.18	39.06	39.70	39.31	39.84	2.31
Lag time, min	-1.54	-1.33	-1.60	-1.64	-1.68	-1.56	0.14
R^2	0.9830	0.9800	0.9861	0.9864	0.9857	0.9842	0.0027

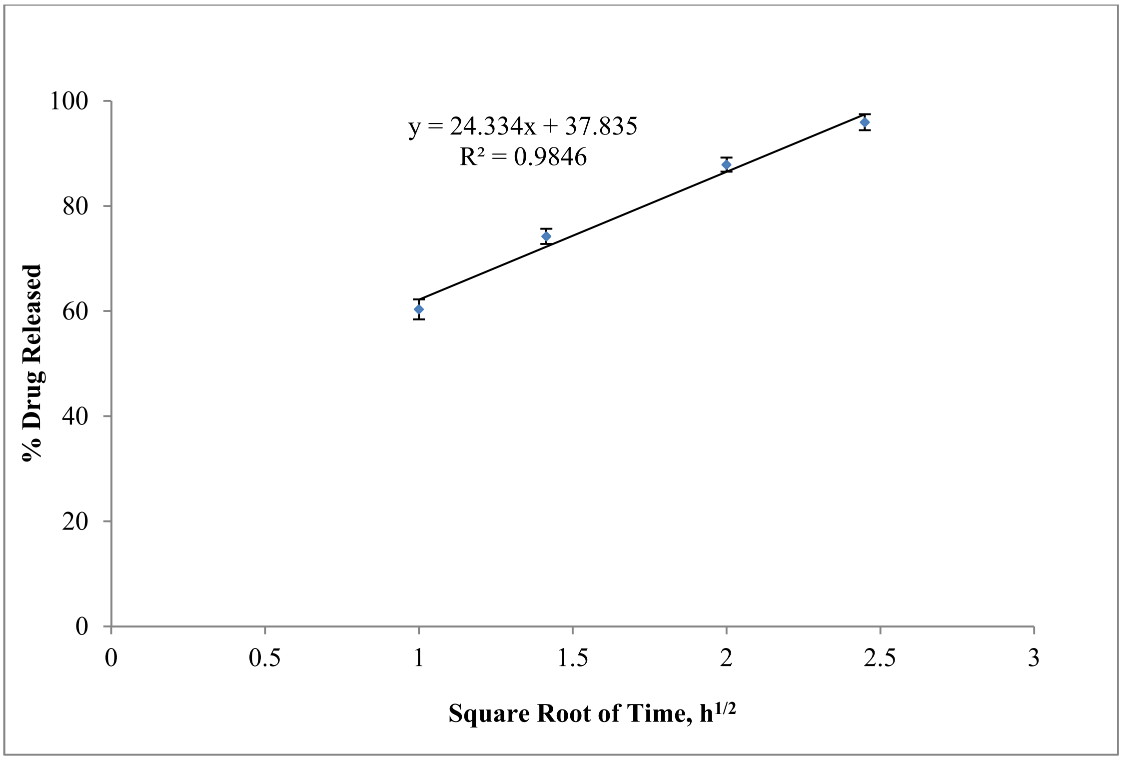


Figure 5.58 The linear regression of mean percentage TMH released and $\sqrt{t}$ for SDL matrices containing GG at mf of 0.15.

Table 5.69 The percent drug released of TMH from matrices using SDL at GG mf of 0.30

Time		**Tablet Number**					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	49.56	48.58	49.58	50.21	50.07	49.60±0.64
2	1.41	64.49	64.55	65.08	66.15	65.50	65.15±0.70
4	2.00	81.98	80.12	81.07	82.80	81.76	81.54±1.01
6	2.45	92.62	90.26	91.54	92.69	90.78	91.58±1.08
8	2.83	96.10	96.70	95.82	96.97	96.15	96.15±0.50
12	3.46	98.85	98.31	100.17	99.75	100.79	99.57±1.00
24	4.90	101.04	101.09	101.27	101.73	101.88	101.40±0.38

Table 5.70 Kinetic constant k, natural convection (Q_0) and R^2 for SDL matrices containing GG at mf of 0.30 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	26.69	28.4	28.68	29.13	27.99	28.78	0.66
Q_0, %	21.22	22.15	22.61	22.97	24.01	22.59	1.03
Lag time, min	-0.71	-0.78	-0.79	-0.79	-0.86	-0.79	0.05
R^2	0.9934	0.9876	0.9906	0.9879	0.9859	0.9891	0.0029

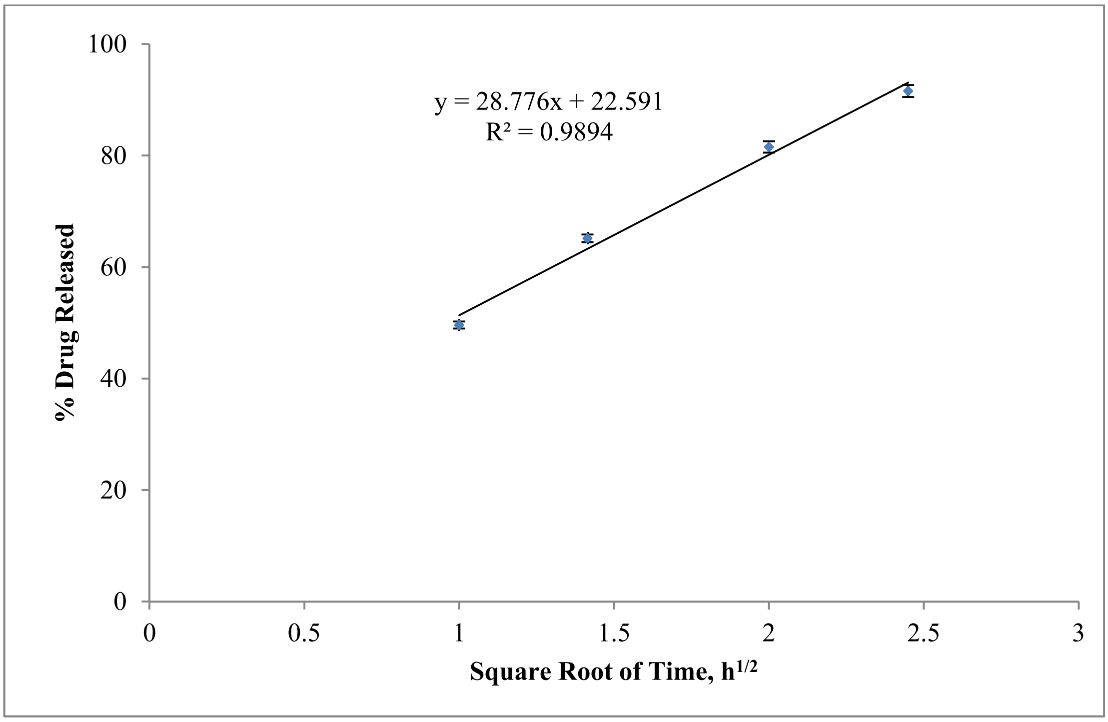


Figure 5.59 The linear regression of mean percentage TMH released and $\sqrt{t}$ for SDL matrices containing GG at mf of 0.30.

Table 5.71 The percent drug released of TMH from matrices using SDL at GG mf of 0.45.

Time		Tablet Number					
h	**$h^{1/2}$**	**1**	**2**	**3**	**4**	**5**	**Mean ± SD**
1	1.00	42.16	44.20	41.59	43.02	42.20	42.63±1.01
2	1.41	56.55	57.64	55.76	56.79	56.20	56.59±0.70
4	2.00	73.17	75.24	73.13	74.46	74.04	74.01±0.89
6	2.45	83.58	85.18	84.76	84.88	85.30	84.74±0.69
8	2.83	91.14	90.87	91.56	92.14	90.35	91.21±0.68
12	3.46	97.18	98.62	97.64	97.80	97.50	97.75±0.54
24	4.90	101.21	101.10	102.04	101.82	101.34	101.50 ± 1.39

Table 5.72 Kinetic constant *k*, natural convection (Q_0) and R^2 for matrices using SDL at GG mf of 0.45 from linear regression analysis of percentage TMH released and $\sqrt{t}$.

	Tablet Number						
	1	**2**	**3**	**4**	**5**	**Mean**	**SD**
k, % $h^{-1/2}$	28.51	28.49	29.75	29.03	29.81	29.12	0.64
Q_0, %	19.94	16.68	12.77	14.97	13.28	14.53	1.55
Lag time, min	-0.52	-0.59	-0.43	-0.52	-0.45	-0.50	0.06
R^2	0.9938	0.9944	0.9970	0.9952	0.9966	0.9954	0.0014

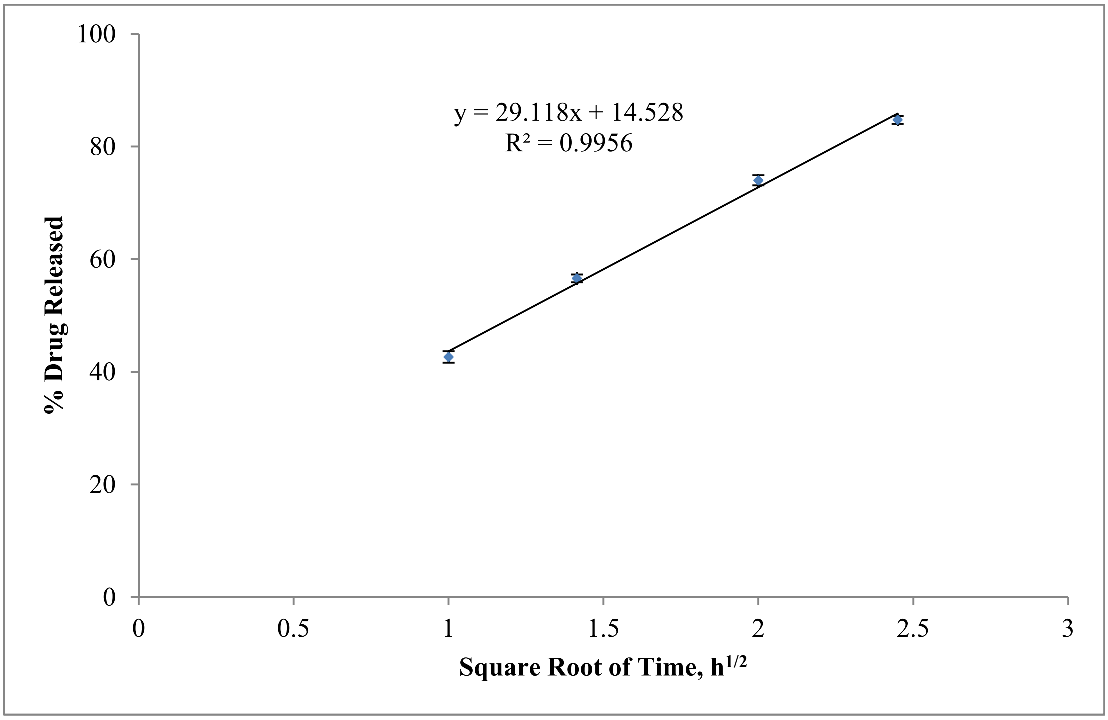


Figure 5.60 The linear regression of mean percentage TMH released and $\sqrt{t}$ for matrices using SDL at GG mf of 0.45.

5.4.23 Jateleela *et al.* Model of Diffusion for Matrices Using SDL at Various mf of GG.

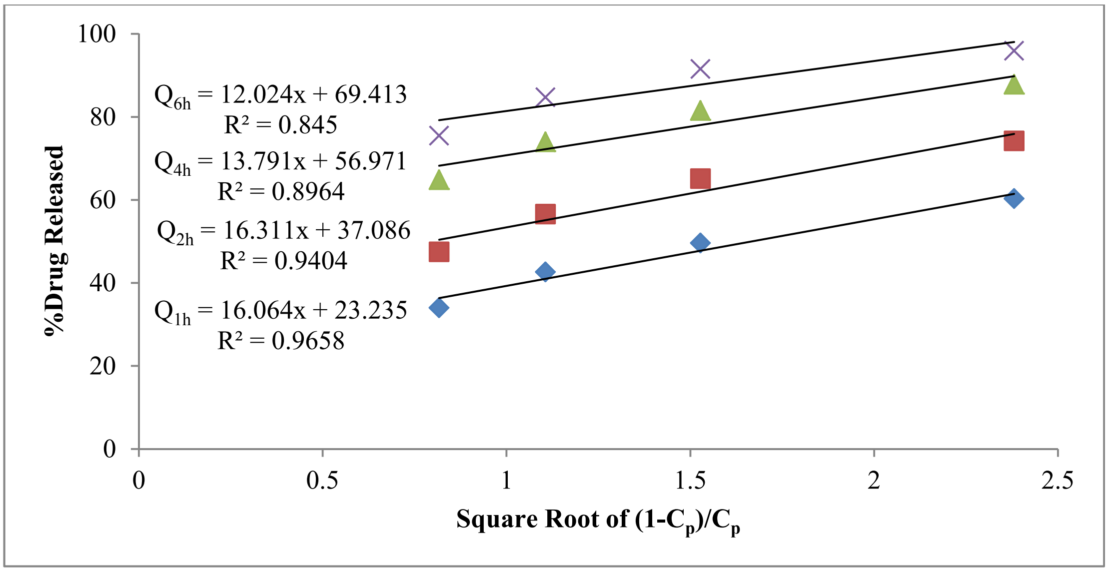


Figure 5.61 Regression analysis of percentage TMH released (*Q*) from SDL matrices and square root of (1-C_p)/C_p of GG at different given times in h. Keys: ♦, 1 h; ■, 2 h; ▲, 4 h; and ✕, 6 h.

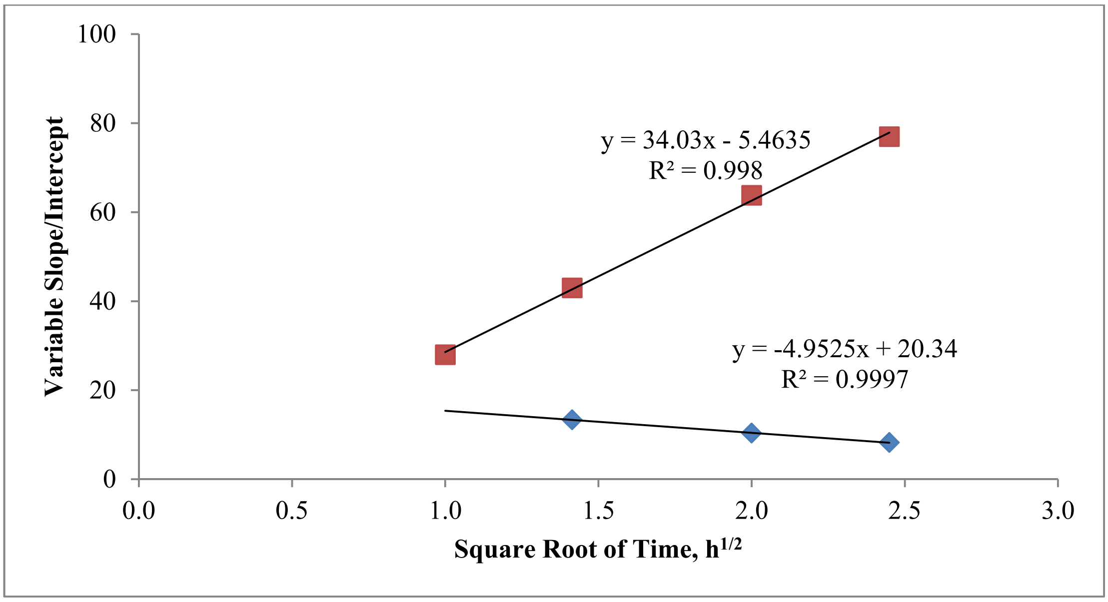


Figure 5.62 Regression analysis of variable kinetic constants (slope b_i and intercept a_i) and $\sqrt{t}$ for matrices using SDL at various mf of GG. Keys: ♦, slope; and ■, intercept.

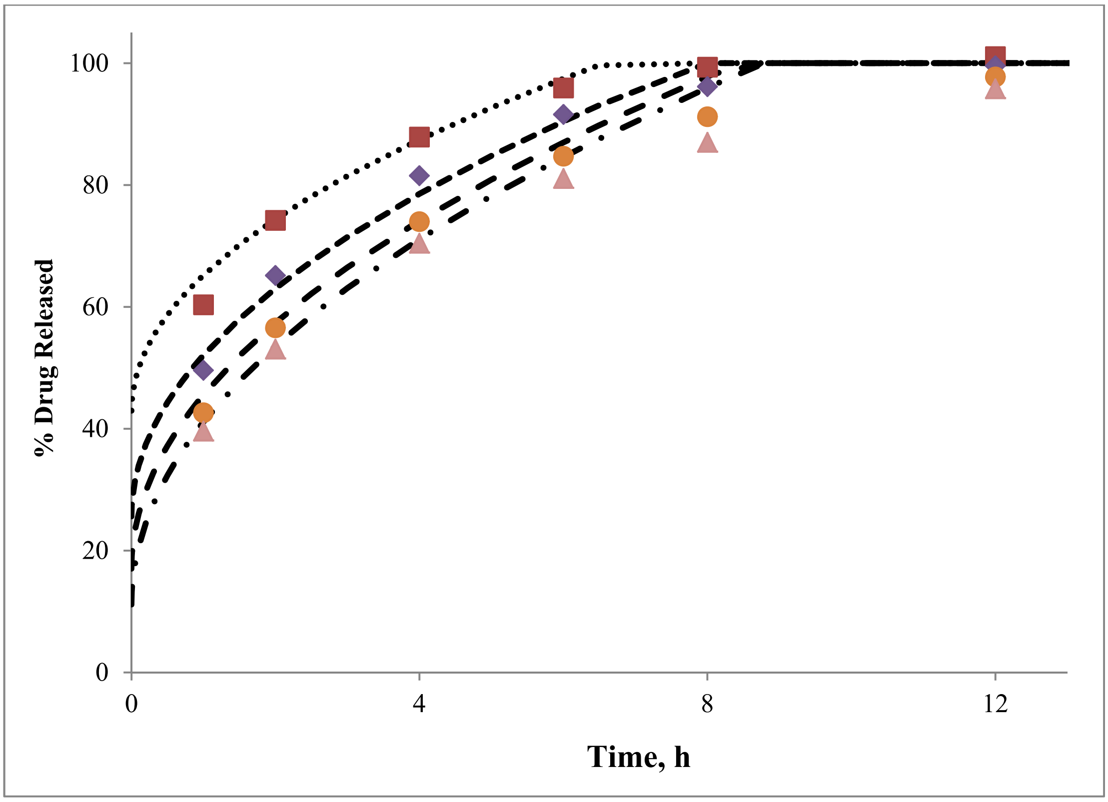


Figure 5.63 Predicted release profiles proposed by Jateleela et al. model versus experimental data for matrices using SDL at various mf of GG. Key: Predictional: ..., 0.15; ----, 0.30; - - -, 0.45; and - · - ·, 0.60. Experimental: ■ 0.15; ♦, 0.30; ●, 0.45; and ▲, 0.60.

5.4.24 Korsmeyer and Peppas model of diffusion: logarithm of percentage drug released versus logarithm of time

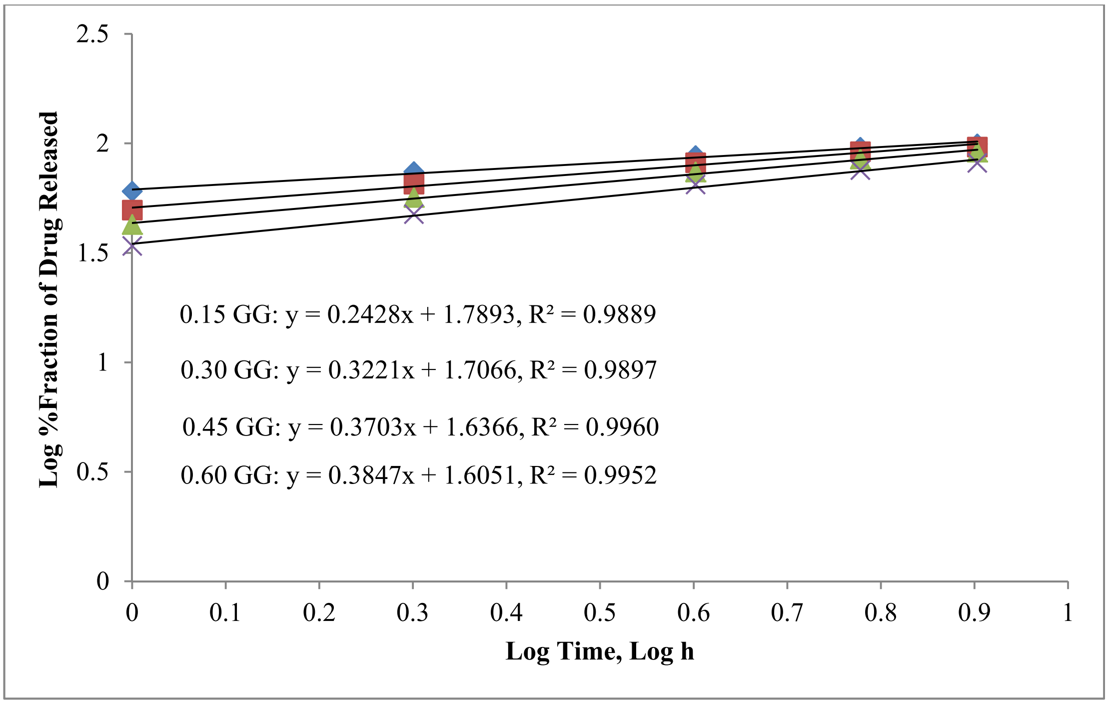


Figure 5.64 The linear relationship between logarithm of percentage drug released and logarithm of time. Keys: ♦, 0.15 GG; ■, 0.30 GG; and ▲, 0.45 GG and ✕, 0.60 XG.

Table 5.73 Characterization of the order of release mechanism by the value of n for matrices using SDL at various mf of GG

Filler	Polymer	mf	Release Exponent (*n*)	Drug Transport Mechanism
SDL	GG	0.15	0.24	quasi-Fickian diffusion
		0.30	0.32	quasi -Fickian diffusion
		0.45	0.37	quasi-Fickian diffusion
		0.60	0.38	quasi-Fickian diffusion

Table 5.74 Rate constant, *k* and ANOVA test of matrices using SDL at various mf of different polymers

Polymer	mf	Release rate, % $h^{-1/2}$				
		1	2	3	4	5
HPMC K4M	0.15	37.75	38.51	36.92	37.99	39.50
	0.30	30.93	30.36	30.57	31.10	30.90
	0.45	27.95	28.11	27.67	28.37	28.00
	0.60	26.29	26.46	26.4	26.95	26.28
HPMC K15M	0.15	36.13	35.31	35.07	34.81	35.51
	0.30	29.65	29.61	29.59	29.68	30.38
	0.45	27.80	27.56	27.79	27.84	27.91
	0.60	27.98	27.61	26.27	27.47	28.02
XG	0.15	25.41	25.38	24.90	25.23	24.91
	0.30	22.67	22.40	22.82	22.78	22.84
	0.45	20.57	19.97	20.42	19.88	20.40
	0.60	16.71	17.33	16.74	17.14	16.75
GG	0.15	24.02	25.65	24.47	24.14	23.39
	0.30	29.69	28.40	28.68	29.13	27.99
	0.45	28.51	28.49	29.75	29.03	29.81
	0.60	29.48	28.96	29.92	28.15	27.95

Source of Variation	**Sum of Square (SS)**	**Degree of Freedom (DF)**	**Mean of Square (MS)**	**F-Ratio**	**p-value**
Between Groups	2005.90	15	133.73	470.57	2.04×10^{-59}*
Within Groups	18.19	64	0.28		
Total	**2024.09**	**79**			

*highly significant difference (p << 0.01)

Table 5.75 Rate constant (*k*) of matrices using SDL as a filler at various mf of different polymer filler, LSD 1% allowance (α = 0.01, 2-tailed).

t = 2.655 at *DF* of 64	LSD 1% allowance = = $t\sqrt{s^2(\frac{1}{n_i}+\frac{1}{n_j})}$ = 0.90															
R_x	0.15 K4M	0.15 K15M	0.30 K4M	0.30 K15M	0.45 GG	0.60 GG	0.30 GG	0.45 K4M	0.45 K15M	0.60 K15M	0.60 K4M	0.15 XG	0.15 GG	0.30 XG	0.45 XG	0.60 XG
1	37.75	36.13	30.93	29.65	28.51	29.48	29.69	27.95	27.80	27.98	26.29	25.41	24.02	22.67	20.57	16.71
2	38.51	35.31	30.36	29.61	28.49	28.96	28.40	28.11	27.56	27.61	26.46	25.38	25.65	22.40	19.97	17.33
3	36.92	35.07	30.57	29.59	29.75	29.92	28.68	27.67	27.79	26.27	26.40	24.90	24.47	22.82	20.42	16.74
4	37.99	34.81	31.10	29.68	29.03	28.15	29.13	28.37	27.84	27.47	26.95	25.23	24.14	22.78	19.88	17.14
5	39.50	35.51	30.90	30.38	29.81	27.95	27.99	28.00	27.91	28.02	26.28	24.91	23.39	22.84	20.40	16.75
Mean($\bar{X}$)	38.13	35.37	30.77	29.78	29.12	28.89	28.78	28.02	27.78	27.47	26.48	25.17	24.33	22.70	20.25	16.93
$\bar{X}$–(%A)	37.23	34.47	29.87	28.88	28.22	27.99	27.88	27.12	26.88	26.57	25.58	24.27	23.43	21.80	19.35	16.03

Table 5.75 Rate constant (*k*) of matrices using SDL as a filler at various mf of different polymers, LSD 1% allowance (α = 0.01, 2-tailed) (continued)

For each mf of polymers:

K4M: 0.15 > 0.30 > 0.45 > 0.60

K15M: 0.15 > 0.30 > 0.45 ≈ 0.60

XG: 0.15 > 0.30 > 0.45 > 0.60

GG: 0.30 ≈ 0.45 ≈ 0.60 > 0.15

For each polymer:

At 0.15: K4M > K15M ≈ XG ≈ GG

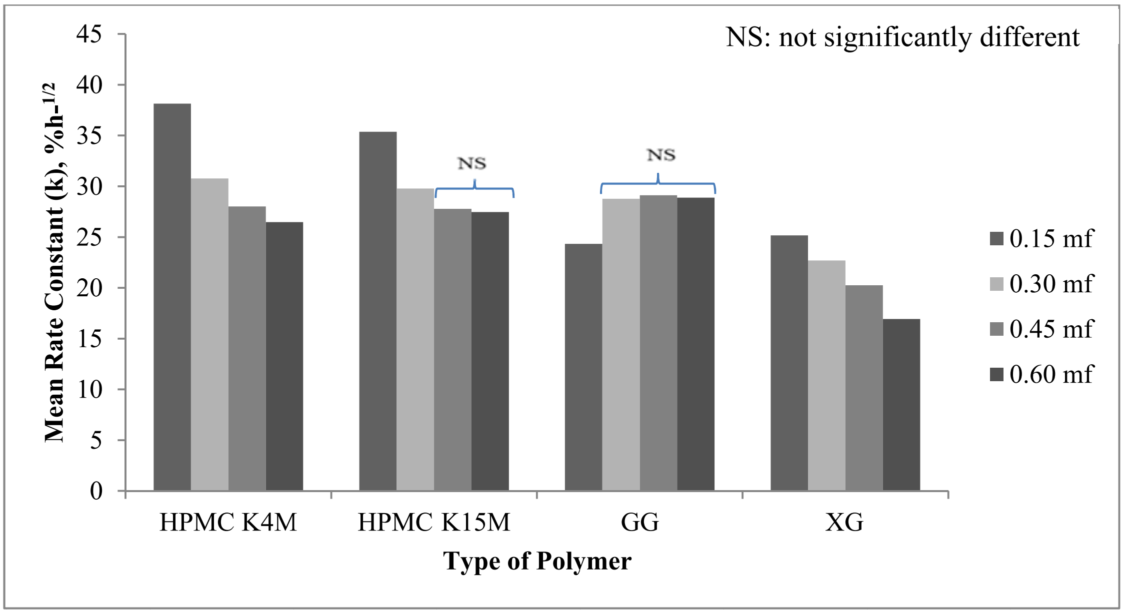
At 0.30: GG ≈ K4M ≈ K15M > XG

At 0.45: GG ≈ K4M ≈ K15M > XG

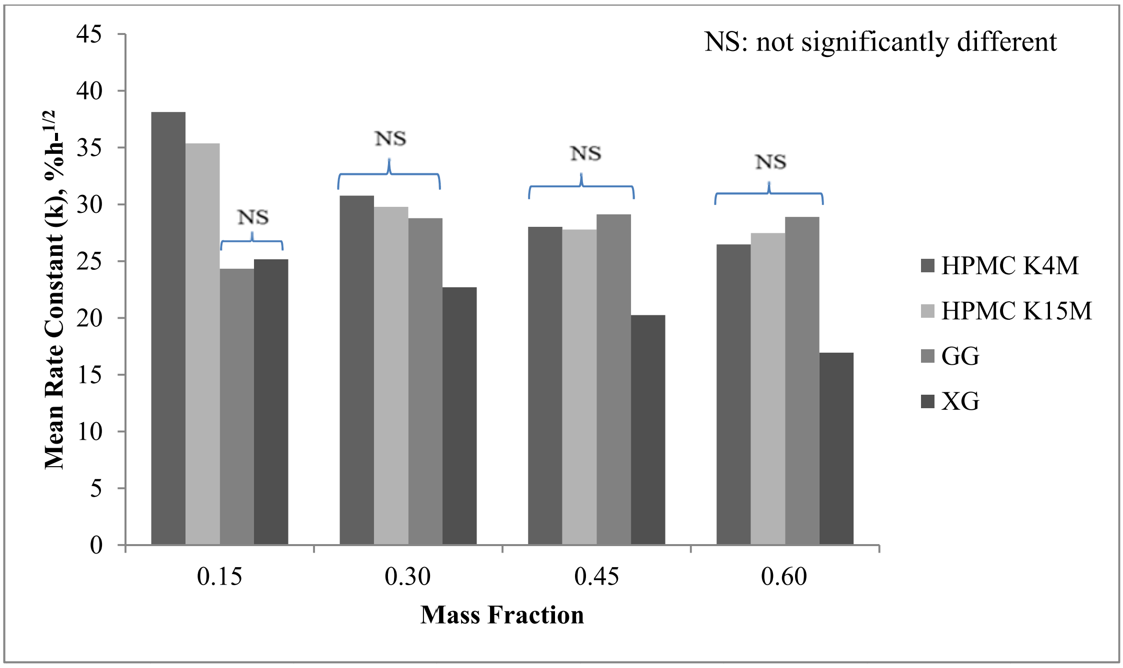
At 0.60: GG ≈ K4M ≈ K15M > XG

The composition of TMH formulations prepared with soluble fillers, SDL containing various polymers are shown in Table 4.2. As depicted in Fig. 5.37 – 5.39 for HPMC K4M matrices, Fig. 5.44 – 5.46 for HPMC K15M matrices, Fig. 5.51 – 5.53 for XG matrices and Fig. 5.58 – 5.60 for GG matrices, plots of mean percentage of drug released from each matrix containing SDL at various mf of different polymers versus square root of time provided a linear relationship. These showed that release of TMH from all matrices obeyed Higuchi's model of diffusion with high regression coefficient (R^2).

From equation (4), the kinetics constants, *k* were received by linear regression analysis between percentage drug release from various matrices and square root of time. From such regression analysis, the data of kinetics constants *k*, natural convection (Q_o), lag time and R^2 were received as shown in Table 5.47, 5.49 and 5.51 for HPMC K4M; Table 5.54, 5.56 and 5.58 for HPMC K15M; Table 5.61, 5.63 and 5.65 for XG and Table – 5.68, 5.70, and 5.72 and for GG respectively. For each polymer, the concentration of polymer, K4M, K15M and XG increased from the mass fraction of 0.15 to 0.45, the release kinetic constant, k decreased.



(a)



(b)

Figure 5.65 (a) The bar chart of mean rate constant (*k*) and type of polymers of matrix tablets using SDL at various mass fraction of polymer.
(b) The bar chart of mean rate constant (*k*) and mass fraction of matrix tablets using SDL as a filler.

Analysis of variance (ANOVA), α = 0.01) of these release data showed a significant difference in k of different formulations. Furthermore, by a multiple-comparison release data of these kinetics constants, it was found that TMH release rate from matrices containing various polymer were ranked as follows: (i) for HPMC K4M and XG: 0.15 > 0.30 > 0.45 > 0.60 respectively; (ii) for HPMC K15M: 0.15 > 0.30 > 0.45 ≈ 0.60, and (3) for GG: 0.30 ≈ 0.45 ≈ 0.60 > 0.15. At each mass fraction of polymers, k of matrices using different polymers might be ranked as follows: (i) at mf of 0.15: K4M ≈ K15M ≈ XG ≈ GG, and (ii) at mf of 0.30 to 0.60: GG ≈ K4M ≈ K15M > XG

As depicted in Fig. 5.40 for HPMC K4M, Fig. 5.47 for HPMC K15M, Fig. 5.54 for XG and Fig. 5.61 for GG, plots of mean percentage of drug released at different given times (1-6 h) from each matrix versus square root of $(1-C_p)/C_p$, showed good linearity. From linear regression analysis from these plots in each figure, the intercept (a_i) and slope (b_i) for each polymer were obtained with high regression coefficients.

Using equation 27, the working equation to predict drug release from matrices containing SDL is as follows:

$Q = (-5.20 + 1.58x) + (20.43 + 7.20x)\sqrt{t}$ for HPMC K4M Eq. (34)

$Q = (-7.10 + 2.47x) + (22.38 + 5.39x)\sqrt{t}$ for HPMC K15M Eq. (35)

$Q = (-7.56 + 5.15x) + (13.14 + 8.19x)\sqrt{t}$ for XG Eq. (36)

$Q = (-5.46 + 20.34x) + (34.03 - 4.95x)\sqrt{t}$ for GG Eq. (37)

where $x = \sqrt{(1 - C_p)/C_p)}$

Fig. 5.42, Fig. 5.49, Fig. 5.56 and Fig. 5.63 showed the predicted TMH release profiles proposed by Jateleela *et al.* versus experimental data for SDL matrices using HPMC K4M, K15M, XG and GG, respectively. The experimental data from release testing are closely matched the predicted release profiles. This implies that the release profiles of TMH from various matrices could be predicted mainly by the diffusion model of Jateleela *et al.* for soluble filler, SDL.

The main parameters for Korsmeyer-Peppas equation (n values) were obtained from linear regression analysis. The n values indicate that which mechanism is prominent in drug release from matrices. For SDL matrices containing HPMC K4M at mf of 0.15 followed Quasi-Fickian diffusion mechanism (*n* < 0.45) and those matrices containing HPMC K4M at mf of 0.30 and 0.45 followed Non-Fickian diffusion mechanism (0.45 < *n* = 0.89) as shown in Table -5.52. For SDL matrices containing HPMC K15M at mf of 0.15, 0.30 and 0.45 followed non-Fickian diffusion mechanism (0.45 <*n* = 0.89) as shown in Table 5.59. For SDL matrices containing XG at mf of 0.15 followed -Fickian diffusion mechanism (*n* < 0.45), mf of 0.30 followed Fickian diffusion (*n* = 0.45) and those matrices containing SDL at mf of 0.45 followed non-Fickian diffusion mechanism as shown in Table 5.66. For SDL matrices containing GG at mf of 0.15, 0.30 and 0.45 followed quasi-Fickian diffusion mechanism (*n* < 0.45) as shown in Table 5.73.

Table 5.76 (a) Natural convection, % (b) ANOVA test of matrices using SDL as a filler at various mf of different polymers.

Polymer	MF	Natural Convection, %				
		1	2	3	4	5
HPMC K4M	0.15	-1.66	-2.48	-1.77	-1.06	-2.69
	0.30	-1.89	-0.83	-1.50	-1.68	-0.94
	0.45	-2.79	-2.58	-3.52	-3.16	-2.51
	0.60	-4.37	-4.57	-4.38	-5.28	-3.57
HPMC K15M	0.15	-2.60	-0.96	-0.56	-1.20	-2.48
	0.30	-2.37	-1.28	-1.63	-2.49	-2.33
	0.45	-30.60	-27.79	-35.12	-30.34	-33.64
	0.60	-7.14	-6.44	-4.69	-6.24	-7.52
XG	0.15	13.56	13.25	14.34	13.85	14.54
	0.30	5.35	6.03	4.87	5.37	5.29
	0.45	0.80	1.16	1.41	1.40	0.87
	0.60	0.09	-1.30	-0.81	-1.30	-0.78
GG	0.15	36.93	34.18	39.06	39.70	39.31
	0.30	21.22	22.15	22.61	22.97	24.01
	0.45	14.94	16.68	12.77	14.97	13.28
	0.60	4.66	5.56	4.99	7.69	8.41

Source of Variation	Sum of Square(SS)	Degree of Freedom (DF)	Mean of Square (MS)	F-Ratio	p-value
Between Groups	10692.39	15	712.83	708.11	4.79×10^{-65}*
Within Groups	64.43	64	1.01		
Total	**10756.82**	**79**			

*highly significantly difference (p << 0.01)

Table 5.77 Natural convection (Q_0), % of matrices using SDL as a filler at various mf of different polymers, LSD 1% allowance (α = 0.01, 2-tailed).

t = 2.69 at DF of 64	LSD 1% allowance = $t\sqrt{s^2(\frac{1}{n_i}+\frac{1}{n_j})}$ = 1.68															
R_x	0.15 GG	0.30 GG	0.45 GG	0.15 XG	0.60 GG	0.30 XG	0.45 XG	0.60 XG	0.30 K4M	0.15 K15M	0.15 K4M	0.30 K15M	0.45 K4M	0.45 K15M	0.60 K4M	0.60 K15M
1	36.93	21.22	14.94	13.56	4.66	5.35	0.80	0.09	-1.89	-2.60	-1.66	-2.37	-2.79	-3.15	-4.37	-7.14
2	34.18	22.15	16.68	13.25	5.56	6.03	1.16	-1.30	-0.83	-0.96	-2.48	-1.28	-2.58	-3.43	-4.57	-6.44
3	39.06	22.61	12.77	14.34	4.99	4.87	1.41	-0.81	-1.50	-0.56	-1.77	-1.63	-3.52	-3.65	-4.38	-4.69
4	39.70	22.97	14.97	13.85	7.69	5.37	1.40	-1.30	-1.68	-1.20	-1.06	-2.49	-3.16	-3.01	-5.28	-6.24
5	39.31	24.01	13.28	14.54	8.41	5.29	0.87	-0.78	-0.94	-2.48	-2.69	-2.33	-2.51	-3.00	-3.57	-7.52
Mean($\bar{X}$)	37.84	22.59	14.53	13.91	6.26	5.38	1.13	-0.82	-1.37	-1.56	-1.93	-2.02	-2.91	-3.25	-4.43	-6.41
$\bar{X}$–(%A)	36.16	20.91	12.85	12.23	4.58	3.70	-0.55	-2.50	-3.05	-3.24	-3.61	-3.70	-4.59	-4.93	-6.11	-8.09

Table 5.77 Natural convection, Q_0 of matrices using SDL as a filler at various mf of different polymers, LSD 1% allowance (α = 0.01, 2-tailed) (continued).

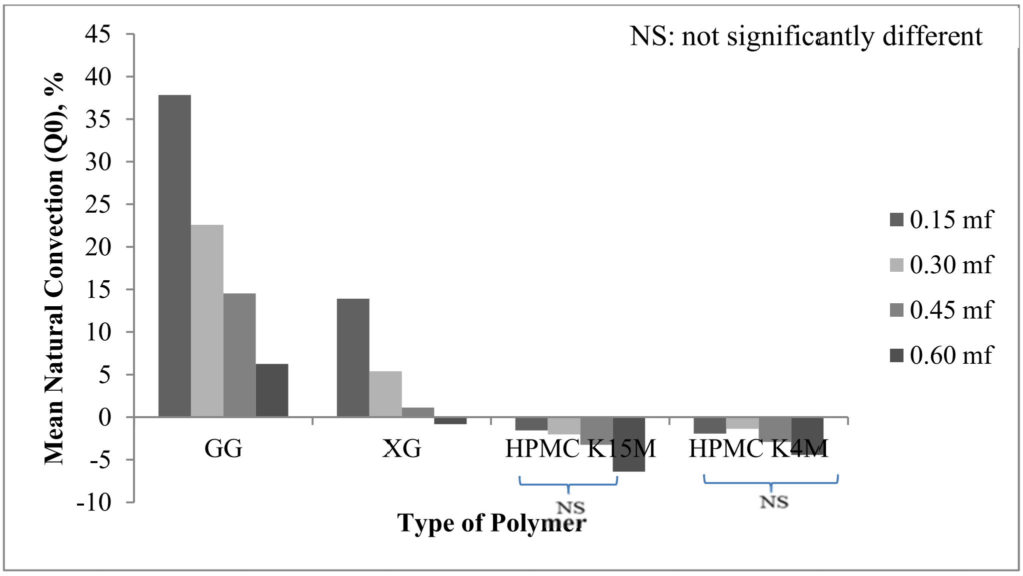
For each mf of polymers:

K4M: 0.15 ≈ 0.30 ≈ 0.45 ≈ 0.60
K15M: 0.15 ≈ 0.30 ≈ 0.45 > 0.60
XG: 0.15 > 0.30 > 0.45 > 0.60
GG: 0.15 > 0.30 > 0.45 > 0.60

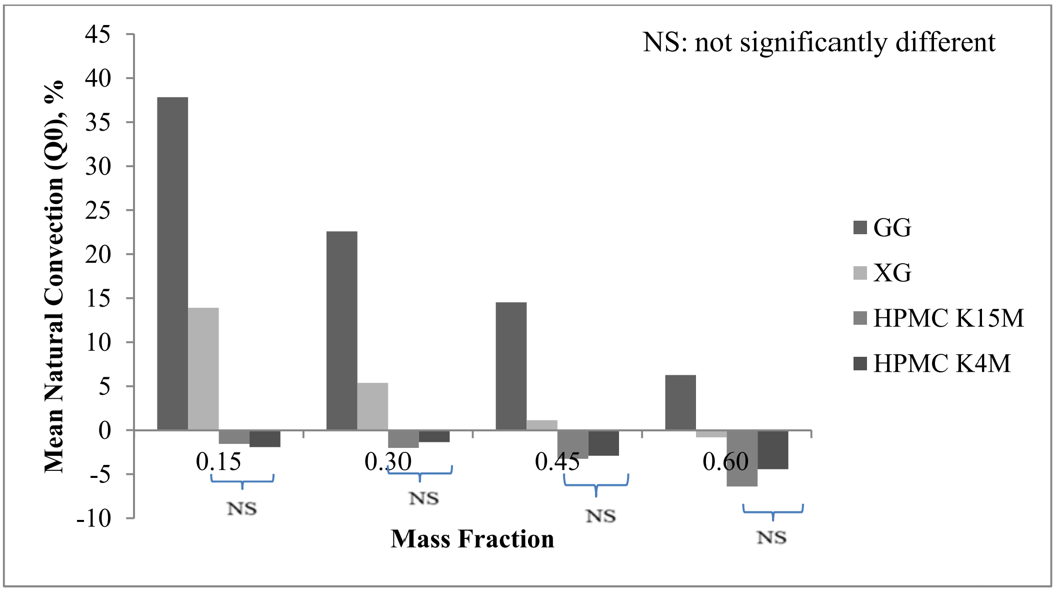
For each polymer:

At 0.15: GG > XG > K15M ≈ K4M
At 0.30: GG > XG > K4M ≈ K15M
At 0.45: GG > XG > K4M ≈ K15M
At 0.60: GG > XG > K4M ≈ K15M

From multiple comparison with LSD procedure, it was found that Q_0 from matrices containing various polymers were ranked as follows: (i) for HPMC K4M and HPMC K15M: 0.15 ≈ 0.30 ≈ 0.45 ≈ 0.60; (ii) for XG and GG: 0.15 > 0.30 > 0.45 > 0.60. At each mf from 0.15 to 0.60, Q_0 from matrices containing various polymers were ranked as follows: GG > XG > K4M ≈ K15M. These indicated that high mass fraction of polymer, XG and GG cause low Q_0 of matrices resulting in low releasing TMH, whereas HPMC K4M and HPMC K15M showed no different significance in Q_0 at different mf of polymers. For various polymers, GG showed highest natural convection and highest TMH released at time zero and in the initial time when soluble filler SDL was used.



(a)



(b)

Figrure 5.66 (a) The bar chart of mean natural convection (Q_0) and type of polymers of matrix tablets using SDL at various mass fraction of polymer.

(b) The bar chart of mean natural convection (Q_0) and mass fraction of matrix tablets using SDL as a filler.

Table 5.78 Lag time, min and ANOVA test of matrices using SDL at various mf of different polymers.

Polymer	MF	Lag time, min				
		1	2	3	4	5
HPMC K4M	0.15	0.12	0.25	0.14	0.05	0.28
	0.30	0.22	0.04	0.14	0.18	0.06
	0.45	0.60	0.51	0.97	0.74	0.48
	0.60	1.66	1.79	1.65	2.30	1.11
HPMC K15M	0.15	0.31	0.04	0.02	0.07	0.29
	0.30	0.38	0.11	0.18	0.42	0.35
	0.45	0.77	0.93	1.04	0.70	0.69
	0.60	3.91	3.26	1.91	3.10	4.32
XG	0.15	-17.09	-16.35	-19.90	-18.08	-20.44
	0.30	-3.34	-4.35	-2.73	-3.33	-3.32
	0.45	-0.09	-0.20	-0.29	-0.30	-0.11
	0.60	0.00	0.34	0.14	0.35	0.13
GG	0.15	-141.83	-106.54	-152.88	-162.28	-169.47
	0.30	-30.65	-36.50	-37.29	-37.31	-44.15
	0.45	-16.48	-20.57	-11.06	-15.96	-11.91
	0.60	-1.50	-2.21	-1.67	-4.48	-5.43

Source of Variation	Sum of Square(SS)	Degree of Freedom(DF)	Mean of Square(MS)	F-Ratio	p-value
Between Groups	102731.6	15	6848.78	167.44	2.52×10^{-45}*
Within Groups	2617.72	64	40.90		
Total	**105349.4**	**79**			

*highly significant difference (p << 0.01)

Table 5.79 Lag time, min of matrices using SDL as a filler at various mf of different polymer, LSD 1%allowance ($\alpha = 0.01$, 2-tailed).

$t = 2.655$ at *DF* of 64	LSD 1% allowance = $t\sqrt{s^2(\frac{1}{n_i} + \frac{1}{n_j})}$ = 10.74															
R_x	0.60 K15M	0.60 K4M	0.45 K15M	0.45 K4M	0.30 K15M	0.60 XG	0.15 K4M	0.15 K15M	0.30 K4M	0.45 XG	0.60 GG	0.30 XG	0.45 GG	0.15 XG	0.30 GG	0.15 GG
1	3.91	1.66	0.77	0.60	0.38	0.00	0.12	0.31	0.22	-0.09	-1.50	-3.34	-16.48	-17.09	-30.65	-141.83
2	3.26	1.79	0.93	0.51	0.11	0.34	0.25	0.04	0.04	-0.20	-2.21	-4.35	-20.57	-16.35	-36.50	-106.54
3	1.91	1.65	1.04	0.97	0.18	0.14	0.14	0.02	0.14	-0.29	-1.67	-2.73	-11.06	-19.90	-37.29	-152.88
4	3.10	2.30	0.70	0.74	0.42	0.35	0.05	0.07	0.18	-0.30	-4.48	-3.33	-15.96	-18.08	-37.31	-162.28
5	4.32	1.11	0.69	0.48	0.35	0.13	0.28	0.29	0.06	-0.11	-5.43	-3.22	-11.91	-20.44	-44.15	-169.47
Mean($\bar{X}$)	3.30	1.70	0.83	0.66	0.29	0.19	0.17	0.15	0.13	-0.20	-0.50	-3.40	-15.19	-18.37	-37.18	-146.6
$\bar{X}$–(%A)	12.02	8.11	5.09	4.31	2.14	1.10	0.96	0.73	0.70	-2.34	-2.43	-2.72	-3.49	-5.28	-16.16	-35.10

Table 5.79 Lag time, min of matrices using SDL as a filler at various mf of different polymers, LSD 1%allowance (α = 0.01, 2-tailed) (cont.)

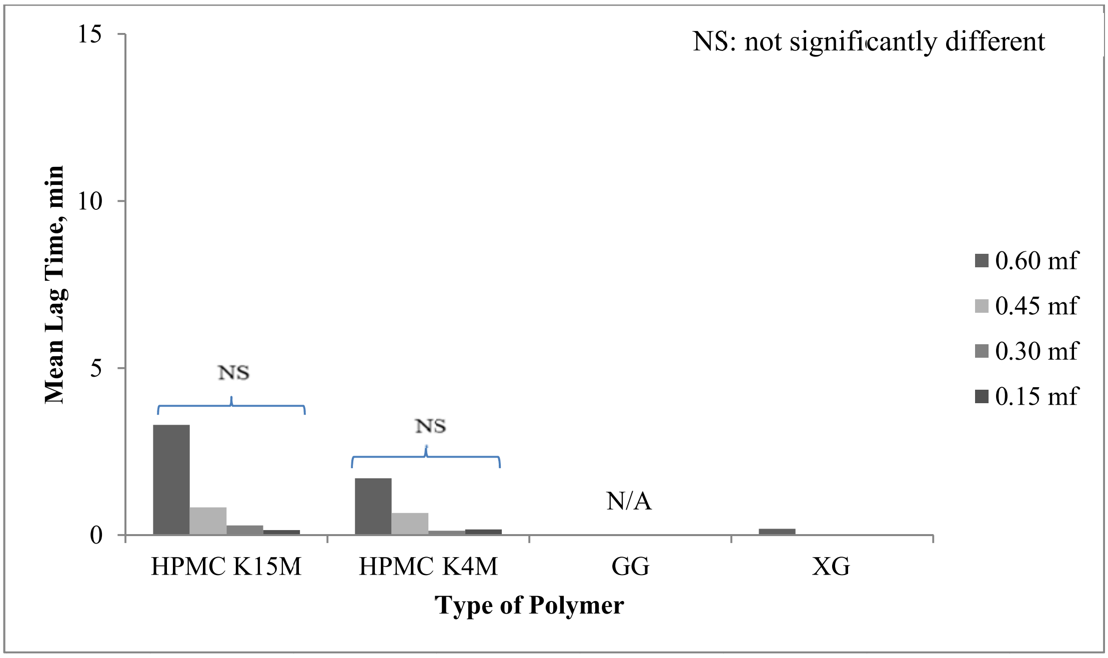
For each mf of polymers:

K4M: 0.60 ≈ 0.45 ≈ 0.15 ≈ 0.30
K15M: 0.60 ≈ 0.45 ≈ 0.30 ≈ 0.15
XG: N/A
GG: N/A

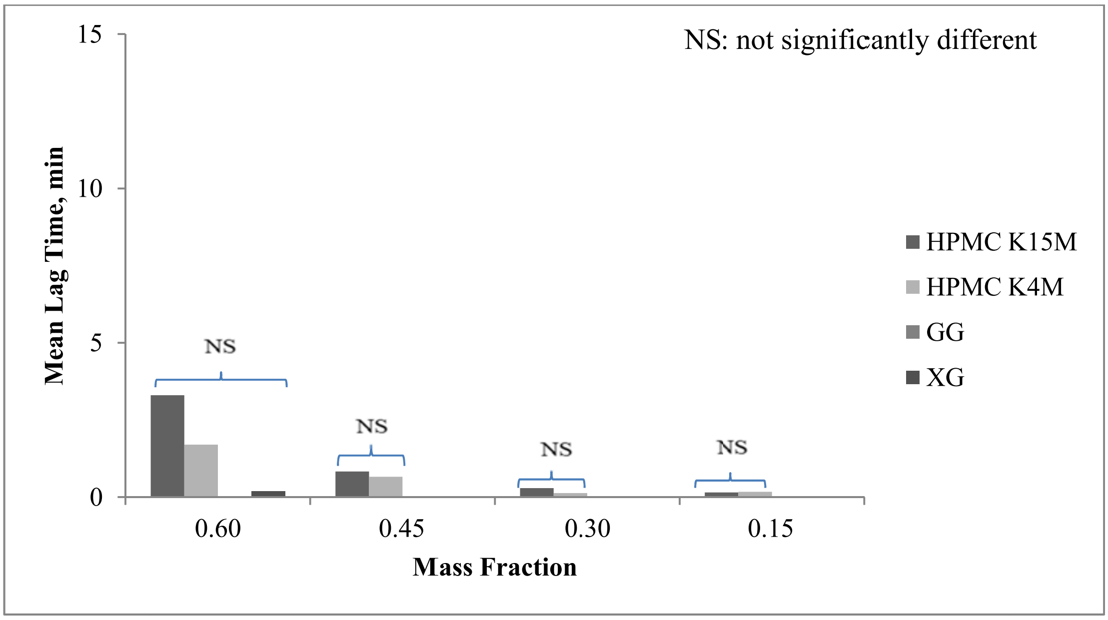
For each polymer:

At 0.15: K4M ≈ K15M
At 0.30: K4M ≈ K15M
At 0.45: K4M ≈ K15M
At 0.60: K4M ≈ K15M ≈ XG

From multiple comparison with LSD, lag times from matrices containing HPMC K4M or HPMC K15M were found to be not significantly different at various mf (0.15 ≈ 0.30 ≈ 0.45 ≈ 0.60). For each mf of either HPMC from 0.15 to 0.60, lag times of matrices using different HPMC were found to be not significantly different.



(a)



(b)

Figrure 5.67 (a) The bar chart of mean lag time and type of polymers of matrix tablets using SDL at various mass fraction of polymer.

(b) The bar chart of mean lag time and mass fraction of matrix tablets using SDL as a filler.

5.5 Construction of Once-daily Dose Controlled Release TMH Matrices

Once-daily dose drug matrices have been widely attented due to therapeutic advantages over conventional dosing that include a probable lower incident of toxicity and can improve patient adherence. Finding the suitable retarding agent and ratio in polymer matrices will be recognized because of characteristics of polymer. The amount of polymer is affected to the drug release rate. Constructing the Once-daily dose controlled release TMH matrices was done by substituted 100% the variable amount of drug released (Q) and 24 h in time (t) in each working equation to get the suitable mass fraction of polymers. In this study, XG was the most appropriate polymers that could be observed, for matrices using XG as a retarding agent, 0.45 mf matrices contained with an insoluble filler, DCPD and 0.60 mf matrices contained with a soluble filler, SDL could retard the drug release until 24 h as shown in Table that match to the calculation from the equations.

Table 5.80 Calculation of *Cp* for once-daily dose by substitute *Q* and *t* by 100% and 24 h in each working equation.

Polymer	Filler	MF of polymer for once-daily dose controlled release TMH matrix
HPMC K4M	DCPD	N/A (>>0.6)
	SDL	N/A (>0.6)
HPMC K15M	DCPD	N/A (>>0.6)
	SDL	N/A (>0.6)
XG	DCPD	0.39
	SDL	0.52
GG	DCPD	-
	SDL	-

From Table 5.80, the mf of XG providing once-daily dose TMH matrices using DCPD and SDL were 0.39 and 0.52, respectively. For matrices using GG as polymer, the results of calculation are too low and not corresponded to the observation, maybe the equation cannot predict the drug release of the matrices using low viscosity polymer. All formulation using HPMC K4M and HPMC K15M as polymer could not maintain the release until 24 h, it released total of drug within 12 h, with correspond to the calculation that mass fraction of polymer using for once-daily dose is higher than 0.60 mf, it cannot be used to formulate the once-daily dose because mf of drug is 0.40. For GG matrices with each filler, the results The equation that predicted the drug release from once-daily dose formulation, was made by replacing *Cp* with all values from Fig 5.23 for XG matrices contained DCPD and Fig. 5.55 for XG matrices contained SDL in working Eq. (32) and Eq. (36)

These new equations were obtained as followed:

$$Q = 2.43 + 19.87\sqrt{t} \text{ for DCPD} \qquad \text{Eq. (38)}$$

$$Q = -2.61 +21.01\sqrt{t} \text{ for SDL} \qquad \text{Eq. (39}$$

From these equations, each operating curve of percentage TMH released at time t is derived for once-daily dose TMH matrices using insoluble filler and soluble filler were depicted in Fig 5.68. The release profiles of matrices using in a soluble filler, DCPD had the release rate 19.87 % $h^{-1/2}$ and the natural convection, Q_0 of 2.43% and the release profiles of matrices using in a soluble filler, SDL had the release rate 21.01 % $h\text{-}^{1/2}$ and the natural convection, Q_0 of -2.61%.

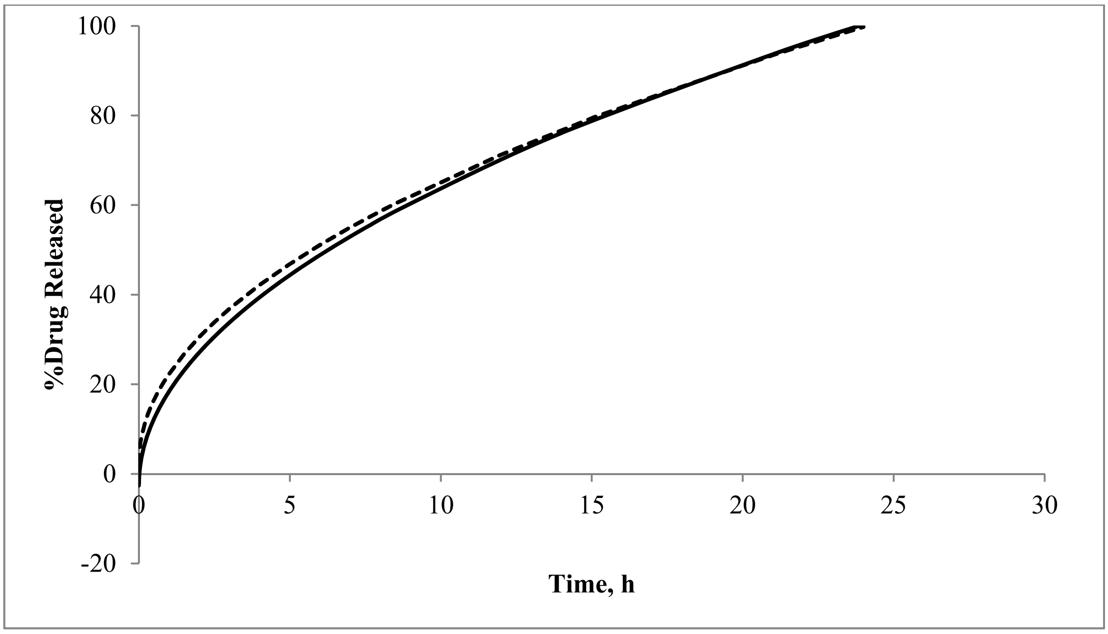


Figure 5.68 Construction of once-daily dose controlled release TMH matrices using DCPD and SDL at mf of 0.39 and 0.52, respectively. Key: ….., DCPD and ____, SDL.

5.6 Determination of Swelling Property of Each Formulation

As depicted in figure 5.69 HPMC K4M, HPMC K15M, and XG could progressively increase the swelling ratio with increasing time within 24 h. At 24 h both HPMC provided 2-fold increasing in swelling ratio whereas XG provided 4-fold increasing. These might due to the gradual hydration of water into matrix using each polymer could cause gradual polymer swelling related to swelling property of each polymer. Matrix using GG showed peak and highest swelling ratio in the initial time and provided non-remarkable decrease in swelling ratio. These might be due to GG was easily contacted with water, and the fast hydration and swelling were subsequently obtained. GG immediately provided peak swelling around 27-fold at initial time, this might be due to low viscosity of GG gel layer which could not retard the hydration into the matrix.

For mixtures using insoluble filler DCPD as depicted in Fig. 5.70, 5.72 and 5.74, as well as those using soluble filler SDL as depicted in Fig. 5.71, 5.73 and 5.75, an increase in polymer mf of either HPMC or XG could increase the swelling ratio profile with increasing time within 24 h. At initial time for DCPD mixture using

0.15 HPMC K4M or K15M, thinning effect was occurred and might be due to the void space in mixture filling with low viscosity of polymer that could not retard the collapsing of mixture powder of DCPD with higher density than that of SDL.

For mixtures using insoluble filler DCPD as depicted in Fig. 5.76, as well as those using soluble filler SDL as depicted in Fig. 5.77, an increase in GG mf could only increase the swelling ratio, but could not increase swelling ratio profile with increasing time within 24 h. These results were similar to effect of GG on swelling profile with increasing time. This might be due to peak swelling of GG at initial time t = 0. For mixtures containing GG at all mf, using SDL showed collapse effect in swelling ratio profile after initial time until 24 h. This might due be the larger void space in soluble matrix formed by sudden dissolving SDL by water uptake into mixture compared to insoluble matrix. However, for DCPD mixture using GG at mf of 0.60 showed collapse effect too because there was no DCPD in mixture that could retard such effect.

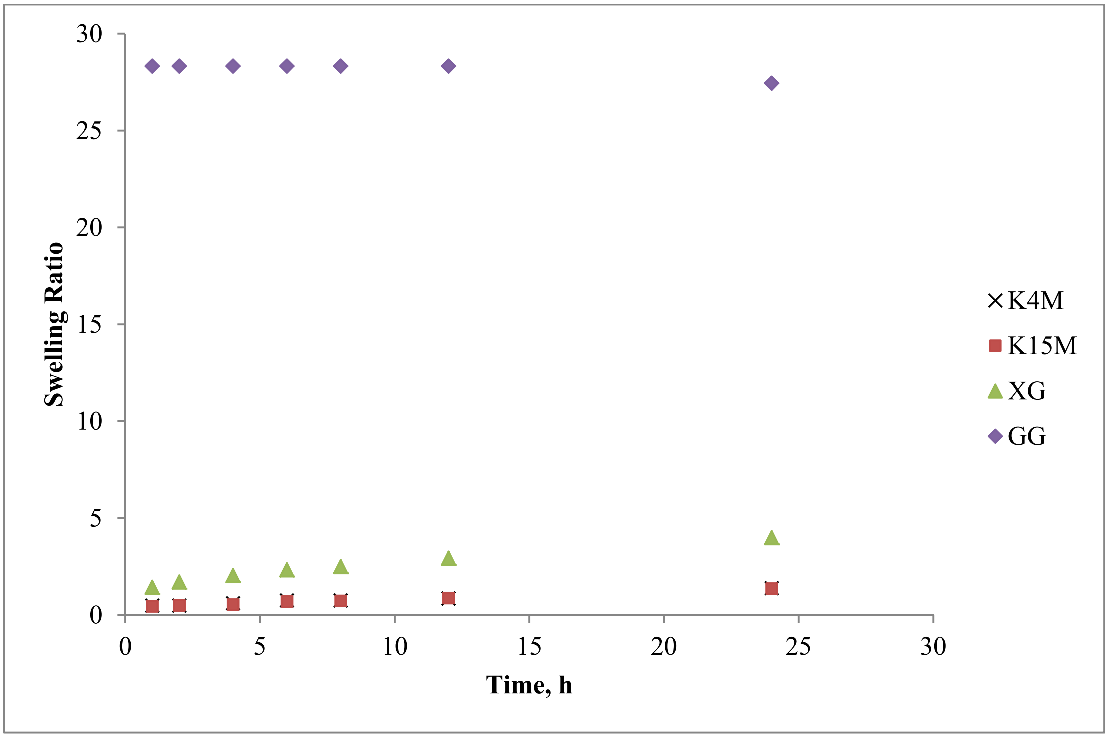


Figure 5.69 The swelling ratio of HPMC K4M, HPMC K15M, XG and GG at different imes (n = 3).

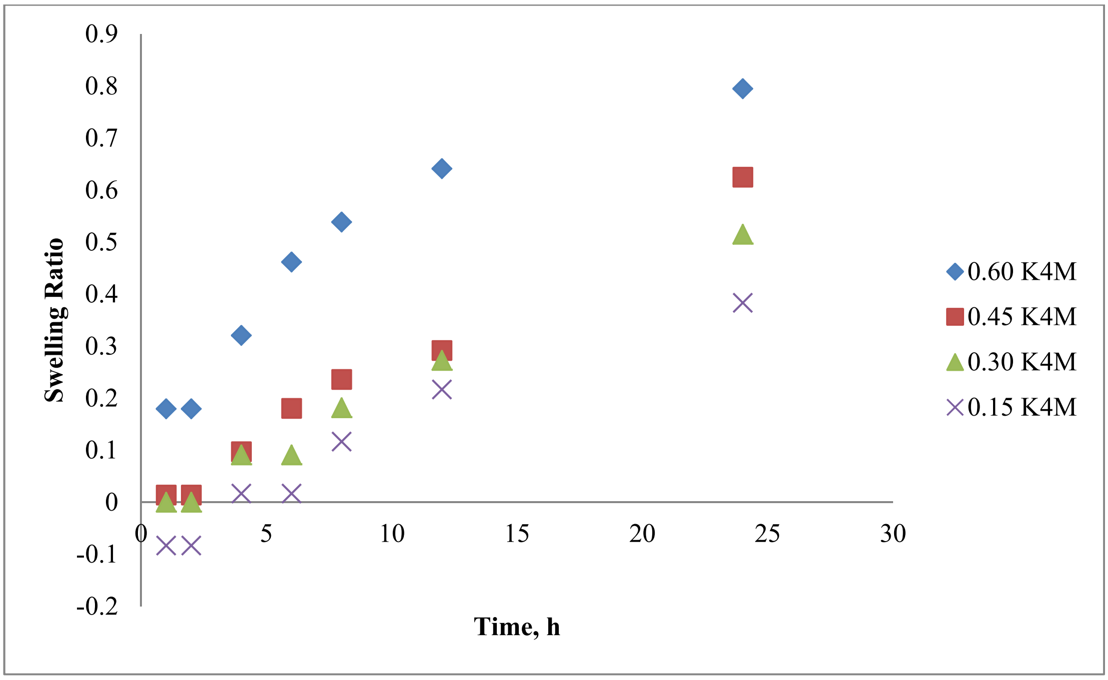


Figure 5.70 The swelling ratio with different mf of HPMC K4M formulations at different times using DCPD (n = 3).

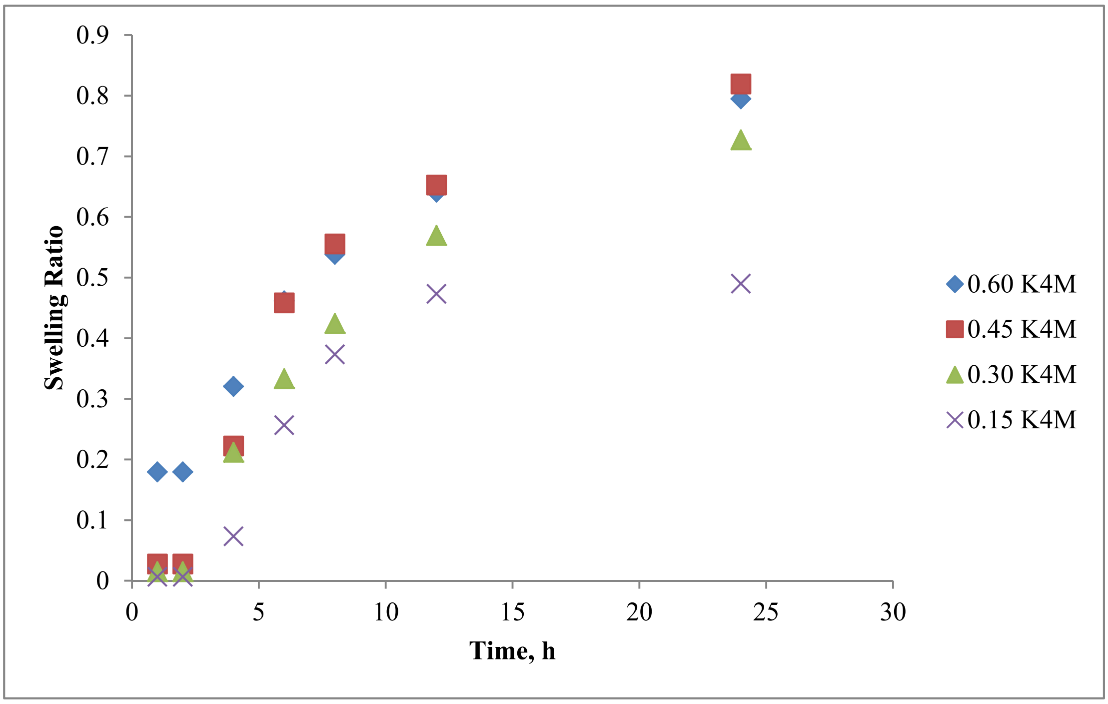


Figure 5.71 The swelling ratio with different mf of HPMC K4M formulations at different times using SDL (n = 3).

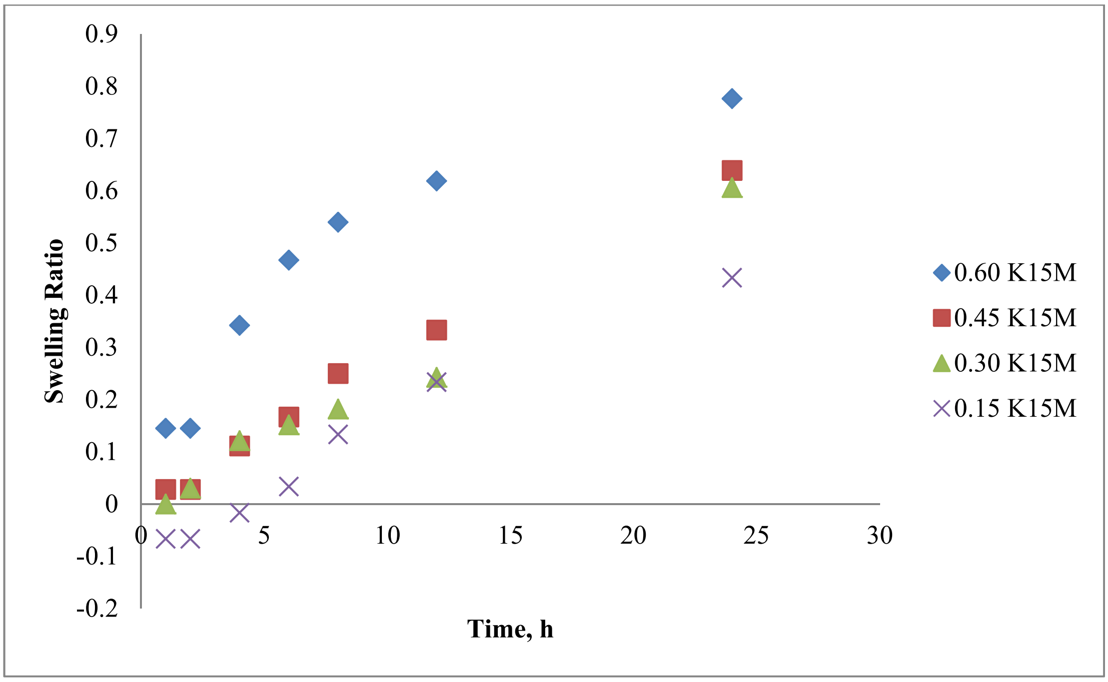


Figure 5.72 The swelling ratio with different mf of HPMC K15M formulations at different times using DCPD as a filler (n = 3).

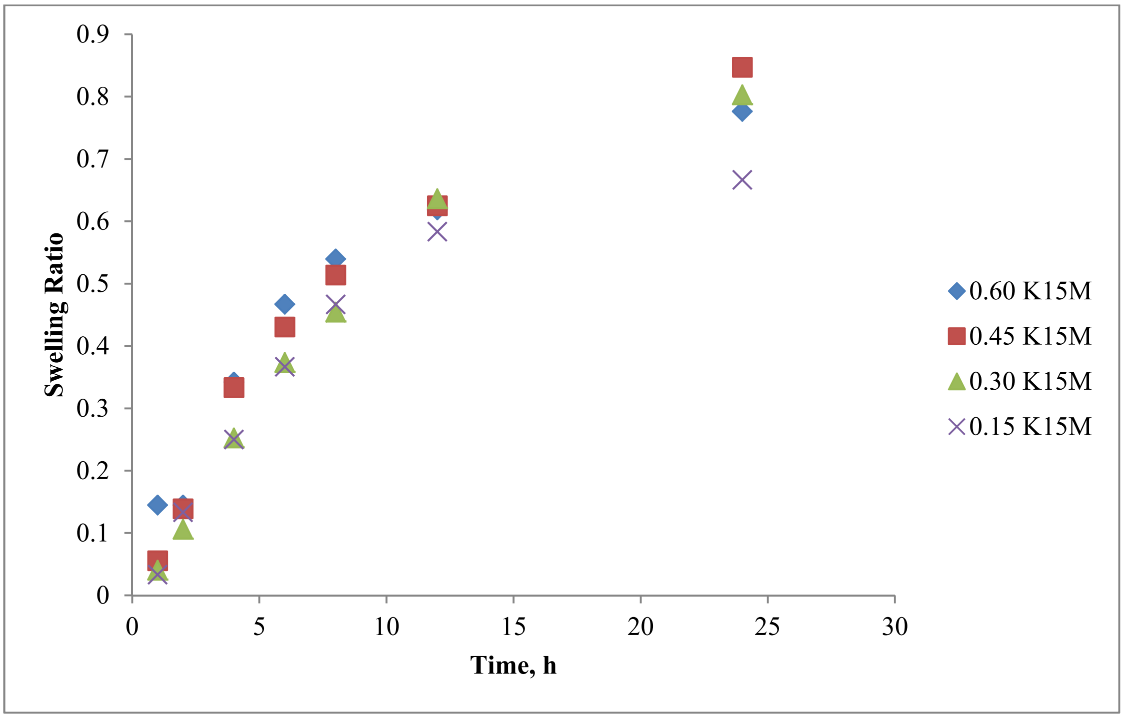


Figure 5.73 The swelling ratio with different mf of HPMC K15M formulations at different times using SDL (n = 3).

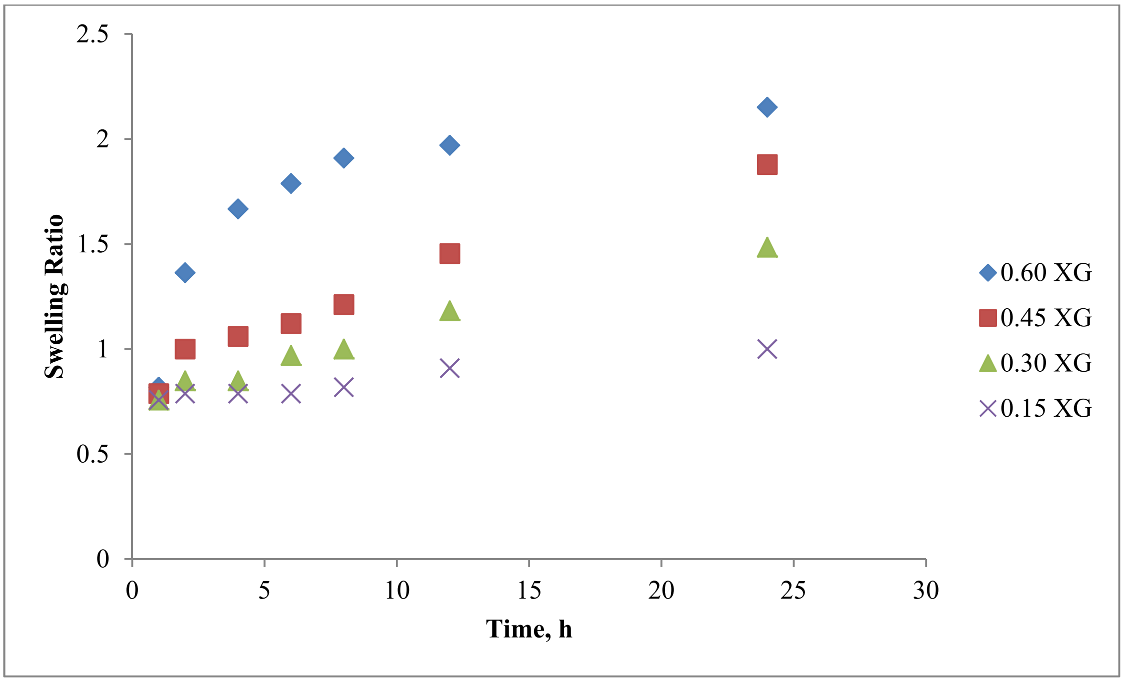


Figure 5.74 The swelling ratio with different mf of XG formulations at different times using DCPD (n = 3).

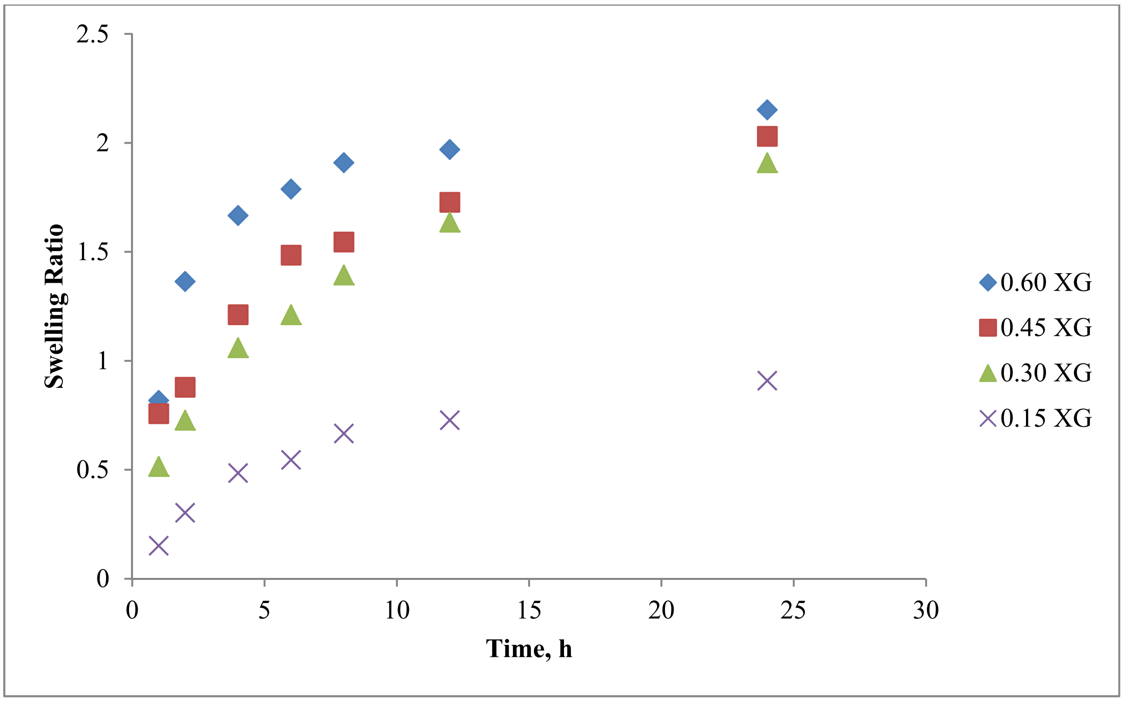


Figure 5.75 The swelling ratio with different mf of XG formulations at different times using SDL (n = 3).

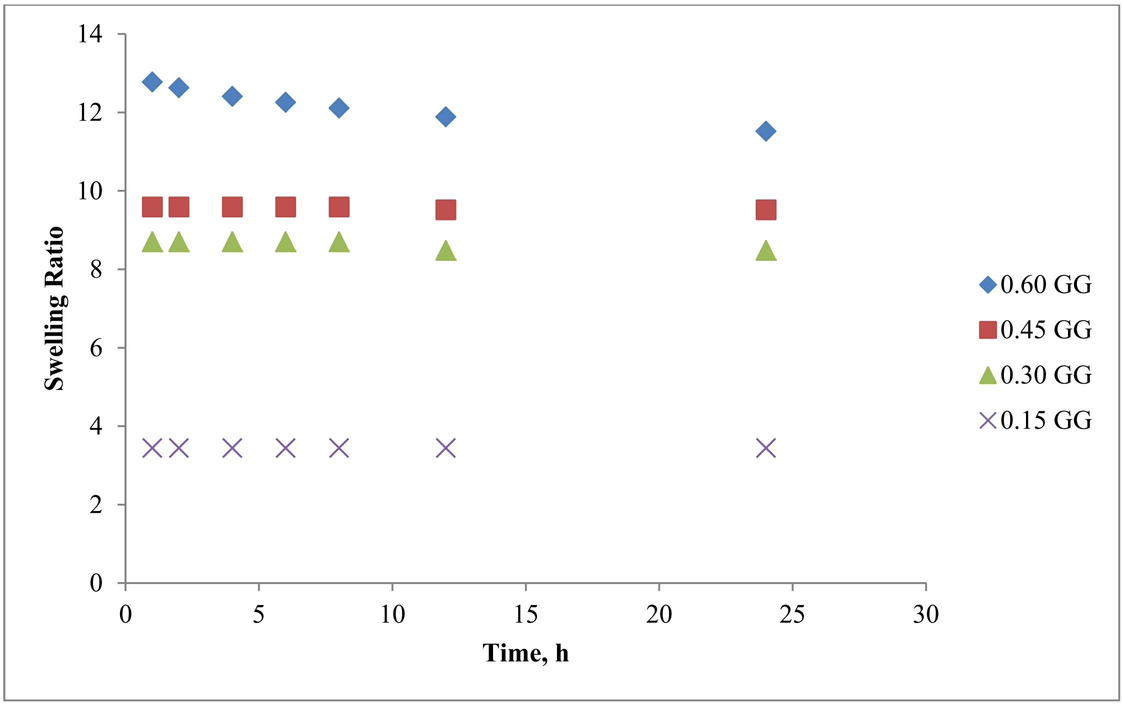


Figure 5.76 The swelling ratio with different mf of GG formulations at different times using DCPD (n = 3).

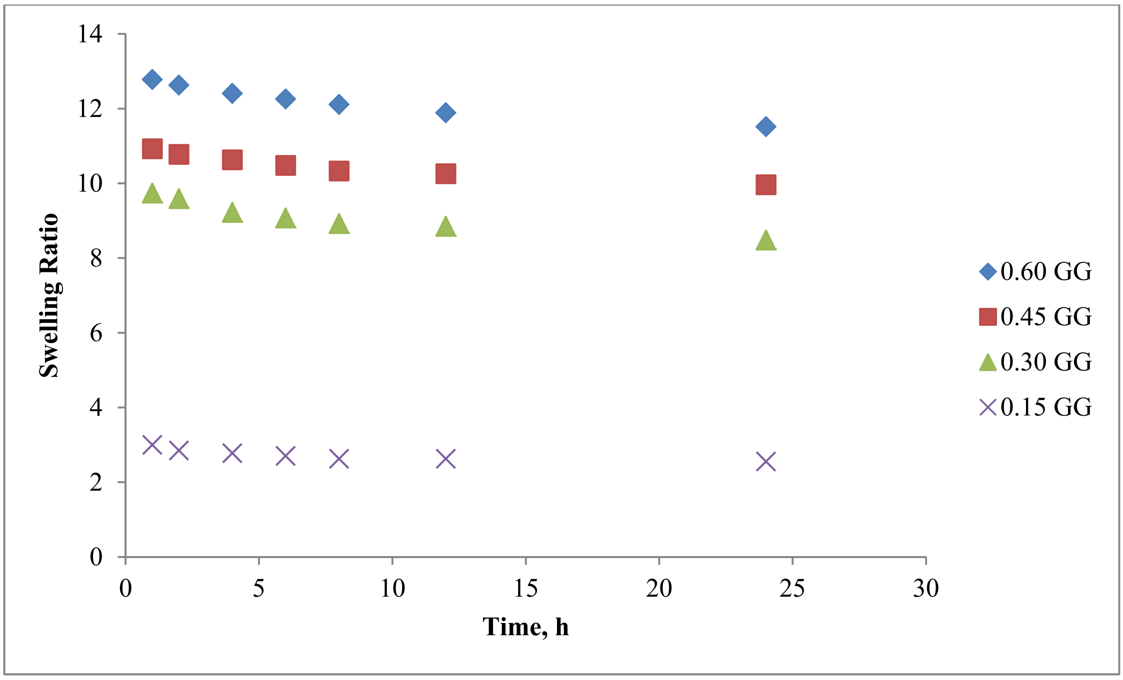


Figure 5.77 The swelling ratio with different mf of GG formulations at different times using SDL (n = 3).

The present study shows that the formulations prepared from HPMC K4M, HPMC K15M, XG and GG could moderate the drug release from TMH matrix tablets. When the concentration of polymer was increased, the release of drug was decreased. XG has the best retardability property for drug at all mf. For different fillers used, insoluble DCPD showed better retardability effect than SDL. The drug release from all formulations of the matrix tablets followed Higuchi model of diffusion. For mechanism of drug transport, most drug release from HPMC matrix tablets transport showed non-Fickian diffusion, XG matrix tablets showed quasi-Fickian and non-Fickian diffusion whereas GG matrix tablets showed only quasi-Fickian diffusion. This finding was consistent with the previous studies, Varshosaz et al studied the different combination of natural gum (guar or xanthan) with HPMC. A triple mixture of these three polymers was also used to provide matrix tablets for sustained release of TMH. The results showed that when only HPMC was used as a retarding agent, Higuchi model and Peppas equation could be used to fit the drug release profile well indicating the Fickian diffusion. This polymer showed less mass loss and water uptake compared with natural gums. The hydration rate of this synthetic polymer relates to its hydroxypropyl substitutes percentage. HPMC K100M contains the greatest amount of these groups and produces strongly viscous gel that plays an important role in drug release especially at the beginning of the release profile. When XG was used as the only retarding hydrophilic polymer, drug release significantly followed a zero-order kinetic model ($p<0.05$). On the other hand, XG shows the highest erosion and water uptake among the formulations studied. From the results obtained in this study, there are 3 mechanisms involved (i.e, swelling, erosion, and diffusion fronts). Therefore a zero-order release was observed. A decrease in the XG concentration resulted in shifts of the drug release kinetic to Higuchi model. When GG was used as the only retarding polymer, the first order release kinetic was observed. GG matrices had neglible mass loss, and a high water uptake after 8 hours. The overall rate of release of tramadol from GG matrices was significantly higher than that from XG matrices ($p<0.05$). These results indicate that XG has higher drug retarding ability than GG. Tablets prepared from XG showed a non-Fickian or anomalous mechanism. GG matrices showed a Fickian-release diffusion (55). Singh et al investigated the release of TMH matrix tablets using different polymers namely GG, XG and Methocel (HPMC K15M and HPMC K100M). From the overall dissolution profile, it was concluded that the drug release rate decreased as concentration of the polymer increased. The type of polymer used also had an effect. The release mechanism of TMH from matrix tablets indicated anomalous (non-Fickian) transport mechanism and followed zero order kinetics (56). Manjula et al investigated TMH matrix tablets containing polymers (gum olibanum, HPMC and XG), either alone or in combinations, by wet granulation. Among the three polymers, cumulative drug release from HPMC matrix was slower when compared to XG and gum olibanum. The drug release in XG matrix tablets was slower when compared to HPMC matrix tablets up to 4 hours of dissolution studies. However, during the remaining 4 hours dissolution studies, incorporation of lactose induced faster drug release when compared to dicalcium phosphate and microcrystalline cellulose. Drug release from XG matrix and HPCM matrix followed first-order kinetics (57). Uddin et al evaluated HPMC K15M as rate retardant polymer to sustain the release of TMH from TMH sustained release tablet matrix. From their study it was observed that zero order release kinetics was the predominant release mechanism than Higuchi and first order kinetics. Among the formulations (drug and polymer ratio, 5:6, 5:5, 5:4, 5:3 and 5:2), a different amont of HPMC K15M polymer can sustain the release of TMH 55.5% to 100% in 8 hours (58). Rao et al developed sustained release matrix tablets of TMH using different polymers (HPMC, Karaya gum and Carragenan). The formulations prepared with drug:polymer ratio 1:1 showed 100% drug release in 6 to 8 hours and formulations prepared with drug:polymer 1:2 could retard the drug release during the desired time period. The formulation which was prepared from HPMC K15M showed 88.87% release in 12 hours. Drug release mechanism from matrix tablets followed non-Fickian (anomalous) transport mechanism (59). Gendle et al. developed sustained release tablets of TMH using polymers (HPMC K100M, HPMC K15M and HPMC K4M) hydrophilic matrix system. The data showed that the formulations are useful for sustained release of TMH due to almost 100 percent drug release obtained after 12 hours. For kinetic release, the data was fitted to Korsmeyer's Peppas equation, n values of 0.42 – 0.59 were obtained, indicating the Fickian and non-Fickian release or anomalous (60).

CHAPTER VI
CONCLUSION

The directly compressed TMH matrix tablets were determined their percentage drug released (Q_i) from matrices in distilled water using the USP dissolution apparatus type II at certain time intervals from 0-24 h, The release profiles between Q_i square root of time were established. From linear regression with high regression constant between Q_i and square root of time, it was indicated that the release of TMH from all matrices obeyed Higuchi's model of diffusion. In the present study, the effect of mass fraction of four different polymers, i.e., HPMC K4M, HPMC K15M and XG on the release kinetics of TMH from hydrophilic swellable matrices containing two different direct compression fillers, i.e. DCPD and SDL were studied.

For insoluble filler DCPD, it was found that the kinetic release rate (*k*) of TMH from matrices containing various mass fractions (mf) of polymer might be ranked as (i) for HPMC K4M, HPMC K15M or XG: 0.15 > 0.30 > 0.45 > 0.60, and (ii) for GG: 0.15 ≈ 0.30 ≈ 0.45 > 0.60. For each MF of polymers, *k* of different polymers might be ranked as (1) at MF of 0.15: GG ≈ K4M≈ K15M > XG, and (2) at MF of 0.30 to 0.60: GG > K4M ≈ K15M > XG. From the values of Y-intercept namely natural convection (Q_0) of TMH from matrices, Q_0 of matrices containing various MF of different polymers might be ranked as: (i) for HPMC K4M, HPMC K15M and GG: 0.15 > 0.30 > 0.45 ≈ 0.60, and (ii) for XG: 0.15 > 0.30 > 0.45 > 0.60. For each mass fraction of polymers, Q_0 of matrices containing different mf of polymers might be ranked as (i) at mf of 0.15, 0.30 and 0.60: GG > XG > K4M > K15M, and (ii) at mf of 0.45: GG > XG > K4M ≈ K15M. From the values of X-intercept namely lag time, the lag times of matrices containing various mf, i.e., 0.30, 0.45 and 0.60 of HPMC K4M or HPMC K15M were found to be not significantly different. Furthermore for any mf of polymers from 0.30 to 0.60, the lag times of matrices containing HPMC K4M and HPMC K15M were found to be not significantly different.

For soluble filler, SDL it was found that kinetic release rate (*k*) from matrices containing various mf of polymers might be ranked as (i) for HPMC K4M and XG: 0.15 > 0.30 > 0.45 > 0.60 respectively; (ii) for HPMC K15M: 0.15 > 0.30 > 0.45 ≈ 0.60, and (iii) for GG: 0.30 ≈ 0.45 ≈ 0.60 > 0.15. For each mass fraction of polymers, *k* of matrices containing different polymers may be ranked as (i) at mf of 0.15: K4M ≈ K15M ≈ XG ≈ GG, and (ii) at mf of 0.30 to 0.60: GG ≈ K4M ≈ K15M > XG. From the values of natural convection (Q_0), Q_0 of matrices containing different mf of polymers might be ranked as: (i) for HPMC K4M or HPMC K15M: 0.15 ≈ 0.30 ≈ 0.45 ≈ 0.60; (ii) for XG or GG: 0.15 > 0.30 > 0.45 > 0.60. For each mass fraction of polymers, Q_0 of matrices containing any mf from 0.15 to 0.60 of polymers might be ranked as: GG > XG > K4M ≈ K15M. From the values of lag time, the lag times of matrices containing various mf from 0.15 to 0.60 of HPMC K4M or HPMC K15M were found to be nonsignificantly different. Furthermore for any mf of polymers from 0.15 to 0.60, the lag times of matrices containing HPMC K4M and HPMC K15M were found to be nonsignificantly different.

For matrices using XG as a retarding agent, both DCPD matrices containing 0.45 XG and SDL matrices containing 0.60 XG could retard the release of TMF until 24 h. From the drug release models proposed by Shah et al for matrices containing an insoluble filler and by Jateleela et al for those containing a soluble filler, mf of XG providing once-daily dose TMH matrices using DCPD and SDL were found to be 0.39 and 0.52, respectively.

The mechanism of drug transport from various matrices were described the release exponent *n* proposed by Kormeyer-Peppas. Increase in polymer mf could increase the release exponent for both matrices containing DCPD and SDL. For matrices using various mf of GG, the mechanism of drug transport of all matrices containing DCPD or SDL was only quasi-Fickian diffusion. For matrices using various mf of HPMC, the mechanism of drug transport of all matrices containing DCPD or SDL was non-Fickian transport, except DCPD matrices using 0.15 HPMC K4M or K15M, and SDL matrices using only 0.15 HPMC K4M were found to be quasi-Fickian diffusion. For matrices using various mf of XG, the mf which turned the transport mechanism from quasi-Fickian diffusion to non-Fickian transport were 0.60 XG for matrices using DCPD and 0.45 XG for matrices using SDL, respectively.

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