Design of Experiment in Practice: Formulation Design and Optimization of Sustained Release Tablet Dosage Form of Ketorolac

A project submitted
by
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Dedicated to my parents

Certification Statement

This is to certify that the project titled "Design of Experiment in Practice: Formulation Design and Optimization of Sustained Release Tablet Dosage Form of Ketorolac" submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Counter signed by the supervisor

_____

Acknowledgement

The blessings and mercy of the Almighty who is the source of our life and strength of our knowledge and wisdom, has helped me to continue my study in full diligence which I hope will reflect in my project.

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Abstract

Oral sustained release drug delivery system is being widely used for the past two decades as a means to provide a drug with improved therapeutic efficacy and also to assure rational drug therapy. The sustained release dosage form allows slow release of the drug followed by the maintenance of a constant therapeutic blood or tissue drug levels for an extended period of time. This characteristic of the dosage form further decreases frequency of drug intake ensuring better patient compliance and often reduces adverse effects associated with drug. The aim of the present study was to design and develop an optimized once daily oral sustained release matrix tablet formulation of a potent non-steroidal anti-inflammatory drug (NSAID), Ketorolac Tromethamine. Ketorolac Tromethamine has a short biological half-life of 4 to 6 hours, so it was considered as a suitable drug for the formulation of sustained release tablet to prolong its therapeutic action and reduce dosing frequency. The experiment was designed to develop nine different formulations of matrix tablets by using combination of hydrophilic Methocel K100M CR and Methocel K4M CR polymers at different ratios. The selection of the excipients was based on IR and DSC studies depending on the compatibility of which the tablets were manufactured by direct compression. The resulting tablets were evaluated for physical properties such as weight variation, hardness, thickness, friability and drug content which complied with the limits specified in USP. *In vitro* dissolution study was performed in order to obtain the drug release profile of the matrix tablets and the outcomes were fitted into various mathematical models for release kinetic analysis. Most of the formulated tablets were found to follow Higuchi drug release kinetics and exhibited non-Fickian type drug release mechanism. Furthermore, in order to obtain an optimum product, a 3^2 full factorial design was employed to systematically optimize the drug release profile with Design Expert software. The analysis of the responses produced by the software revealed that the polymer combination used at different ratios has control on the drug release. F4 was selected as the optimum formulation significantly on the basis of desirability criterion and graphical analysis.

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List of acronyms

API = Active Pharmaceutical Ingredient

BCS = Biopharmaceutics Classification System

CR = Controlled Release

DSC = Differential Scanning Calorimetry

EM = Electromagnetic

FT-IR = Fourier Transform Infrared Radiation

FDA = Food and Drug Administration

FI = Factor interaction

GI = Gastrointestinal

HPMC = Hydroxypropyl methyl cellulose

IR = Infrared

KT = Ketorolac Tromethamine

LBD = Loose Bulk Density

MDT = Mean Dissolution Time

NSAID = Non-steroidal anti-inflammatory drug

PRESS = Predicted residual sum of square

R-squared = Multiple correlation coefficient

SD = Standard Deviation

TBD = Tapped Bulk Density

USP = United State Pharmacopeia

UV= Ultraviolet

Introduction

Oral drug delivery system is considered to be the most convenient route of drug administration. There are several techniques by which such drugs can be designed based on some interrelated variables such as type of delivery system, the disease being treated, the patient, the length of therapy and physicochemical properties of drug (Etman et al., 2008). A conventional dosage form of the drug usually do not maintain the therapeutic range of plasma drug level for extended period of time and often require multiple-dose therapy. This approach of repetitive dosing, however, exhibits some drawbacks such as frequent administration especially for drugs with short biological half-life, patient non-compliance with multiple dosage regimens and sometimes, under medication or over medication at certain disease states (Gennaro, 2000).

In order to minimize these limitations of a conventional dosage form, oral sustained release drug delivery system is being widely used for the past two decades as a means to provide a drug with improved therapeutic efficacy and also to assure rational drug therapy. The sustained release dosage form allows slow release of the drug followed by the maintenance of a constant therapeutic blood or tissue drug levels for an extended period of time (Figure 1.1). Further benefits of this drug delivery system include reduction in dose frequency and adverse side effects, increase in patient compliance, better therapeutic performance and even reduced healthcare cost when compared with that of conventional dosage form. Overall, administration of sustained release dosage form enables increased reliability of therapy eliminating the potential threat for both under and over dosing (Etman et al., 2008).

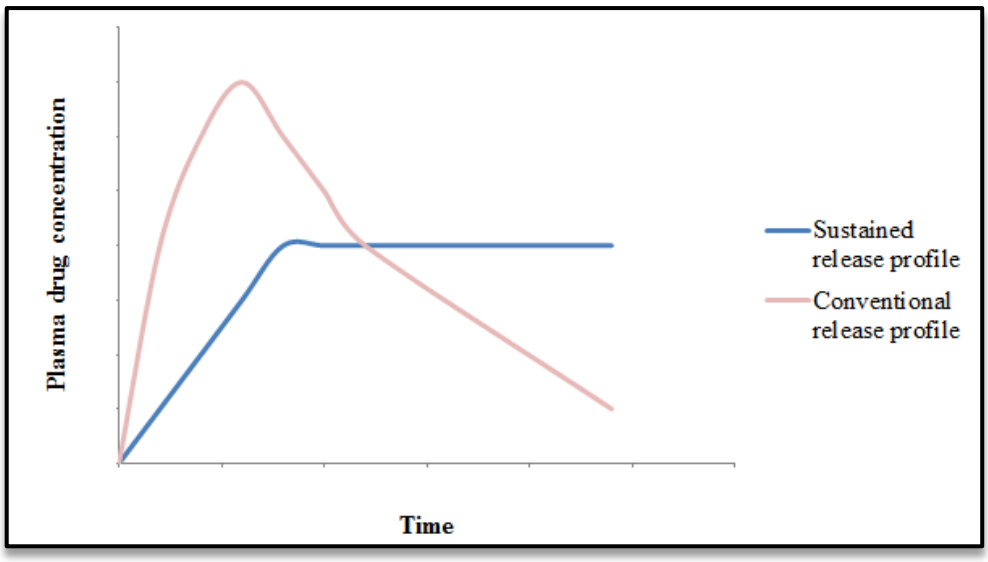

Figure 1.1: Comparison of conventional and sustained release profiles

There are several methods by which a sustained release tablet can be manufactured and the selection of the manufacturing process depends on the physicochemical properties of the components used in the formulation. A relatively easier and cost effective approach to the manufacture of the dosage form involves the direct compression of the mixture of drug, polymer and excipients to form a tablet in which the drug is embedded in a matrix core of the retardant. Alternatively, granulation of the mixture can be done prior to compression if required (Bose, Wong, & Singh, 2013).

The present study involves the formulation of sustained release matrix tablet of a non-steroidal anti-inflammatory drug (NSAID), Ketorolac Tromethamine through the use of different grades of natural hydrophilic polymers at various combinations which is eventually followed by release kinetic study and optimization of formulation so that a once daily sustained release tablet formulation could be obtained.

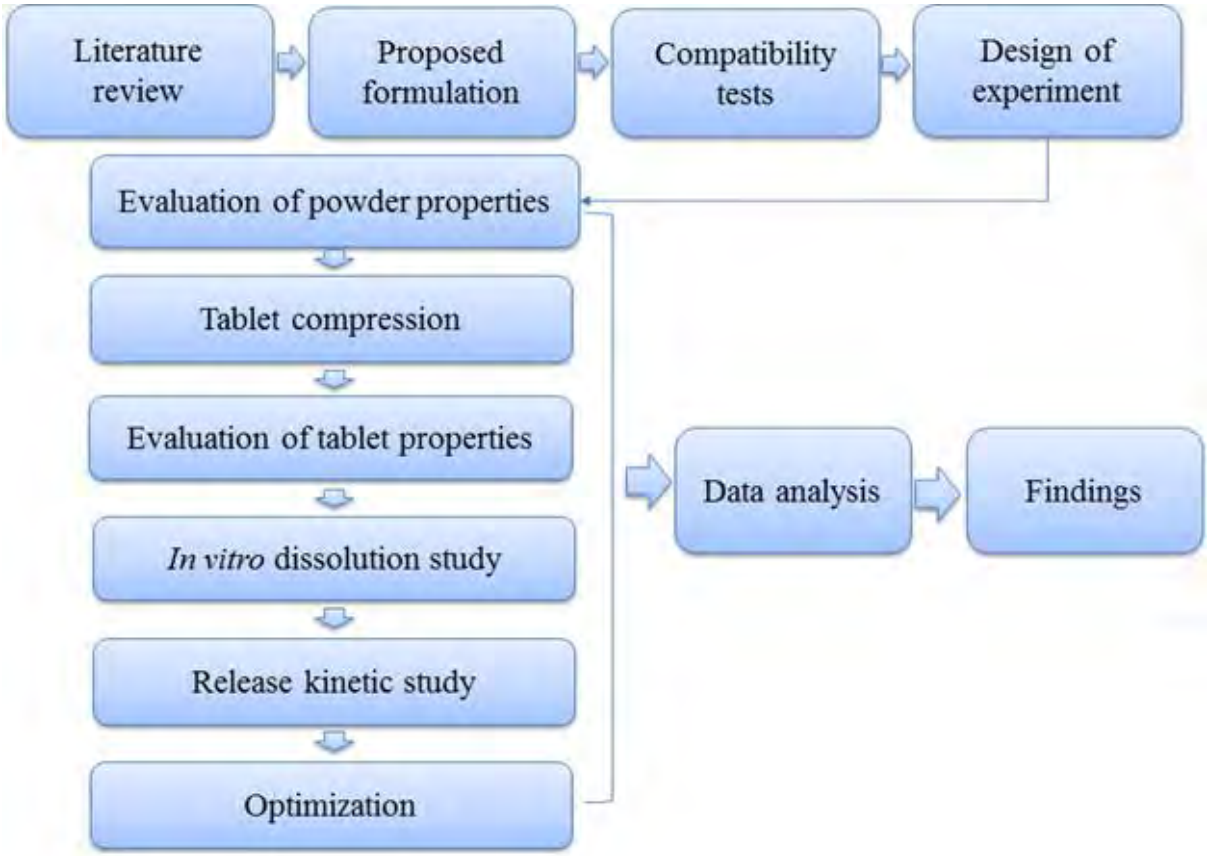

Figure 1.2: Flowchart of the study design of the project

1.1 Rationale of the study:

It is well recognized that a drug with a short half-life may be eliminated from the body at a faster rate resulting in a plasma level concentration insufficient to produce therapeutic effect. On the other hand, the development of the sustained release dosage form maintains constant therapeutic blood or tissue drug level for an extended period of time through prolongation of drug release. Therefore, such modified release drug delivery system is considered to be the most convenient mode of drug administration which can be achieved through the formation of a matrix system. In this system, the rate and the mechanism of drug release is controlled by the type and concentration of polymers used in the tablet formulation. There are four types of matrix system that can be used to design the sustained release dosage form which includes matrix composed of insoluble inert polymer, insoluble erodible polymer, hydrophilic polymer or hydrogel polymer. A hydrophilic polymer matrix system is widely used to prolong the drug release because of

its ability to undergo rapid hydration, good compression and gel forming characteristics, easy availability and cost effectiveness (Diwedi, Alexander, & Chandrasekar, 2011). It is a dynamic system which is dependent on polymer wetting, hydration, gel formation, swelling and dissolution. Simultaneously, the water soluble component of the tablet diffuses through the tablet core while the insoluble materials are released through tablet erosion as shown in Figure 1.3 (DOW, 2006).

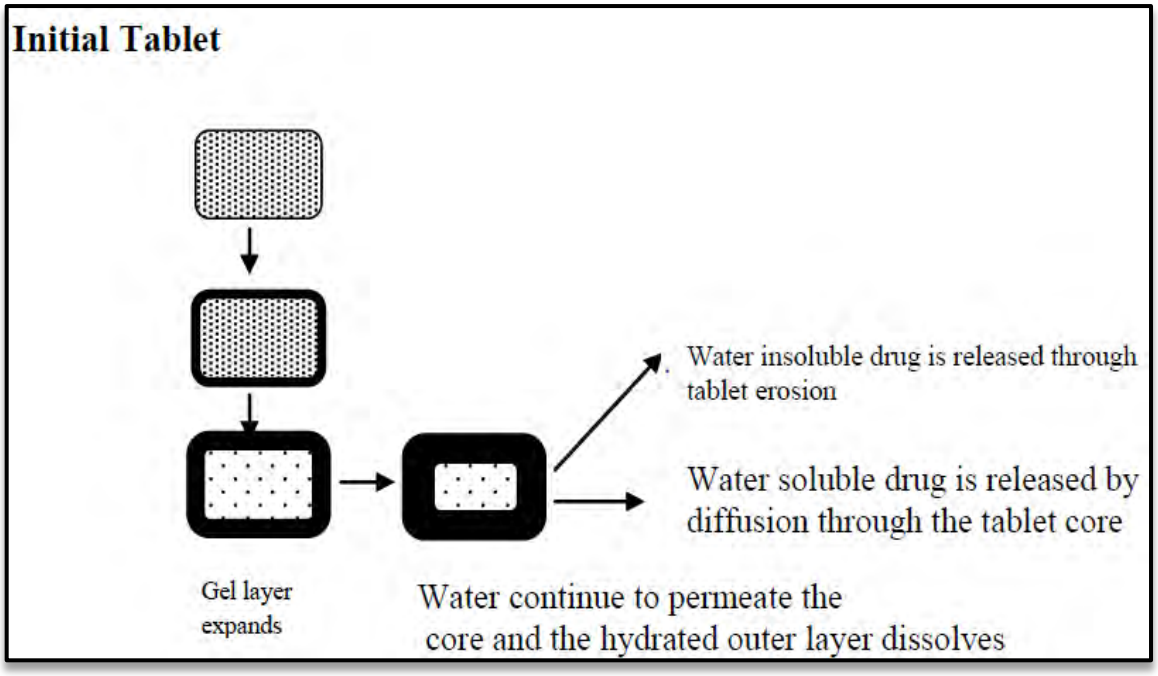

Figure 1.3: Drug release from a hydrophilic matrix tablet

Ketorolac Tromethamine (KT) is commercially available as immediate release oral tablet dosage form. It has a short biological half-life of 4 to 6 hours which makes it susceptible to frequent administration per day to maintain the therapeutic effect. This multiple dosing regimen often leads to gastrointestinal (GI) adverse effects such as GI bleeding, GI perforation or peptic ulcer. Hence, the sustained release formulation of this drug can be thought of as a most suitable method to minimize GI side effects, reduce dosing frequency and increase patient compliance (El-Gizawy, Zein El Din, Donia, & Yassin, 2014). Moreover, since the dosage regimen of conventional tablet of Ketorolac Tromethamine is 10mg every 4 to 6 hours i.e. 3 to 4 times a day due to its short half-life, a once daily sustained release form of the drug can overcome the problems associated with increased dose frequency, patient incompliance and adverse GI effects. In addition, KT has a similar potency as an analgesic to that of opioids often used for post-operative

pain relief. Therefore, intake of KT spares the patient from the adverse effects of opioids which includes respiratory depression, psychomotor disturbances, ataxia, sedation, constipation, tolerance, and dependence (Vadivelu et al., 2015). So, the successful formulation of a sustained release dosage form of KT may be potentially beneficial to the patient"s health.

In this study of sustained release oral tablet formulation development of KT, compatibility study of the drug with each excipient was performed by Fourier Transform Infrared Radiation (FT-IR) to support product development and justify the use of the selected excipients. Further confirmation of compatibility was conducted by a thermo analytical technique known as Differential Scanning Calorimetry (DSC) study. This led to direct compression of the powder blend into tablet followed by *in vitro* dissolution of the tablet whose results were analyzed and deployed to obtain once daily optimum formulation of KT.

1.2 Drug profile:

Ketorolac Tromethamine:

Ketorolac Tromethamine (KT) is a potent non-steroidal anti-inflammatory drug (NSAID) that belongs to the pyrrolizine group. It was the first NSAID commercialized in the United States for parenteral use in 1990 and later was approved by the FDA for administration as an immediate release oral tablet in 1991. Currently, it is available as oral, intramuscular, intravenous, ophthalmic dosage form. KT shows potent analgesic and mild anti-inflammatory activity in the treatment of moderate to severe acute pain by inhibiting the action of cyclooxygenase enzyme responsible for prostaglandin synthesis. Ketorolac Tromethamine is a racemic mixture of [-S] and [+R] enantiomeric forms, with the S-form having analgesic activity (Vadivelu et al., 2015).

1.3 Literature review:

Extensive literature review was initially done to select the drug, polymer, excipients, solvent, experimental conditions along with the study of release kinetic models and method of optimization to formulate oral sustained release matrix tablet of Ketorolac Tromethamine. Following are the list of journals that were searched for the present study:

1. Journal of Applied Pharmaceutical Science
2. International Journal of Pharmaceutical Science and Research
3. Bangladesh Journal of Scientific and Industrial Research
4. Acta Poloniae Pharmaceutica-Drug Research
5. International Journal of Pharmaceutical Research and Bio-science
6. Asian Journal of Pharmaceutical and Clinical Research
7. Pakistan Journal of Pharmaceutical Sciences
8. Saudi Pharmaceutical Journal
9. World Journal of Pharmaceutical Sciences
10. International Journal of Pharmacy and Pharmaceutical Sciences
11. Dhaka University Journal of Pharmaceutical Science
12. Asian Journal of Pharmaceutical Sciences
13. Advanced Drug Delivery Reviews
14. Journal of Analytical and Bioanalytical Techniques
15. Advanced Drug Delivery Reviews
16. American Journal of drug delivery
17. Journal of Thermal Analysis and Calorimetry
18. Pain Practice

Methodology

The research methodology of this project has been developed based on a proposed sustained release formulation of Ketorolac Tromethamine. In the study, Ketorolac Tromethamine, a member of NSAID has been amalgamated with Methocel K100M CR and Methocel K4M CR of different ratios to form matrix tablets. Excipients chosen for the formulation have been subjected to compatibility study and their compatibility with the active ingredient has been verified. The proposed formula of the sustained release tablet of Ketorolac Tromethamine is given in Table 2.1.

Table 2.1: Proposed formula of the drug

Active Pharmaceutical Ingredient	**Amount**
Ketorolac Tromethamine	30mg
Excipients	**Justification (of use)**
Methocel K100M CR	Rate controlling polymer
Methocel K4M CR	Rate controlling polymer
Starch 1500	Binder
Avicel PH 101	Filler
Magnesium stearate	Lubricant
Talc	Glidant

2.1 Standardization of Ketorolac Tromethamine by UV-Visible spectrophotometer:

10mg of Ketorolac Tromethamine was accurately weighed and dissolved in100ml of distilled water to obtain a concentration of 100µg/ml. From the above mixture 8ml, 9ml, 10ml, 11ml and 12ml solution was withdrawn and diluted to 100ml to obtain concentrations in the range 8.4µg/ml to 12.6µg/ml respectively. This was followed by the measurement of absorbance with UV-Visible spectrophotometer for each concentration at 322nm (Table 3.1).

2.2 Drug-Excipient compatibility study:

A formulation is considered appropriate when no interactions between drug-excipient and excipient-excipient occur. The evaluation of drug-excipient compatibility is an essential part in the development of any stable dosage form as incompatibility between drug and excipients can lead to the alteration of absorption and bioavailability of the drug, thereby, affecting the stability, safety and/ or efficacy of the drug delivery system (Gupta & Chadha, 2015). So during the development of dosage form various excipients are studied for compatibility with API. FT-IR spectroscopy and DSC are frequently employed as a rapid method to ascertain any possible interaction between the formulation components and therefore facilitate the selection of excipients with suitable compatibility.

2.2.1 FT-IR study:

FT-IR, Fourier Transform Infrared spectroscopy is the study of the interaction of electromagnetic radiation from the IR region of the EM spectrum (4000-400) cm^{-1} with a molecule through which IR radiation is passed. The nature of interaction depends upon the functional groups present in the substance. Compounds of different structure usually exhibit different IR spectrum. Any interaction between the drug and the excipient may lead to change in the molecular structure thereby generating a different IR spectrum to that of the pure drug and hence, indicates incompatibility. For the purpose of drug-excipient compatibility test by FT-IR, six FT-IR test samples were prepared by mixing each drug entities separately with the individual excipient in the ratio of 1:1. The pure Ketorolac Tromethamine was also passed through FT-IR for reference. The IR spectrum obtained for each prepared sample within 4000-400cm^{-1} region was recorded and studied for any interaction between the drug and the excipients. The tests were designed in 1:1 ratio as follows:

1. Ketorolac Tromethamine + Methocel K100M CR

2. Ketorolac Tromethamine + Methocel K4M CR

3. Ketorolac Tromethamine + Starch 1500

4. Ketorolac Tromethamine + Avicel PH101

5. Ketorolac Tromethamine + Magnesium stearate

6. Ketorolac Tromethamine + Talc

2.2.2 DSC study:

The samples for DSC, Differential Scanning Calorimetry analysis were prepared in 1:1 ratio with the same composition as for FT-IR. In DSC analysis, DSC curves were obtained for the pure drug and drug with each of the excipients by placing 3mg of the sample into a disc followed by its insertion inside the machine. The samples were run under nitrogen atmosphere at a flow rate of 30ml/min and a heating rate of 10°C in the temperature range 30-300°C.

2.3 Evaluation of powder flow properties:

The powder blends prepared for compression into sustained release tablets were evaluated for their compressibility and flow properties.

2.3.1 Bulk density:

The loose bulk density (LBD) and tapped bulk density (TBD) of the powder for each proposed formulation were determined by taking a quantity of about 10gm of powder from each formulation into a 100ml measuring cylinder. After the initial volume of the powder was noted, the cylinder was allowed to tap several times until no further change in the volume was observed. LBD and TBD were calculated by using the following formulae:

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{bulk volume of the powder}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the powder}}$$

2.3.2 Carr's index and Hausner ratio:

Carr"s Index and Hausner ratio were calculated from bulk density to determine the flow and compressibility characteristics of the powder blend as given in the formulae below:

$$\text{Carr's Index (\%)} = \frac{(\text{TBD} - \text{LBD}) \times 100}{\text{TBD}}$$

$$\text{Hausner ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Table 2.2: Relationship between Carr's index and powder flow

Carr's index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

Source: Aulton, 2002

Table 2.3: Relationship between Hausner ratio and powder flow

Hausner ratio	Powder flow
< 1.25	Good
1.25-1.5	Fair to passable
>1.5	Poor

Source: Aulton, 2002

2.3.3 Angle of repose:

The angle of repose of the powder was determined for each proposed formulation by the funnel method. In this method, the powder was allowed to flow through the funnel clamped at a fixed height (h) of 3cm, until the apex of the heap of powder just touched the tip of the funnel. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan\emptyset = \frac{h}{r}$$

where, h = height of the powder cone, r= radius of the powder cone, Ø = angle of repose

Table 2.4: Relationship between angle of repose and powder flow properties

Angle of repose	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

Source: Aulton, 2002

2.3.4 Moisture content:

The presence of moisture in the powder affect its flow characteristics as the particles become cohesive due to moisture absorption and often the powder shows poor flowability. So the powder blend of each formulation was subjected to drying in oven and also its moisture content was determined with the moisture analyzer prior to evaluation of the flow properties of the powder.

2.4 Polymer combination of matrix tablet formulations using 3^2 full factorial design:

A 3^2 randomized full factorial design was used in the present study. In this design, 2 factors were evaluated, each at 3 levels (low, mid and high), and experimental trials were performed for all 9 possible combinations. The amounts of Methocel K100M CR (A) and Methocel K4M CR (B) were selected as independent variables in 3^2 full factorial design while the percentage of drug released from tablets of different polymer ratio were taken as dependent variables (Bushra, Shoaib, Aslam, Hashmat, & Rahman, 2008). The 3^2 full factorial design layout for the trial batches (F1-F9) is shown in Table 2.5 and 2.6.

Table 2.5: 3^2 full factorial design layout

Coded value	Actual values	
	A (%)	B (%)
-1 (low level)	30	5
0 (mid level)	35	7.5
+1 (high level)	40	10

A and B indicates the amount of Methocel K100M and Methocel K4M respectively

Table 2.6: Polymer combinations of formulation (F1-F9)

Formulation	Batch Code		K100M:K4M (%)	
	A	B		
F1	-1	-1	30	5
F2	-1	0	30	7.5
F3	-1	+1	30	10
F4	0	-1	35	5
F5	0	0	35	7.5
F6	0	+1	35	10
F7	+1	-1	40	5
F8	+1	0	40	7.5
F9	+1	+1	40	10

2.5 Preparation of matrix tablets:

Drug, polymer and excipients were weighed separately for 15 tablets for each formulation as shown in Table 2.7. The proposed formulations were coded as F1, F2, F3, F4, F5, F6, F7, F8 and F9. After weighing, polymer and excipients for each formulation were mixed thoroughly followed by the addition of the API with further mixing to ensure homogenous distribution of the particles. The powder mixture of each formulation was passed through a 40 mesh sieve. The sieved mass was poured in the hopper of the tablet compression machine and the die and punch were adjusted to get the desired weight of the tablet (300 mg). Finally, the weights and hardness of the resulting tablets per formulation were checked.

Table 2.7: Formulation of Ketorolac Tromethamine sustained release matrix tablets

Components	Amount (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketorolac Tromethamine	10	10	10	10	10	10	10	10	10
Methocel K100M CR	30	30	30	35	35	35	40	40	40
Methocel K4M CR	5	7.5	10	5	7.5	10	5	7.5	10
Starch 1500	26.5	25.25	24	24	22.75	21.5	21.5	20.25	19
Avicel PH 101	26.5	25.25	24	24	22.75	21.5	21.5	20.25	19
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total	100								

2.6 Evaluation of physical properties of matrix tablets:

The matrix tablets manufactured was assessed for quality control parameters to ensure its compliance with pharmacopoeial specifications.

2.6.1 Weight variation:

To determine the weight variation among tablets, 10 tablets for each matrix formulation were weighed individually using the electronic balance and the average weight of the 10 tablets was calculated. Then the percentage of weight variation was determined by using the following formula:

$$\% \text{ Weight variation} = \frac{(\text{Average weight} - \text{Individual weight}) \times 100}{\text{Average weight}}$$

Table 2.8: Pharmacopeial specifications for tablet weight variation

Average weight of tablets (mg) (USP)	Maximum % difference
Less than 130	10
130-324	7.5
More than 324	5

Source: Lieberman & Kanig, 1986

2.6.2 Tablet hardness:

The hardness of the tablets for each formulation was determined by applying a diametric compression force on the tablets with the hardness tester.

2.6.3 Tablet friability:

The initial weight of five tablets for each proposed formulation was measured and then the tablets were allowed to rotate in a friabilator at 100 rpm for 4 minutes. The tablets were dedusted and reweighed. Percentage friability was calculated from the loss in weight as given in the equation below:

$$\% \text{ Friability} = \frac{(\text{Initial weight of tablet} - \text{Final weight of tablet}) \times 100}{\text{Initial weight of tablet}}$$

The United State Pharmacopoeia states that the friability value of tablets should be less than 1% (Nasrin, Asaduzzaman, Mowla, Rizwan, & Alam, 2011).

2.6.4 Tablet thickness and diameter:

The thickness and diameter of six randomly selected matrix tablets were determined using a vernier caliper.

2.6.5 Tablet drug content:

To prepare the standard solution of Ketorolac Tromethamine, 30mg of the drug was dissolved in distilled water upto the volume of 100ml. The solution was diluted 10 times and absorbance was taken at λ_{max}= 322nm. For the purpose of sample solution preparation, three tablets were crushed using motor and pestle. The powder weight equivalent to single tablet was dissolved in distilled water and the volume was made upto 100ml. This solution also went through 10 times dilution followed by measurement of

absorbance at λ_{max}= 322nm. Then the drug content per dosage unit was calculated by the following equation:

Ketorolac Tromethamine content (mg / dosage unit),

$$= \frac{\text{Absorbance of sample} \times \text{Weight of standard} \times \text{Average weight}}{\text{Absorbance of standard} \times \text{Weight of sample}}$$

2.7 *In vitro* dissolution study:

Dissolution testing plays an important role in the drug formulation development especially in the establishment of *in vitro–in vivo* relationships between release of drug from the dosage form and drug absorption. Furthermore, the physicochemical properties of the drug, excipients used or their combination as well as manufacturing conditions selected to prepare the tablet influences the dissolution rate from a tablet (Etman et al., 2008).

2.7.1 Preparation of dissolution medium:

To prepare phosphate buffer of pH 6.8, 6.8gm potassium hydrogen phosphate (KH_2PO_4) and 0.94gm sodium hydroxide (NaOH) were dissolved in distilled water to make the volume upto 1000ml. The pH of the solution was adjusted by using dilute orthophosphoric acid or NaOH as required.

2.7.2 Preparation of the sample for dissolution:

900ml phosphate buffer dissolution medium was poured into the dissolution vessels. Then the media was allowed to warm to a temperature of 37°C ± 0.5°C. Three tablets of each of the 9 formulations were weighed and immersed into the media, which positioned itself between the paddle and the bottom of the vessel. The apparatus was operated at 100 rpm and observed for 8 hours. Samples of about 5ml were withdrawn after 0.5, 1, 2, 4 and 8 hours and same quantity was then replaced with fresh dissolution medium. Afterwards the collected samples were filtered through the filter paper and their absorbance was measured by UV-Visible spectrophotometer at 322nm. By using the absorbance reading and the standard curve equation of Ketorolac Tromethamine, the percentage of drug released from the matrix tablet of various polymer ratios was calculated. The following formulae were used for the calculation:

Equation of the standard curve:

$$Y = 52.19X + 0.0422$$

Where, Y = Absorbance and X = Concentration (mg/ml)

$$X = Y - 0.0422 / 52.19$$

$$\% \text{ drug release} = X \text{ (mg/ml)} \times 900 \text{ (ml)} \times 100 / \text{ weight of API (mg)}$$

The release data were analyzed using different kinetic equations which include zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models.

2.8 *In-vitro* dissolution release kinetic study of matrix tablets:

The drug release data obtained from *in vitro* dissolution of matrix tablets F1 to F9 for 8 hours were fitted into various mathematical models to determine the release mechanism and find the model that best fits the drug release profile. For the drug release kinetic study, the models (Ahamed, Banik, & Hossain, 2013) that have been employed include:

i. Zero order model: Cumulative percentage of drug release *versus* time.
ii. First order model: Log cumulative percentage of drug remaining *versus* time.
iii. Higuchi model: Cumulative percentage of drug release *versus* square root of time.
iv. Korsmeyer-Peppas model: Log fraction of drug release *versus* log of time.
v. Hixson-Crowell model: Cubic root of percentage drug release *versus* time.

Mathematical equations that represent the release kinetics are described below:

2.8.1 Zero order equation:

The zero-order model describes the systems where the drug release rate is independent of its concentration. The equation assumes the cumulative amount of drug release *versus* time. The equation is as follows:

$$\mathbf{C = K_0 t} \quad \text{[equation 1]}$$

where, C = drug concentration at „t“time

K_0 = zero order rate constant expressed in unit concentration/time

t = time in hour

A graph of concentration against time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes (Talukder, Ahmed, Haque, & Chowdhury, 2010).

2.8.2 First order equation:

The first order model describes the release from systems where the release rate is concentration dependent. The release behavior of first order equation is expressed as log cumulative percentage of drug remaining *versus* time (Talukder, Ahmed, Haque, & Chowdhury, 2010).The equation may be as follows:

$$\log C = \log C_0 - K t / 2.303 \quad \text{[equation 2]}$$

where, C= amount of drug remaining at „t“ time

C_0 = drug concentration at t = 0

K = first order rate constant

2.8.3 Higuchi square root law:

Higuchi model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. The Higuchi release model is described as cumulative percentage of drug release *versus* square root of time. The equation is as follows:

$$Q = K_h t^{½} \quad \text{[equation 3]}$$

where, Q = (100-C) i.e. the amount of drug released at time „t“

K_h = the constant reflecting the design variables of the system

Hence, drug release rate is proportional to the reciprocal of the square root of time (Talukder, Ahmed, Haque, & Chowdhury, 2010).

2.8.4 Korsmeyer-Peppas model:

The Korsmeyer-Peppas model is generally used to analyze the release of a drug molecule from a polymeric matrix using the following equation:

$$\log (M_t/M_f) = \log K + n \log t \quad \text{[equation 4]}$$

where, M_t = amount of drug release at time „t“

M_f = amount of drug release after infinite time

K = release rate constant incorporating structural and geometric characteristics of the dosage form

n = diffusional exponent indicative of the mechanism of drug release

The log value of percentage drug dissolved is plotted against log time for each formulation according to the equation (Talukder, Ahmed, Haque, & Chowdhury, 2010). The process responsible for the drug release from the matrix tablet can be determined from the diffusional exponent (n) which is influenced by the shape of the tablet. Based on the „n" value of a spherical shaped tablet (Table 2.9), drug transport mechanism from the tablet is classified into four types (Siepmann & Peppas, 2001) which are as follows:

i. Fickian (case I) diffusion: Diffusion-controlled drug release.
ii. Case II transport: Drug release controlled by polymer relaxation.
iii. Non-Fickian or anomalous transport: Both diffusion and erosion regulated drug release.
iv. Super case II transport: Erosion-controlled drug release.

Table 2.9: Diffusional exponent as an indicator of release mechanism

Diffusional exponent (n)	Mechanism of transport
0.43	Fickian (case I) diffusion
0.43<n<0.85	Anomalous / non – Fickian transport
0.85	Case II / Zero order transport
>0.85	Super case II transport

Source: Siepmann & Peppas, 2001

2.8.5 Hixson-Crowell cube root law:

It is the law that describes the release from systems where there is a change in surface area and diameter of the particles or tablets. This law is expressed as the cube root of the percentage of initial drug minus the cube root of the percentage of drug remaining in the matrix, as a function of time (Dash, Murthy, Nath, & Chowdhury, 2010). The equation is as follows:

$$\mathbf{Q_0}^{1/3} - \mathbf{Q\ t}^{1/3} = \mathbf{K_{HC}.\ t} \quad \text{[equation 5]}$$

where, Q_0 = initial amount of the drug in the tablets

Q_t = the amount of drug remaining in time „t"

K_{HC} = rate constant for the Hixson-Crowell cube root law

2.9 Successive fractional dissolution time:

To characterize the drug release rate in different experimental conditions, time required for 25% ($T_{25\%}$), 50% ($T_{50\%}$) and 80% ($T_{80\%}$) of drug release were calculated from dissolution data according to the following equations:

$$\mathbf{T_{25\%} = (0.25/K)^{1/n}}$$

$$\mathbf{T_{50\%} = (0.5/K)^{1/n}}$$

$$\mathbf{T_{80\%} = (0.8/K)^{1/n}}$$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher drug retaining ability of the polymer is indicated by a higher MDT value and *vice-versa.* The MDT value is also a function of polymer loading, polymer nature and physicochemical properties of the drug molecule (Talukder, Ahmed, Haque, & Chowdhury, 2010).

MDT can be calculated by the following equation:

$$\mathbf{MDT = (n/n+1).\ K^{-1/n}}$$

2.10 Optimization of sustained release formulation of Ketorolac Tromethamine:

Optimization is considered as an efficient and economical method to understand the relationship between independent and response variables (Bushra, Shoaib, Aslam, Hashmat, & Rahman, 2008). For the purpose of optimization, a 3^2 full factorial design comprising 9 full factorial design points was employed to systematically optimize drug release profile. During the experimental design, Methocel K100M CR (A) and Methocel K4M CR (B) were taken as the independent variables while the percentage of drug released after 1 hour (Y_{1hr}), 4 hours (Y_{4hr}) and 8 hours (Y_{8hr}) were considered as response variables. The relationship between responses and independent variables of all designed formulations were processed by Design Expert software. Statistical analysis was performed and contour plots were displayed to postulate the effects of the independent variables on responses followed by selection of the optimum formulation on the basis of desirability criterion and graphical analysis.

Result and Discussion

3.1 Standardization of Ketorolac Tromethamine:

The standardization of Ketorolac Tromethamine generated a linear calibration curve from the plot of absorbance *versus* concentration graph with a correlation coefficient (R^2) of 0.9958 as shown in Figure 3.1.

Table 3.1: Standardization of Ketorolac Tromethamine

Concentration (mg/ml)	Absorbance (λ_{max}= 322 nm)
0.0084	0.481
0.00945	0.53
0.0105	0.594
0.01155	0.652
0.0126	0.694

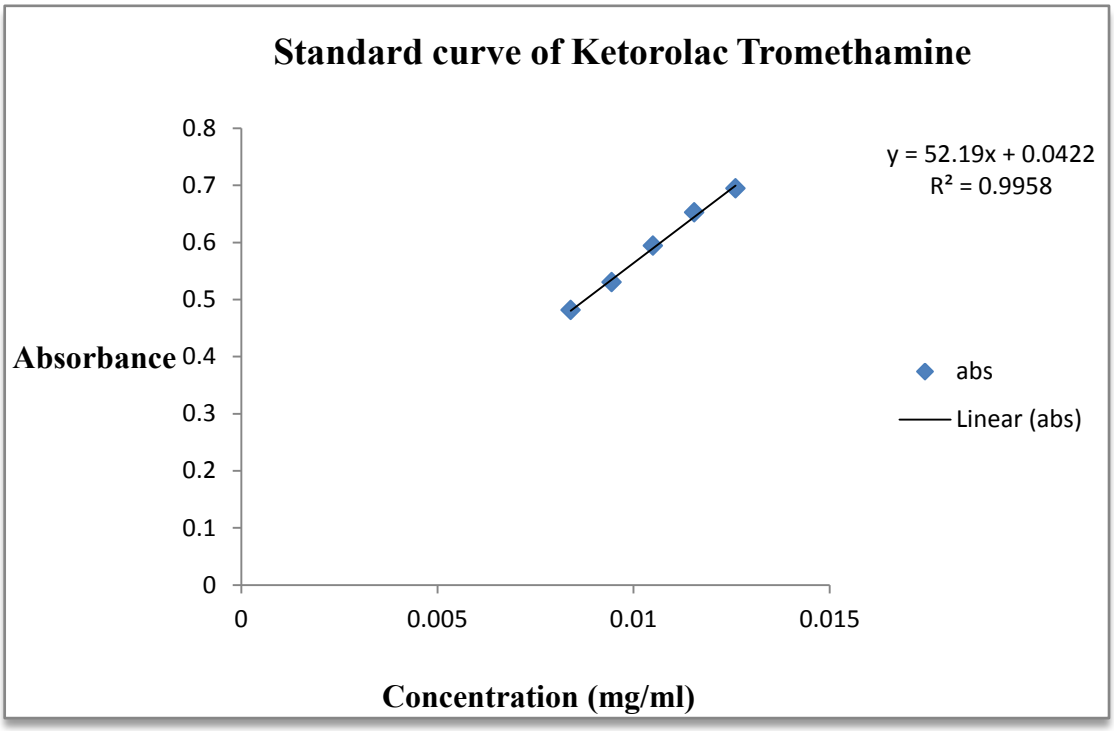

Figure 3.1: Standard curve of Ketorolac Tromethamine

3.2 Evaluation of drug-excipient compatibility study:

3.2.1 FT-IR characterization:

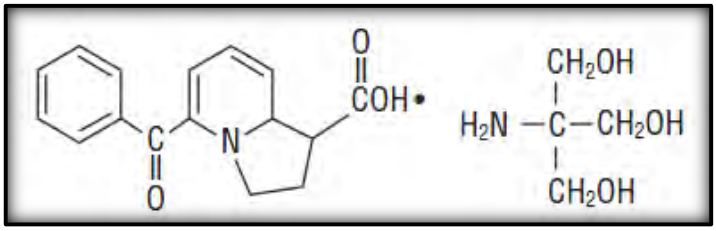

Figure 3.2: Structure of Ketorolac Tromethamine

Table 3.2: Principal functional groups of Ketorolac Tromethamine

Functional group	Frequency (cm^{-1})
Ketone (C=O stretching)	1720-1705
Aromatic ring (C=C stretching)	1600 and 1475
Carboxylic acid (C=O stretching)	1725-1700
Carboxylic acid (O-H stretching)	3400-2400
Amine (N-H stretching)	3500-3100
Amine (C-N stretching)	1350-1000

Source: Pavia, Lampman, Kriz, & Vyvyan, 2008

The principal peaks of Ketorolac Tromethamine were observed at 3349.50cm^{-1} for N-H stretching of primary amine; 3079.46 cm^{-1} for O–H stretching of alcohol; 1594.22 cm^{-1} and 2898.14 cm^{-1} for C=O and O–H stretching of carboxylic acid respectively; 1471.74cm^{-1} for C=C stretching of aromatic ring and 1385.9cm^{-1} for C-N stretching (Table 3.2). IR studies showed no interaction between drug and excipients selected for the study. However, additional peaks were observed in the spectrum of physical mixtures of drug and excipients but with no significant change in the original peak position and indicated that there was no chemical interaction between Ketorolac Tromethamine and other excipients. The spectra of the pure drug and drug-excipients are given in Figure 3.3 to Figure 3.9.

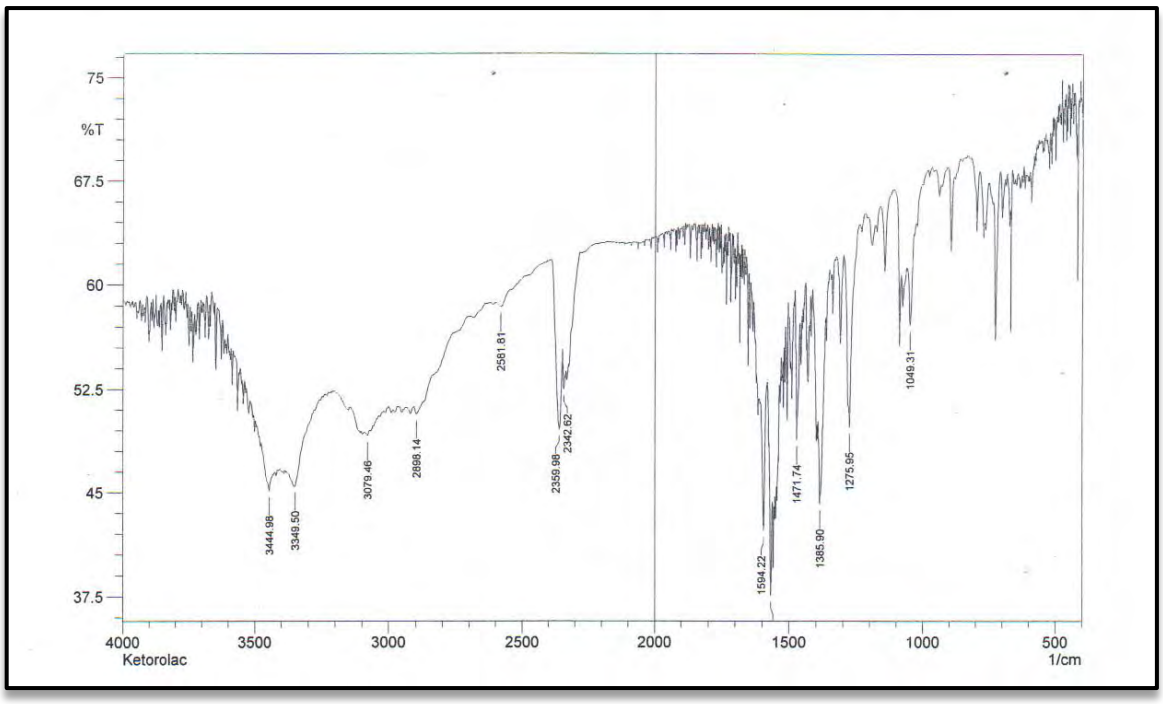

Figure 3.3: FT-IR spectrum of Ketorolac Tromethamine (pure drug)

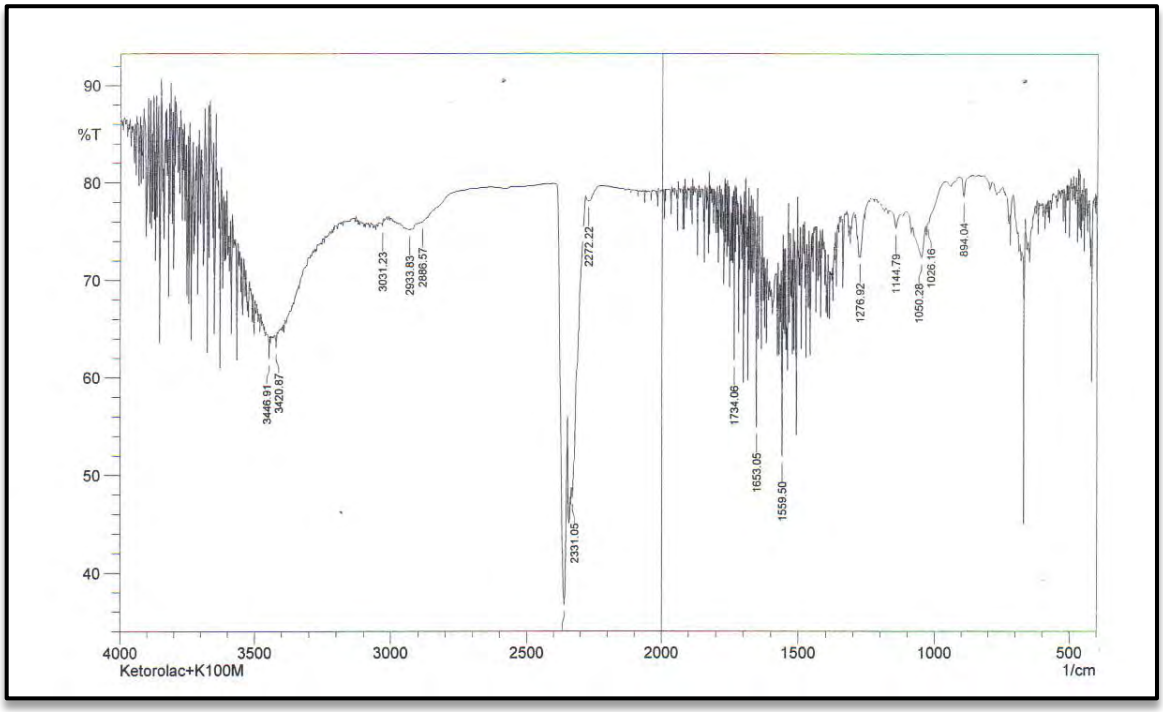

Figure 3.4: FT-IR spectrum of Ketorolac Tromethamine + Methocel K100M CR

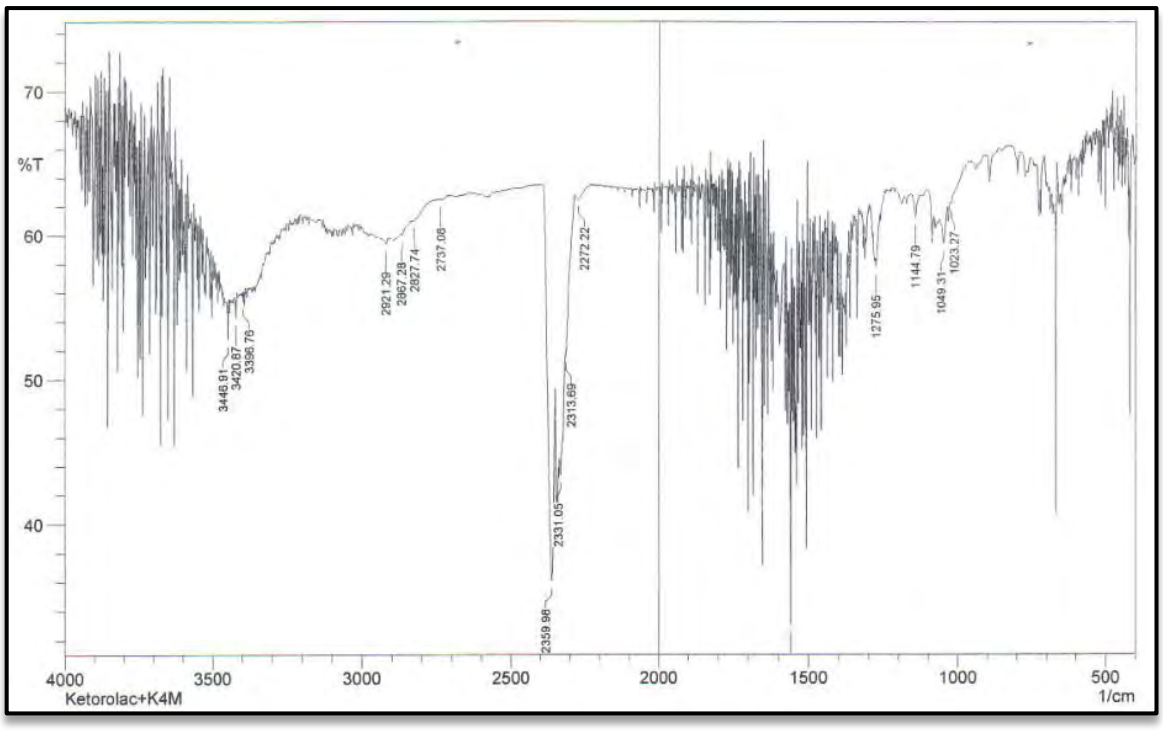

Figure 3.5: FT-IR spectrum of Ketorolac Tromethamine + Methocel K4M CR

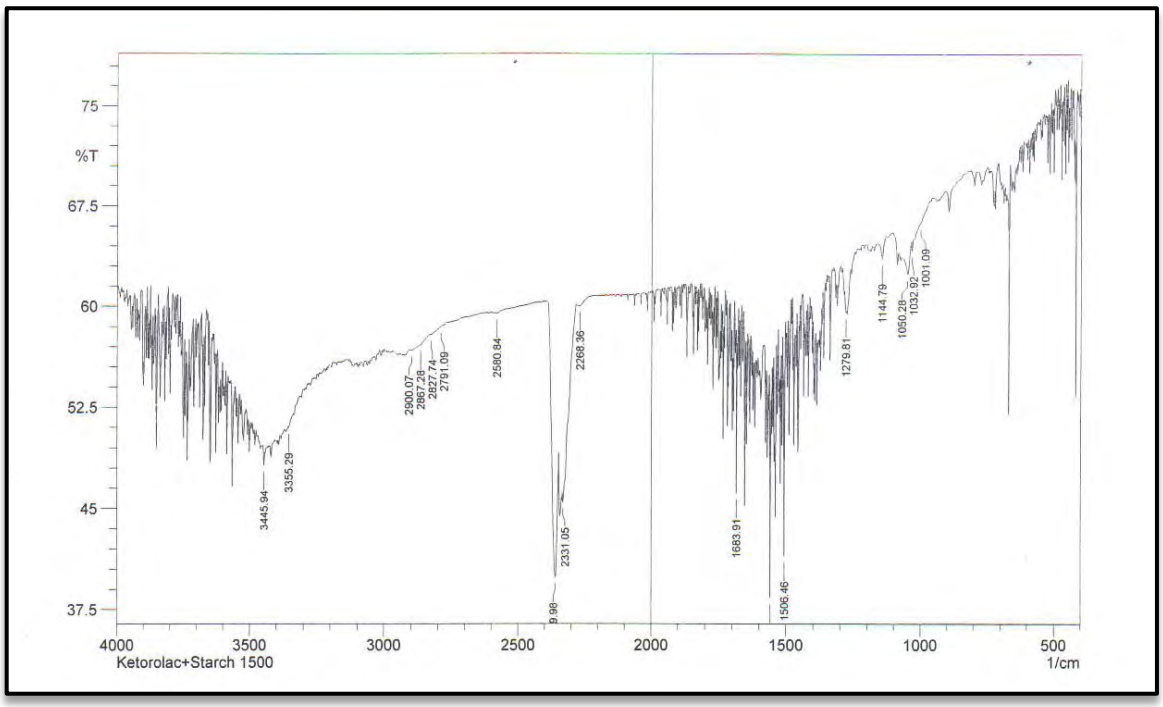

Figure 3.6: FT-IR spectrum of Ketorolac Tromethamine + Starch 1500

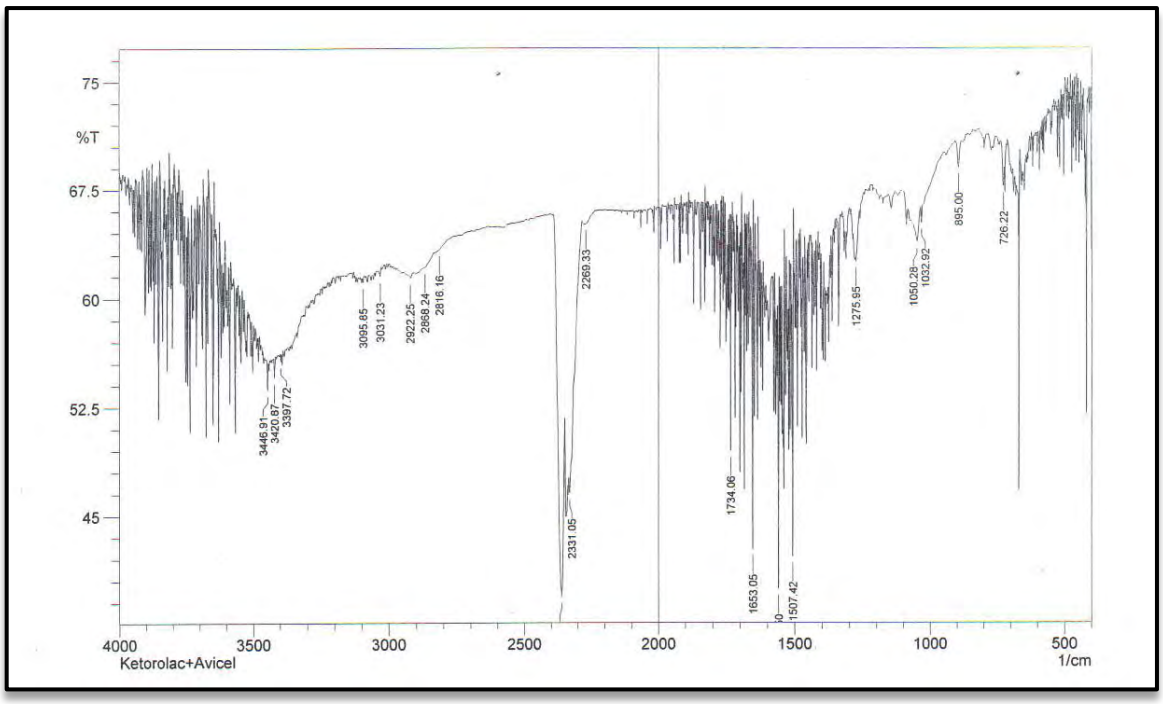

Figure 3.7: FT-IR spectrum of Ketorolac Tromethamine + Avicel PH 101

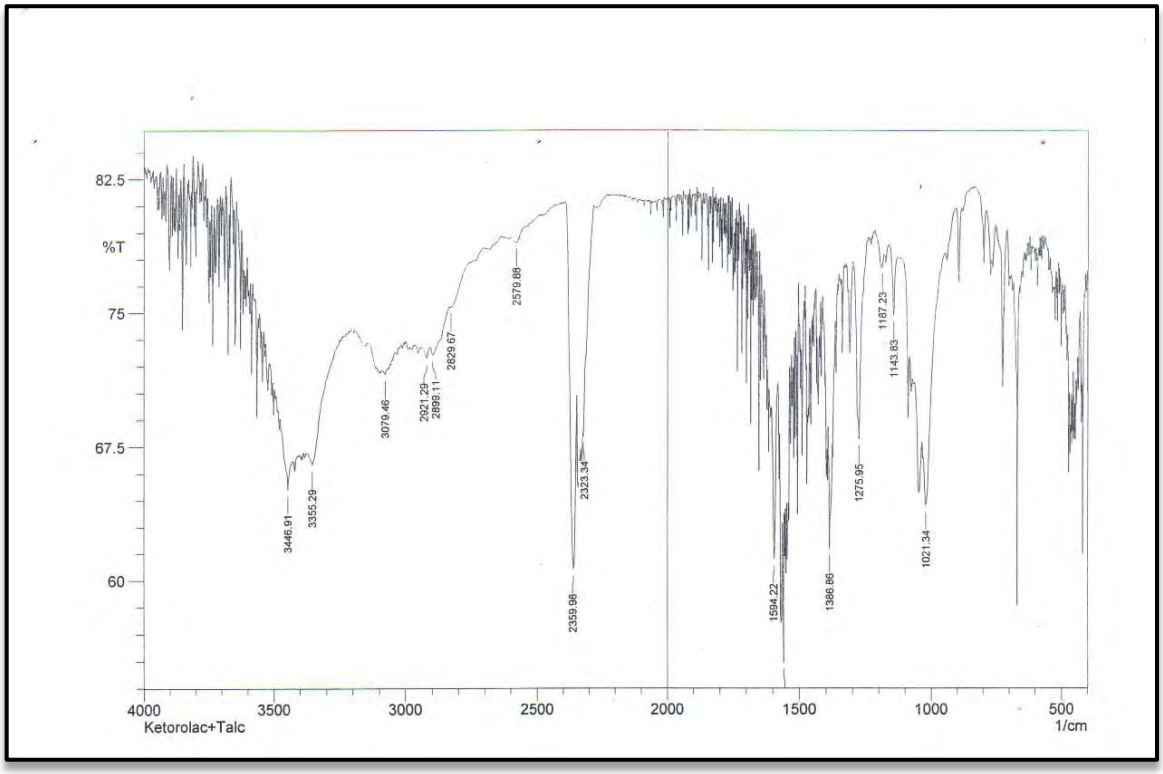

Figure 3.8: FT-IR spectrum of Ketorolac Tromethamine + Talc

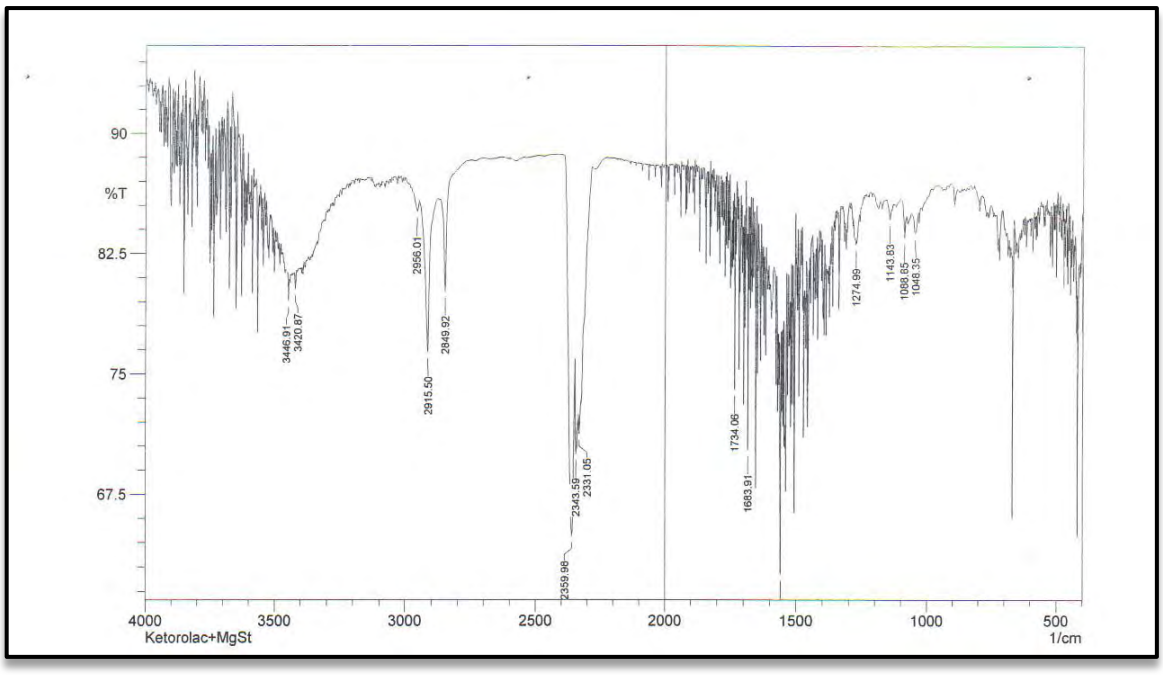

Figure 3.9: FT-IR spectrum of Ketorolac Tromethamine + Magnesium stearate

3.2.2 DSC characterization:

The careful selection of excipients plays a significant role in the successful formulation of a stable and effective dosage form. DSC is an effective method to identify any physicochemical interaction between the ingredients used in the formulation and is therefore, widely used for the selection of suitable chemically compatible excipients. The absence of incompatibility between the drug and the excipients is seen when the thermograms of mixtures show patterns corresponding to the individual components. In contrast, any interaction may be indicated by the appearance or elimination of one or more new peaks when compared with the thermogram obtained from pure drug (Nanjwade, Manjappa, Murthy, & Pol, 2009).

The DSC thermograms of KT showed long and sharp characteristic endothermic peak at 165.98^{o}C associated with the melting of KT (Figure 3.10). DSC scans of physical mixtures also showed characteristic endothermic peak corresponding to the pure drug which have been presented in Figure 3.11 to 3.16 respectively. These findings indicate that no interaction occurred between drug and the excipients which made it suitable for use in formulation of Ketorolac Tromethamine sustained release matrix tablet. However, there was a slight change in characteristic peak that may be due to fusion of excipients present in the physical mixture (Nanda, Saroha, & Sharma, 2014).

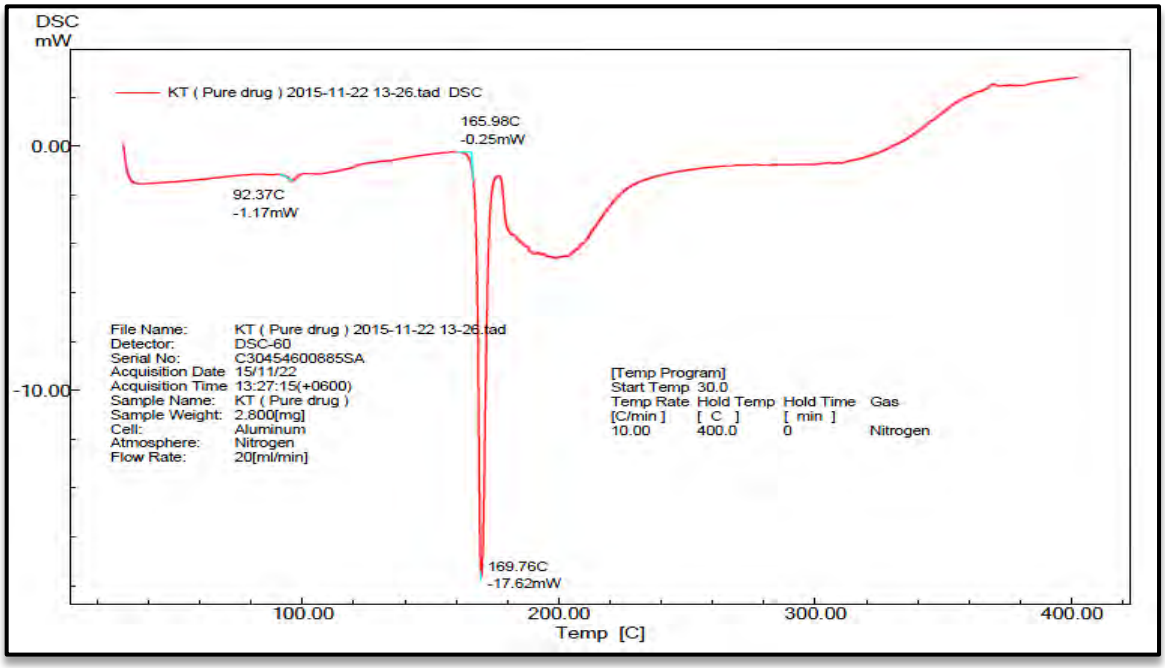

Figure 3.10: DSC thermogram of Ketorolac Tromethamine (pure drug)

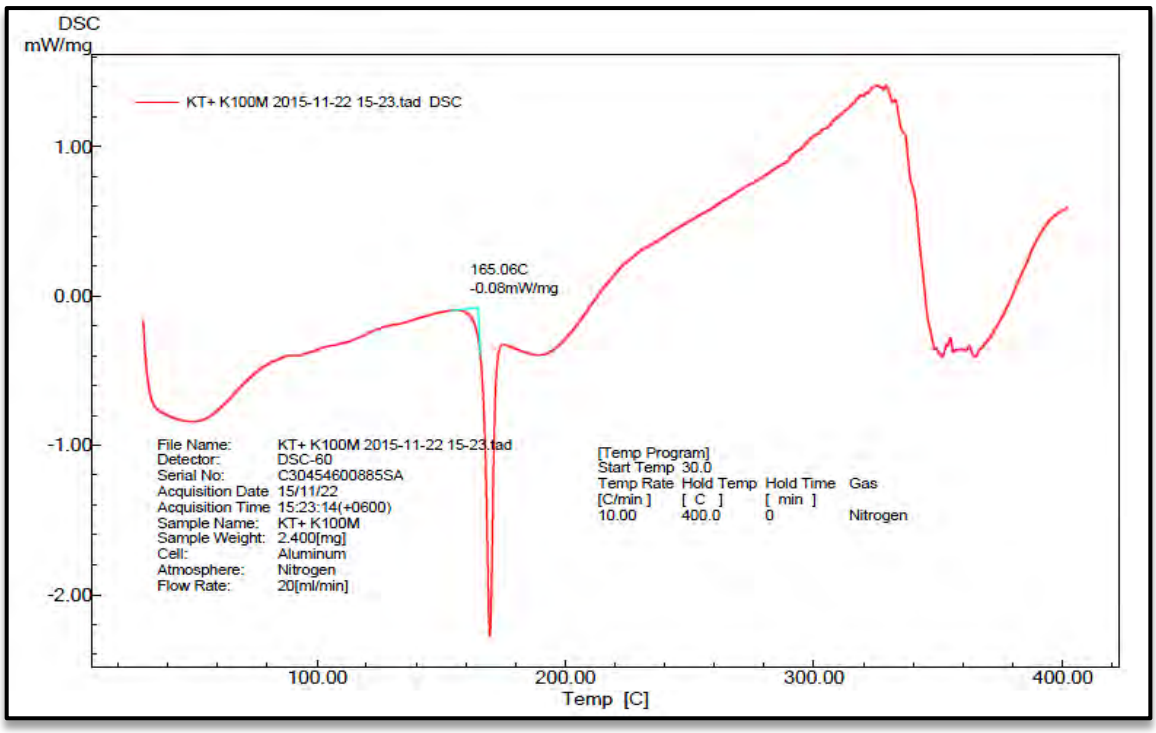

Figure 3.11: DSC thermogram of Ketorolac Tromethamine + Methocel K100M CR

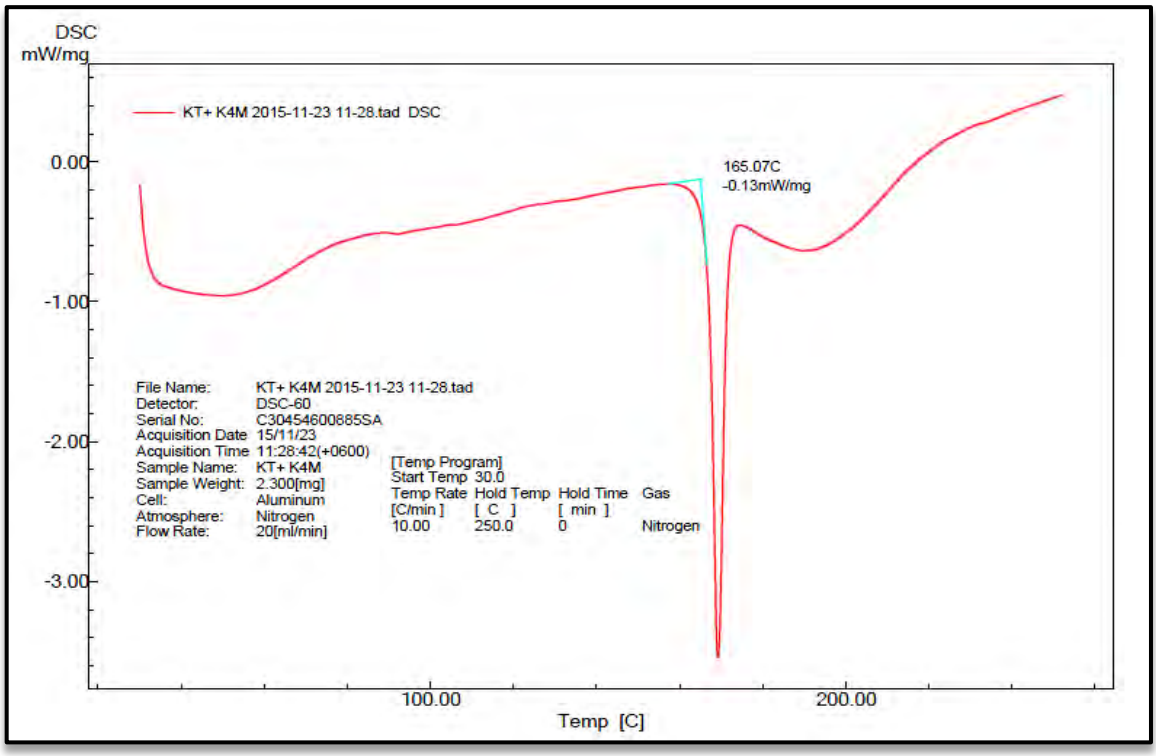

Figure 3.12: DSC thermogram of Ketorolac Tromethamine + Methocel K4M CR

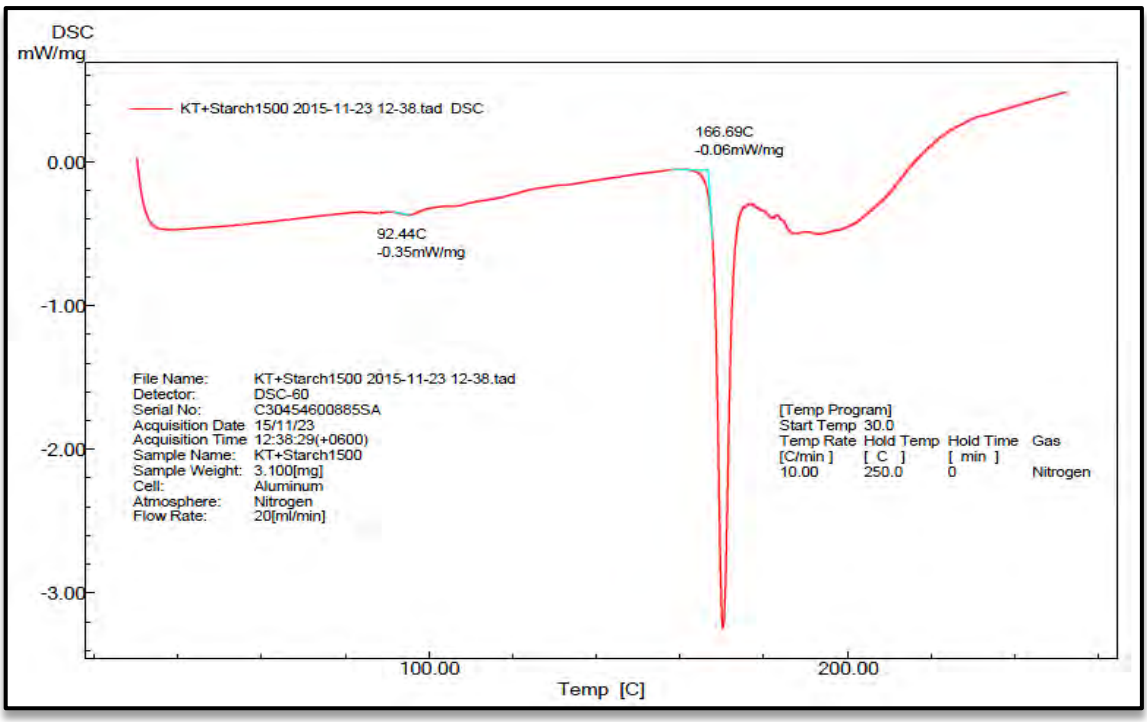

Figure 3.13: DSC thermogram of Ketorolac Tromethamine + Starch 1500

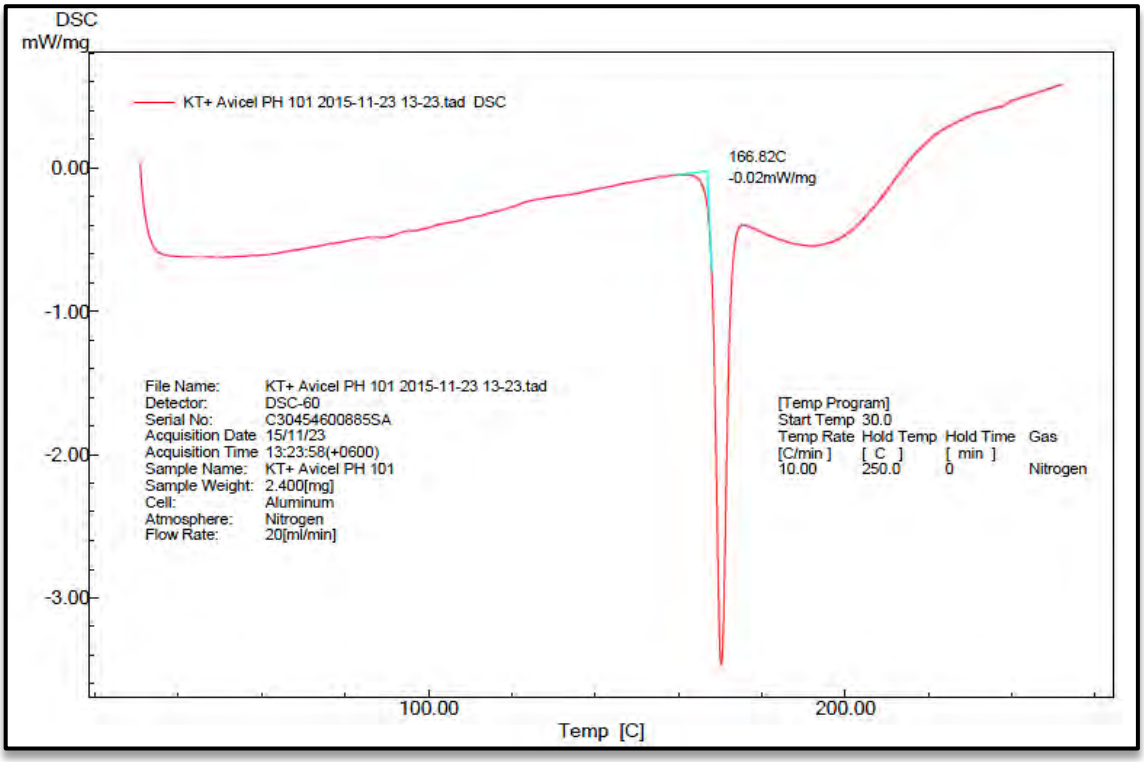

Figure 3.14: DSC thermogram of Ketorolac Tromethamine + Avicel PH 101

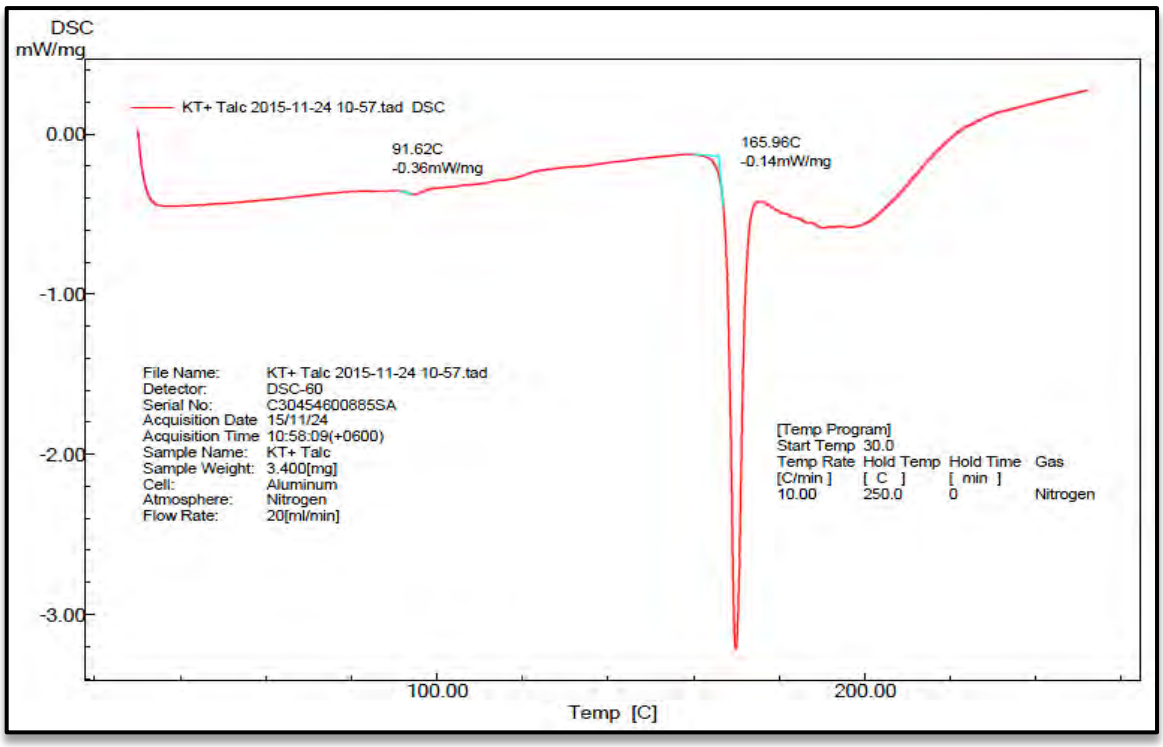

Figure 3.15: DSC thermogram of Ketorolac Tromethamine + Talc

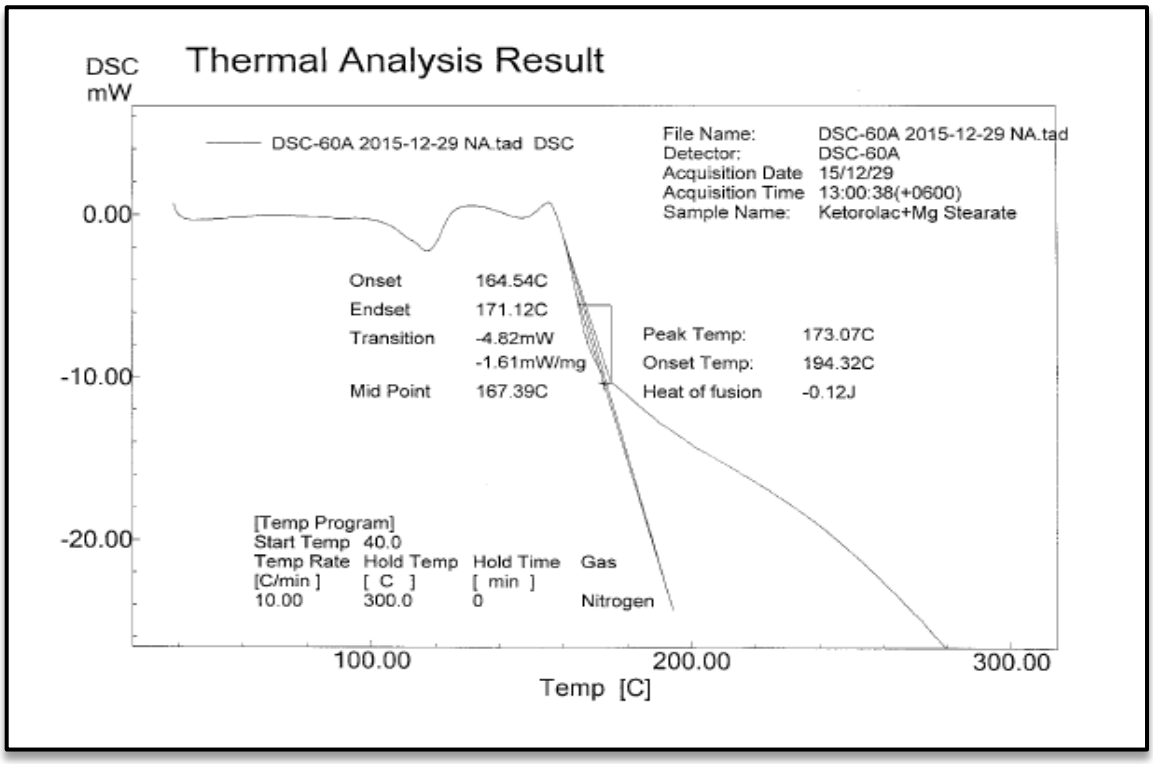

Figure 3.16: DSC thermogram of Ketorolac Tromethamine + Magnesium stearate

3.3 Evaluation of powder flow properties:

In this experimental study, an attempt has been taken to develop "once daily" sustained release tablet of Ketorolac Tromethamine by direct compression method using two different viscosity grades of cellulose derivatives i.e. Methocel K100M CR and Methocel K4M CR as the rate retarding agents. According to the trial tablet formulations, powder blends of F1 to F9 were prepared and tested for powder flow properties. The powder blends of proposed formulations (F1 to F9) were evaluated for LBD, TBD, Carr"s index, Hausner ratio and angle of repose as shown in Table 3.3. The results of LBD and TBD ranged from 0.339 ± 0.006 to 0.356 ± 0.011 (gm/ml) and 0.431 ± 0.005 to 0.460 ± 0.005 (gm/ml) respectively. The results of Carr"s compressibility index ranged from 18.56 ± 2.36 to 24.00 ± 1.82 (%) with Hausner ratio between 1.27 ± 0.007 and 1.32 ± 0.04. The results of angle of repose ranged from 42.19 ± 0.085 to 45.47 ± 0.230 (°). All these results indicated that the powder possessed fairly good flow and compressibility properties.

Table 3.3: Factors determining powder flow characteristics (F1 to F9)

Formulation	Loose bulk density (gm/ml) ± SD	Tapped bulk density (gm/ml) ± SD	Carr's index (%) ± SD	Hausner Ratio ± SD	Angle of repose (º) ± SD
F1	0.356±0.011	0.460±0.005	22.61±1.55	1.29±0.03	42.19±0.085
F2	0.342±0.003	0.450±0.015	24.00±1.82	1.32±0.04	42.51±0.205
F3	0.351±0.007	0.445±0.01	21.12±3.24	1.27±0.06	43.44±0.06
F4	0.351±0.006	0.445±0.01	21.12±0.425	1.27±0.007	42.49±0.159
F5	0.351±0.007	0.431±0.005	18.56±2.36	1.23±0.04	42.52±0.415
F6	0.339±0.006	0.445±0.01	23.82±0.36	1.31±0.007	43.44±0.06
F7	0.350±0.005	0.450±0.006	22.22±2.07	1.29±0.04	45.47±0.230
F8	0.351±0.006	0.445±0.01	21.12±0.425	1.27±0.007	42.65±0.280
F9	0.339±0.006	0.440±0.004	22.95±1.64	1.30±0.03	44.72±0.185

3.4 Evaluation of physical properties of matrix tablets:

The tablets of the proposed formulations (F1 to F9) were subjected to various evaluation tests like thickness, diameter, hardness, weight variation, friability and drug content as shown in Table 3.4. The hardness was found to be uniform in all tablets and percentage friability of the tablets of all the formulations was below 1% indicating that the friability was within the official limits. The average percentage weight variation and the drug content of tablets were found to be within pharmacopoeial limits.

Table 3.4: Physical properties of matrix tablets (F1 to F9)

Formulation	Average weight (mg) ± SD	Diameter (mm)	Thickness (mm) ± SD	Hardness (kg/cm^2)	Friability (%)	Potency (%) ± SD
F1	307±0.8	9	5.28±0.03	7	0.33	98.39±0.003
F2	304.67±1.75		5.20±0.03		0.15	101.32±0.003
F3	308.33±0.14		5.85±0.05		0.16	100.66±0.0008
F4	309.33±1.22		5.47±0.04		0.17	101.98±0.001
F5	306.33±0.80		5.15±0.06		0.16	102.64±0.003
F6	302.33±0.81		5.15±0.06		0.67	98.39±0.004
F7	308±0.65		5.72±0.04		0.32	101.98±0.002
F8	308±0.65		5.65±0.04		0.16	99.43±0.004
F9	307.33±0.14		5.68±0.04		0.49	102.53±0.003

3.5 Drug release kinetic studies of Ketorolac Tromethamine matrix tablets:

A polymer‟s ability to retard the drug release primarily depends on its viscosity and other processing factors like particle size, hardness, compressibility index, etc. Hence, Methocel K100M CR and Methocel K4M CR were used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlling delivery of drugs (Kabir, Halder, Shuma, & Rauf, 2012). The drug release data (Table 3.5 to 3.9) obtained from dissolution study was extrapolated by zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the drug release kinetics followed by the nine formulations (Figure 3.17 to 3.21).

3.5.1 Zero order plot:

Table 3.5: Zero order release profile of nine formulations of matrix tablets

Time (hour)	Cumulative % of drug released ± SD								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	14.90± 1.27	17.96± 0.21	15.71± 0.028	14.75± 0.50	15.95± 1.29	15.29± 1.15	13.25± 0.07	13.13± 0.63	15.06± 0.48
1	23.40± 0.72	22.59± 0.30	23.05± 0.45	23.53± 0.14	29.76± 5.78	22.30± 0.19	21.15± 1.48	22.50± 1.29	24.54± 1.89
2	36.62± 0.59	37.29± 1.61	35.02± 0.75	35.71± 0.70	38.39± 0.24	35.18± 1.77	31.31± 0.52	33.82± 0.64	31.23± 0.40
4	56.91± 0.56	57.25± 0.23	54.39± 1.45	54.15± 0.31	57.83± 1.07	47.71± 2.31	50.28± 0.54	52.07± 1.90	58.24± 0.62
8	77.59± 1.17	80.66± 0.25	75.55± 1.25	77.37± 0.48	73.28± 1.27	65.67± 3.47	71.34± 1.53	74.09± 1.88	77.76± 1.72

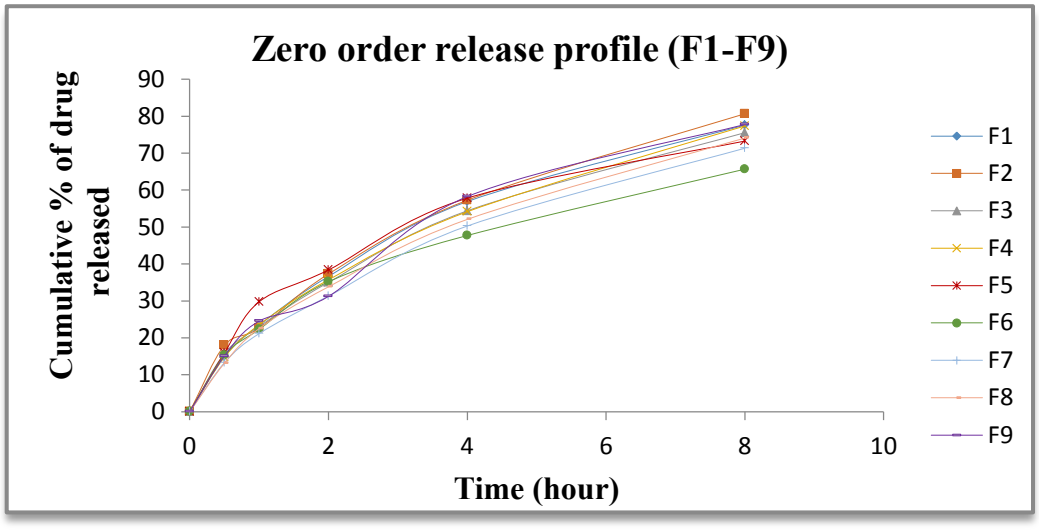

Figure 3.17: Zero order plot of release kinetics of Ketorolac Tromethamine matrix tablets

3.5.2 First order plot:

Table 3.6: First order release profile of nine formulations of matrix tablets

Time (hour)	Log cumulative % of drug remaining								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
0.5	1.93	1.91	1.93	1.93	1.92	1.93	1.94	1.94	1.93
1	1.88	1.89	1.89	1.88	1.85	1.89	1.90	1.89	1.88
2	1.80	1.80	1.81	1.81	1.79	1.81	1.84	1.82	1.84
4	1.63	1.63	1.66	1.66	1.63	1.72	1.70	1.68	1.62
8	1.35	1.29	1.39	1.35	1.43	1.54	1.46	1.41	1.35

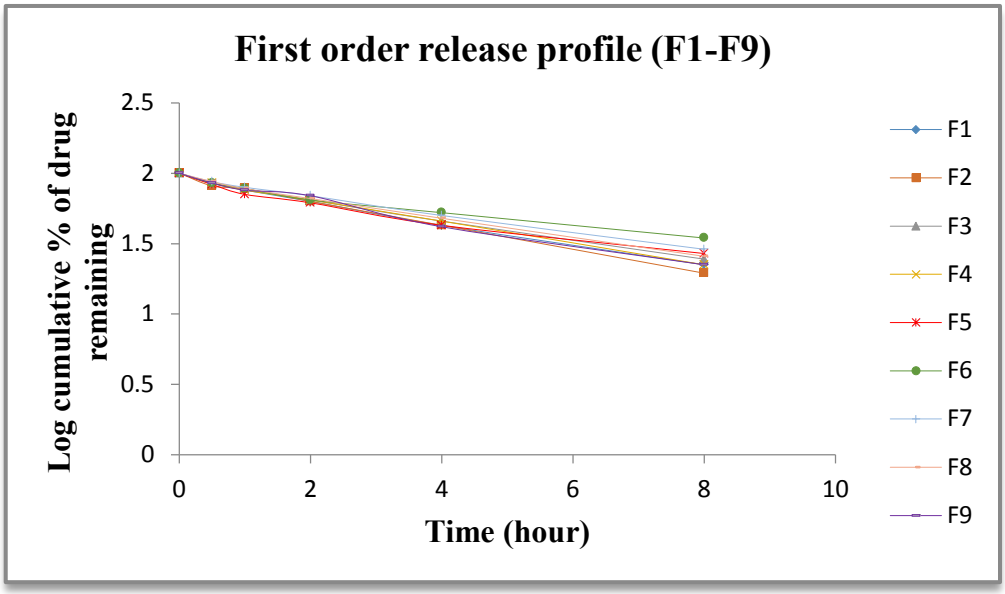

Figure 3.18: First order plot of release kinetics of Ketorolac Tromethamine matrix tablets

3.5.3 Higuchi plot:

Table 3.7: Higuchi release profile of nine formulations of matrix tablets

Square root of time (hour)	Cumulative % of drug released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.71	14.90	17.96	15.71	14.75	15.95	15.29	13.25	13.13	15.06
1	23.40	22.59	23.05	23.53	29.76	22.30	21.15	22.50	24.54
1.41	36.62	37.29	35.02	35.71	38.39	35.18	31.31	33.82	31.23
2	56.91	57.25	54.39	54.15	57.83	47.71	50.28	52.07	58.24
2.83	77.59	80.66	75.55	77.37	73.28	65.67	71.34	74.09	77.76

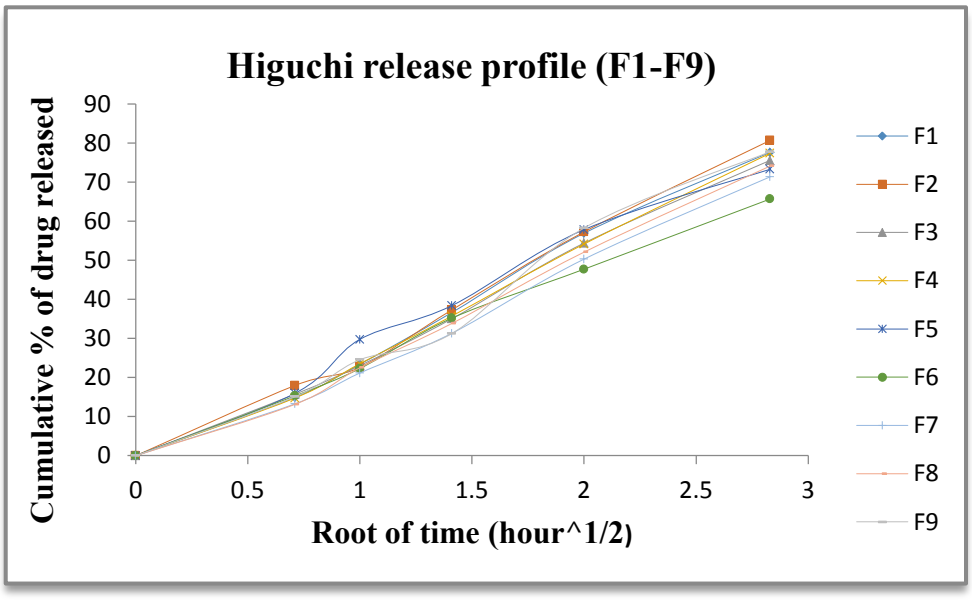

Figure 3.19: Higuchi plot of release kinetics of Ketorolac Tromethamine matrix tablets

3.5.4 Korsmeyer-Peppas plot:

Table 3.8: Korsmeyer-Peppas release profile of nine formulations of matrix tablets

Log of time (hour)	Log fraction of drug released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
-0.30	-0.83	-0.74	-0.80	-0.83	-0.80	-0.82	-0.88	-0.88	-0.82
0	-0.63	-0.65	-0.64	-0.63	-0.53	-0.65	-0.67	-0.65	-0.61
0.30	-0.44	-0.43	-0.46	-0.45	-0.42	-0.45	-0.50	-0.47	-0.51
0.60	-0.24	-0.24	-0.26	-0.27	-0.24	-0.32	-0.30	-0.28	-0.23
0.90	-0.11	-0.09	-0.12	-0.11	-0.14	-0.18	-0.15	-0.13	-0.11

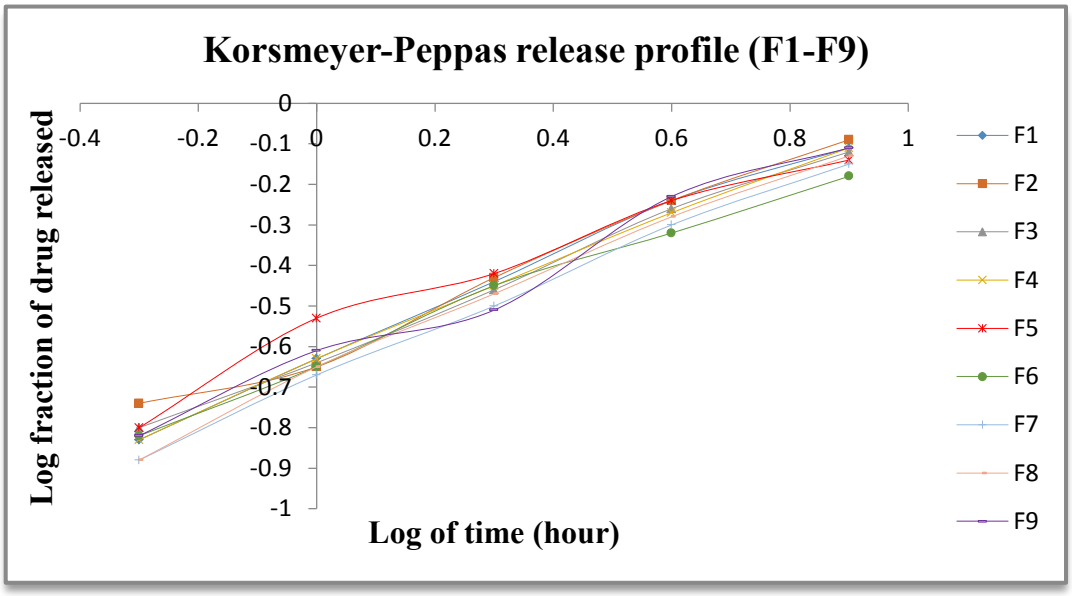

Figure 3.20: Korsmeyer-Peppas plot of release kinetics of Ketorolac Tromethamine matrix tablets

3.5.5 Hixson-Crowell plot:

Table 3.9: Hixson-Crowell release profile of nine formulations of matrix tablets

Time (hour)	Cubic root of total amount of drug (%) - Cubic root of drug remaining (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.24	0.30	0.26	0.24	0.26	0.25	0.21	0.21	0.24
1	0.39	0.38	0.39	0.40	0.52	0.37	0.35	0.38	0.42
2	0.65	0.67	0.62	0.64	0.69	0.62	0.55	0.60	0.54
4	1.14	1.14	1.07	1.06	1.16	0.76	0.96	1.01	1.17
8	1.82	1.96	1.74	1.81	1.65	1.39	1.58	1.68	1.83

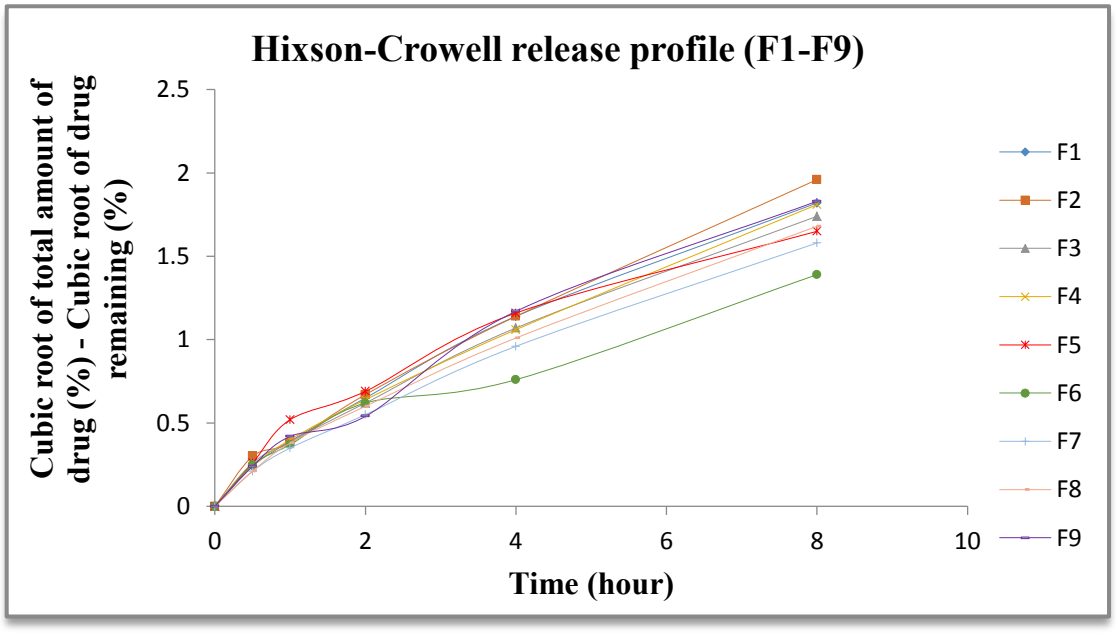

Figure 3.21: Hixson-Crowell plot of release kinetics of Ketorolac Tromethamine matrix tablets

3.6 Interpretation of release rate constants and R^2 values for different formulations:

The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined (Table 3.10). In this experiment, the *in vitro* release kinetics of drug could be best expressed by Higuchi model (R^2: 0.984 to 0.997) as the relevant plot showed high linearity for most of the formulations, followed by first order model (R^2: 0.968 to 0.996) and Hixson-Crowell model (R^2: 0.939 to 0.987) as shown in Table 3.10. It was clearly evident that the formulations did not follow zero order release pattern because the R^2 value did not show relatively high linearity. To confirm the drug release mechanism from the matrix tablets, the data were fitted into Korsmeyer-Peppas equation which is often used to describe the drug release behavior from the polymeric systems. When plotted according to Korsmeyer-Peppas equation, the formulations F1, F3, F4, F6, F7 and F8 showed high linearity (R^2 >= 0.995), with slope (n) values between 0.537 and 0.623 (Table 3.11), which appears to indicate that diffusion as well as erosion was the predominant mechanism of drug release for the tablets.

Hence, diffusion coupled with erosion might be the proposed mechanism for the release of drug from Methocel K100M and Methocel K4M based sustained release matrix tablet of Ketorolac Tromethamine.

Table 3.10: Drug release rate constants and R^2 values for different formulations

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	K_0	R^2	K	R^2	K_h	R^2	n	R^2	K_{HC}	R^2
F1	9.101	0.951	0.183	**0.994**	28.492	**0.993**	0.610	**0.995**	0.221	0.979
F2	9.358	0.932	0.198	**0.996**	29.154	**0.994**	0.570	0.987	0.235	0.987
F3	8.773	0.927	0.171	**0.994**	27.427	**0.996**	0.580	**0.998**	0.208	0.980
F4	9.002	0.933	0.181	**0.996**	28.045	**0.995**	0.600	**0.998**	0.217	0.985
F5	8.320	0.867	0.157	0.968	26.796	0.988	0.537	0.970	0.195	0.939
F6	7.424	0.896	0.125	0.970	23.630	**0.997**	0.537	**0.993**	0.158	0.956
F7	8.368	0.939	0.151	**0.995**	25.958	**0.993**	0.610	**0.997**	0.190	0.983
F8	8.679	0.934	0.165	**0.995**	27.004	**0.994**	0.623	**0.995**	0.202	0.982
F9	9.186	0.927	0.185	**0.990**	28.538	0.984	0.600	0.982	0.223	0.978

Table 3.11: The best fitted model and drug release mechanism followed by the matrix tablets of Ketorolac Tromethamine

Formulation	Best fitted model	n value (Korsmeyer-Peppas model)	Release mechanism
F1	Korsmeyer-Peppas, First order, Higuchi, Hixson-Crowell and Zero order	0.610	Anomalous/Non-Fickian Release
F2	First order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell and Zero order	0.570	Anomalous/Non-Fickian Release
F3	Korsmeyer-Peppas, Higuchi, First order, Hixson-Crowell and Zero order	0.580	Anomalous/Non-Fickian Release
F4	Korsmeyer-Peppas, First order, Higuchi, Hixson-Crowell and Zero order	0.600	Anomalous/Non-Fickian Release
F5	Higuchi, Korsmeyer-Peppas, First order and Hixson-Crowell	0.537	Anomalous/Non-Fickian Release
F6	Higuchi, Korsmeyer-Peppas, First order and Hixson-Crowell	0.537	Anomalous/Non-Fickian Release
F7	Korsmeyer-Peppas, First order, Higuchi, Hixson-Crowell and Zero order	0.610	Anomalous/Non-Fickian Release
F8	Korsmeyer-Peppas, First order, Higuchi, Hixson-Crowell and Zero order	0.623	Anomalous/Non-Fickian Release
F9	First order, Higuchi, Korsmeyer- Peppas, Hixson-Crowell and Zero order	0.600	Anomalous/Non-Fickian Release

3.7 Analysis of successive fractional dissolution time:

Successive fractional dissolution time and MDT of the nine formulations (F1 to F9) of Ketorolac Tromethamine matrix tablets are mentioned in Table 3.12 and depicted in Figure 3.22. The $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and MDT values showed very little increase in the drug retaining ability of the polymers for some formulations. The time taken to release 25%, 50% and 80% of the drug from the matrix tablet was found to increase with rise in amount of Methocel K4M CR for F1 to F3 and F4 to F6 respectively thereby reflecting retardation of drug release rate and hence higher MDT value as the concentration of the polymer increased. However, the formulations F7 to F9 showed slight deviation from the general phenomena of retarding capacity with increase in polymer loading. Similarly, $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and MDT for F1, F4, F7 and F2, F5, F8 were found to increase with the rise in loading of Methocel K100M CR although a deviation was observed for F9 when compared with values of F3 and F6.

Table 3.12: Successive fractional dissolution time of nine formulations of Ketorolac Tromethamine matrix tablets

Formulation	$T_{25\%}$ (hour)	$T_{50\%}$(hour)	$T_{80\%}$(hour)	MDT (hour)
F1	1.124	3.501	7.565	4.132
F2	0.996	3.359	7.662	4.115
F3	1.117	3.691	8.301	4.477
F4	1.148	3.644	7.976	4.339
F5	0.937	3.411	8.188	4.334
F6	1.202	4.374	10.501	5.558
F7	1.357	4.228	9.137	4.991
F8	1.281	3.894	8.276	4.546
F9	1.139	3.616	7.916	4.306

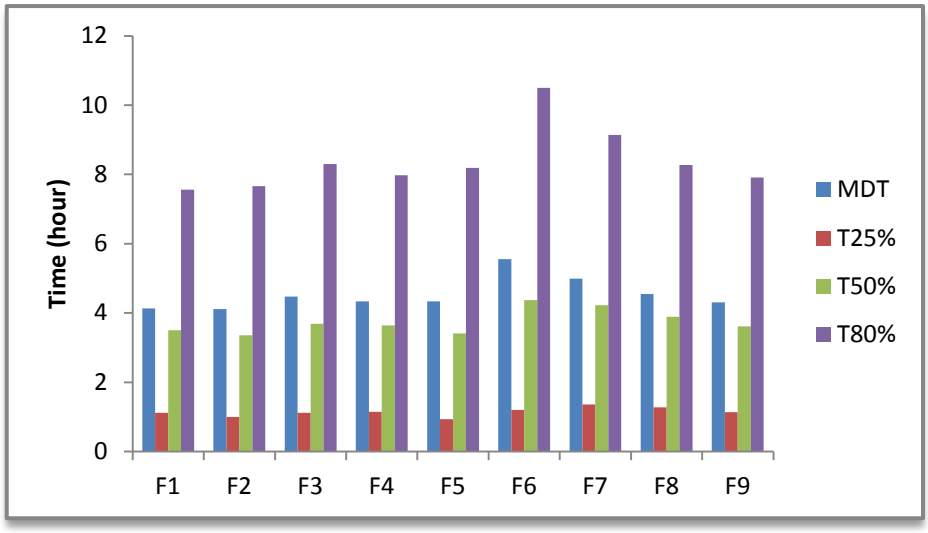

Figure 3.22: Comparison of MDT, $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ values of different formulations

3.8 Optimization of formulation using 3^2 full factorial design:

3.8.1 Summary of the design:

The optimization of the formulation was carried out using 3^2 full factorial design by means of Design Expert software where Factor 1 and Factor 2, represented by Methocel K100M CR (A) and Methocel K4M CR (B) respectively were taken as two independent variables. The levels were set as low (-1), medium (0) and high (1) followed by input of *in vitro* drug release data to analyze the extent of dependence of drug release on the polymers after 1, 4 and 8 hours (Figure 3.23 and 3.24).

Select	Std	Run	Factor 1 A:Methocel K100M %	Factor 2 B:Methocel K4M %	Response 1 After 1 hr %	Response 2 After 4 hr %	Response 3 After 8 hr %
	9	1	1	1	24.54	58.24	77.76
	4	2	-1	0	22.59	57.25	80.66
	6	3	1	0	22.5	52.07	74.09
	5	4	0	0	29.76	57.83	73.28
	10	5	0	0	29.76	57.83	73.28
	2	6	0	-1	23.53	54.15	77.37
	8	7	0	1	22.3	47.71	65.67
	7	8	-1	1	23.05	54.39	75.55
	3	9	1	-1	21.15	50.28	71.34
	1	10	-1	-1	23.4	56.91	77.59

Figure 3.23: The actual design of the experiment

Design Summary

File Version	9.0.6.2		
Study Type	Response Surface	Runs	10
Design Type	3 Level Factorial	Blocks	No Blocks
Design Mode	Quadratic	Build Time (r	15.00

Factor	Name	Units	Type	Subtype	Minimum	Maximum	Coded	Values	Mean	Std. Dev.
A	Methocel K100	%	Numeric	Continuous	-1	1	-1.000=-1	1.000=1	0	0.816497
B	Methocel K4M	%	Numeric	Continuous	-1	1	-1.000=-1	1.000=1	0	0.816497

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Trans
R1	After 1 hr	%	10	Polynomial	21.15	29.76	24.258	3.0316	1.40709	None
R2	After 4 hr	%	10	Polynomial	47.71	58.24	54.666	3.63948	1.22071	None
R3	After 8 hr	%	10	Polynomial	65.67	80.66	74.659	4.19401	1.22826	None

Figure 3.24: Summary of the design

3.8.1.1 Graph column:

The graph column determines the correlation between the individual polymer content and release of the drug after 1, 4 and 8 hours. Figure 3.25 to 3.27 shows plot of Factor 1 (Methocel K100M CR) *versus* response after 1, 4 and 8 hours which depicted that the polymer loading is weakly correlated with the release of the drug at low, mid and high level because the increase in amount of Methocel K100M CR do not show significant control on drug release of some formulations. In contrast, the graph of Factor 2 (Methocel K4M CR) against response after 1, 4 and 8 hours showed better influence of polymer loading compared to Factor 1 at all levels (Figure 3.28 to 3.30).

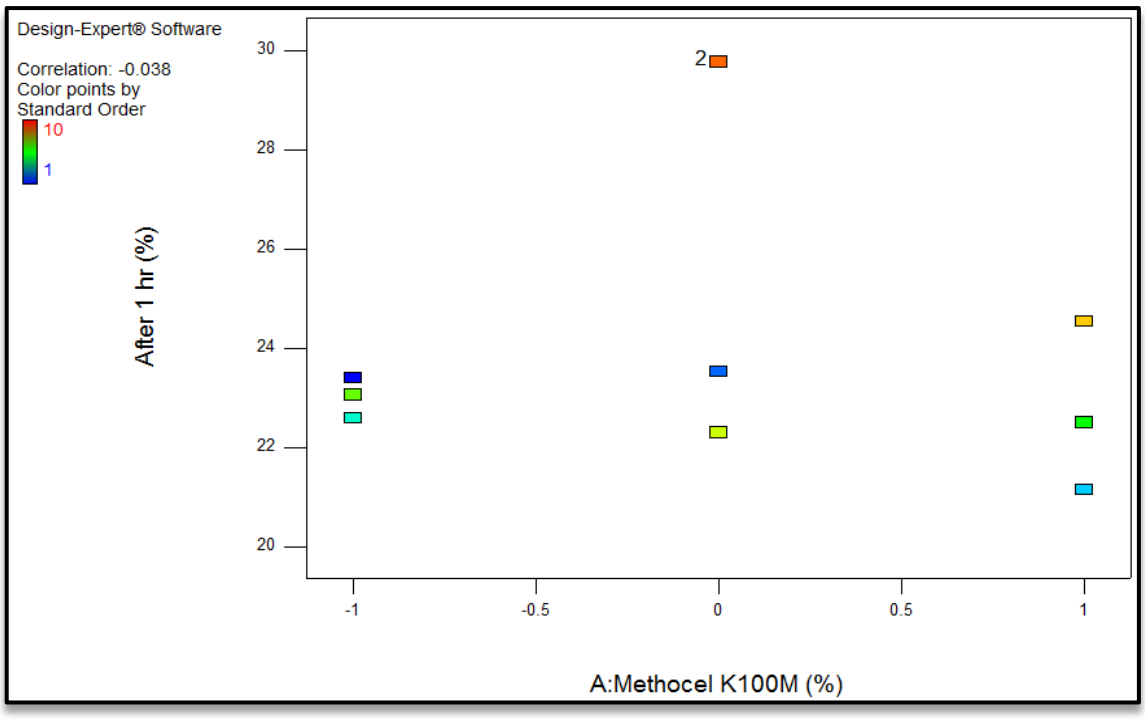

Figure 3.25: The graph column of Methocel K100M CR (A) after 1 hour

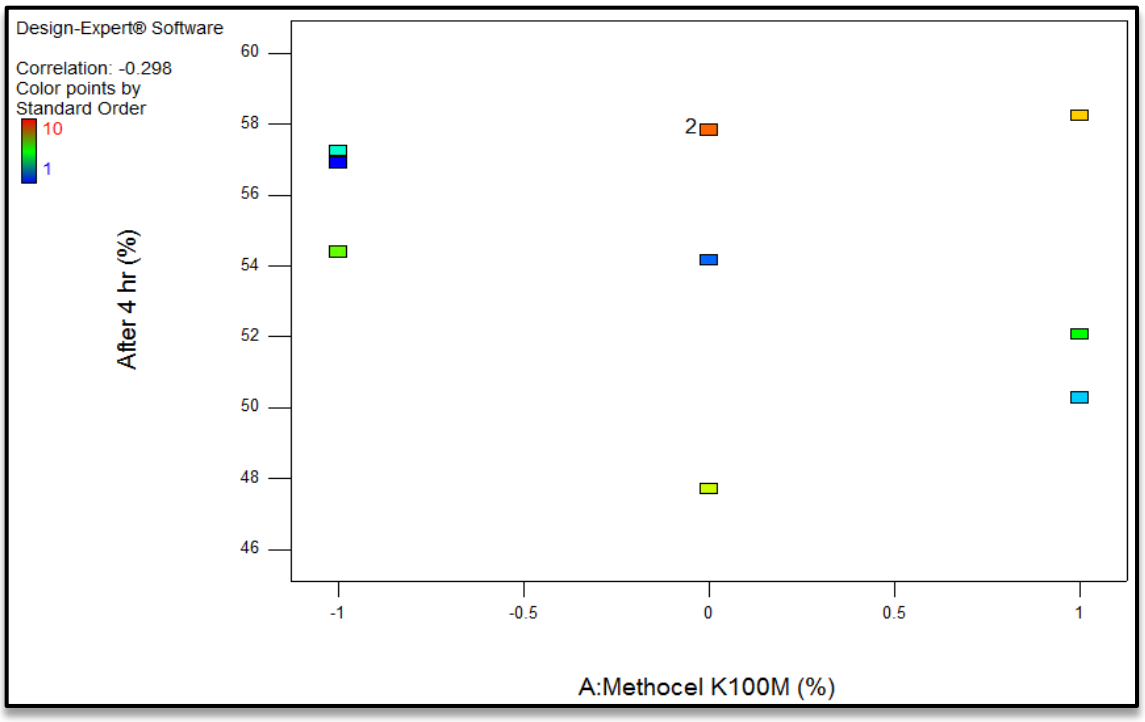

Figure 3.26: The graph column of Methocel K100M CR (A) after 4 hours

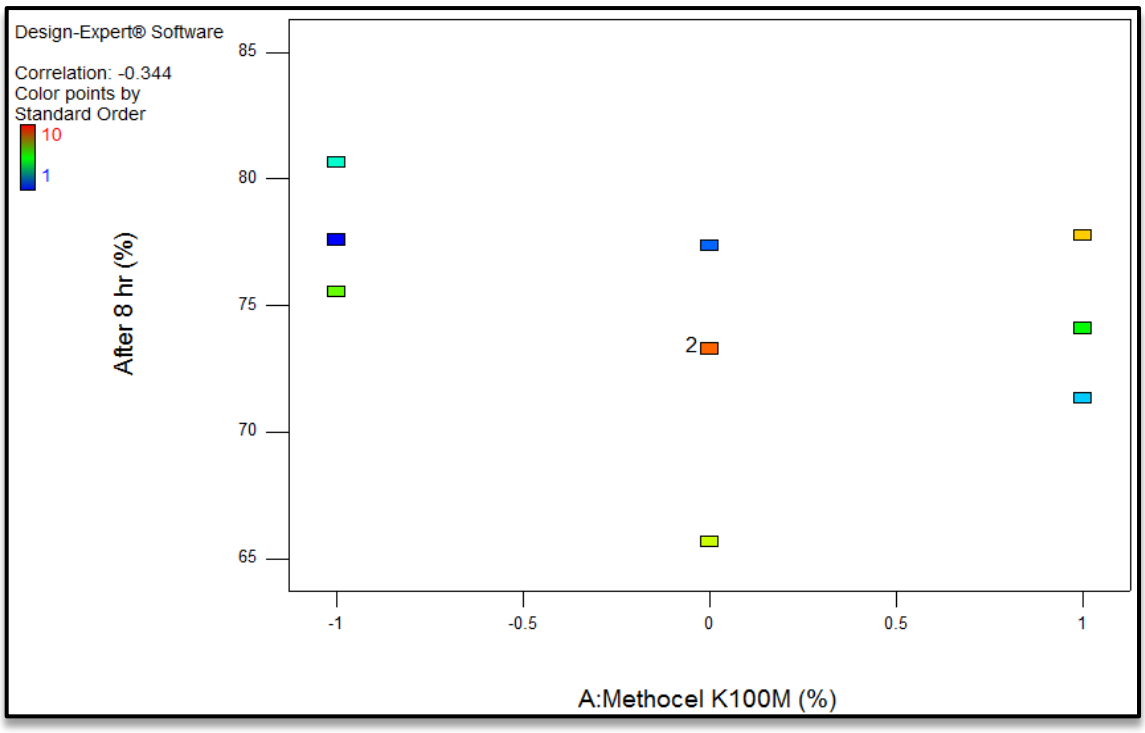

Figure 3.27: The graph column of Methocel K100M CR (A) after 8 hours

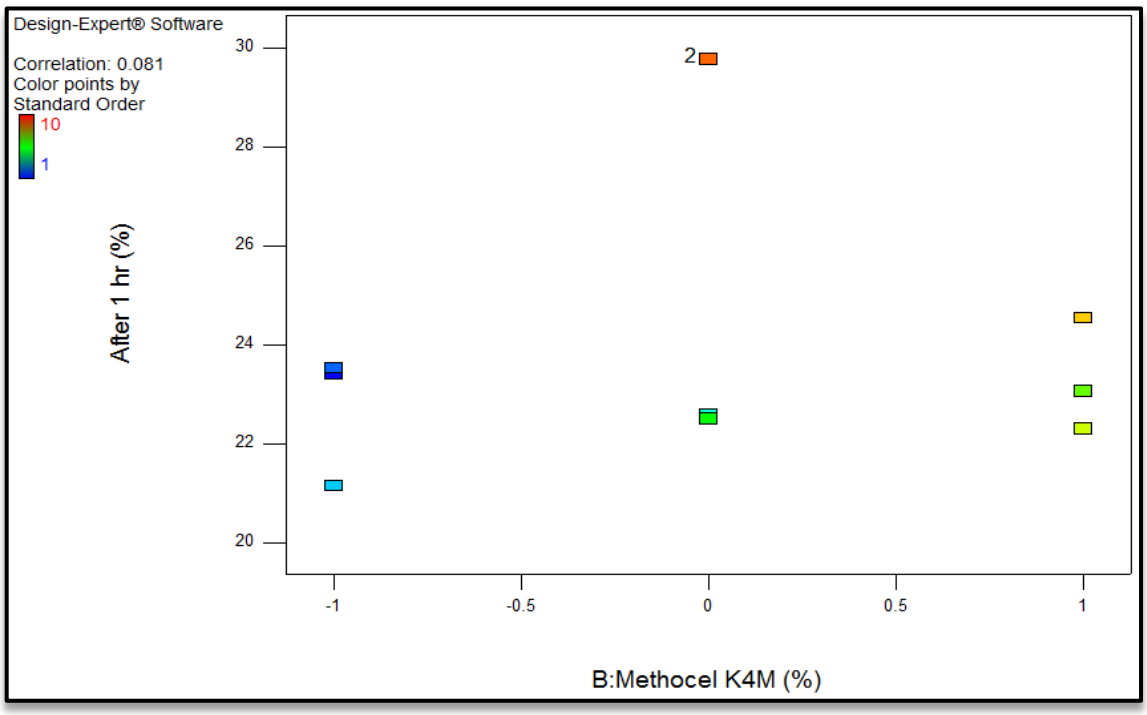

Figure 3.28: The graph column of Methocel K4M CR (B) after 1 hour

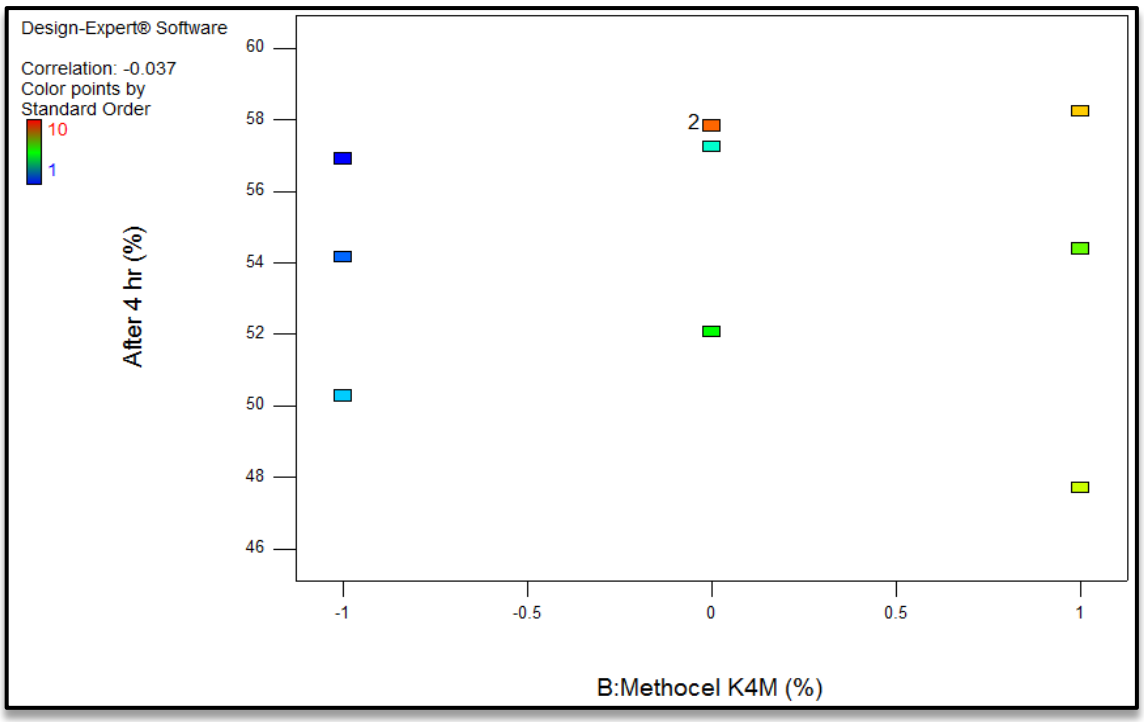

Figure 3.29: The graph column of Methocel K4M CR (B) after 4 hours

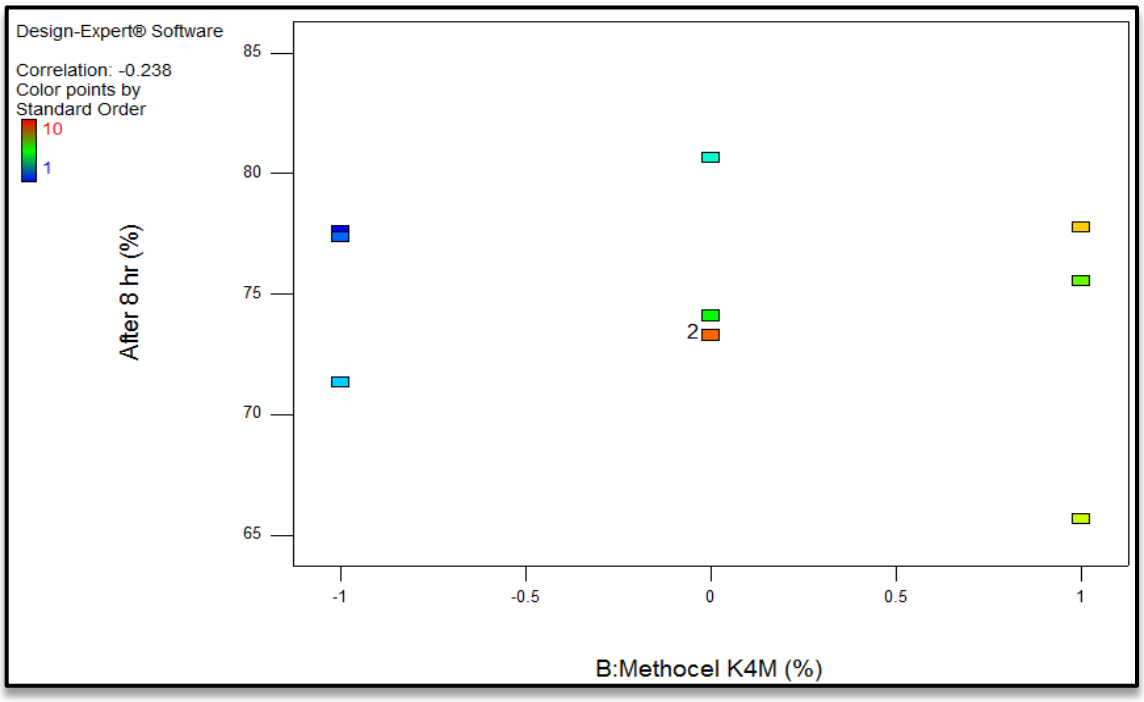

Figure 3.30: The graph column of Methocel K4M CR (B) after 8 hours

3.8.2 Analysis of the full factorial design:

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses as represented by the following equation:

$$Y= b_0 + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2$$

where,

Y is the dependent variable,

A, B are the coded levels of the independent variable,

b_0 is the intercept representing the arithmetic mean response of the 9 runs,

b_1 to b_5 are the estimated coefficients computed from the observed experimental response values of Y.

The main effects (A and B: Linear) represent the average result of changing one factor at a time from its low to high values. The interaction terms (AB: 2 FI) show how the response changes when two factors are simultaneously changed. The polynomial terms (A^2 and B^2: Quadratic) are included to investigate nonlinearity of the model.

3.8.2.1 Response after 1 hour:

After 1 hour, for each source of terms (intercept, A, B, AB, A^2, B^2), the probability value (p-value) was examined to choose the statistical model that best evaluates the response. So far, the Design Expert software predicted that the release pattern after 1 hour (Y_{1hr}) followed a quadratic model as the p-value for this model was found to be lower i.e. 0.1796 relative to linear, 2 FI and cubic models (Figure 3.31). Similarly, lack of fit test and model summary statistics displayed by the software suggested less lack of fitness for the quadratic model as it exhibits low standard deviation (Std. Dev), high "R-Squared" value and a low "PRESS" (Figure 3.32).

Sequential Model Sum of Squares [Type I]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Mean vs Total	5884.51	1	5884.51			Suggested
Linear vs Mear	0.67	2	0.33	0.028	0.9721	
2FI vs Linear	3.50	1	3.50	0.27	0.6238	
Quadratic vs 2	45.26	2	22.63	2.72	0.1796	Suggested
Cubic vs Quad	2.55	2	1.27	0.083	0.9234	Aliased
Residual	30.74	2	15.37			
Total	5967.22	10	596.72			

Figure 3.31: Suggested statistical model for response after 1 hour

Lack of Fit Tests

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Linear	82.05	6	13.67		
2FI	78.55	5	15.71		
Quadratic	33.29	3	11.10		
Cubic	30.74	1	30.74		
Pure Error	0.000	1	0.000		

"Lack of Fit Tests": Want the selected model to have insignificant lack-of-fit.

Model Summary Statistics

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	3.42	0.0081	-0.2754	-0.5438	127.69	
2FI	3.62	0.0503	-0.4245	-0.9786	163.66	
Quadratic	2.89	0.5975	0.0944	-1.8314	234.20	Suggested
Cubic	3.92	0.6283	-0.6726	-51.2931	4325.43	Aliased

Figure 3.32: Fit summary report for response after 1 hour

The response after 1 hour was also statistically analyzed by analysis of variance (ANOVA) at the 5% significance level. From the ANOVA for response surface quadratic model, the ability of the model to provide adequate information on the dependence of drug release on polymer was determined. The p-value for the model was

found to be 0.4464 (p>0.05) indicating that the model is not significant and the chance of error is more than 5% (Figure 3.33).

Response 1 After 1 hr

ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	49.42	5	9.88	1.19	0.4464	not significant
A-Methocel K	*0.12*	*1*	*0.12*	*0.014*	*0.9101*	
B-Methocel K	*0.55*	*1*	*0.55*	*0.066*	*0.8105*	
AB	*3.50*	*1*	*3.50*	*0.42*	*0.5522*	
A^2	*21.33*	*1*	*21.33*	*2.56*	*0.1847*	
B^2	*16.43*	*1*	*16.43*	*1.97*	*0.2327*	
Residual	33.29	4	8.32			
Lack of Fit	*33.29*	*3*	*11.10*			
Pure Error	*0.000*	*1*	*0.000*			
Cor Total	82.72	9				

Std. Dev.	2.89	R-Squared	0.5975
Mean	24.26	Adj R-Squared	0.0944
C.V. %	11.89	Pred R-Square	-1.8314
PRESS	234.20	Adeq Precisior	3.157

Figure 3.33: ANOVA statistics for response after 1 hour

The polynomial equation represents the quantitative effect of factors (A and B) upon the response. Coefficients with one factor (A or B) represent the effect of that particular factor while the coefficients with more than one factor (AB) and those with second order terms (A^2 and B^2) represents the interaction between those factors and the quadratic nature of the model respectively. A positive sign in front of the terms indicates accelerating effects while the negative sign indicates retarding effects of the factor.

The predicted equation for Y_{1hr} in terms of coded factors is mentioned below:

$$\mathbf{Y_{1hr} = 27.66 - 0.14A + 0.30B + 0.94AB - 3.02A^2 - 2.65B^2}$$

According to the above equation, coefficient b_1 bears a negative sign which means that „A" decreased the response by 0.14 times. So increasing the amount of the Methocel K100M CR polymer in the formulations increased the time taken by the drug to leave the formulation and retarded release of drug into the medium. Coefficient b_2 bear positive sign indicating that „B" increased the response by 0.3 times. Moreover, combination of A

and B increased the drug release by 0.94 times. Therefore, both „A" and „B" were responsible for the response after 1 hour but „A" participated in the retarding effect of the polymer.

The quadratic model generated for Y_{1hr} was used to construct two dimensional (2D) contour plot and three dimensional (3D) surface response plot in which the response parameter was represented by a curvature surface as a function of „A" and „B." The 2D contour plot as well as the 3D response surface plot in Figure 3.34A and 3.34B shows the effect of polymer on drug release after 1 hour.

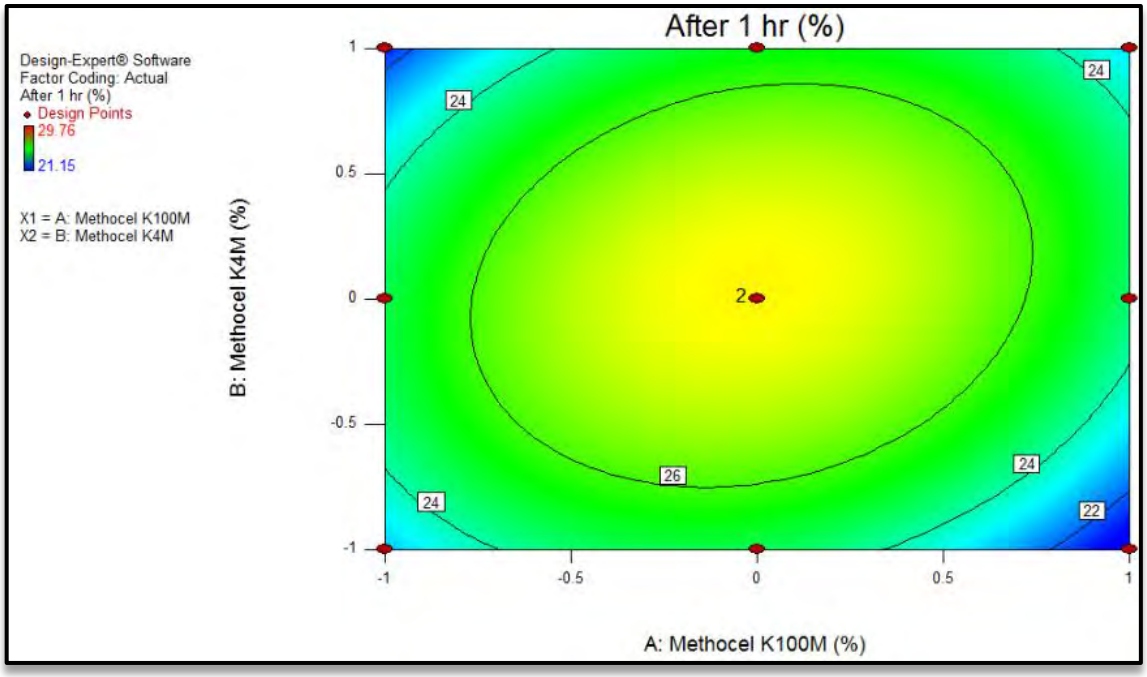

Figure 3.34A: 2D contour plot of drug release after 1 hour

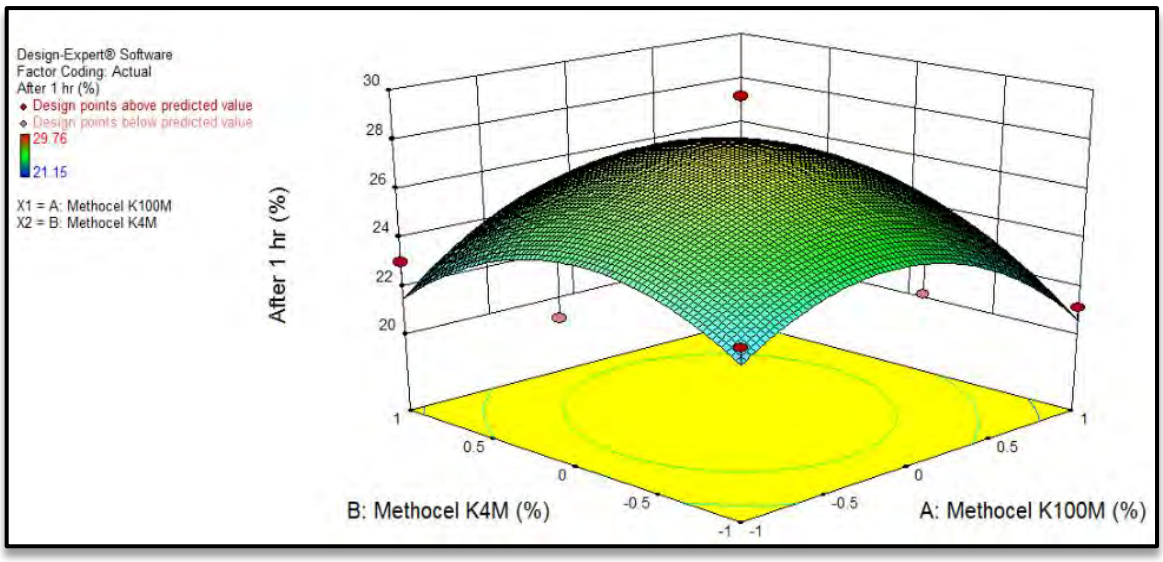

Figure 3.34B: 3D surface plot of drug release after 1 hour

The diagnostic--normal plot of residuals determines the linearity of the data points and for the 1st hour, the practical response values for all the formulations were found in close proximity with the theoretical values, thereby, showing linearity (Figure 3.35).

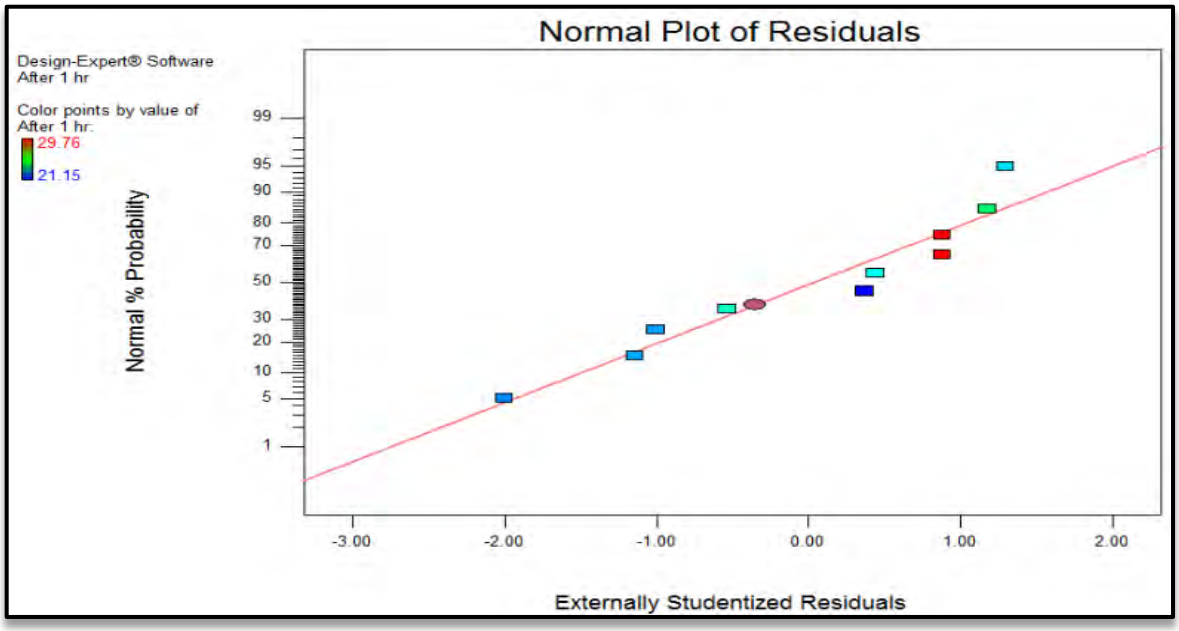

Figure 3.35: Normal plot of residuals after 1 hour

3.8.2.2 Response after 4 hours:

For the response after 4 hours (Y_{4hr}), only b_0 with a value of 54.67 was obtained indicating that the polymer has no control on the release of drug after 4 hours. The contour and surface plots also supported the statistical model which showed that the release was independent of the polymer loading (Figure 3.36A and 3.36B). The normal plot of residuals illustrated linear relationship between experimental and theoretical response data (Figure 3.37).

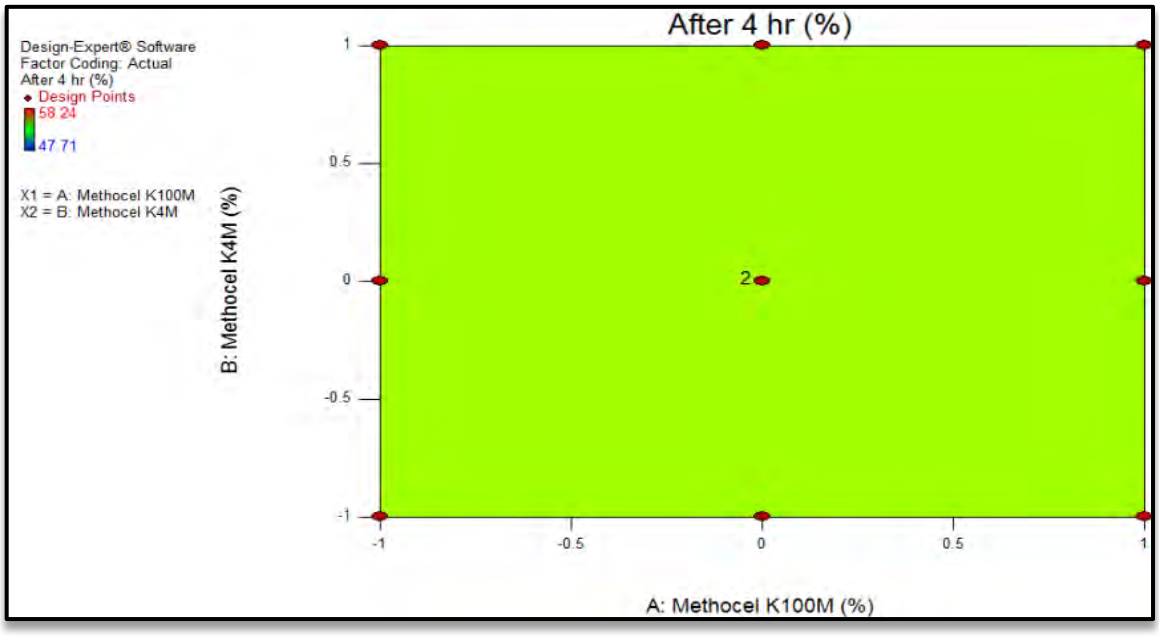

Figure 3.36A: 2D contour plot of drug release after 4 hours

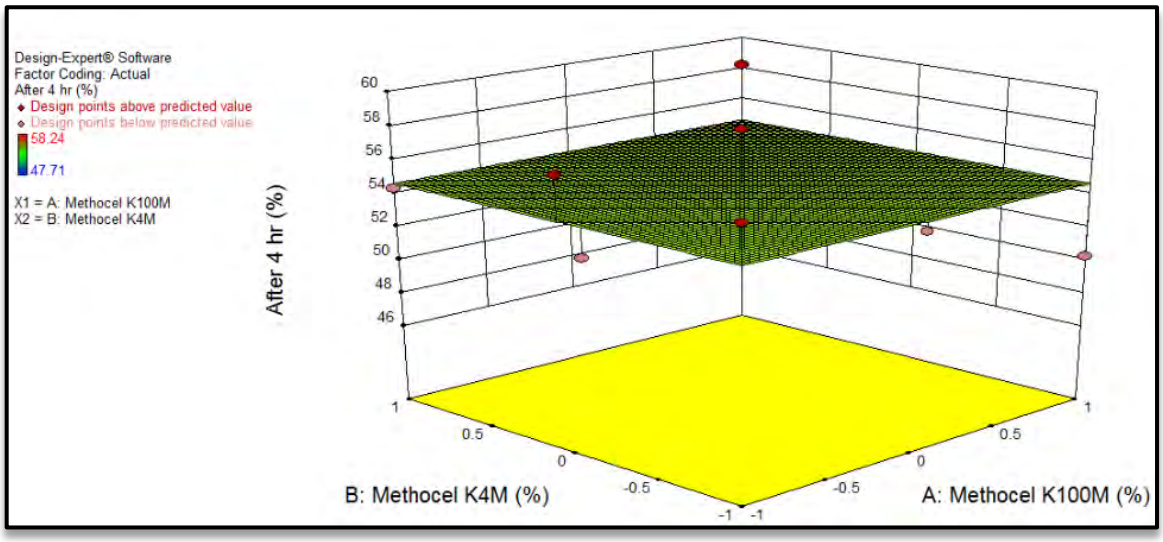

Figure 3.36B: 3D surface plot of drug release after 4 hours

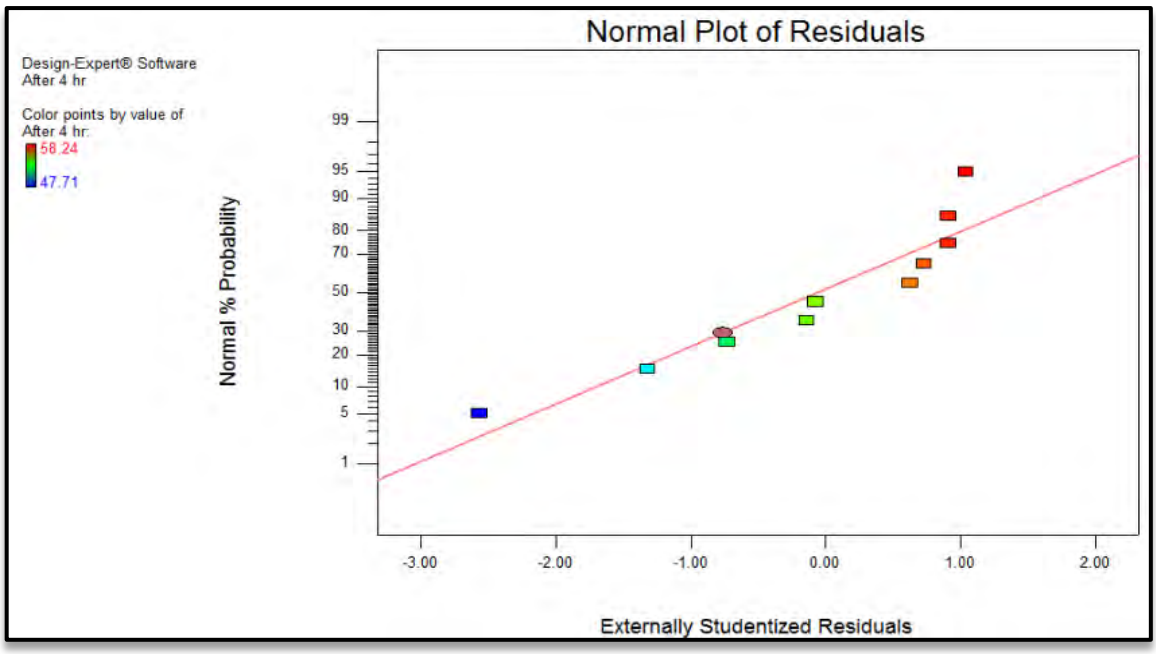

Figure 3.37: Normal plot of residuals after 4 hours

3.8.2.3 Response after 8 hours:

For the response after 8 hours (Y_{8hr}), only b_0 with a value of 74.66 was obtained indicating that the polymer has no control on the release of drug after 8 hours. The contour and surface plots also supported the statistical model which showed that the release was independent of the polymer loading (Figure 3.38A and 3.38B). The normal plot of residuals depicted linear relationship between experimental and theoretical response data (Figure 3.39).

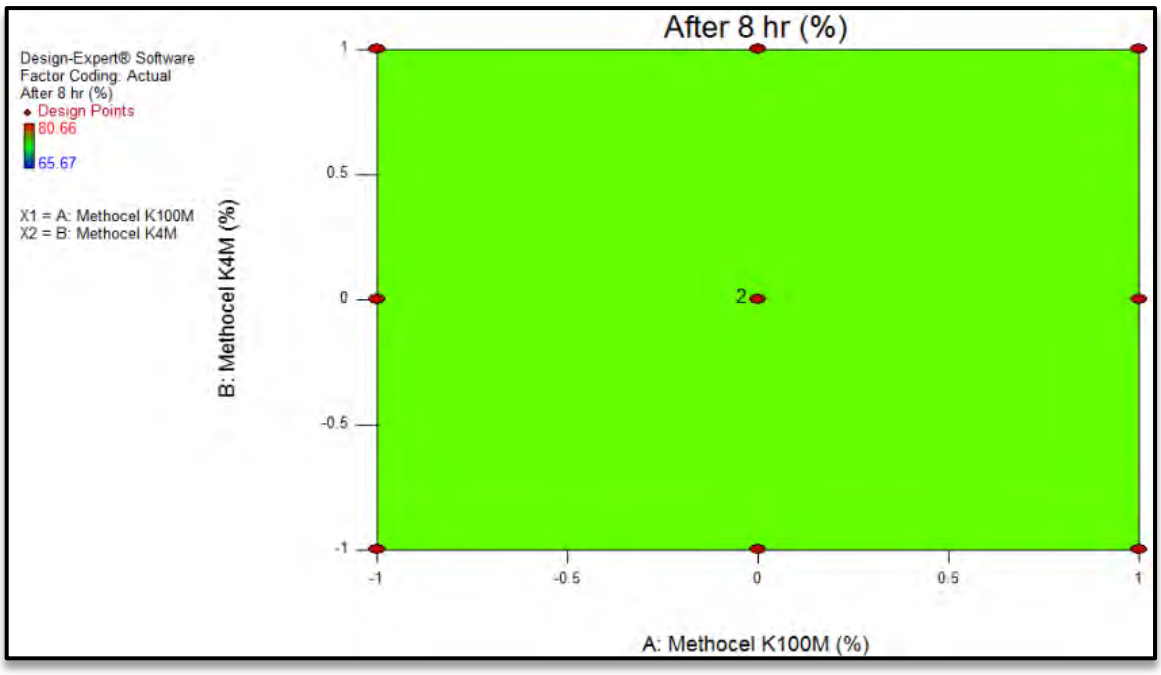

Figure 3.38A: 2D contour plot of drug release after 8 hours

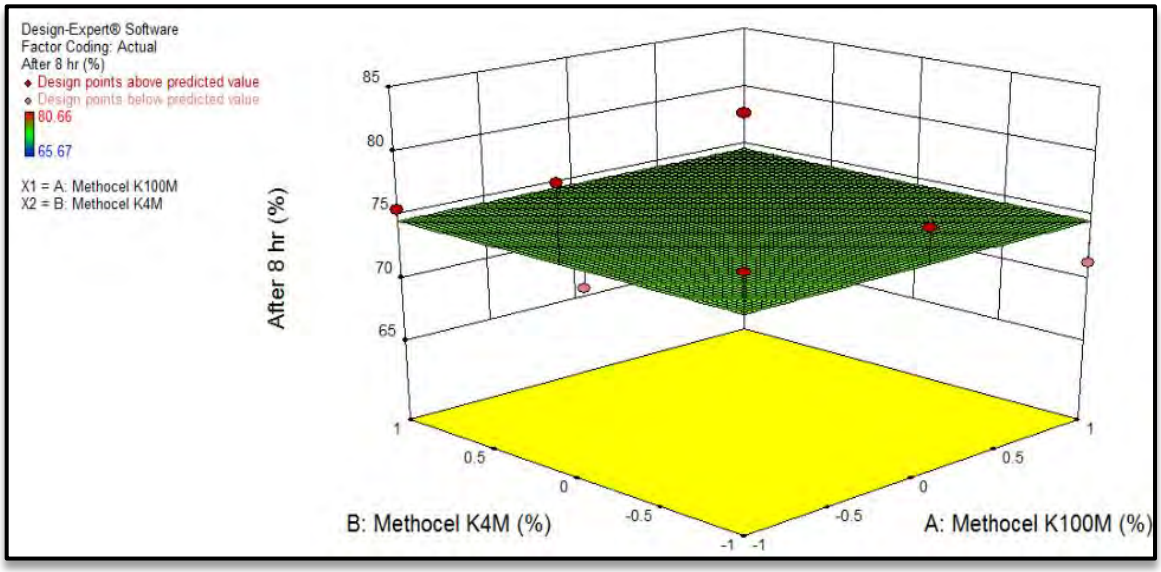

Figure 3.38B: 3D surface plot of drug release after 8 hours

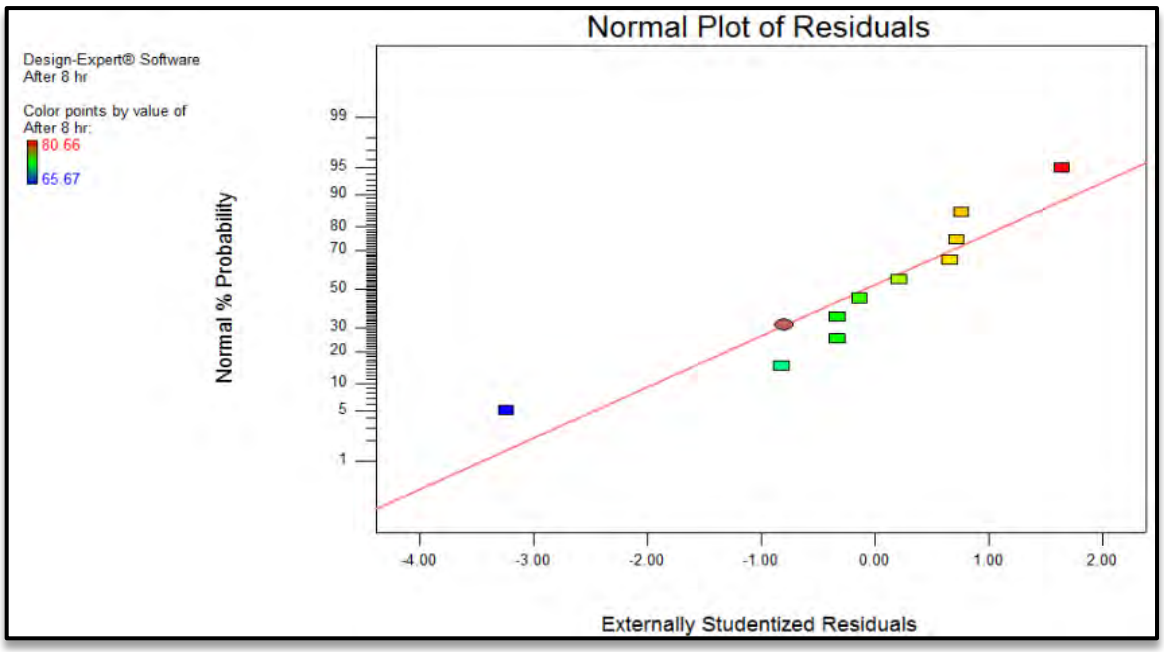

Figure 3.39: Normal plot of residuals after 8 hours

Response	Intercept	A	B	AB	A^2	B^2
After 1 hr	27.6643	-0.141667	0.301667	0.935	-3.02357	-2.65357
p=		0.9101	0.8105	0.5522	0.1847	0.2327
After 4 hr	54.666					
p=						
After 8 hr	74.659					
p=						
Legend		p <.01	.01<= p <.05	.05<= p <.10	p >=.10	

Figure 3.40: Summary of the responses after 1, 4 and 8 hours

3.8.3 Optimization of the formulation:

For optimization, a numerical technique was employed to generate formulation with desired responses. As a result, the desirable ranges of these responses were restricted to 21%<Y_{1hr}<25%, 45% <Y_{4hr}<55% and 65% <Y_{8hr}<75%. The optimum coded levels of each independent variable were based on the desirability criterion and graphical analysis. An overlay plot was obtained that displayed a yellow region for the possible optimum formulations (Figure 3.41).

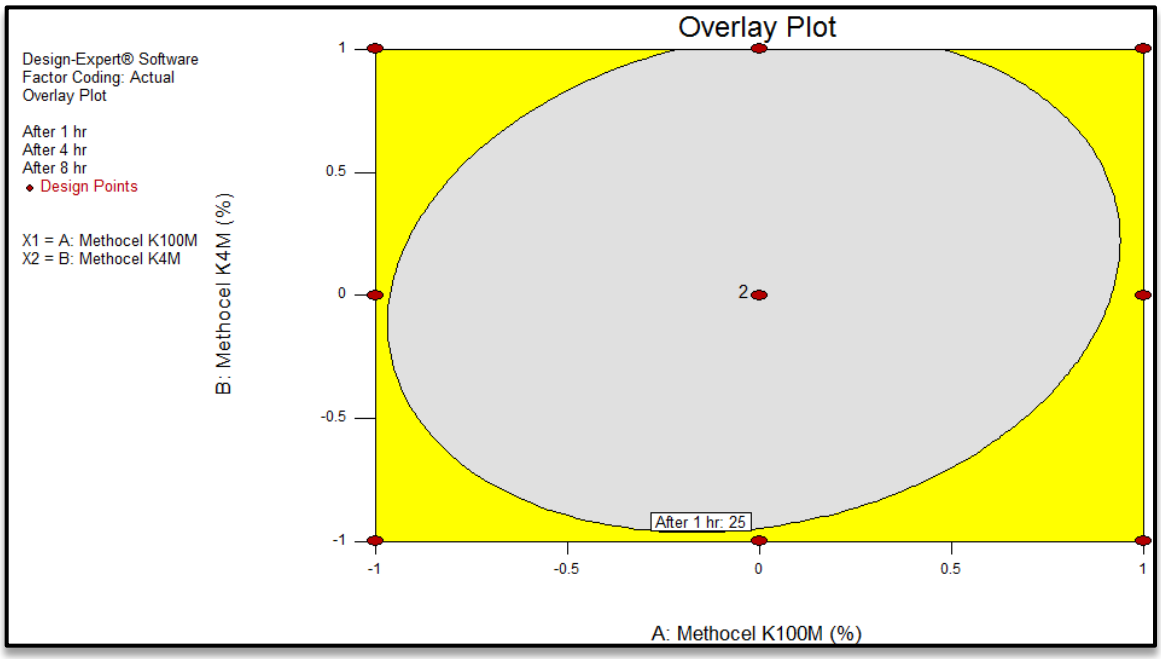

Figure 3.41: The overlay plot of the optimization area

The optimum formulation was chosen to be F4, primarily on the basis of desirability criterion and graphical analysis of the formulation (Figure 3.42 and 3.43) where the observed responses were found to be in close agreement with the predicted values for the optimized formulation (Table 3.13). Moreover, $T_{25\%}$ was also considered as a parameter for the selection because the time taken to release 25% of drug was 1.148 hour (Table 3.12). The Korsmeyer-Peppas model also showed significant R^2 value for F4 (Table 3.10). The physical parameters evaluated for F4 were also found to be satisfactory and within the specifications (Table 3.3 and 3.4).

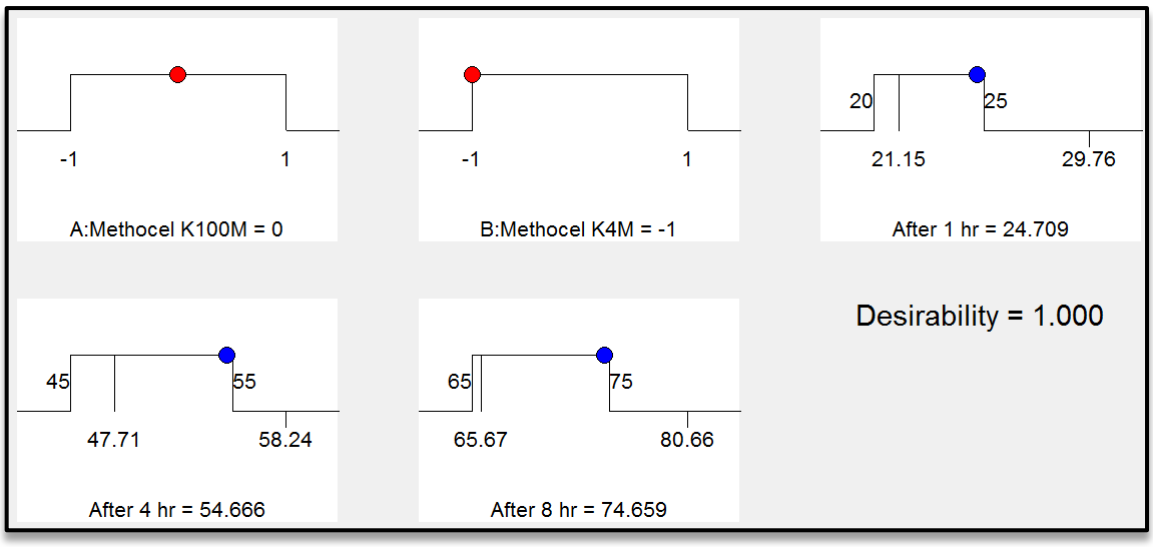

Figure 3.42: Optimum formulation with predicted drug release profile

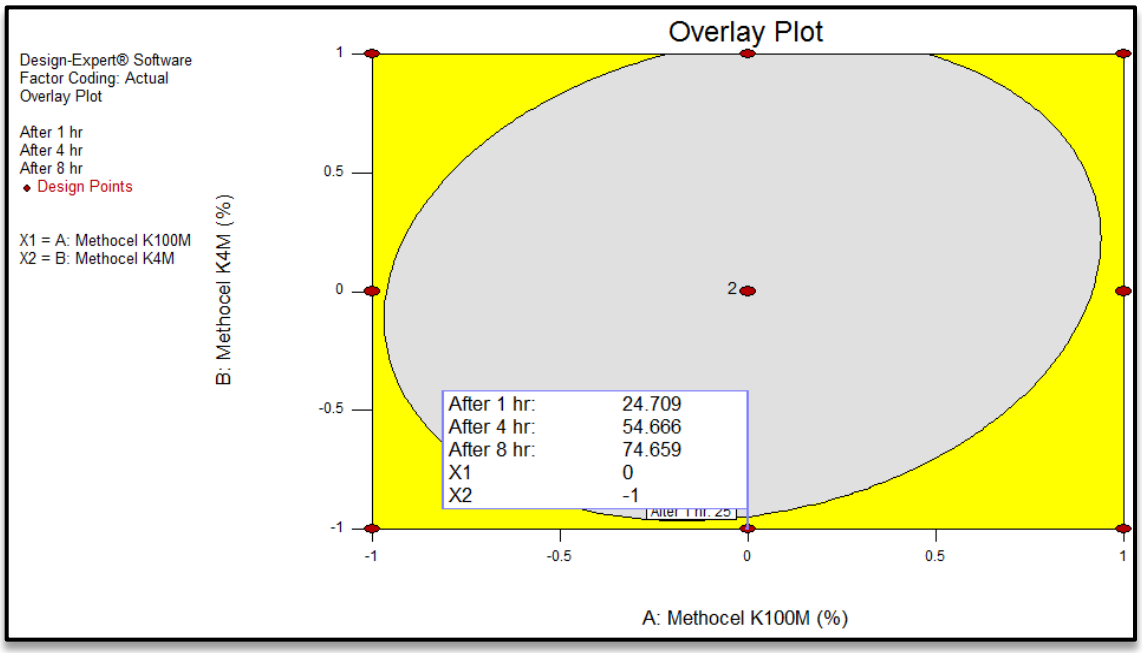

Figure 3.43: The overlay plot of the optimum formulation

Table 3.13: Composition of the optimum formulation with the predicted and experimental values of response variables

Composition Methocel K100M CR: Methocel K4M CR	Response variables	Experimental value (%)	Predicted value (%)	Prediction error (%)
F4= 35:5	Drug release after 1 hour	23.53	24.709	3.56
	Drug release after 4 hours	54.15	54.666	3.82
	Drug release after 8 hours	77.37	74.659	4.40

Conclusion

In the present study, a sustained release oral tablet dosage form of Ketorolac Tromethamine was successfully formulated. The design of this experiment involved the formulation of nine trial batches of the matrix tablet using different ratio of hydrophilic polymers for each. All the components of the formulation showed compatibility with each other and the physical parameters of the tablets were found to comply with the specifications. *In vitro* dissolution study of the tablets performed for eight hours generated drug release profile for the nine formulations, which were fitted into several mathematical models to identify the release kinetics and drug transport mechanism that is followed by the matrix tablets. Finally, optimization of the formulation was carried out by using Design Expert software and hence, a once daily oral sustained release tablet formulation was obtained.

Recommendation

Due to time constraint, further trial batches with different polymer combinations could not be investigated. Thus, this leaves behind a scope to carry out extensive work on the formulations.

Appendix

Appendix 1

Ketorolac Tromethamine

Ketorolac Tromethamine is a tromethamine salt of Ketorolac which enhances the solubility of Ketorolac to help in absorption. It is a member of non-steroidal anti-inflammatory drug (NSAID) and is indicated for the short-term management of moderate to severe pain, especially post-operative pain. Ketorolac Tromethamine is rapidly absorbed and hence exhibit bioavailability of 80% to 100%. More than 99% of the drug in plasma is protein bound over a wide concentration range. It is metabolized in the liver via glucuronidation and para-hydroxylation followed by approximately 90% of the drug elimination in urine, and around 6% to 8% in the feces.

Chemical Name: (±)-5-Benzoyl-2,3-dihydro-1Hpyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol
Molecular formula: $C_{19}H_{24}N_2O_6$
Molecular weight: 376.40 g/mol
Melting point: 162°C
Appearance: White or off-white crystalline powder
BCS classification: Class I accompanied by high solubility and high permeability
Solubility: Freely soluble in water and methanol, slightly soluble in ethanol and practically insoluble in acetone, methylene chloride and toluene
pKa: 3.46
pH: The pH of a 1% (w/v) solution in distilled water is 5.7-6.7 (Vadivelu et al., 2015).

Dosage and administration:
Ketorolac Tromethamine tablets are indicated only as continuation therapy to Ketorolac Tromethamine injection, and the combined duration of use of Ketorolac Tromethamine injection and Ketorolac Tromethamine tablets should not exceed 5 days, because of the increased risk of serious adverse events. The recommended dosage regimen is 10mg every four to six hours and should not exceed 40 mg per day (Roche, 2008).

Appendix 2

Ultraviolet-Visible spectrophotometry

UV-Visible spectrophotometry is one of the most frequently employed techniques in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measures the ratio, or function of ratio, of the intensity of the incident and transmitted beams of light in the UV-Visible region is called UV-Visible spectrophotometer. In qualitative analysis, organic compounds can be identified by the use of spectrophotometer, if any recorded data is available, and quantitative spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer-Lambert law.

Beer‟s law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially with the number of absorbing molecules. In other words, absorbance is proportional to the concentration.

Lambert‟s law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially as it passes through a medium of homogeneous thickness.

A combination of these two laws yields the Beer - Lambert law.

Beer-Lambert law: When beam of light is passed through a transparent cell containing a solution of absorbing substance, reduction of the intensity of light may occur. Mathematically, Beer - Lambert law is expressed as

$$A = a\ b\ c$$

Where, A = absorbance

a = absorptivity or extinction coefficient

b = path length of radiation through sample

c = concentration of solute in solution.

Both „a‟ and „b‟ are constant, so „A‟ is directly proportional to the concentration „c‟ (Behera, Ghanty, Ahmad, Santra, & Banerjee, 2012).

Appendix 3

FT-IR

FT-IR or Fourier Transform Infrared spectroscopy is the study of the interaction of electromagnetic radiation from the IR region of the EM spectrum (4000-400) cm^{-1} with a molecule through which IR radiation is passed. The nature of interaction depends upon the functional groups present into the substance. When IR radiation passed through a sample (solid, liquid or gas), certain frequencies of the radiation are absorbed by the atoms of the substance leading to molecular vibration. The frequencies of absorbed radiation are unique for each atom or group of atom, which provide the characteristics of bonds associated with a substance. The resulting IR spectrum represents the molecular absorption and transmission, which can be divided into two approximate regions:

- Functional group region (4000-1500 cm^{-1}), valuable information are obtained from this region to interpret any spectrum.
- Fingerprint region (<1500 cm^{-1}), usually consists of a very complicated series of absorption that are characteristic for a particular compound. Like a fingerprint no two unique molecular structures produce the same infrared spectrum**.**

As the frequency of vibration of a bond in a molecule depends on the nature of the atoms joined by the bond, arrangement of atoms within the molecule (i.e. environment), mass of the atom and strength of the bonds, no two molecule of different structure have exactly the same infrared spectrum. For this reason, the Infrared spectrum can be used for molecules much as a fingerprint can be used for humans (Pavia, Lampman, Kriz, & Vyvyan, 2008; Mubtasim, Kabir, Podder, & Bhadra, 2015).

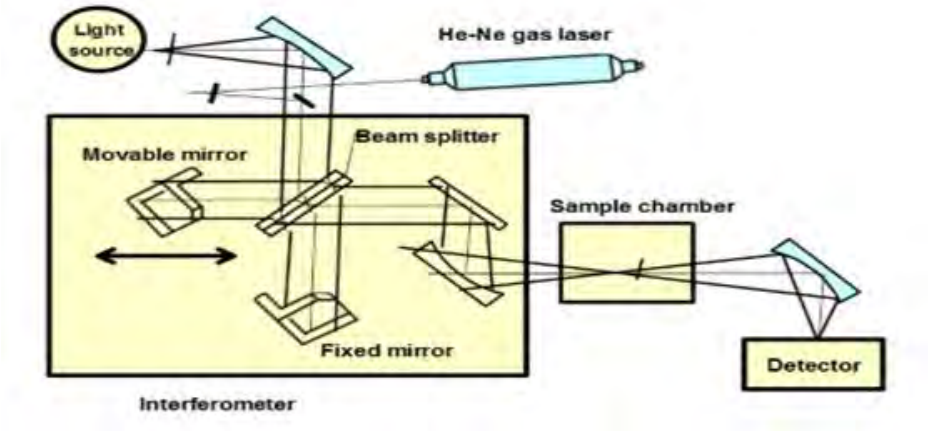

Figure: Schematic diagram of FT-IR spectrometer

Appendix 4

DSC

Differential Scanning Calorimetry, or DSC, is a thermal analysis technique that looks at how a material‟s heat capacity (Cp) is changed by temperature. A sample of known mass is heated or cooled and the changes in its heat capacity are tracked as changes in the heat flow. This allows the detection of transitions such as melts, glass transitions, phase change, and curing. Because of this flexibility, since most materials exhibit some sort of transitions, DSC is used in many industries, including pharmaceuticals, polymers, food, paper, printing, manufacturing, agriculture, semiconductors, and electronics. The biggest advantage of DSC is the ease and speed with which it can be used to see transitions in materials (Satpute & Sayed, 2015).

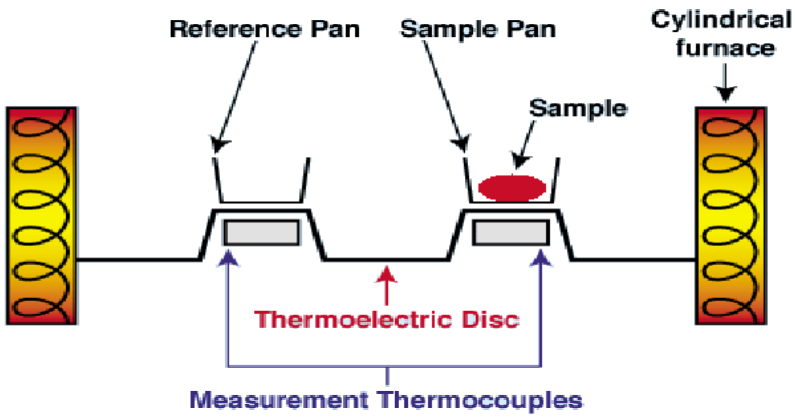

Figure: Schematic diagram of the interior of a DSC

Appendix 5

Dissolution

Dissolution test is required to evaluate the release of drug from a pharmaceutical dosage form as a predictor of the in vivo performance of a drug product. A dissolution test is a simple concept, where a tablet or capsule is placed into a known volume of media and as it dissolves the resulting solution is sampled over time, and assayed (often by HPLC or by spectrophotometry) for the level of active pharmaceutical ingredient (API) present. The choice of apparatus is also a matter of consideration during the method development

which is based on the dosage form performance in the *in vitro* test system (Vaghela, Kayastha, Bhatt, Pathak, & Rathod, 2011).

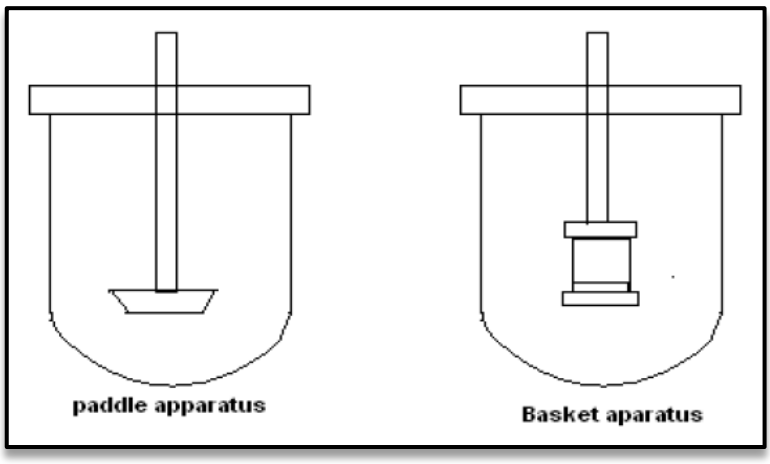

Figure: Dissolution apparatus

Dissolution is evaluated by measuring rate release profile or the amount dissolved over time. So, duration is another important criteria need to be considered during the method development of dissolution. For immediate release dosage forms, the procedure duration is usually 30 to 60 minutes and in most cases, single time point specification is adequate. On the other hand, for extended release dosage forms, at least three test time points are typically chosen to characterize the in vitro drug release profile (Vaghela, Kayastha, Bhatt, Pathak, & Rathod, 2011). At last, for analyzing the dissolution test samples, spectrophotometric (UV) determinations and HPLC are most commonly used. When a method is developed for particular testing of any specific dosage form, that method needs to be validated for the consistency of the results for further conductance of the process.

Appendix 6

Hydrophilic Matrix Systems

Hydrophilic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug release profile and are cost effective. Hydroxypropyl methylcellulose (HPMC), also known as Hypromellose according to USP or Methocel designated by Dow Company, provides the release of a

drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect (Phadtare, Phadtare, Nilesh, & Asawat, 2014). To achieve controlled release through the use of a water-soluble polymer such as Hypromellose, the polymer must quickly hydrate on the outer tablet surface to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core. Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role (Varma, Kaushal, Garg, & Garg, 2004).

Table: Typical properties of selected Methocel K100M CR and Methocel K4M CR grade products

Methocel product grade	Methoxyl (%)	Hydroxypropoxyl (%)	Apparent viscosity, 2% in water at 20°C (cP)
K100M CR	19-24	4-12	80000-120000
K4M CR	19-24	4-12	3000-5600

Source: Siepmann & Peppas, 2001

Factors affecting the kinetics and mechanism of drug release from the matrix tablet:

Drug characteristics: Drug solubility, dose/drug content, molecular weight and size, particle size and shape.

Polymer variables: Polymer type, polymer viscosity grade, polymer proportion, particle properties, polymer combinations.

Formulation aspects: Formulation geometry, processing technique, excipients/additives (Varma, Kaushal, Garg, & Garg, 2004).

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