# FORMULATION AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF DEXKETOPROFEN TROMETAMOL

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**ABSTRACT:**

**Objective:** The intension behind the formulation of theses dosage form is due to and sustained release of drug for effective treatements. The attempt is going to developed gastroretentive floating systems by using suitable polymer. In the present research work we are using the polymer such as HPMC for maintaining the sustained release action and enhancing the floating behaviours. In the study we have formulated nine batches for formulating the concentration of polymer and other excipients with acceptable sustained release action. **Method:** The optimized batch are formulated by using the excipients as drug,gas generating agent as sodium bicarbonate, polymer as HPMC which showing the sustained action, have enhancing the floating behaviours and these batch show the 12 hours sustained release action about 99% release of drug. **Result:** The prepared tablet are evaluated by pre-compressional and post-compressional parameter. From all of formulated batchs the F6 batch show the optimized results in these formulation polymer ratio is 1:1 ratio they resulted as 99% drug release action, having the floating lag time 18 second and floated upto 12 hours. **Conclusion:** From above experimental results the gastro retentive drug delivery system of dexketoprofen trometamol tablet are successfully prepared and shows several advantages.

1. **Keyword:** Dexketoprofen Trometamol, Floating drug delivery system,HPMC.

## I. INTRODUCTION:

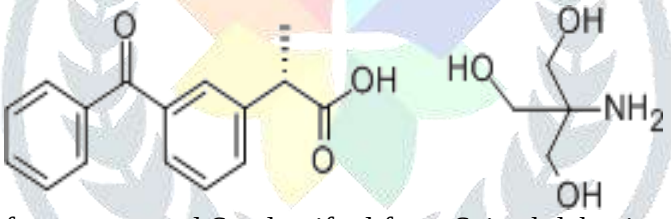
### 2. Floating drug delivery system

Oral formulations however experience problems such as poor pharmacokinetics due to gastro heterogeneity Digestive system, pH, dosage form, diameter, and enzymatic activity gastrointestinal residence time. For human administration due to its various advantages like ease of administration, versatility in design, cost-effectiveness, the efficiency of storage and transportation, and high patient compliance. Systems in conventional medication distribution can not solve gastrointestinal tracts (GIT) issues such as the inadequate release of medication, decreased efficacy of dosage, and demand for frequent dosage.[1] Furthermore, GRDDS can boost the managed by constantly releasing drugs the medication at the target rate for a prolonged duration They are unsteady, alkaline and poorly soluble pH, have an effective GRDDD-Release including super porous hydrogel, bio/mucoadhesive, raft-forming, magnetic, ion-exchange, expandable, low and highdensity formats Different formulate systems are unstable and low-solution and are of lowdensity local activity in the higher part of the intestines for Helicobacter pylori eradication.[2] A few plan methodologies have been utilized to structure effective controlled discharge GRDDS including super porous hydrogel, bio/mucoadhesive, pontoon shaping, attractive, particle trade, expandable, and low-and high-thickness system Various detailing related factors, for example, polymer types (nonionic, cationic, and anionic polymers), polymer organization in dose structure, consistency grade, the atomic load of the polymer, and medication dissolvability can influence the nature of the gastroprotective measurement structure Moreover, the physicochemical idea of excipients assumes a significant job in different GRDDSThe density of excipients and floating agent pieces, for instance, are essential factors in the floating formulation. Also, process factors can affect the nature of the gastro-protective dosing structure, as a result of the super porous hydrogel system, which involves, for example, crospovidone and sodium carboxymethylcellulose, which can form a super porous hydrogel.[3]

## 3. GASTRORETENTIVE DRUG

There has been considerable research over the last decade on the possibility of controlled and site-specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastroretentive drug delivery system. Such gastroretentive drug delivery system possesses the ability of retaining the drug in GIT particularly, in the stomach for long periods. The ideal of gastroretention stems from the need to localize drugs at a specific region of GIT such as stomach in the body. Often, the extent of drug absorption is limited by the residence time of the drug at the absorption site. The transit time in GIT i.e., from the mouth to the anus, varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological conditions of the alimentary canal. In addition, the relatively brief GI transit time (8-12 h) for most of the drugs impedes the formulation of once daily dosage form(Welling P. et al., 2000; Singh B. et al., 2000) Many drugs show poor bioavailability in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium.[4] Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon (Berner B. et al., 2003). Another problem associated with the performance of controlled release systems is that some drugs are absorbed in a particular portion of the GIT only or are absorbed to a diff\erent extent in various segments of the GIT. Such drugs show 'absorption window', which signifies the region of GIT from where absorption occurs primarily[5] An absorption window exists because of physiological, physicochemical or biochemical factors. Drugs having site-specific absorption are difficult to design as oral controlled release drug delivery system because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption(Ahuja A. et al., 1997) After crossing the absorption window, the released drug goes waste with negligible or no absorption.[6] This phenomenon drastically decreases the time available for drug absorption after its release and jeopardize the success of the delivery system. The gastroretentive drug delivery system can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability[7]

Dexketoprofen trometamol is a water-soluble salt of the dextrorotatory enantiomer of the nonsteroidal anti-inflammatory drug (NSAID) ketoprofen. It is use as analgesic and an anti-inflammatory agent, and is one of the most potent in vitro inhibitors of prostaglandin synthesis.




**III. MATERIAL** : Dexketoprofen trometamol,Samle gifted from Scitech lab, sinnar and all other excipients from Dodal chemical ennterprices, Aurangabad Hydroxypropyl methyl cellulose (HPMC K4M), Sodium Alginate, Sodium bicarbonate, Cellulose microcrystalline, Magnesium stearate

## IV. PREFORMULATION STUDY:

Preformulation can be defined as the Pre-development process in which the science of chemistry determines the physic-chemical and mechanical condition of novel drugs, creating durable, safty and effectiveness. Ideally, in the preliminary phase at the start of such an appropriate physical discovery process, chemical information are available to assist in the selection of new substances studied in this study to evaluate the interactions and interactions of various ingredients designed to be used in the final dose form and considered in current research.[8]

Organoleptic character of color such as tree, aroma, taste, and appearance play a major role in sample identification and therefore should be documented in a descriptive statement.

### 1. Melting point:

By using capillary process melting point was calculated a small quantity of API is taken and put in the apparatus and the melting point is calculated and matched with the specifications.[9]

### 2. Determination of λmax of Dexketoprofen trometamol:

Accurately weighted Dexketoprofen trometamol (100mg) was mixed in 100 ml of 0.1N HCL The concentration of solution (1000µg/ml), the aliquots of 1 ml from solution were pipetted out into 10 ml volume flask thus the concentration of (100µg/ml) solution of API was prepared. Again 1 ml of aliquots was dissolve to 10 ml (10µg/ml).

Then the absorbance spectrum was taken on the U.V Spectrophotometer in range 200-400 nm against the blank 0.1N HCl[10]

**3. FTIR Spectroscopy:**

The IR spectrum of Dexketoprofen trometamol was record using the fourier Transform Infra-Red spectrophotometer. The Dexketoprofen trometamol were potassium bromide in 1:5 ratio. The scans were obtained at a resolution from 4000-to 400 cm-1.[11]

**4. Differential scanning calorimetry:**

Differential Scanning Calorimetry (DSC) parameter were conducted with DSC instrument name PerkinElmer 4000, For analysis aluminium pan were used, sample weight was 1 mg. Done under nitrogen purning, flow rate:20ml/min. Heating range:30-300oC. Rate of heating -10oC/min used for analysed the thermal behaviour of Drug

**5. Construction of calibration curve for Dexketoprofen trometamol (0.1N hydrochloric acid) The standard solution of pure drug was prepared in hydrochloric acid (0.1 N)**

The prepared solution was scanned between 400-200 nm by UV- visible spectrophotometer.

(i) Preparation of Hydrochloric acid (0.1 N): Place 0.85 ml of concentrated hydrochloride acid in a 100 ml volumetric flask, add distilled water to make volume upto 100 ml.

(ii) Preparation of standard stock solution: 10 mg of Dexketoprofen trometamol was first dissolved in 10 ml of hydrochloric acid (0.1 N) in 100 ml volumetric flask. The volume of solution was made up by using the hydrochloric acid (0.1 N) to give a solution of concentration 100 µg/mL.

(ii) Working stock solution: The standard stock solution was then appropriately diluted with hydrochloric acid (0.1 N), to obtain a series of dexketoprofen trometamol solution in the concentration range of 5-30 µg/mL. The absorbance of all the solutions was measured against blank at 260 nm using double beam spectrophotometer. A standard plot of absorbance v/s concentration of drug in µg was plotted. This graph was used for the estimation of drug concentration in-vitro drug release studies.

**5.1 Construction of calibration curve for dexketoprofen trometamol (methanol)**

I. Preparation of standard stock solution: 10 mg of Dexketoprofen trometamol was first dissolved in 10 ml methanol in 100 ml volumetric flask. The volume of solution was made up by using the methanol to give a solution of concentration 100 µg/mL.

II. Working stock solution: The standard stock solution was then appropriately diluted with methanol, to obtain a series of dexketoprofen trometamol solution in the concentration range of 5-30 µg/mL. The absorbance of all the solutions was measured against blank at 260 nm using double beam spectrophotometer. A standard plot of absorbance v/s concentration of drug in µg was plotted. This graph was used for the estimation of drug concentration in-vitro drug release studies.[12]

**6. Determination of solubility:**

A solvent under consideration (water, 0.1N HCl and phosphate buffer solution pH 6.8) was saturated with the drug powder and the vials were allowed to stand at room temperature (25°C) for 7 days with frequent shaking. The solution was filtered using Whatmann filter paper. The filtrate was analyzed for drug content using Ultraviolet (UV) spectroscopy.

**7. Drug Excipients Compatibility:**

**7.1. Physical compatibility studies:**

The drug is in mix with one or more excipients in the tablet dosage form; the latter could affect the drug's stability. Awareness of drug excipient reactions, thus very helpful in choosing the correct excipients for the formulator. API was well blended with the excipients according to the formula chosen for the tabletting and held small portion of this mixed powder in cleaned and dry vials at 40oC±2o C/75±5RH and room temperature in the stabilization chamber. For 7 days physical tests is carried out visually.[13]

### 7.2. Fourier transform infra red (FTIR) spectroscopy study:

Infrared spectrophotometry is a valuable analytical tool used to test the chemical reaction between the API and other formulating excipients. The Formulation, combined with dry powdered potassium bromide in the ratio (1:10), was compressed to automated IR press at 10 tone pressure to form clear pellet. The pellet IR spectrum was then recorded by scanning using FTIR spectrometer in the 4000-400 cm-1 wavelength range.[14]

### 7.3. Differential scanning calorimetry (DSC):

Differential scanning calorimetry equipped with an intracooler and refrigerated cooling systems was used to analyse the thermal behaviour API and other excipients in range 30-300°C. Alumina standard was used to calibrate the DSC tempreture. Nitrogen was purged at 20 ml / min through cooling units.

## II. Experimental design:

Optimization design that is factorial design 32 was applied to develop the controlled release formulation of dexketoprofen trometamol for 12 hours. Based on the results obtained with preliminary formulations, 32 randomized full factorial design was applied in the present study. In this design 2 factors will be evaluated, each at 3 levels, and experimental trials will be performed at all 9 possible combinations. The amount of polymer that is HPMC K4M and Sodium alginate, was selected as independent variables. The probable formulations using 32 randomized full factorial design[15]

**Table 1: Factor levels:**

| Coded level | -1 | 0 | +1 |
|---|---|---|---|
| HPMC K4M (X1) | 100 | 120 | 140 |
| Sodium Alginate (X2) | 50 | 70 | 90 |

So the possible combinations of two independent factors having three levels can be given as,

**Table 2: Factor levels and variable**

| Independent Variable | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| X1 | -1 | -1 | -1 | 0 | 0 | 0 | +1 | +1 | +1 |
| X2 | -1 | 0 | +1 | -1 | 0 | +1 | -1 | 0 | +1 |

### 1. Preparation of powder blend:

Powder blend were prepared for the preparation of floating tablet by direct compression method. All the ingredients were weighed accurately and mixed by passing through 60 # sieve. Mixing was again done by spatulation and tumbling in glass morter and pestle

### 2. Formulation of Tablets:

Formulations were prepared by using nine different combinations of two factors as shown in the Table 8.3. Mixing of drug, polymers and other ingredients was done by geometric mixing. Tablets were prepared by direct compression method using rotary press (lab press). Compression force for all the Tablets was adjusted to get Tablets of hardness 3.5- 6 kg/cm$^2$. Weight of Tablets was adjusted to 400mg.[16,17]

**V. Drug powder characterization:[18,19]**

**1. Pre-Compressional evaluation of Dexketoprofen Trometamol Gastro Retentive tablet:**

**1.1 Angle of repose:**

Angle of repose is the maximum angle of a stable slope determined by the joint, joint, and particle formation. The internal angle between the overlay width and the upper surface is known as the angle of repose and is related to the mass, surface area, and stiffness of the uncoated material.

Method: Using the funnel process the Angle of repose is calculated. The funnel height was altered so the funnel nail barely touched the mound of sheets. A well-proportioned joint needed to cross the canal on the surface with ease. The height and diameter of the powder mass was determined, and the resting angle was estimated using the equation below.

$$\Theta = \tan^{-1} ( h / r )$$

Where, h = height of heap, r = radius of the heap, Θ = angle of repose.

**1.2 Bulk density:**

Density is defined as the size of the powder divided by the mass of the pile. The mass of the mass depends largely on the particle shape, when the particle becomes more circular, the mass of the mass increases. In addition as the size of the granule increases the size of the masses decreases.

Method: approximate weight of powder ingredient (API) transferred to a 100 ml cylinder without tapping during transfer. The value determined by the API was estimated. The mass of the mass is measured using a formula

**Bulk Density = Bulk Mass / Bulk Volume**

**1.3 Tapped density:**

Compressed compression is obtained by tapping the measuring stone consists the powder sample. After viewing the first volume, the cylinder is held by the machine and the volume is read until certain volume changes are considered by pressing the machine by raising the cylinder and letting it drop below its weight for some distance. A device that rotates the device during a stroke may be preferred to minimize any weight separation during the stroke.

**1.4 Cylinder dropping distance:**

At average droplets / minute the cylinder pulse length is 14 ± 2 mm. Unless otherwise mentioned, initially pour the cylinder 500 times and measure the volume of Va, the nearest graduated unit. Re-tap an additional 750 times to the closest graduated unit and calculate the target number, Vb. When there is less than 2 per cent difference between the two volumes, Vb is the last allowable volume, Vf. Repeat for the expansion of 1250 taps as needed, less than 2 percent range the gap between successive measurements. Calculate inequality in composition, in gm by ml,

**Tapped Density = m / Vf**

Where, m = initial weight Vf = volume of material after tapping.

**1.5 Measurement of Powder Compressibility:**

The compressability Index and Hausner's estimates are measures of the height of the powder to be suppressed. As such, they are measures of the relative importance of inter-individual communication. In a free flowing powder, such interactions often lack the density and the transition will be close to the value. The scarce material that flows the most, has the mostNinterdisciplinary connections, and the biggest difference between a large and a molded number. This difference is shown in the Pressure Index

Hausner's ratio: = Vo / Vf

Where, Vf = final tapped volume, Vo = initial un tapped volume.

**2. Post-Compressional Evaluation of Dexketoprofen Trometamol Gastro Retentive tablet:[20,21]**

**2.1 Tablet thickness and Diameter:**

The size and width of the tablets were important for tablet size uniformity.Thickness and width were measured using vernier callipers.

**2.2 Hardness :**

This test is used to determine the hardness of the tablet that may pass through the fracture or rupture during storage, transport and handling. Of these six tablets were selected randomly and the hardness of each tablet was measured by a Monsanto hardness examiner. Weight is usually measured in kg / cm2.

**2.3Friability:**

The friability test was performed to assess the hardness and durability at once in the Roche Friabilator. Here twenty (Wo) tablets were placed first and placed in a flushing and changing drum. Afterwards, they are thrown down from a height of 6 inches. After completing 100 cycles i.e., 25 rpm for 4 minutes, the tablets were weighed again (w). Percentage weight loss or friability (F) is calculated by the formula

**F= (1-W/Wo) x 100**

F= friability, Wo= initial weight

**2.4 Weight variation:**

This test is performed to match the weight of each tablet to be within a specified range. This is done by randomly sampling and weighing 20 tablet and the average weight is calculated. No more than one weight loss from the average weight is more than 11 percent and no deviation is more than two percent. The standard deviation and deviation were specified

**2.5 Content Uniformity:**

This test is performed to maintain the weight similarity of the active ingredient in each tablet that should be on the prescribed list according to the Indian Pharmacopoeia. The test was done by taking 20 pills and instructions, weighing and powder. An amount of powdered tablet equal to 40 mg of API is dissolved in 0.1 N HCL in a 100ml volumetric flask. Purified and the absorbance measured at 221 nm using 0.1 N HCL

**2.5 In vitro buoyancy Study:**

The floating features of GFDDS are important, as they have an impact on the in vivo behavior of the drug delivery system. However, there seemed to be no reduction in the float system to keep floating under the body because of the later compression.

**2.6 Floating Lag Time:**

The time taken by the tablet to leave the surface of the fluid after moving to the melting point at 0.1N HCL, temperature 37 ± 0.5˚C, paddle rotating at 50 rpm.

**2.7 Water uptake studies:**

The swelling behavior of a mass unit can be calculated by observing either its stability, weight gain or water absorption. The fluid formulation study was performed using a USP purification equipment in 900ml of distilled water stored at 37o + 0.5oc, rotated at 50 rpm. At certain times the tablet is withdrawn and weighted. Percentage saturation of tablet removed; compressed as percent water

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

**2.8 In vitro dissolution studies:**

Reports of the dissolution were carried out using dissolution devices from USP II. The accelerator speed was 50 rpm. N Hydrochloric acid (900ml) is used as a precipitate. This is placed at roughly 37 ± 1 C. 5ml of fresh medium precipitate samples is available at fixed times, diluted and supplemented with 5ml. Where appropriate, the samples obtained were thoroughly mixed with the removal fluid and analyzed using a wide sensor UV spectrum at 221 nm. Every analysis on dissolution was performed with defined values in triplicate.

**2.9 Kinetic model fitting:[22,23]**

There are several nonlinear kinetic models to explain the release mechanisms (Higuchi, the Peppas model) and the discharge order (Zero and First order).

**2.9.1 Zero order kinetics:**

The elimination of drugs from the dosage forms of the drug that do not correspond to the slow release of the drug can be represented by the following equation

$$W0 - Wt = K0t$$

Where W0 =initial dose, Wt =drug dose at that time t and k =always the same.

Partitioning this method into W0 also makes it easier ft = k0t When ft = 1 - (Wt / W0) and ft represent the drug fraction dissolved at time t and k0 the rate of transparent dissolution or zero order is always given in this way, the image showing that the soluble fraction is a drug is time-sensitive.

**2.9.2 First order kinetics:**

This kind of model for analyzing a drug ablation study. The relation that illustrates this model

$$Log\ Qt = Log\ Q0 + K1t / 2.303$$

Where Qt =amount of drug released in time, Q0 =first dose of the drug in the solution K1 =first dose of the regular drug release.

In this way the tensile relationship between the percentages of logs remaining drug and time so that the first order is always off the slope. The doses of drugs that follow this dissolution profile, such as some that contain water-soluble

drugs in porous matrices release the drug in proportion to the amount of the drug that resides in them, as a result of which the amount of drug released per unit of time decreases.

**2.9.3 Korsmeyer Peppas Model:**

Korsmeyer et al., (1983) developed a simple semi-empirical model, related to drug release in the past (t) **Qt / Qα = Kktn**

Where Kk is a constant factor combining the composition and geometry of the drug dosage form and n is the main output, indicating the process of drug release..

**2.9.4 Higuchi Model:**

$$Qt = KHt1 / 2$$

Where Qt = number of drugs release time t and KH = Higuchi output ratio;

The causal relationship between the square root of the opposition and time is concerned with the fact that drug release follows strong Fickian resistance. For the purpose of data treatment, the above equation is usually reduced to:

$$Q = Kt1 / 2$$

Therefore the graph of the drug dose derived from the square root of time will be continuous if various constraints are added to the drug release from the matrix. Alternatively, the rate of drug release is equal to that of square time origin. A major advantage of the equations above is its simplicity.

**2.10 Stability protocol:**

The final conditions used for the stability parameter were the instantaneous conditions (40 ° C ± 2 ° C / 75% ± 5% RH) .Exercise studies were performed to construct the optimum. Tablets for optimization were assembled and then stored in a stabilizer chamber for 3 months at specified temperature.[24,25,26]

## VI. RESULTS AND DISCUSSIONS

### 1 PRE-FORMULATION STUDIES

**1.1 Organoleptic properties**

**Table 3: Organic Properties of Drug**

| Identification test | Results of sample obtained | Reported standards |
|---|---|---|
| Appearance | Fine powder | Fine powder |
| Colour | White | White |
| Odour | Odourless | Odourless |
| Taste | Tasteless | Tasteless |
| Melting point | $108^0C$ | $103 – 107^0C$ |

Organic Properties of API like Color And odour are studied. The drug Complies with Specification hence it take for further study.

### 1.2 Melting point of drug

The Melting Point calculated by capillary process, melting point found to be 103-107 ° C. Melting point follows USP guidelines and it has concluded that the drug is pure and the same.

### 1.3 Determination of λmax of Dexketoprofen trometamol:

UV Spectrophotometer use for Determination of λmax of Dexketoprofen trometamol. UV Analysis is done by using Shimadzu (1800) double beam UV Spectrophotometer. It shows absorbance maxima (λmax) at 260nm in 0.1 N HCL. UV spectrum shows peak at 221 nm which complies with the USP standard value. Thus drug take for further study such as Dissolution study

### 1.4 FTIR Spectroscopy:

FTIR Spectroscopy done by using Shimadzu (8400S) by Potassium bromide (KBr) pellet method shows peaks as in table, that gives conformity of structure of drug.

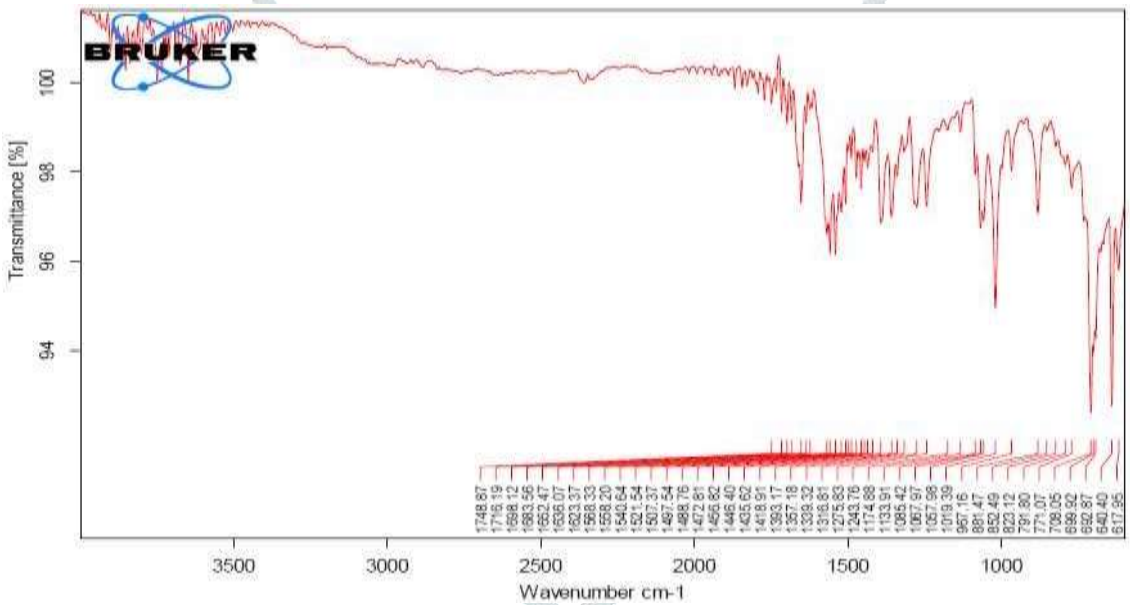



**Figure 1: IR spectra of Dexketoprofen trometamol**

**Table 4: Comparison of functional group observed in IR spectra of Dexketoprofen trometamol.**

| Sr. No. | Functional group | Standard IR Range ($cm^{-1}$) | Assessment of peak ($cm^{-1}$) |
|---|---|---|---|
| 1 | C=C stretch of aromatic | 1600-1450 | 1580 |
| 2 | C-N stretch | 1500-1400 | 1425 |
| 3 | C-O stretch of secondary alcohol | 1350-1100 | 1275 |

| | | | |
|---|---|---|---|
| 4 | C=O stretch of ketone | 1725-1705 | 1716 |
| 5 | C=O stretch of carboxylic acid | 1725-1700 | 1716 |
| 6 | O-H stretch of alcohol | 3550-3200 | 3550 |

The FTIR spectral analysis showed that there is change in percent transmittance which may be due to change in crystallinity and there is no disappearance of any characteristics peaks of pure drug Dexketoprofen trometamol we concluded that functional group are represents in this IR that the given drug are pure and identical.

### 1.5 Differential scanning calorimetry

The DSC thermogram of the drug depicts a sharp endothermic peak at 108.43°C corresponding to the melting transition temperature and decomposition of Dexketoprofen trometamol. Such sharp endothermic peak signifies that Dexketoprofen trometamol used was in pure state. The DSC thermogram of Dexketoprofen trometamol which confirms melting point to reported value and from these concluded that the gives API is the Identical and pure

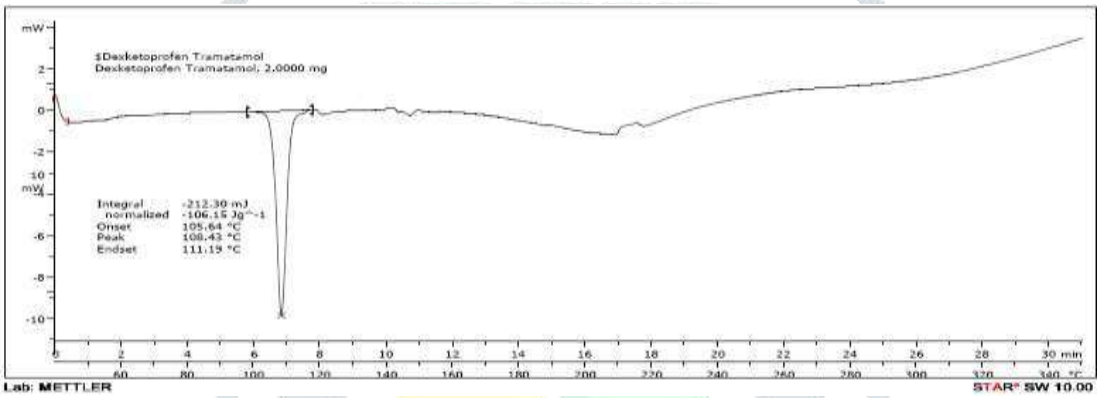



**Figure 2: Differential scanning calorimetry**

### 1.6 Ultraviolet (UV) spectroscopy:

Ultra-Violet (UV) absorption spectroscopy is mostly used for quantitative analysis but this may be used to characterize the drug. The drug sample showed good absorptivity in UV range of the radiation. Wavelengths of maximum absorbance (λmax) were found to be matching with the reported values as shown in Figure

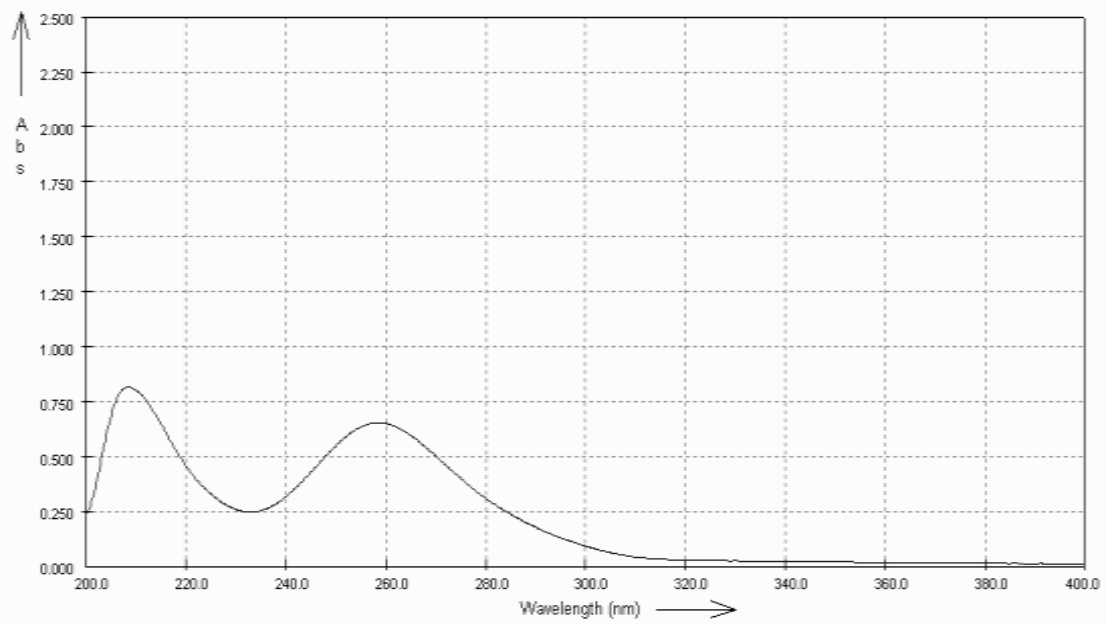



**Figure 3: UV Spectra of Dexketoprofen trometamol in 0.1 N HCL**

The calibration curve of Dexketoprofen trometamol was prepared in HCL (0.1 N) solution. Dexketoprofen trometamol showed maximum absorption at wavelength 258.3 nm.

**Table 5: Data for Calibration Curve of Dexketoprofen trometamol in 0.1N HCl**

| Sr. No. | Conc. (µg/ml) | Absorbance at 258.3 nm |
|---|---|---|
| 1. | 5 | 0.194 |
| 2. | 10 | 0.325 |
| 3. | 15 | 0.459 |
| 4. | 20 | 0.622 |
| 5. | 25 | 0.767 |

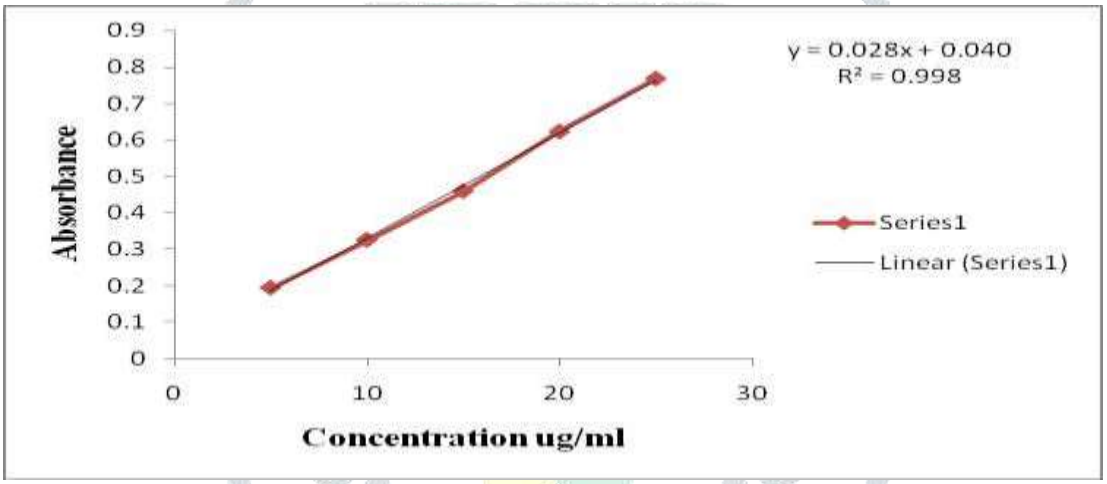



**Figure 4: Standard curve of Dexketoprofen trometamolo in 0.1N HCl λ max = 258.3 nm**

**UV Spectra of Dexketoprofen trometamol in Methanol.**

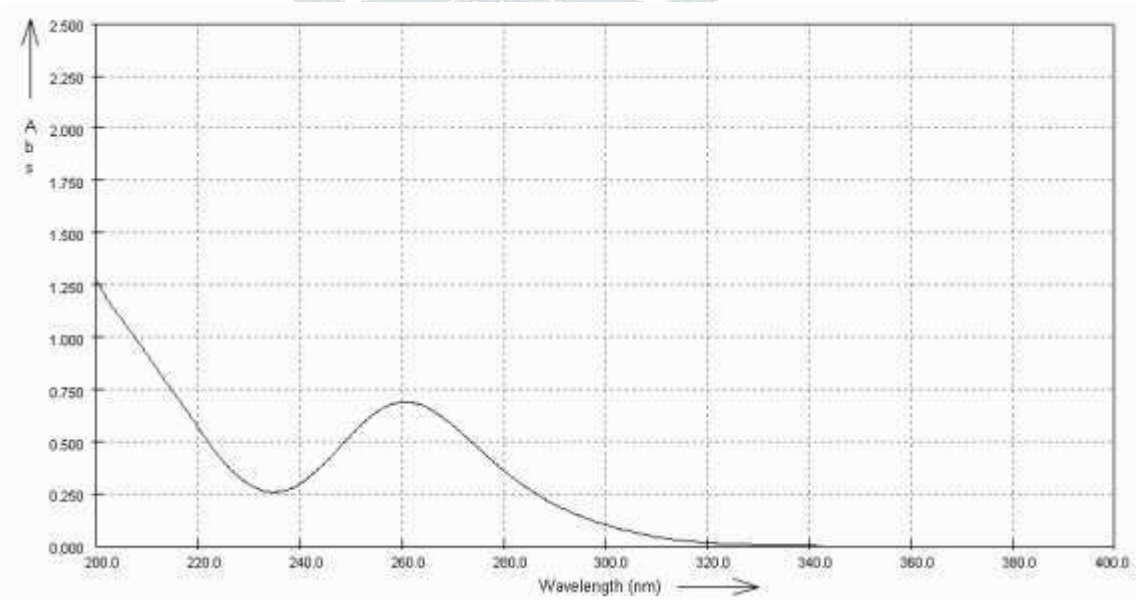



**Figure 5: UV Spectra of Dexketoprofen trometamol in Methanol**

The calibration curve of Dexketoprofen trometamol was prepared in methanol solution. Dexketoprofen trometamol showed maximum absorption at wavelength 260 nm.

**Table 6: Data for Calibration Curve of Dexketoprofen trometamol in Methanol**:

| Sr. No. | Conc. (µg/ml) | Absorbance at 260 nm |
|---|---|---|
| 1. | 5 | 0.074 |
| 2. | 10 | 0.250 |
| 3. | 15 | 0.426 |
| 4. | 20 | 0.611 |
| 5. | 25 | 0.801 |

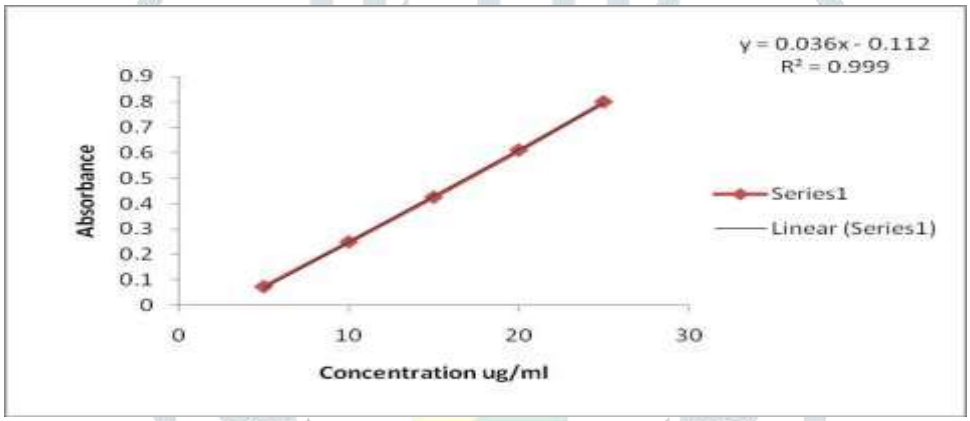



**Figure 6: Standard Curve of Dexketoprofen trometamol in Methanol- λ max = 260 nm**

## 2. Drug Excipients Compatibility:

### 2.1 FTIR of Drug And Excipients:

- **IR spectra of Dexketoprofen trometamol + HPMC K4M**

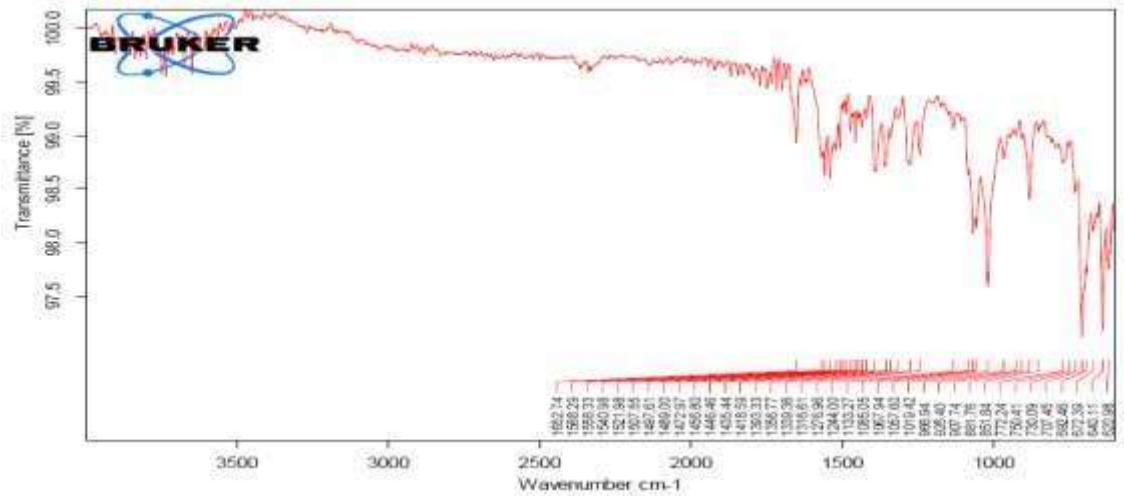



**Figure 7: IR spectra of Dexketoprofen trometamol + HPMC K4M**

**Table 7: Interpretation of IR spectra of Dexketoprofen trometamol + HPMC K4M**

| Sr. No. | Functional group | Standard IR Range ($cm^{-1}$) | Assessment of peak ($cm^{-1}$) |
|---|---|---|---|
| 1 | O-H stretch alcohol | 3100-3600 | 3590 |
| 2 | C-O stretch ether | 1150-1070 | 1133 |
| 3 | C=C stretch aromatic | 1600-1450 | 1507 |
| 4 | C-O stretch secondary alcohol | 1350-1100 | 1244 |

❖ **IR spectra of Dexketoprofen trometamol + Sodium Alginate**

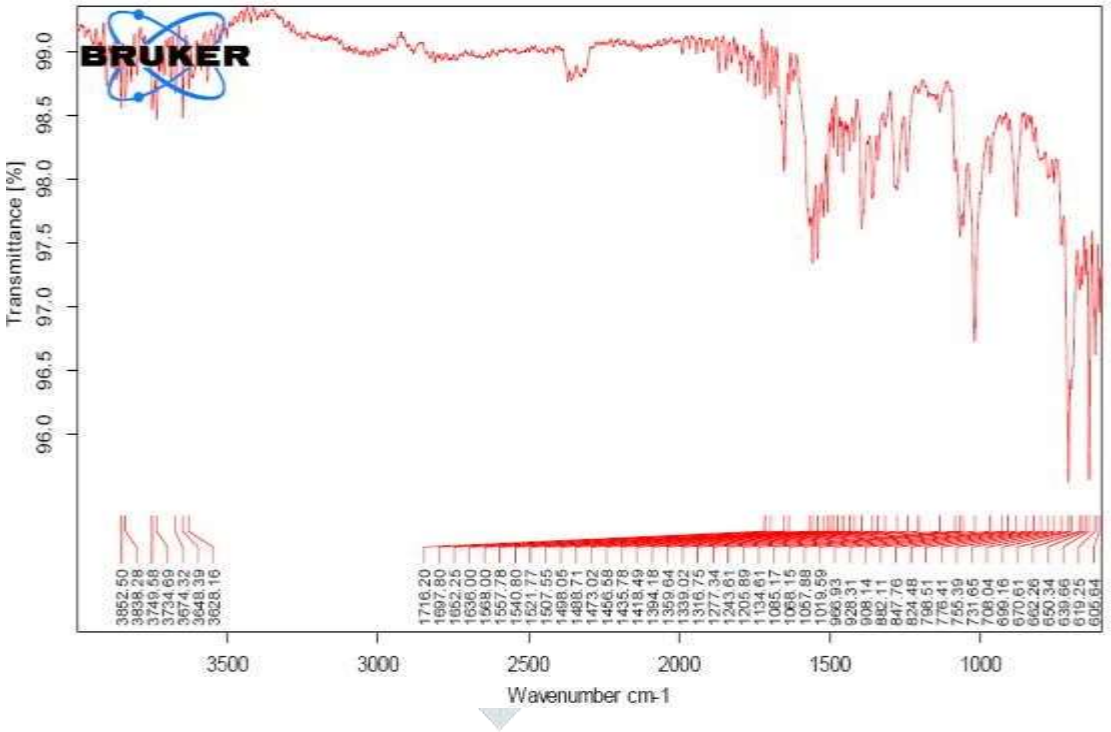



**Figure 8: IR spectra of Dexketoprofen trometamol + Sodium Alginate**

**Table 8: Interpretation of IR spectra of Dexketoprofen trometamol +Sodium Alginate**

| Sr. No. | Functional group | Standard IR Range ($cm^{-1}$) | Assessment of peak ($cm^{-1}$) |
|---|---|---|---|
| 1 | C=O stretch carboxylic acid | 1725-1700 | 1716 |
| 2 | O-H stretch alcohol | 3100-3600 | 3628 |
| 3 | C-O stretch ether | 1150-1070 | 1134 |
| 4 | C=C stretch aromatic | 1600-1450 | 1489 |
| 5 | C-O stretch secondary alcohol | 1350-1100 | 1316 |

❖ **IR spectra of Dexketoprofen trometamol + Microcrystalline cellolose:**

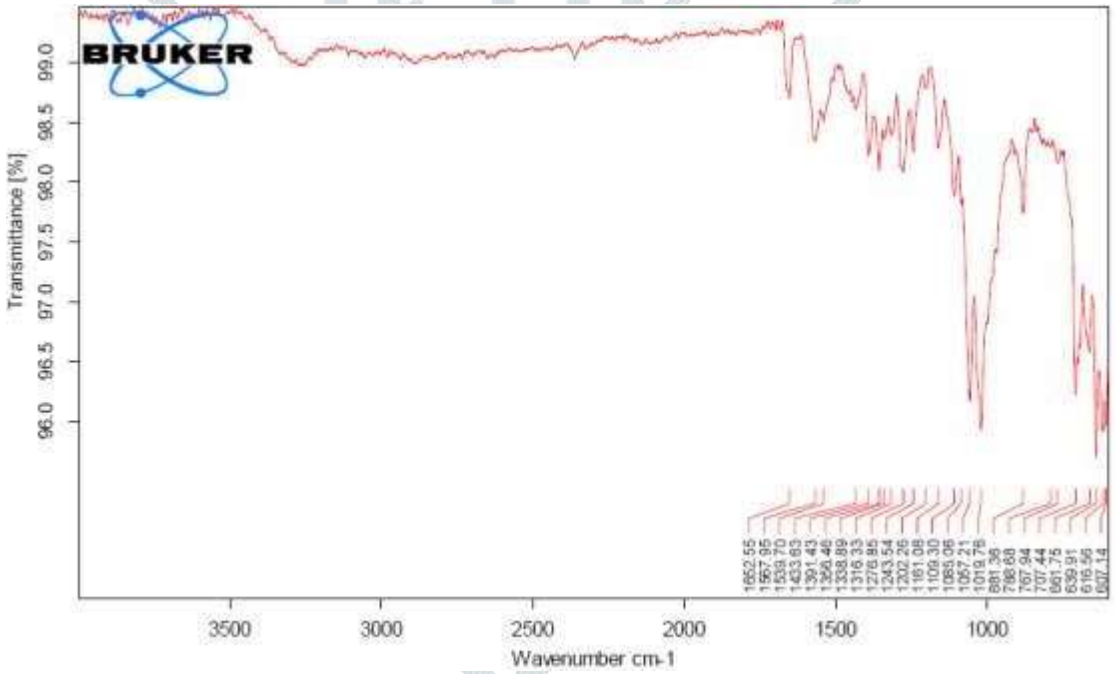



**Figure 9: IR spectra of Dexketoprofen trometamol + Microcrystalline cellolose**

**Table 9: Interpretation of IR spectra of Dexketoprofen trometamol + Mcc**

| Sr. No. | Functional group | Standard IR Range ($cm^{-1}$) | Assessment of peak ($cm^{-1}$) |
|---|---|---|---|
| 1 | C=C stretch aromatic | 1600-1450 | 1433 |
| 2 | C-O stretch ether | 1150-1070 | 1085 |
| 3 | C-O stretch secondary alcohol | 1350-1100 | 1278 |

❖ **IR spectra of Physical Mixture:**

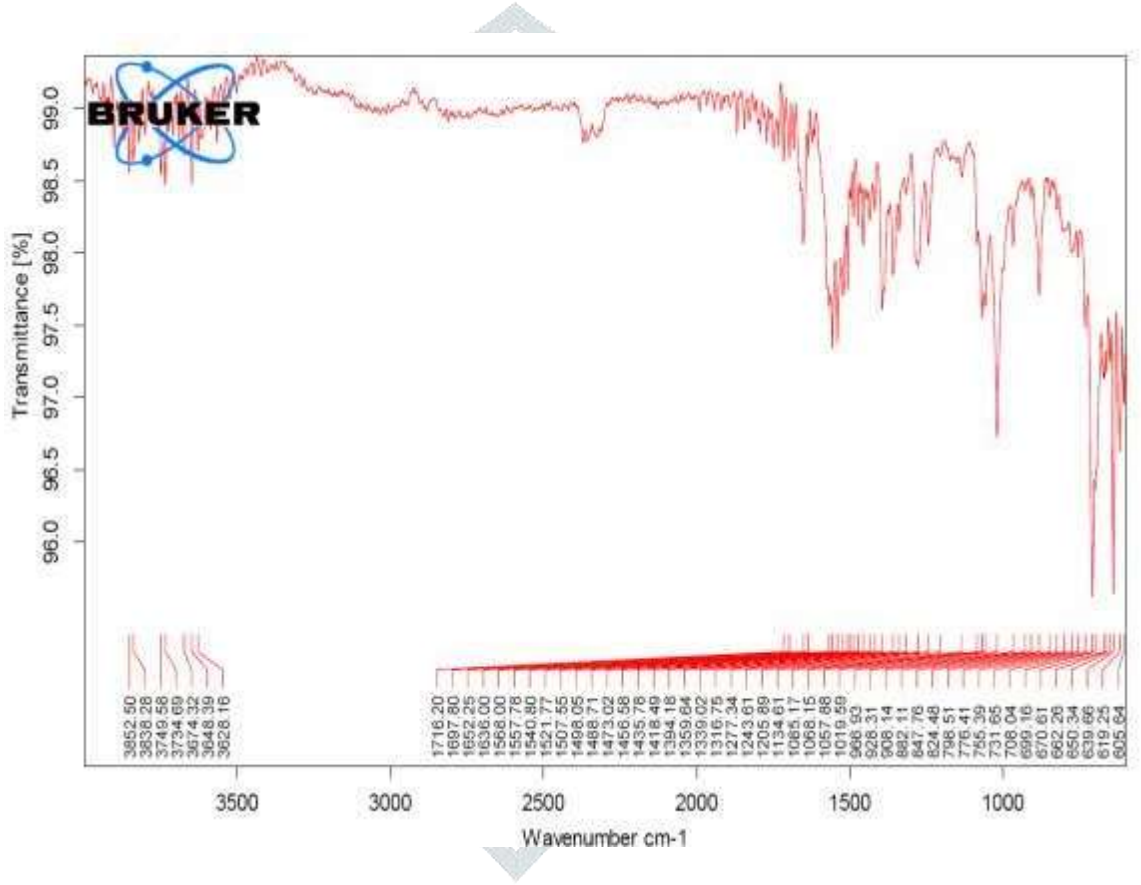



**Figure 10: IR spectra of Physical Mixture**

**Table 10: Interpretation of IR spectra of Physical Mixture:**

| Sr. No. | Functional group | Standard IR Range ($cm^{-1}$) | Assessment of peak ($cm^{-1}$) |
|---|---|---|---|
| 1 | C=O stretch carboxylic acid | 1725-1700 | 1716 |
| 2 | O-H stretch alcohol | 3100-3600 | 3628 |
| 3 | C-O stretch ether | 1150-1070 | 1134 |
| 4 | C=C stretch aromatic | 1600-1450 | 1489 |
| 5 | C-O stretch secondary alcohol | 1350-1100 | 1316 |

The FTIR spectral analysis showed that there is change in percent transmittance which may be due to change in crystallinity and there is no disappearance of any characteristics peaks of pure drug Dexketoprofen trometamol and in the physical mixture of drug to polymer. This confirms the absence of chemical interaction between drug and polymers.

**2.2 Differential scanning calorimetry (DSC) of Drug and Mixture:**

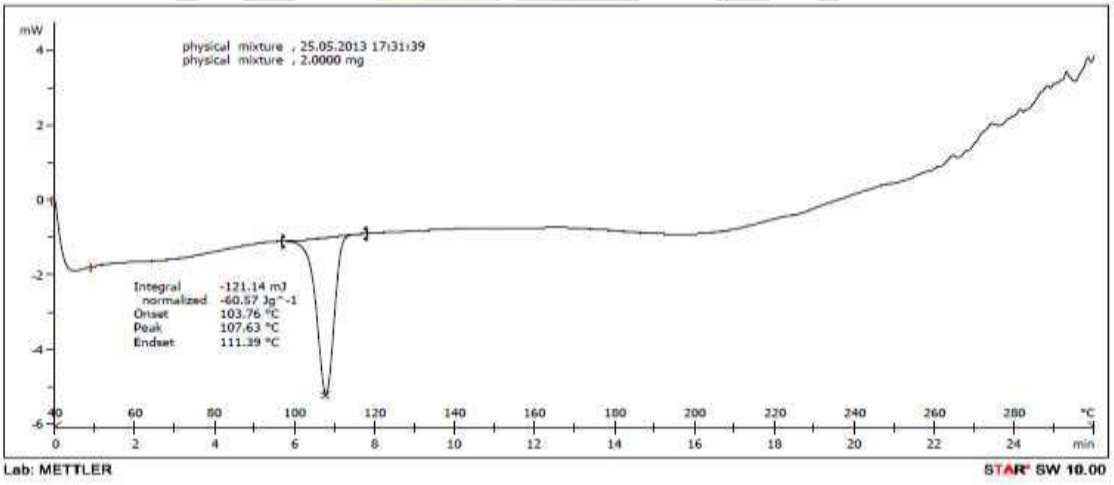



**Figure 11: DSC thermogram of Physical mixture**

The above DSC in figure 9.10 showed the thermogram of the drug depicts a sharp endothermic peak at 108.43 °C and the above DSC in figure 9.11 showed the thermogram of the physical mixture depicts a sharp endothermic peak at 107.63°C. The thermogram showed individually for drug dexketoprofen trometamol nearly unchanged as compared to thermogram of physical mixture. Hence, it can be concluded that there was no interaction between drug and physical mixture.

## VI. Drug powder characterization:

### 1. Pre-Compressional evaluation of Dexketoprofen Trometamol Gastro Retentive tablet:

**Table 11: Evaluation parameter of powder blend:**

| Formulation Code | Angle of Repose ($^0$) ± SD* | LBD ($gm/cm^2$) ± SD* | TBD ($gm/cm^2$) ± SD* | Compressibility index (%) ± SD* | Hausner's ratio ± SD* |
|---|---|---|---|---|---|
| **F1** | 34.04±0.51 | 0.400±0.005 | 0.500±0.012 | 20.00±0.53 | 1.25±0.07 |
| **F2** | 32.66±0.46 | 0.416±0.003 | 0.526±0.005 | 20.91±0.29 | 1.28±0.02 |
| **F3** | 33.34±0.32 | 0.434±0.001 | 0.555±0.009 | 21.80±1.14 | 1.30±0.09 |
| **F4** | 34.77±0.21 | 0.446±0.008 | 0.520±0.002 | 20.10±0.98 | 1.25±0.03 |
| **F5** | 32.00±0.89 | 0.434±0.004 | 0.550±0.001 | 21.09±0.23 | 1.29±0.05 |
| **F6** | 31.37±0.65 | 0.466±0.007 | 0.552±0.007 | 21.01±0.47 | 1.26±0.09 |
| **F7** | 34.12±0.55 | 0.430±0.002 | 0.550±0.003 | 21.81±0.64 | 1.27±0.08 |
| **F8** | 33.68±0.71 | 0.454±0.006 | 0.569±0.001 | 20.21±0.34 | 1.25±0.01 |
| **F9** | 32.66±0.33 | 0.426±0.003 | 0.554±0.008 | 23.18±0.69 | 1.30±0.007 |

The powder mixtures for all nine formulations were evaluated for bulk density which ranged from 0.400 to 0.466 (g/ml), tapped density ranged from 0.500 to 0.569 (g/ml), Carr's index ranged from 20.00% to 23.18%, angle of repose ranged from 31.37º to 34.77° and the Hausner's ratio was found in the range of 1.25 – 1.30. All these results indicated that, the powder blend showed good flow properties into the die cavity and compressibility properties and complies with the acceptable limits.

**1. Floating properties:**

The tablet were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was taken floating lag time. The floating lag time found to be 10 to 20. All these results were tabulated in Table 9.14**.**

**A. Immediately after adding the tablet**


**B. After 18 sec**

**Figure 12: Floating tablet buoyancy time study**

**Table 12: Result of Floating Property of Dexketoprofen trometamol tablet:**

| Formulation code | Floating lag time (sec.) | Total floating duration ( hr.) |
|---|---|---|
| **F1** | 20 | 12 |
| **F2** | 19 | 12 |
| **F3** | 18 | 12 |
| **F4** | 10 | 12 |
| **F5** | 12 | 12 |
| **F6** | 18 | 12 |
| **F7** | 19 | 12 |
| **F8** | 15 | 12 |
| **F9** | 20 | 12 |

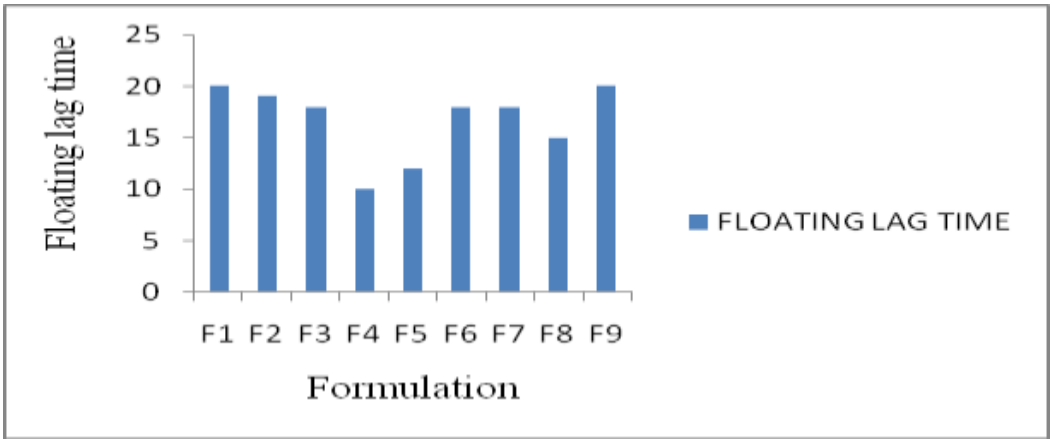



**Figure 13: Floating Lag Time of tablet formulation**

**2. Swelling index of tablet formulations:**

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was 0.1 N HCL, 900 ml rotated at 50 rpm. The

medium was maintained at 37±0.5 $^0$C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed.

**Table 13: Swelling index of tablet:**

| Formulation code | Percent hydration or swelling index In hours | | |
|---|---|---|---|
| | **4** | **8** | **12** |
| **F1** | 13 | 28 | 42 |
| **F2** | 22 | 39 | 51 |
| **F3** | 42 | 60 | 75 |
| **F4** | 54 | 70 | 82 |
| **F5** | 27 | 43 | 55 |
| **F6** | 61 | 78 | 86 |
| **F7** | 55 | 74 | 88 |
| **F8** | 39 | 55 | 66 |
| **F9** | 61 | 78 | 90 |

From above table it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates

and swell and gel barrier are formed at the outer surface. As the gelatinous layer dissolves or dispersed, the hydration swelling process is continuous toward new exposed surfaces, thus maintaining the integrity of dosage Form.

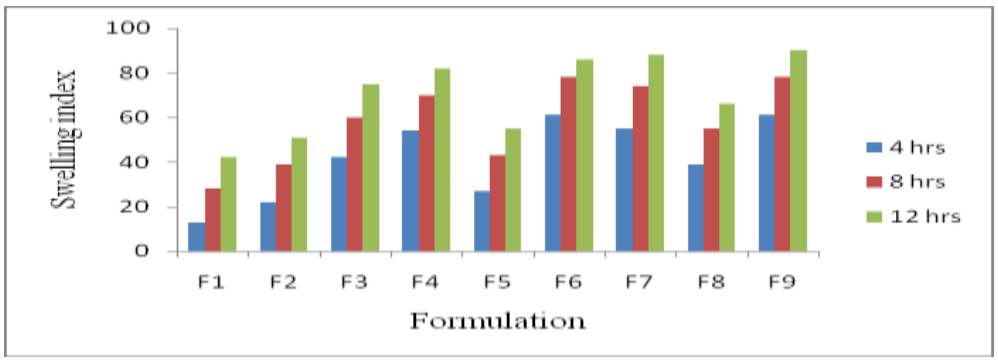



**Figure 14: Swelling index of tablet.**

### 3. *In vitro* drug release study

**Table 14: *In vitro* drug release from tablets:**

| Formulation Code | Percent drug release at time (hr) (n = 3) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **4** | **6** | **8** | **10** | **12** |
| **F1** | 39.12±0.431 | 40.79±0.685 | 47.85±0.265 | 59.51±0.357 | 69.06±0.296 | 81.12±0.540 | 88.60±0.174 |
| **F2** | 35.80±0.941 | 38.71±0.785 | 54.09±0.456 | 62.82±0.594 | 72.80±0.174 | 85.22±0.327 | 92.34±0.751 |
| **F3** | 32.05±0.456 | 36.21±0.125 | 49.52±0.248 | 63.85±0.875 | 70.72±0.562 | 85.20±0.296 | 91.93±0.892 |
| **F4** | 38.29±0.213 | 42.03±0.985 | 50.76±0.854 | 58.34±0.459 | 68.64±0.493 | 80.29±0.658 | 90.68±0.321 |
| **F5** | 35.38±0.387 | 37.46±0.654 | 46.67±0.485 | 61.64±0.215 | 71.55±0.296 | 82.37±0.174 | 95.67±0.359 |
| **F6** | 37.46±0.587 | 41.26±0.265 | 50.76±0.321 | 64.90±0.369 | 73.63±0.358 | 84.86±0.546 | 99.00±0.296 |
| **F7** | 35.38±0.659 | 38.71±0.754 | 47.85±0.548 | 56.17±0.985 | 68.23±0.174 | 80.29±0.985 | 93.59±0.671 |
| **F8** | 32.05±0.615 | 37.46±0.258 | 55.34±0.357 | 66.15±0.785 | 73.63±0.756 | 84.86±0.296 | 94.42±0.789 |
| **F9** | 36.63±0.214 | 39.54±0.159 | 49.01±0.659 | 64.49±0.564 | 76.96±0.174 | 85.69±0.785 | 97.33±0.786 |

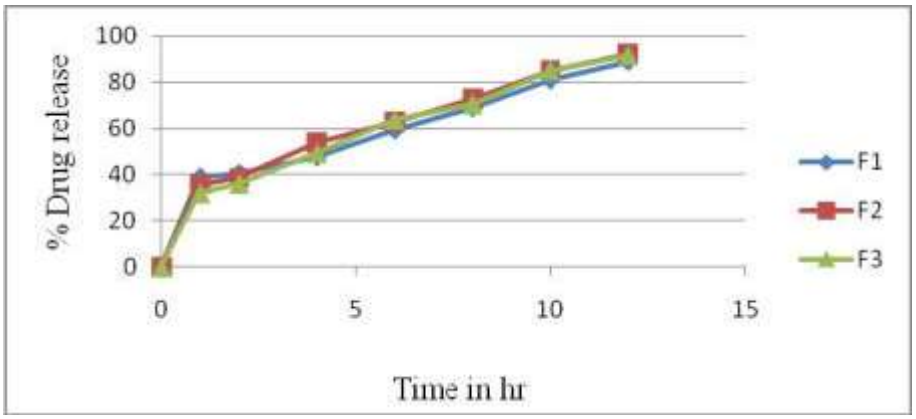



**Figure 15: Percent drug release from formulation F1, F2, F3**

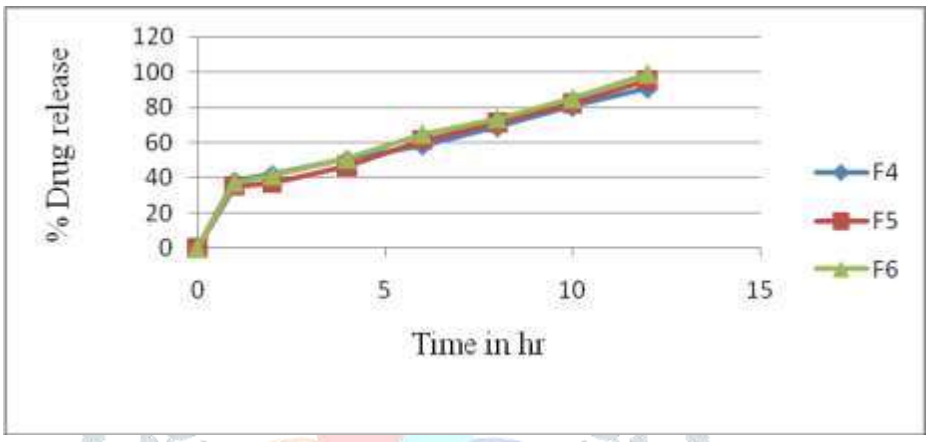



**Figure 16: Percent drug release from formulation F4, F5, F6**

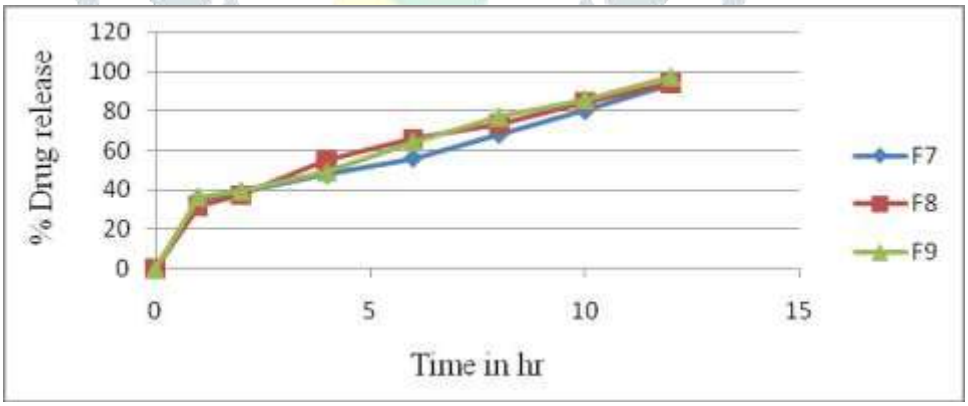



**Figure 17: Percent drug release from formulation F7, F8, F9**

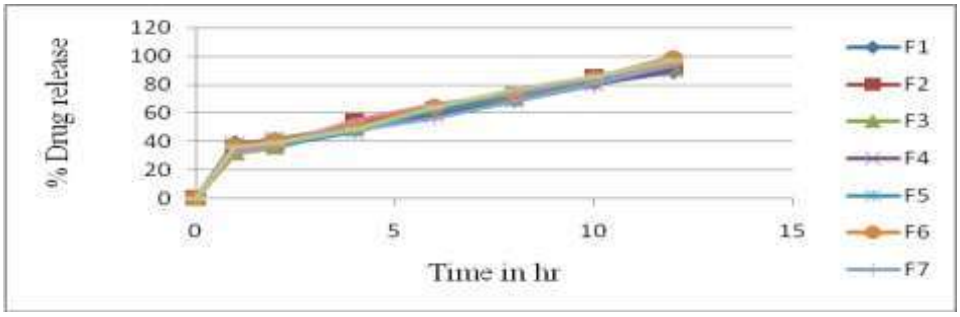



**Figure 18: Comparative *In Vitro* release profile of F1 – F9 Formulation**

**Table 15: Drug release kinetics of tablet formulations:**

| Formulation code | $R^2$ Value | | | |
|---|---|---|---|---|
| | Zero order | First order | Higuchi | Korsmey-Peppas |
| **F1** | **0.983** | 0.992 | 0.907 | 0.856 |
| **F2** | **0.994** | 0.971 | 0.975 | 0.957 |
| **F3** | **0.993** | 0.961 | 0.983 | 0.967 |
| **F4** | **0.993** | 0.992 | 0.955 | 0.926 |
| **F5** | **0.994** | 0.986 | 0.958 | 0.925 |
| **F6** | **0.996** | 0.987 | 0.963 | 0.936 |
| **F7** | **0.992** | 0.981 | 0.945 | 0.919 |
| **F8** | **0.986** | 0.936 | 0.991 | 0.986 |
| **F9** | **0.993** | 0.978 | 0.964 | 0.932 |

The dissolution kinetics of all batch was applied to various dissolution models such as Zero order, First order, Higuchi and Korsemayer-peppas. The cumulative drug relese values of all batch gives the highest $R^2$ value and least slope value in Zero order. Thus, Zero order fits best for the dissolution data of the all batches as it showed the highest value for $R^2$.

From the above dissolution data it was concluded that the formulation F6 gave the better drug release 99.00%, than other eight formulations. So, formulation F6 was found to be optimize formulation.

**4. Graphs of kinetic model of formulation F6**

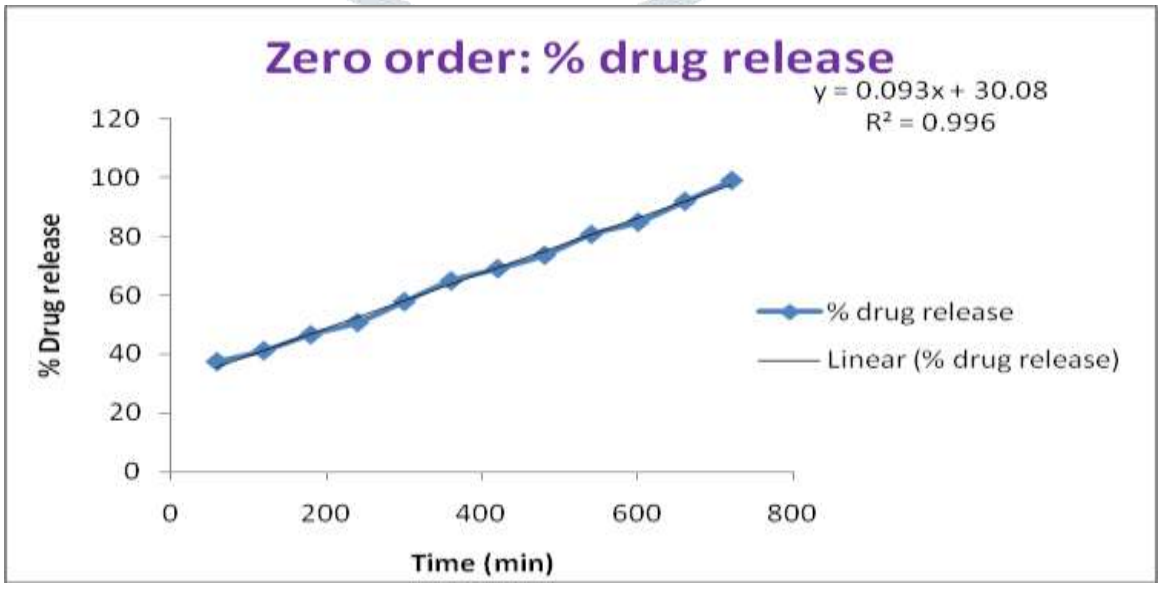



**Figure 19: Zero order kinetics of formulation F6**

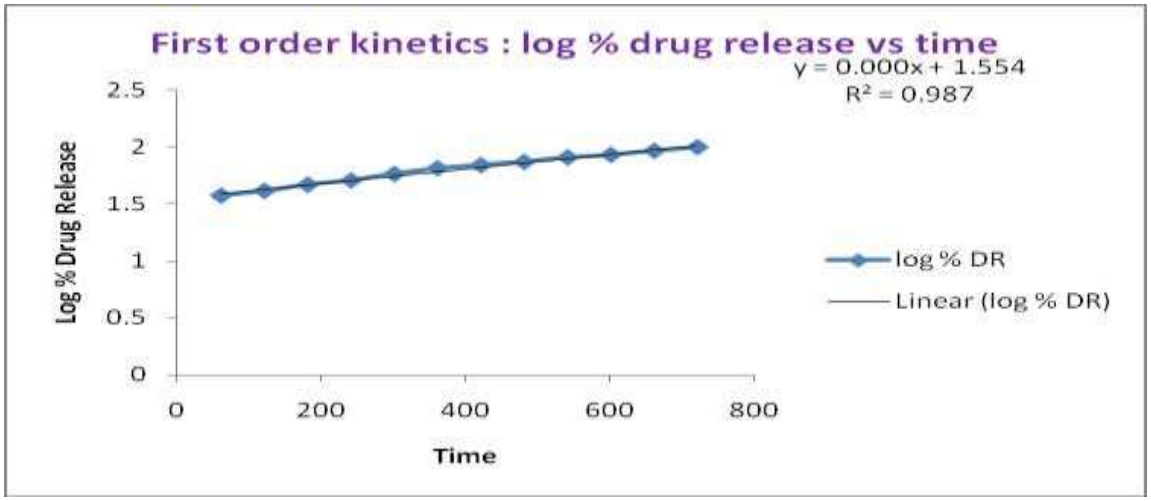



**Figure 20: First order kinetic of formulation F6**

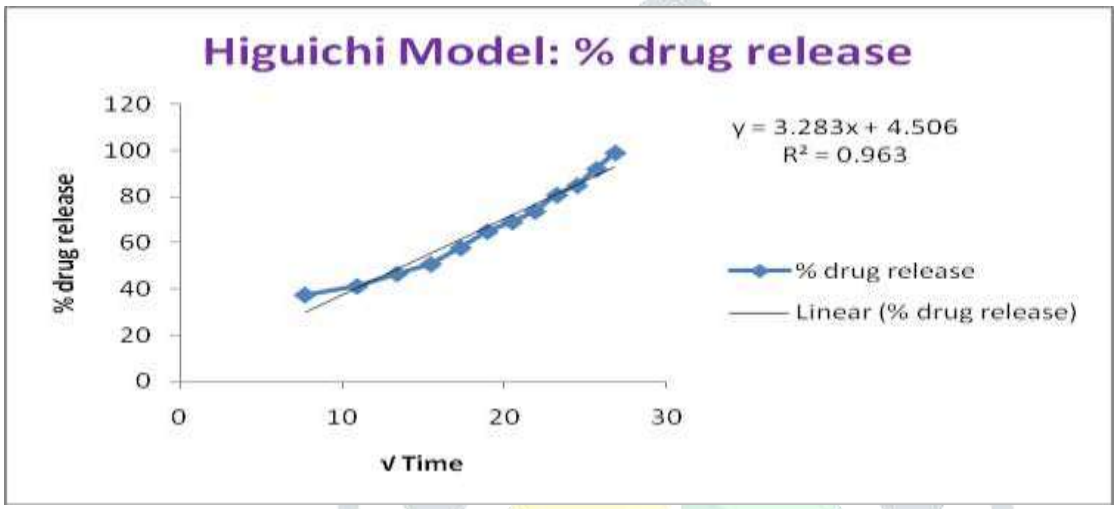



**Figure 21: Higuichi Model kinetic of formulation F6**

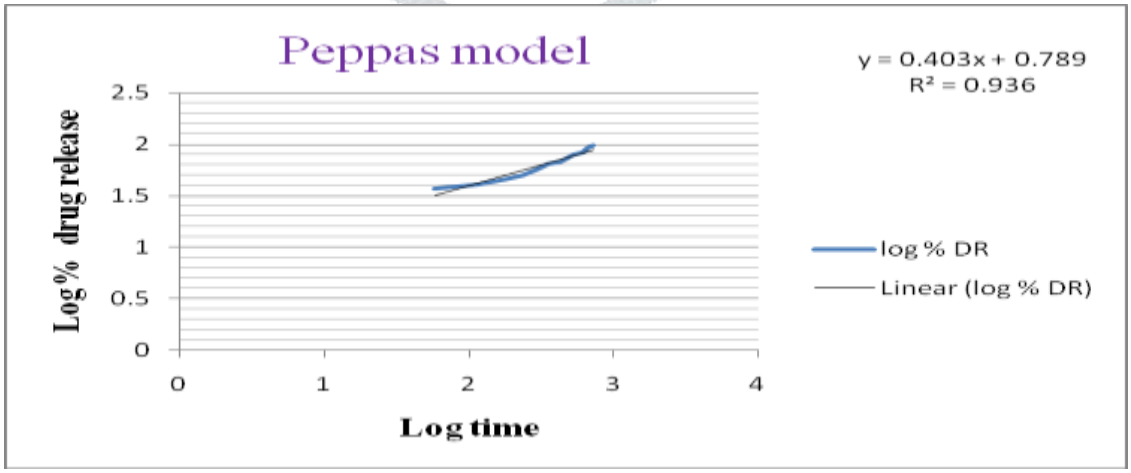



**Figure 22: Peppas Model kinetic of formulation F6**

## VII. STABILITY STUDY:

The optimized Formulation F6 was subjected to stability studied at 40ºC under humidity conditions (75%) for a period of 3 months. Samples were analyzed for colour changes appearance, drug content and release characteristics.

**Table 16: Evaluation of formulation (F6) kept for stability at $40^0$C /75%RH:**

| Parameter | 0 week (n = 3) | 1 month (n = 3) | 2 month (n = 3) | 3 month (n = 3) |
|---|---|---|---|---|
| **Appearance** | White | White | White | White |
| **Hardness (Kg/cm$^2$)** | 4.29±0.03 | 4.23±0.028 | 4.18±0.021 | 4.11±0.02 |
| **Lag time (sec)** | 18 | 18 | 18 | 20 |
| **Duration of Floating** | 12 | 12 | 12 | 12 |
| **Drug content (%)** | 99.9±0.57 | 99.8±0.89 | 99.6±0.98 | 99.2±0.95 |

From the result it was observed that there was no significant change in physiochemical properties as well as in drug release profile even after storage at 40ºC for four week. It may be inferred that there was no degradation and change in the matrix system.

**Table 17: In-vitro drug release study of formulation (F6) kept for stability at $40^0$C /75%RH:**

| Time (Hrs) | Cumulative % drug released (n = 3) | | | |
|---|---|---|---|---|
| | 0 month | 1 month | 2 month | 3 month |
| 1 | 37.46±0.256 | 37.00±0.426 | 36.89±0.658 | 36.45±0.562 |
| 2 | 41.20±0.354 | 40.85±0.584 | 40.23±0.231 | 40.10±0.645 |
| 4 | 50.76±0.483 | 50.11±0.784 | 49.95±0.845 | 49.35±0.854 |
| 6 | 64.90±0.862 | 64.22±0.852 | 63.91±0.741 | 63.25±0.356 |
| 8 | 73.63±0.745 | 73.00±0.321 | 72.45±0.521 | 72.00±0.797 |
| 10 | 84.86±0.321 | 84.12±0.514 | 83.99±0.321 | 83.10±0.262 |
| 12 | 99.00±0.512 | 98.99±0.649 | 98.71±0.213 | 98.40±0.623 |

After stability study, *in-vitro* release dissolution test of Formulation F6 is represented

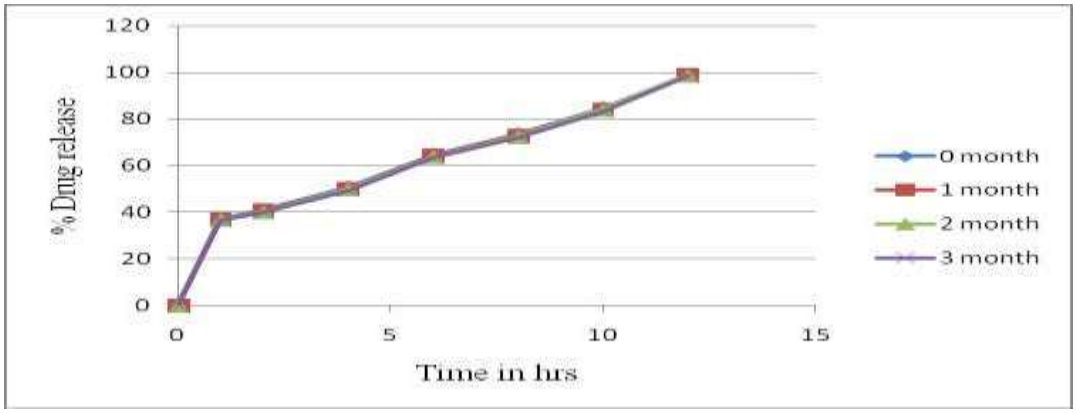



**Figure 23: Comparative dissolution profile of formulation F6 after stability study.**

## VIII .SUMMARY AND CONCLUSION

In the present study Dexketoprofen trometamol floating tablets were prepared by using Sodium Alginate and HPMC K4M as a release retarding polymers.Preliminary studies carried out then drug interaction studies carried out by FTIR and by DSC. FTIR showed no additional peak in FTIR spectra of physical mixtures indicates not any interactions in drug and Excipients. DSC study revealed that there is no interaction between the drug and excipients. The DSC curve of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in drug in the formulation. Preliminary studies for powder blend such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were carried out and the results revealed that the powder blend was having free flowing property.

The formulations were studied for evaluation parameters such as colour, odour, taste, weight variation, hardness, friability and thickness were carried out for the tablets. The powder was white, odourless and tasteless. All the batches complied with Pharmacopoeial and other acceptable standards required for weight variation, thickness, hardness, friability, drug content uniformity and possess sufficient mechanical strength. The formulation F6 gave 99.0% drug release up to 12 hours, that's why it was selected as better optimized formulation. The floating tablet of Dexketoprofen trometamol is a new pharmaceutical formulation to be taken orally and offering a Regulated drug release in zero-order manner. High Floating ability of the formulation is likely to increase its GI residence time, and eventually, prolonged the drug release and reduces dosing frequency. However, appropriate balancing between various levels of the two polymers is imperative to acquire proper controlled release and byouncy. Gastroretentive dosage form of Dexketoprofen trometamol will reduce the frequency of administration of drug as well as prolonged its action and helps to minimize dose of drug thus increase the patient complianc

## IX. ACKNOWLEDGEMENT

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