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Formulation and evaluation of sustained release matrix tablet of ketoprofen

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Abstract

The aim of the study was the formulation of the sustained release matrix tablet of Ketoprofen. The sustained release tablet was prepared by wet-granulation method. The tablets were formulated using hydrophilic polymer HPMC K4M and xanthan gum. Preformulation compatibility studies indicate that there is no interaction between the excipient and the drug. Total seven batches were prepared and powder blends before compression was subjected for evaluation of flow properties. All the parameter was found to be within the limit showing good flow property. After compression, the entire tablet batch was evaluated for thickness, hardness, friability, weight variation, drug content uniformity, swelling index, *In-vitro* release pattern. The thickness of tablet indicates that die fill was uniform in all the formulation and the formulation possessed sufficient hardness & friability indicating a good mechanical strength of the development formulation. The weight of the all the formulation were found to be with in pharmacopeial limit. The *In-Vitro* dissolution profile of all the formulation of Ketoprofen was controlled over an extended period of time. The optimized formulation of F7 containing combination of HPMC K4M and xanthan gum was consider as the best formulation with respect to its sustained in vitro drug release for 12 hrs, total sustained release time & improved bioavailability. The developed formulation was found to be stable during the stability studies of 3 month indicating good stability of the tablets.

Keywords: Ketoprofen, Stability studies, swelling index, *In-Vitro* release

1. Introduction

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out [1,2]. With proper control of manufacturing process, reproducible release profiles are possible. There is no risk of "dumping" of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable. Their capacity to incorporate active principle is large, which suits them to delivery of large dosage[3] . Monolithic devices or matrices represent a substantial part of drug delivery systems. Matrices containing swellable polymers are referred to as Hydrogel matrices, Swellable control release systems. Hydrophillic matrix tablet. Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic microparticulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymers. The release of drug from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug –polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The

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central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration. Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.[4, 5]

Nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting the cyclooxygenase (COX) enzymes (COX-1 and COX-2), leading to a decrease in the synthesis of prostaglandins, which are mediators of inflammation, pain, and fever. Rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations typically occurring within 0.5 to 2 hours post-administration [6]

2. Materials and Methods

2.1. Materials

Ketoprofen was obtained as gift sample from Dr. Reddy's Lab., Hydrabad. HPMC K4M Gifted by Colorcon Asia PvtLtd.All other chemicals are Analytical Grade.

2.2. Methods

2.2.1. Preformulation Studies

A preformulation study is a crucial preliminary stage in the drug development process, aiming to evaluate the physicochemical properties of a drug substance before formulating it into a dosage form. This stage provides valuable insights into the drug's intrinsic characteristics, which are essential for designing an effective and stable formulation Preformulation testing's main goal is to produce data that will help the formulator create a dosage form that is safe, effective, and stable. Preformulation research was therefore done on the drug sample in order to identify it and determine compatibility. Preformulation studies are essential for establishing a solid foundation for subsequent formulation development and optimization efforts. They help in identifying potential formulation challenges and risks early in the development process, allowing for proactive problem-solving and mitigation strategies. Comprehensive preformulation data enable rational decision-making regarding formulation design, excipient selection, and process optimization to ensure the development of safe, effective, and stable drug products.[7]

2.2.2. Determination of Melting Point

Melting point of Ketoprofen was determined by capillary method. Fine powder of Ketoprofen was filled in the glass capillary tube which was sealed at end. The capillary tube is tied to thermometer and the thermometer was placed in melting point apparatus. The powder at what temperature it will melt was noticed as melting temperature of drug.

2.2.3. Solubility

Solubility of Ketoprofen was determined in different aqueous and non-aqueous solvents. Solubility studies performed by taking excess amount of Ketoprofen in different beakers containing the solvents.

2.2.4. UV Spectroscopy

A stock solution of Ketoprofen was prepared by using phosphate buffer pH 7.4. Then UV Spectrum was scanned in the range 200-400nm by using Shimadzu 1601.[8]

2.2.5. Preparation of Standard Curve of Ketoprofen

Weighed accurately 100 mg of Ketoprofen was taken and dissolved in a suitable quantity phosphate buffer pH 7.4in 100 ml volumetric flask. Then the volume was made up to 100 ml with phosphate buffer pH 7.4, which gives 1000 µg/ml concentration. The standard stock solution was then serially diluted with phosphate buffer pH 7.4 to get 2 to 18 µg/ml of Ketoprofen. The absorbance of the solutions was measured against buffer solution as blank at 260 nm using spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.[9,10]

2.2.6. Drug Excipients Compatibility Studies

Drug-excipient compatibility studies are an essential part of preformulation and formulation development processes in the pharmaceutical industry. These studies assess the compatibility of a drug substance with various excipients that are used to formulate the final dosage form. he primary purpose of drug-excipient compatibility studies is to evaluate

potential interactions between the drug substance and excipients. These studies aim to identify any chemical, physical, or mechanical interactions that could affect the stability, efficacy, or safety of the final dosage form. By assessing compatibility early in the development process, formulation scientists can make informed decisions regarding excipient selection, formulation design, and process optimization. Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.[11,12]

2.2.7. Formulation of Ketoprofen Sustained Release Matrix Tablets

Sustained release matrix tablets of ketoprofen were prepared by wet granulation method using different concentrations (10%, 20% and 30%) of hydrophilic polymer like HPMC K4M and Xanthan gum. All excipients expect talc and magnesium stearate were accurately weighted and passed through 40 mesh. Calculated the amount of drug, polymer, PVP and microcrystalline cellulose were mixed thoroughly in mortar. A sufficient volume of the isopropyl alcohol as granulating agents were added slowly to achieve enough cohesive mass. The granules were prepared by passing the wet mass through a sieve no 16 #. The resultant granules were then dried in hot air oven at 60^{o} for 30 min. The granules were collected and passed through 20 mesh. Finally, dried granules were lubricated with magnesium stearate and talc my mixing properly in mortar. The lubricated granules were compressed using 9 mm round standard concave punches (Chamunda Press). The composition of different formulation of Ketoprofen sustained release tablets is shown in the table 1.

Table 1 Composition of Sustained Release Matrix Tablets of Ketoprofen

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Ketoprofen	200	200	200	200	200	200	200
Xanthan Gum	40	80	120	-	-	-	20
HPMC K4M	-	-	-	40	80	120	100
PVP K30	20	20	20	20	20	20	20
Talc	4	4	4	4	4	4	4
Mg. stearate	4	4	4	4	4	4	4
Microcrystalline Cellulose	152	92	52	152	92	52	52
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight	400	400	400	400	400	400	400

2.3. Evaluation of Powder Blend (Precompression Parameters) 12, 13

2.3.1. Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml.

2.3.2. Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for multiple times and the tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml.

2.3.3. Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.[14]

$$\tan(\theta) = h / r$$

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

Where, θ is the angle of repose.
h is the height in cms
r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definiteheight (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

2.3.4. % Compressibility

The Carr's compressibility index, also known as the Carr index or Carr's index, is a parameter used to assess the compressibility and flow properties of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the bulk density and tapped density of the powder and provides insights into its flowability and compaction characteristics. It indicates powder flow properties.

2.3.5. Hausner Ratio

Hausner's ratio is a parameter used to assess the flowability of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the tapped density and bulk density of the powder and provides insights into its flow properties. The Hausner ratio is defined as the ratio of tapped density to bulk density. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). [18,19]

2.4. Evaluation of Sustained Release Tablets

2.4.1. Weight Variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The average weight per unit is then calculated by dividing the total weight by the number of units in the sample.

2.4.2. Hardness

The hardness test is a crucial quality control measure in pharmaceutical manufacturing, particularly for solid oral dosage forms like tablets. Tablet hardness, often measured in terms of breaking force or resistance to crushing, provides an indication of the mechanical strength and robustness of the tablet. Hardness testing ensures that tablets can withstand handling, packaging, and transportation without breaking or crumbling, thereby maintaining their integrity and appearance throughout their shelf life. Hardness or tablet crushing strength ie the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

2.4.3. Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.[16]

2.4.4. Content Uniformity

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and quantity of powder equivalent to 100 mg of drug was taken and transfer it to 10 ml of phosphate buffer pH 7.4.The resulting solution was then diluted appropriately and measured using a UV-Visible spectrophotometer at 260 nm.[17]

2.4.5. In-Vitro Dissolution Study

The *In-Vitro* dissolution study was carried out in USP dissolution test apparatus type II (paddle) with a dissolution medium of 900 ml of phosphate buffer pH 7.4, at 50 rpm (37±0.5°C). 5 ml aliquot was withdrawn at the specified time interval, filtered through whatman filter paper, and measured spectrophotometrically after suitable dilution at 260 nm using UV-Visible spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37°C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The results in the form of percent cumulative drug released was calculated.[18]

2.4.6. Swelling Index

The swelling behaviour of a dosage unit was measured by studying its weight gain.The swelling index of tablets was determined by placing the tablets in the basket ofdissolution apparatus using dissolution medium as phosphate buffer pH 7.4 at 37 ± 0.5 °C. After 1, 2,3, 4, 5, and 6h, each dissolution basket containing tablet was withdrawn, blotted withtissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula[19]

$$\text{Swelling index} = \frac{(W_t - W_0)}{W_0} \text{X } 100$$

Where
W_t = Weight of tablet at time t.
W_0 = Initial weight of tablet

2.5. Stability study

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40 °Cand 75% RH for the period of 3 months. The Tablet were evaluated before and after 3 months for change in appearance, Hardness, disintegration time, drug content and in -vitro drug release.

3. Result and Discussion

3.1. Preformulation Study

3.1.1. Determination of Melting Point

The melting point of Ketoprofen was determined by capillary method, melting point of Ketoprofen was found to be 94 to 96 °C. Melting point of drug was compared with pharmacopoeial standards, that confirmed the purity of drug sample.

3.2. Solubility

Ketoprofen was found to be practically insoluble in water; soluble in alcohol, acetone, and chloroform

3.3. UV-Spectroscopy (Determination of λ max)

The solution containing 10 ug/ml of Ketoprofen in phosphate buffer pH 7.4. was prepared and scanned over 200 -800 nm against phosphate buffer pH 7.4. solution as a blank using Shimadzu UV spectrophotometer. The maximum wave length was observed at 260 nm, which match with reported wave length.

3.4. Standard Calibration Curve of Ketoprofen

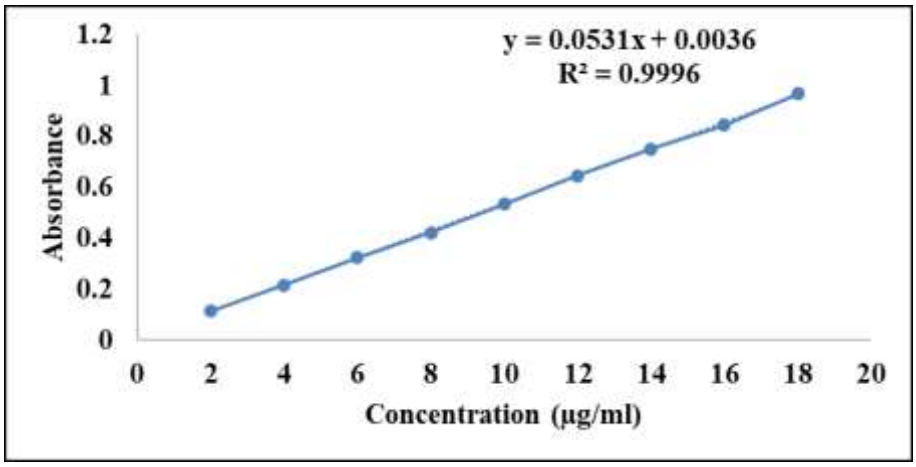

Figure 1 Standard Calibration Curve of Ketoprofen in phosphate buffer pH 7.4

The stock solution is used to prepare 2 to 18 µg/ml of Ketoprofen in phosphate buffer pH 7.4 and analysed at 288 nm. The graph v/s concentration was plotted and data was subjected to linear regression analysis. The data of absorbance figure 1. The standard calibration curve of Ketoprofen in the concentration 2 µg/ml to 18 µg/ml was straight line. The absorbance increased with increased in concentration. Thus the standard curve follows the Beer-Lamberts Law.

3.5. Compatibility Studies (FT-IR)

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and Ketoprofen. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

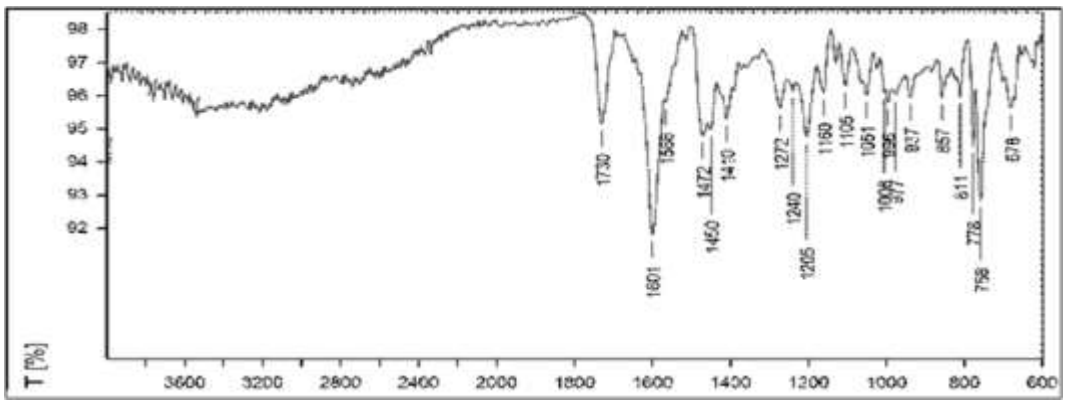

Figure 2 IR spectra of pure drug Ketoprofen

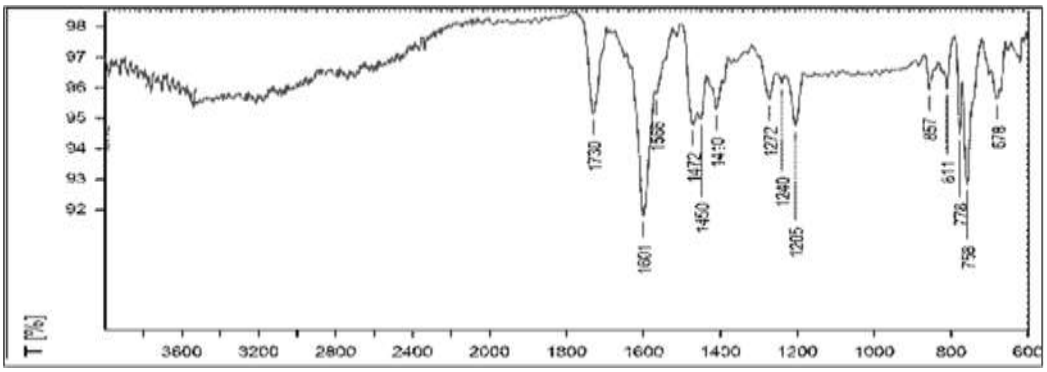

Figure 3 IR Spectra of Ketoprofen sustained Release Tablets (F7)

3.6. Evaluation of Sustained Release Tablets

3.6.1. Pre compression Parameter

The results of micromeritic properties of powder blend were showed in table 2. Bulk density values for all batch powder blend was obtained in the range from 0.43 - 0.45 gm/cc and the tapped density values obtained in the range from 0.52 - 0.56 gm/cc. Angle of repose value for all the formulation ware found in the range between 25.12 – 28.32$^{\theta}$ showing good flow properties for all batch powder blends. The compressibility index and Hausner's ratio was further calculate to determine the flowability of powder blend. The % compressibility index value for all batch powder blends was found in the range of 15.38 to 20.37 indicating excellent to good flow properties for all batch.Hausner ratio for all batch powder blend was found below 1.25 showing excellent flow properties of powder blends of all batches. Thus from the micromeritics study it was found that all batch formulation exhibiting the good flow properties of the powder blend. Thus the powder showed better flow properties and were non aggregated.

Table 2 Micromeritics properties of powder blend (F1 to F7)

Batch	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	27.12±0.12	0.471±0.16	0.512±0.56	15.75	1.18
F2	28.32±0.21	0.451±0.15	0.560±0.43	19.46	1.24
F3	26.12±0.16	0.433±0.33	0.545±0.31	20.55	1.25
F4	25.54±0.23	0.452±0.21	0.548±0.10	17.51	1.21
F5	27.62±0.31	0.448±0.24	0.554±0.16	19.13	1.23
F6	26.38±0.19	0.465±0.81	0.562±0.25	17.25	1.20
F7	25.16±0.25	0.432±0.42	0.530±0.27	18.50	1.22

3.7. Post Compression Parameters

The weight variation test for all tablets formulation (F1 to F7) was passed and found within pharmacopoeial standards. Passing the weight variation test ensures that each tablets was within a batch contains the specified amount of active pharmaceutical ingredient (API) and excipients. This ensures uniform dosing and therapeutic efficacy for patients consuming the medication. The hardness of tablets for all batch formulation (F1 to F7was found in the range from 4.5 to 5 kg/cm2, which was found to be optimum and indicate tablets able to withstand mechanical shock. It was found from the range of 5.10 to 6.12 mm for formulation F1 to F7 is found to be optimum and indicated well distribution of pure drug. Tablet thickness directly influences the amount of active pharmaceutical ingredient (API) and excipients contained within each tablet. Consistent tablet thickness ensures uniformity of dosage across the batch, contributing to predictable and reliable therapeutic outcomes for patients. The friability value of all tablets batch formulation F1 to F7 were found to be less than 1% indicating good mechanical strength of tablets. Passing the friability test ensures that tablets maintain their physical integrity and withstand mechanical stress under normal handling conditions. Good uniformity of drug content was found within and among the different batches of tablet formulation. The values ranged from 95.26 to 99.80% which ware in pharmacopoeial limits.

Table 3 Post Compression parameters of Sustained Release Tablets of Ketoprofen

Batch	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/Cm^2)	Friability (%)	Drug Content Uniformity (%)
F1	404.12±0.27	4.56±0.11	6.5±0.42	0.43±1.1	98.64±1.1
F2	405.34±1.10	4.57±0.13	6.5±0.18	0.50±0.9	98.62±1.2
F3	402.45±0.57	4.60±0.14	6.0±0.30	0.36±0.12	97.34±1.1
F4	401.26±0.44	4.60±0.12	6.5±0.80	0.51±0.18	99.26±1.1
F5	406.12±1.32	4.58±0.13	6.0±0.35	0.57±0.27	97.32±1.3
F6	405.63±1.20	4.56±0.15	6.5±0.81	0.48±0.16	97.56±0.4
F7	400.45±0.74	4.57±0.14	6.5±0.24	0.34±0.31	101.31±1.04

(SD ± Mean of n=3)

3.8. *In-Vitro* Dissolution Study

In vitro drug release study of prepared sustained release tablets of Ketoprofen was determined in phosphate buffer pH 7.4 as dissolution medium. Formulations F1, F2 and F3 prepared with xanthan gum showed 96.24%, 96.60% and 97.41% drug release respectively in 6, 8 and 10 hrs respectively and fail to sustain the drug release up to 12 hrs. Formulation F4, F5, and F6 prepared with HPMC K4M showed 98.42%, 97.34% and 86.17 % drug release respectively in 8, 10 and 12 hrs respectively. Formulation F4 and F5 was not able to sustained the drug release up to 12 hrs. While formulation F6 prepared with 30% concentration of HPMC showed very slow release of drug, this might be due to high concentration of HPMC K4M. Batch F7 prepared with combination of both HPMC K4M and xanthan gum as a rate control polymer was found to be effective in holding the drug in polymer matrix for longer duration, along with desirable release

of drug in 12 hrs. Batch F7 showed drug release of 99.13% in 12 hrs. All batch formulation showed sustaining the drug release for extended period of time.

Among the different formulations, batch F7, prepared with combination of HPMC K4M and xanthan gum, showed sustained release of drug for the periods of 12 hrs. From the results it was observed that, as the concentration of both grade of polymer increases, the drug release decreases. Data for in vitro drug release of sustained release tablets was shown in figure 4.8.

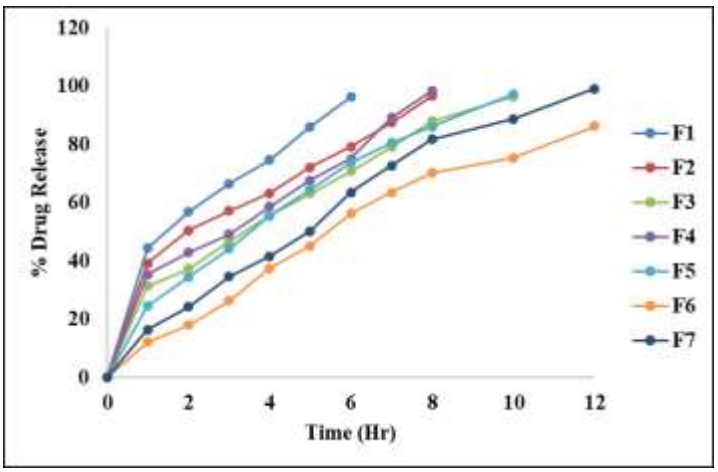

Figure 4 Comparative In vitro Dissolution Profile of formulation F1to F7

3.9. Swelling Index

Swelling study was performed on all the batches (F1 to F7) for 10 hr. The results of swelling index were plotted in figure. 5. Swelling index study showed that the swelling increases with the time, because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batch F6 containing 30% of HPMC K4M. It was found that swelling index was higher for high viscosity grade polymer. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as sustained release capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

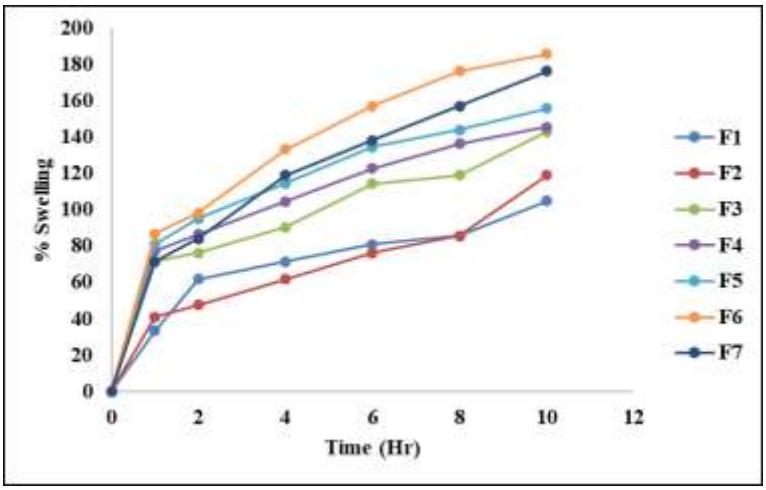

Figure 5 Swelling Index of Ketoprofen Sustained Release Tablet

3.10. Stability Study

Ketoprofen Sustained release tablets formulation showing promising results in term of lowest sustained release lag time and sustained drug release, was selected for stability studies. According to ICH guidelines, optimized formulations

F7 were stored at 40^{0}C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for appearance, Hardness, drug content, sustained release lag time, total sustained release time and In vitro drugrelease. At the end of 3 months no significant difference was observed in tested parameters. From the stability study it was concluded that Ketoprofen Sustained release tablets formulation F7 was found to be stable. The results of stability data were shown in table 4.

Table 4 Stability data of Optimized formulation F7

Formulation Code	Parameter	Before storage (0 month)	After storage (3 month)
F7	Hardness (kg/cm2)	6.5±0.24	6.5±0.36
	Drug Content (%)	101.31±1.04	99.16±0.17
	% Drug Release	99.13 ±1.70	98.32±1.51

4. Conclusion

From the present study following conclusion were observed The Sustained release tablet of Ketoprofen can be prepared by wet-granulation method by using HPMC K4M, and Xanthan gum as a gas generating agent. The entire prepared tablet was found to be good without capping and chipping. IR-spectroscopic studies indicate no drug-excipient interaction in formulation. The in vitro dissolution profile of all the prepared sustained release tablets formulation of Ketoprofen were found to extend the drug release over a period of 6 to 12 hrs. In vitro dissolution study showed that as the concentration of polymer increases the drug release decreases. Use of combination of polymer effectively controlled the release of drug over 12 hrs periods. Comparing all the formulation batch F7 was consider as the ideal formulation which exhibited (99.13%) drug release in 12 hrs. Future details investigation is required to establish in vivo efficiency of Ketoprofen sustained release tablet and long term stability need to be confirm the stability of sustained release Ketoprofen tablets.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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