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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF KETOPROFEN USING NATURAL GUMS

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ABSTRACT

Sustained release tablets of Ketoprofen is a non steroidal anti-inflammatory drug. Designing a sustained release formulation for the drug ketoprofen may prolong therapeutic concentration of drug in the blood and decrease the frequency of dosing and also improve the efficacy of drug and patient compliance. Ketoprofen sustained release matrix tablets were prepared by wet granulation method. The effect of gum damar concentration was studied by using three different drug polymer ratios. Gum damar was used as a hydrophilic release retarding polymer, and talc was used as a lubricant. The grannules were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density and Carr's index. This shows that the grannules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets. The tablets were evaluated for hardness, weight variation, friability, drug content uniformity, in *vitro* dissolution studies and model fitting analysis. The *in vitro* releases of ketoprofen from the prepared tablets were studied in pH 1.2 for 2 hr and phosphate buffer pH 6.8 for 6 hr. It was found that the formulation batch F_2 showed good release profile as compared to other two formulations. F_1 showed initial burst effect after two hours. The formulation batch F_3 showed about 85% drug release it might be due to high ratio of drug to polymer or high swelling of gum damar which retard the drug release. From all the prepared formulations, the promising formulation was selected based on physicochemical properties and *in vitro* release studies.

KEYWORDS: Ketoprofen, Gum Damar, Micro crystalline cellulose, Dibasic calcium phosphate, Sustained release matrix tablets.

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on infield of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. The advantages of natural plant based excipients include low cost, natural origin, free from side effects, biocompatible, bioacceptable, renewable source; environmental friendly processing, local availability, better patient tolerance as well as public acceptance. They improve the national economy by providing inexpensive, formulations to people, using locally available materials.

Ketoprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. It is insoluble in water, freely soluble in alcohol (ethanol) at 20°C, freely soluble in chloroform, acetone and ether, soluble in strong alkali. Ketoprofen is rapidly and well-absorbed orally, with peak plasma levels occurring within 0.5 to 2 hours. Rapidly and extensively metabolized in the liver, primarily via conjugation to glucuronic acid. No active metabolites have been identified. Less than 1% excreted as unchanged drug, Biotransformation is mainly hepatic, eliminated via the kidneys, as a conjugated metabolite and also as unchanged drug, Following parenteral administration 80% eliminated within 24 hours, mainly as conjugated metabolite, minimal elimination in milk.99% bound, primarily to albumin. Ketoprofen is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. Ketoprofen has pharmacologic actions similar to those of other prototypical NSAIDs, which inhibit prostaglandin synthesis. Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and alleviate moderate pain.[1]

Damar gum is obtained from the Dipterocarpaceae family of trees in India and East Asia, principally those of the genera Shorea, Balanocarpus or Hopea. Most is produced by tapping trees; however, some is collected in fossilized for the ground. The gum varies in colour from clear to pale yellow, while the fossilized form is grey-brown. The gum is stable, probably combustible, and incompatible with strong oxidizing agents. Its toxicity is low, but inhalation of dust may cause allergies.

It is used in foods, as a clouding or glazing agent, and in incense, varnish, and other products. Dammar varnish, made from dammar gum mixed with turpentine, was introduced as a picture

varnish in 1826. It is commonly used in oil painting, both during the painting process and after the painting is finished.[2]

MATERIALS AND METHODS

Materials: Ketoprofen was purchased from all fine chemicals, Mumbai. Gum dammar was collected from mumbai. HPMC was purchased from Ahmedabad. Talc was purchased from Loba chemie pvt. Ltd. Microcrystalline cellulose, Sodium hydroxide, Potassium chloride and PVPK-30 were purchased from Chemdyes Corporation, Ahmedabad. Potassium hydrogen ortho- phthalate was purchased from S.D Fine chemicals Ltd, Mumbai. Other materials used were of analytical grade, and procured from commercial sources. Preformulation studies Development of calibration curve for Ketoprofen: A stock solution of Ketoprofen was prepared by dissolving 100mg of drug in 100ml of phosphate buffer of pH 6.8 (1 mg/ml). From this stock solution, 0,5,10,15,20 µg/ml dilutions were prepared. The λmax of the drug was determined by scanning one of the dilutions between 400 to 200 nm using a UV- visible spectrophotometer. Compatibility Studies A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm-1 in a Perkin Elmer FTIR spectrophotometer.

Preparation of sustained release matrix tablets

All the ingredients including drug and gum damar were weighed accurately and mixed thoroughly on a butter paper with the help of a stainless steel spatula and then transferred it into mortal pester. After that water has been added until wet mass has been produced. Then pass the wet mass from sieve no 16 to produce granules. After that dried in hot air oven at 40° for 60 minutes. After that granules was passed through sieve no 18 and add 2% talc. The prepared granules were transferred in to the rotatory 10 stations tablet compression machine which has upper and lower punches of 8 mm size.

Batch details for the formulations of Diclofenac sodium sustained release matrix tablets

Table no:-1. Compostion of Ketoprofen sustained release matrix tablets.

Ingredients	Formulation Batches		
	F_1	F_2	F_3
Ketoprofen(mg)	200	200	200
Gum Damar(mg)	100	150	201
Talc(mg)	6	7	8
Total weight(mg)	**306**	**357**	**408**

Table no:-2. Composition of tablet formulations containing fillers.

Ingredients	Formulation Batches		
	F_4	F_5	F_6
Ketoprofen (mg)	200	200	200
Gum Damar (mg)	150	150	150
MCC (mg)	35	_	_
DCP (mg)	_	35	_
Lactose (mg)	_	_	35
Talc (mg)	8	8	8
Total weight(mg)	**393**	**393**	**393**

Evaluation of Diclofenac sodium SR matrix tablets

Evaluation of granules

Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\textbf{Tan } \theta = h/r \text{ ---------- (1)}$$

Therefore, $\theta = \tan^{-1} h/r$

Where, θ = Angle of repose,

h = Height of the pile,

r =Radius of the pile base[3]

Bulk Density

Weigh accurately 25 g of drug (M), which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0).Bulk density was calculated using the following formula:[4]

$$\text{Bulk density}(\rho t) = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

Tapped Density: Weigh accurately 25 g of drug, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight. Tap the cylinder for 50 times initially and measure the tapped volume (V_1) to the nearest

graduated units, repeat the tapping an additional 100 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2) tapped density was calculated using the following formula

$$\text{Tapped density}(\rho t) = \frac{\text{weight of powder}}{\text{Tapped volume of the powder}}$$

5.6.4 Carr's index: It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by[3]:-

$$\text{Carr's index (\%)} = [(\text{TBD} - \text{LBD}) \times 100]/\text{TBD}$$

Where,

LBD = Lose Bulk Density.

TBD = Tapped Bulk Density.

Evaluation of Sustained Release Matrix Tablets of Ketoprofen

Hardness Test: The crushing strength (kg/cm^2) of tablets was determined by using Monsanto hardness tester. In all the cases, mean of three replicate determinations were taken. According to standards the ideal hardness of uncoated tablets were between 6-8 kg/ cm.[2,5]

Friability test: Take the tablets with average weight of 6.5g Dedust the tablets carefully and weighed accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weighed them accurately. A maximum loss of weight not greater than 1.0 percent was acceptable for most of tablets.[6]

$$\%\ \text{friability} = \frac{\text{Weight(Final)} - \text{Weight(Original)}}{\text{Weight(Original)}}\ \text{X}\ 100$$

Weight Variation Test: Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. According to Indian Pharmacopoeia ± 5% difference is allowed.[7]

Disintegration test: This test determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Tablets were placed in the disintegration test apparatus containing disc and basket-rack assembly. Generally distilled water used as a liquid medium. The volume of liquid is such that the wire mesh at its highest point is at least 25 mm below the surface of the liquid, and its lower point

is at least 25 mm above the bottom of the beaker. Introduce tablet into each tube and add a disc to each tube. Suspend the assembly in the beaker containing distilled water for the specified time. Remove the assembly from the liquid. The tablets pass the test if all of them have disintegrated.[8]

Uniformity of drug content: Tablets were powdered in a glass mortar and the powder equivalent to 10 mg of drug was placed in a stopper 500 ml conical flask. The drug was extracted with 500 ml of pH 1.2. Absorbance was measured at 257 nm in UV visible spectrophotometer against an appropriate blank (pH 1.2).[7]

In vitro dissolution studies: *In vitro* dissolution studies of ketoprofen matrix tablets were carried out in USP tablet dissolution test apparatus II (paddle method) rotating stirrer at 50 rpm using 900 ml of pH 1.2 for 2 hr and pH 6.8 phosphate buffer for 6 hr at 37±0.5ºC as dissolution medium. After every one hour 10 ml of the samples were withdrawn by means of a syringe fitted with pre-filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 257 nm using Shimadzu UV-1800 spectrophotometer after suitable dilutions with pH 1.2 and 6.8 phosphate buffer respectively. All the studies were conducted in triplicate.[9]

Drug Release Kinetics: The results of *in vitro* release profiles obtained for all the sustained release matrix tablet formulation batches were fitted into different models which are described as follows[10]

Zero order equation

$$Q_t = k_0.t$$

Where,

Q_t is the percentage of drug released at time "t"

k_0 is the release rate constant

First order equation

$$\text{Log } Q_t = \log Q_0 - kt/2.303$$

Where,

Q_t is the percentage of drug released at time "t"

kt is the release rate constant;

Higuchi's equation

$$Qt = kH.t1/2$$

Where,

kH is the Higuchi release rate constant;

Hixson-Crowell

$$W_0^{1/3} - W_t^{1/3} = K_S t$$

Where,

K_s is the Hixson-Crowell rate constant.

Korsmeyer-Peppas model

$$Qt/Q\infty = Kt^n$$

Where,

$Qt/Q\infty$ is the fraction of drug released at time t,

K is a constant compromising the structural and geometric characteristics of the device, n, the release exponent, which is indicative of the mechanism of drug release.

For the case of cylindrical geometries such as tablets, n=0.45 corresponds to a Fickian diffusion release (Case I), 0.45<n<0.89 to a non-Fickian (Anomalous) transport, n = 0.89 to a zero order (Case II) release kinetics (32) and n>0.89 to a super Case II transport (10). For fitting the release data to the equations, only the points within the interval 10%-70% were used. In the case of Higuchi model, the range was 10%-60%.

Drug-Excipients Compatibility Studies

Drug-excipients compatibility were done by

1. Differential Scanning Calorimetry (DSC)
2. Fourier Transform Infrared spectroscopy (FTIR)

Differential Scanning Calorimetry (DSC)

Thermal analysis of pure drug ketoprofen, gum dammar and physical mixures of ketoprofen and gum damar were assessed by DSC using DSC-60 instrument.

Fourier Transform infrared Spectroscopy (FTIR)

IR spectroscopy is one of the most powerful analytical techniques, which offers the possibility of the chemical identification. The IR spectrum of ketoprofen drug sample and

gum damar and promising formulations (Batch F_2) were carried out by using flourier transform infrared spectroscopy.

RESULTS AND DISCUSSION

Preformulation studies

Physical Characterization of Gum Damar

Various physico-chemical properties of gum damar were studied. The result are shown in table no.3

Table no. 3: Physical characterization of Gum Damar.

Characteristic	Result
Colour	Yellow
Ash Value	25%
Loss on Drying	4%
Melting Point	141-143ºC

Solubility behavior

Solubility behavior of gum damar in different solvents was carried out. The result are shown in table no. 4.

Table no. 4: Solubility Behavior of gum damar.

Solvent	Solubility (gm/ml)
Chloroform	0.68
Acetone	0.45
Ethanol	0.32
Water	Insoluble
Isopropyl alcohol	0.36

Micromeritical study

Various micromeritical properties of gum damar was studied such as bulk density, tapped density, percentage compressibility and angle of repose. The result are shown in table no.5.

Table no. 5: Micromeritical Study gum damar.

Bulk Density	0.63 ± 0.04 gm/cm^3
Tapped Density	0.76 ± 0.02 gm/cm^3
Percentage Compressibility	17.10 ± 0.03 %
Angle of repose	40.6 ± 0.04

Values were expressed as Mean±SD.

Results of the physical characterization of gum damar are summarized in table 3,4, and 5. Total ash value of gum damar indicates its better chemical stability. Absence of sharp melting

point indicates amorphous nature of the gum damar (table 3). Gum damar exhibited good solubility in almost all the organic solvents and insoluble in water. Results of Micromeritical study showed that gum damar exhibits passable flow properties.

IR Spectroscopy Characterization: The spectra of pure gum damar were taken by using FTIR spectrophotometer.

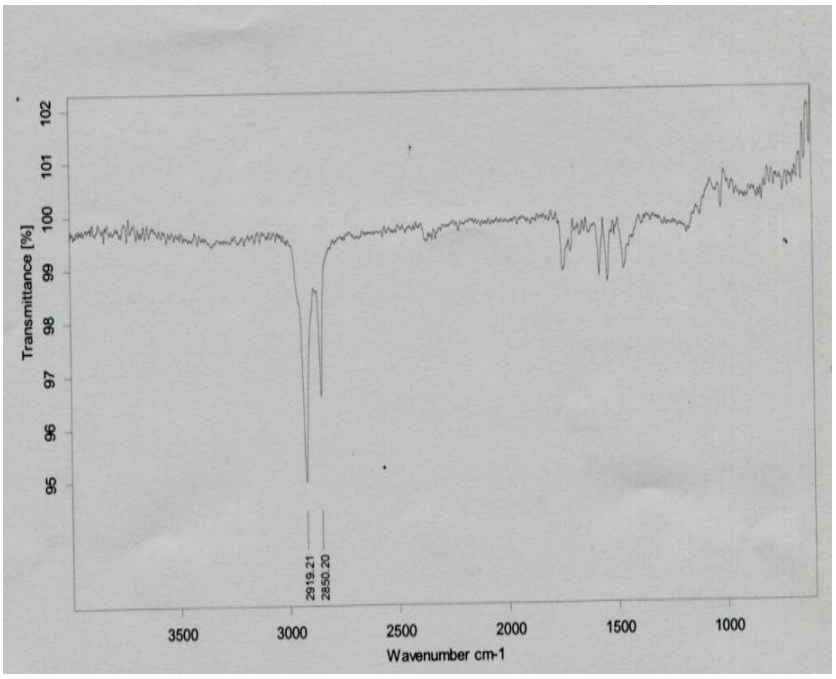

Figure no. 1: FTIR spectra of gum damar.

Swelling study

Swelling study of gum damar was carried out by using water as dissolution medium. The percentage swelling of gum damar at different time of intervals obtained is shown in table no. 6 and figure no. 2.

Table no. 6: Swelling Study.

Time (hours)	Swelling (%)
1	122
2	157
3	170
4	192
5	201
6	213

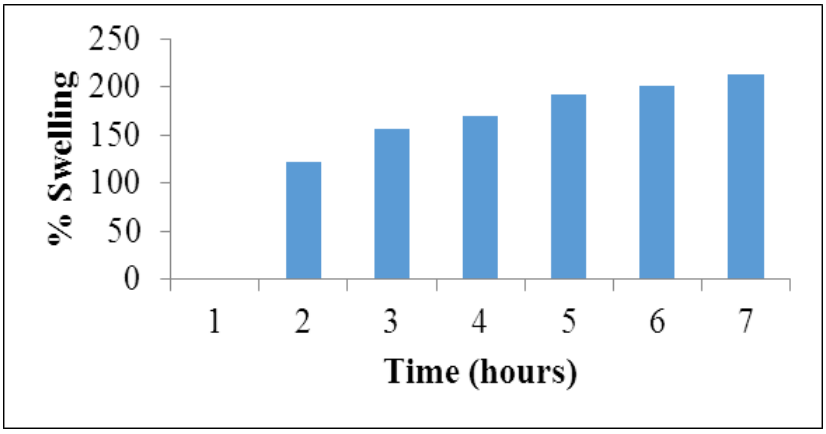

Figure no. 2: swelling study.

The swelling study of gum damar tablets in distilled water are shown in Figure no. 2. As shown in the above figure, tablets containing gum damar has the highest swelling rate in water, with the maximum swelling of 213% after 6 hour.

Preparation of Calibration Curves of Ketoprofen in pH 1.2 and pH 6.8 Buffers

Scanning of Drug

The pure drug ketoprofen when scanned over a range 200-400 nm to determine its $\lambda_{max,}$ the peak was observed at the 257 nm.

Preparation of Standard Calibration Curve of Ketoprofen

The standard calibration curve of ketoprofen in phosphate buffer pH 1.2 and pH 6.8 was successfully developed. The standard curve is shown in Figure no: 6.1 and 6.2. The standard calibration curve was found to be accurate and follow the beers lambert law. The curve was found to be linear in the range of 5-50 µg/ml at λ_{max} 257nm.

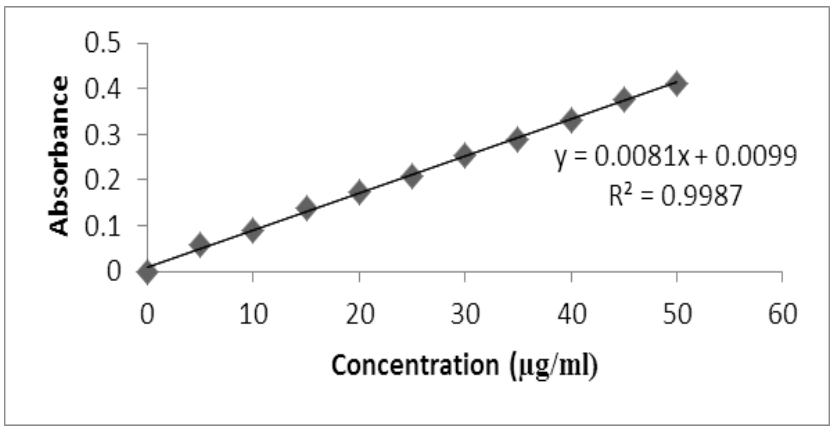

Figure no. 3 Calibration curve for the estimation of Ketoprofen in pH 1.2 buffers.

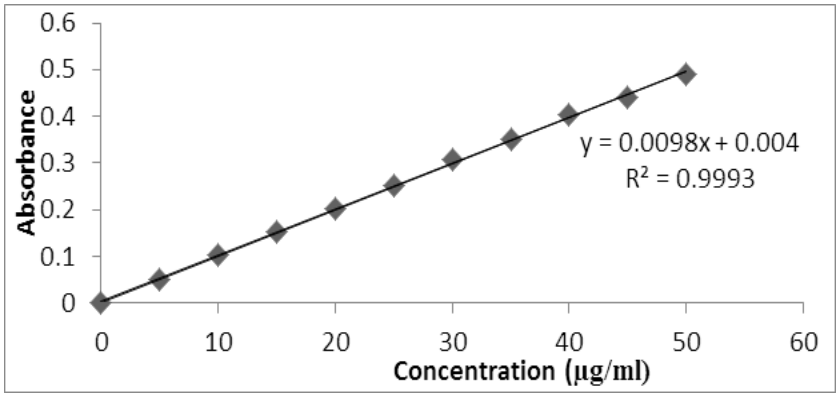

Figure no. 4: Calibration curve for the estimation of Ketoprofen in pH 6.8 buffers.

Evaluation of Physical Properties of Drug Loaded Granules

The dried granules of different formulations (F_1 to F_3) were studied for various micromeritical properties such as angle of repose, bulk density, tapped density, carr's index and hausner ratio. The result are shown in table no 7.

Table no: 7. Evaluation of physical properties of drug loaded granules

Formulations Batches	Evaluation parameters				
	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index %	Hausner Ratio
F_1	24.41±0.02	0.50±0.02	0.56±0.04	10.64±0.03	1.12±0.02
F_2	22.91±0.02	0.48±0.04	0.57±0.03	15.1±0.03	1.18±0.04
F_3	23.95±0.03	0.47±0.03	0.55±0.03	14.95±0.01	1.17±0.03

All values were expressed as Mean±SD.

Table showed the results obtained for pre-compression parameters. The values of angle of repose were found to be in the range of 22.41 to 24.91^0. All formulations showed the angle of repose within 25^0. It indicates that all formulations showed good flow properties.

The bulk density and tapped density for all the formulations varied from 0.47 gm/cm^3 to 0.50gm/cm^3 and 0.55 gm/cm^3 to 0.57 gm/cm^3 respectively.

The percent compressibility of powder was determined by Carr's compressibility index. The percent compressibility for all the four formulations lies within the range of 9.97 to 20 %. All formulations showed good compressibility.

Evaluation of Sustained Release Matrix Tablets of Ketoprofen

All the tablet formulations were subjected to Hardness, friability, weight variation, and drug content test according to IP. The result are shown in table no: 8.

Table no. 8: Tablet Evaluation parameters for formulation batches F_1, F_2 and F_3.

Batch Code	Hardness* (Kg/cm2) Mean ± S.D	Friability*** (%) Mean ± S.D	Weight Variation*** (%) Mean ± S.D	Drug Content (%) Mean ± S.D
F_1	5.2±0.15	0.30±0.03	0.65±0.02	97.23±0.03
F_2	5.4±0.12	0.28±0.04	0.96±0.01	96.5±0.21
F_3	5.5±0.08	0.29±0.02	0.76±0.03	95.28±0.13

* n=3, *** n=20

Hardness Test: Hardness test was performed by Monsanto tester. Hardness was found to be within 5 kg/cm^2 to 5.5 kg/cm^2. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.

Friability Test: The result was found within the approved range (<1%) for all the formulations batches. Results revealed that the tablets passed the fribility test.

Weight Variation Test: All the formulations batches passed weight variation test as per the pharmacopoeial limits of ± 5 %. The weight of all the tablets was found to be uniform.

Uniformity of drug content: Drug content estimation for all the batches was determined. It was found to be pharmacopoeial limit.

***In vitro* Dissolution Studies** In vitro dissolution studies of formulations batches ($F_1$to F_3) were carried out in a USP type II dissolution apparatus**.** Result are shown in table no. 9 and figure no. 5.

Table no. 9: *In vitro* Dissolution profiles of ketoprofen sustained release tablets of formulation Batches F_1, F_2 and F_3.

Time (hours)	% Cumultive drug release (Mean± S.D) n=3		
	F_1	F_2	F_3
0	0.00	0.00	0.00
1	41.43 ±0.65	17.69±0.96	17.42±0.36
2	48.97±0.34	31.10±1.29	25.43±0.84
3	49.42±0.47	51.44±0.92	40.92±0.79
4	62.18±0.49	62.41±1.21	50.99±0.68
5	73.60±0.58	74.50±1.09	60.62±0.54
6	82.56±0.73	83.01±0.83	68.68±0.81
7	91.74±0.82	92.18±0.63	79.20±0.29
8	95.99±0.31	98.23±0.59	85.92±0.31

- *In vitro* release profile of formulation batch F_1 showed the initial burst effect, it might be due to initial, slow swelling and high erosion properties of gum damar.
- The formulation batch F_2 and F_3 showed about 98.23 and 85.92 % drug release at the end of 8 hours respectively. It indicates that the formulation batch F_2 showed higher release as compared to batch F_3.
- We conclude that the ratio of drug:gum damar in formulation batch F_2 and F_3 was 1:0.75 and 1:1 respectively. The formulation batch F_3 showed about 85% drug release it might be due to high ratio of drug to polymer or percentage swelling of gum damar which retard the drug release.
- The formulation batch F_2, showed good and optimum release and used as an optimized batch for further study.

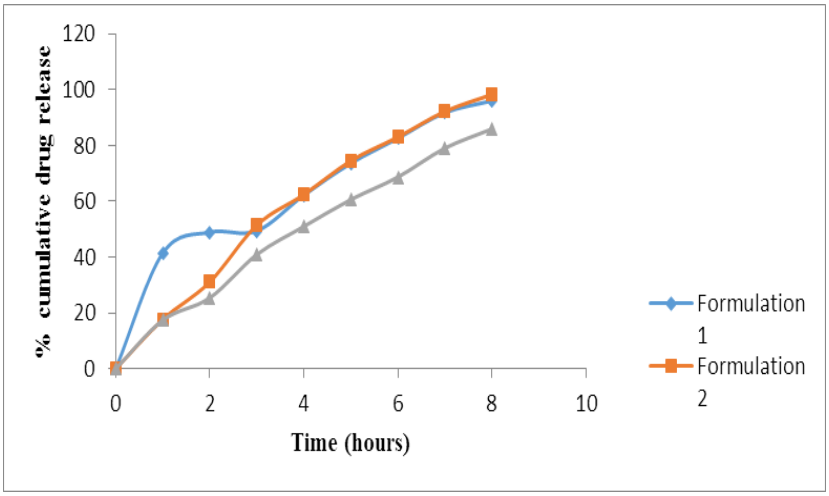

Figure no. 5: In-vitro release profile of F1 to F3 formulations.

Drug Release Kinetics: To determine the mechanism of drug release from the formulations batches (F_1 to F_3). The in vitro release data were subjected to various drug release kinetic models. The result are shown in table no.10.

Table no. 10: Drug Release Kinetics.

Formulations	Zero order	First order	Higuchi	Hixcon-Crowell	Korsmeyer-Peppas	
	R2	R2	R2	R2	N	R2
F1	0.9321	0.9754	0.9857	0.9976	0.5210	0.9580
F2	0.9937	0.9993	0.9761	0.9998	0.5321	0.9917
F3	0.9564	0.9761	0.9994	0.9658	0.5469	0.9861

Formulation batches (F_1 to F_3) was subjected to model fitting analysis to know the mechanism of drug release. In the formulation batch F_1 and F_2, release of ketoprofen

followed the Hixon crowell model with R^2 value obtained was 0.9976 and 0.9998 respectively. Similarly, in the formulations batch F_3, the drug release followed Higuchi model with R^2 value of 0.9994.

Effect of Filler Excipients

The optimize batch F_2 was used to see the effect of filler excipients like MCC, Lactose and Dicalcium Phosphate on sustained release matrix tablets of ketoprofen.

Evaluation of Physical Properties of Drug Loaded Granules Using Fillers

The dried granules of different formulations (F_4 to F_6) were studied for various micromeritic properties such as angle of repose, bulk density, tapped density and carr's index which described as follows.

Table no. 11: Evaluation of physical properties of drug loaded granules using fillers.

Formulations code	Evaluation parameters				
	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index %	Hausner Ratio
F_4	24.09±0.04	0.48±0.04	0.55±0.02	12.11±0.02	1.14±0.02
F_5	22.82±0.02	0.46±0.02	0.54±0.01	11.25±0.03	1.17±0.04
F_6	23.04±0.01	0.45±0.01	0.56±0.01	11.72±0.02	1.24±0.03

All values were expressed as Mean±SD

Table no: 11 showed the results obtained for pre-compression parameters. The values of angle of repose were found to be in the range of 22.82 to 24.09^0. All formulations showed the angle of repose within 25^0. It indicates that all formulations showed good flow properties.

The bulk density and tapped density for all the formulations varied from 0.45 gm/cm^3 to 0.48gm/cm^3 and 0.54 gm/cm^3 to 0.56 gm/cm^3 respectively.

The percent compressibility of powder was determined by Carr's compressibility index. The percent compressibility for all the three formulations lies within the range of 11 to 12 %. All formulations showed good compressibility.

Evaluation of Sustained Release Matrix Tablets of Ketoprofen Using Fillers

All the tablet formulations were subjected to Hardness, friability, weight variation, and drug content test according to IP. The result are shown in table no: 12.

Table no. 12: Evaluation parameters of formulation batches F_4, F_5 and F_6.

Batch Code	Hardness* (Kg/cm^2) Mean ± S.D	Friability*** (%) Mean ± S.D	Weight Variation *** (%) Mean ± S.D	Drug Content (%) n=5± S.D
F_4	5.3±0.34	0.51±0.03	0.86±0.02	98.05±0.04
F_5	5.5±0.18	0.42±0.01	0.66±0.04	97.01±0.03
F_6	5.2±0.09	0.49±0.02	0.94±0.01	97.08±0.04

* n=3, *** n=20

DISCUSSION

Hardness Test: Hardness test was performed by Monsanto tester. Hardness was found to be within 5 kg/cm^2 to 5.5 kg/cm^2. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.

Friability Test: The result was found within the approved range (<1%) for all the formulations batches. Results revealed that the tablets passed the fribility test.

Weight Variation Test: All the formulations batches passed weight variation test as per the pharmacopoeial limits of ± 5%. The weight of all the tablets was found to be uniform.

Uniformity of drug content: Drug content estimation for all the batches was determined. It was found to be pharmacopoeial limit.

***In vitro* Dissolution study:** In vitro dissolution studies of formulations batches (F_4 to F_6) were carried out in a USP type II dissolution apparatus**.** Result are shown in table no.13 and figure no 6.

Table no. 13: *In vitro* Dissolution profiles of ketoprofen sustained release tablets of formulation batches F_4, F_5 and F_6.

Time (hours)	% Cumulative drug release (Mean± S.D) n=3		
	F_4	F_5	F_6
0	0.00	0.00	0.00
1	20.47±0.65	16.30±0.72	21.30±0.85
2	24.83±0.36	20.40±0.98	25.40±0.68
3	43.23±0.47	27.10±0.25	45.10±0.47
4	57.11±0.89	42.60±0.16	59.20±0.61
5	72.68±0.75	56.80±0.28	74.82±0.78
6	90.26±0.78	73.20±0.42	89.40±0.39
7	93.05±0.14	78.30±0.47	94.20±0.75
8	97.11±0.63	82.00±0.69	98.00±028

- Tablets containing MCC absorbed water through the capillaries leading to swelling and disintegration.
- Dicalcium phosphate (DCP) is insoluble, non swelling and tablets are intact throughout the dissolution process. Drug release was through via small inter and intra granular spaces.
- Lactose containing tablets exhibited crack on the sides of tablets during dissolution process. Drug diffusion was promoted due to the pores and channels that were created following the solubilization of lactose.

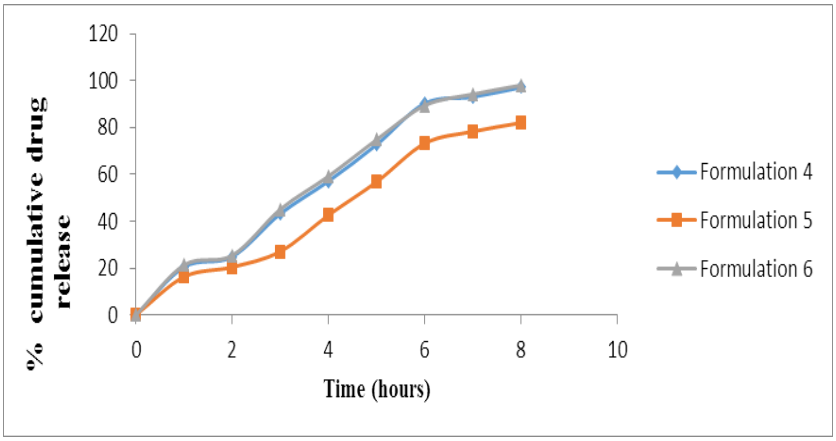

Figure no.6: In-vitro release profile of F_4 to F_6 formulations.

Drug release kinetics

To determine the mechanism of drug release from the formulations (F_4 to F_6) the data were subjected to various drug release kinetic models results are shown in table no.14.

Table no. 14: Drug release kinetics.

Formulation	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	N	R^2
F_4	0.9810	0.9730	0.9805	0.9424	0.5120	0.9907
F_5	0.9467	0.9357	0.9718	0.9821	0.5324	0.9640
F_6	0.9882	0.9487	0.9701	0.9589	0.4674	0.9629

Each formulation was subjected to model fitting analysis to know the mechanism of drug release. In the formulation F_4, release of ketoprofen followed the korsmeyer Peppas with R^2 value obtained was 0.9907. In the formulation F_5, drug release fitted in the Hixon crowell model with R^2 value obtained as 0.9821. Similarly, in the formulations batch F_6 the drug release followed Zero order model with R^2 value 0.9882.

Drug-Excipients Compability Studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug ketoprofen, damar gum, granules of damar gum with ketoprofen are shown in Fig. 1,7 and 9 respectively.

FTIR spectra of pure drug and damar gum were compared with FTIR spectra of granules. FTIR peaks (in cm^{-1}) and its functional groups are given in Table 15.

Table 15: FTIR peaks and functional groups.

Sr. No.	Material	Peaks (cm^{-1})	Characteristic functional groups
1.	Ketoprofen	i) 1700 – 1650 ii) 1750 iii) 3350 – 3200 iv) 3000 – 2900 v) 3100 – 3000	CO str. Esteric CO str. NH str. Aliphatic (CH_3, CH_2, CH) str. Aromatic CH str.
2.	Damar gum	i) 3400 – 3200 ii) 3000 – 2900	OH str. Aliphatic CH str.
3.	Granules of ketoprofen with gum dammar	i) 1700 – 1650 ii) 1750 iii) 3400 – 3200 iv) 3000 – 2900 v) 3100 – 3000	CO str. Esteric CO str. OH str. Aliphatic (CH_3, CH_2, CH) str. Aromatic CH str.

*Str – stretching

From the above table it was concluded that there were no changes in the peak shape and no shift of peaks. So the drug was compatible with the polymer.

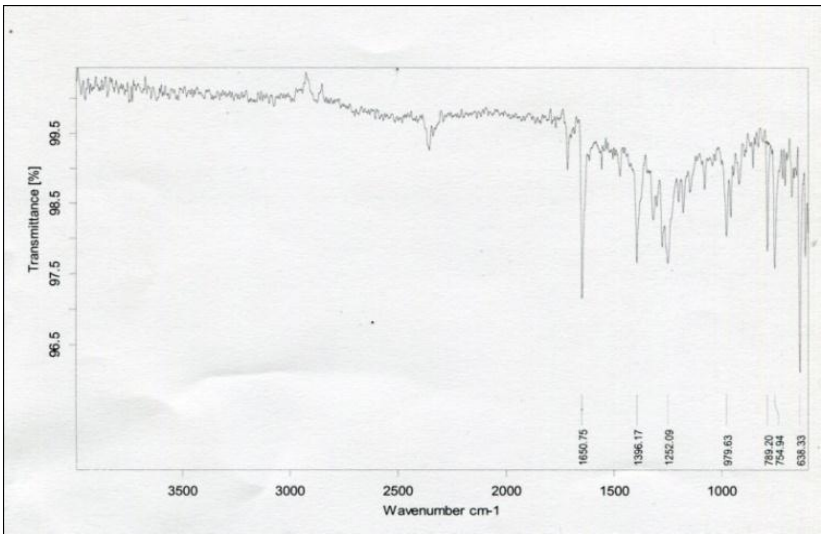

Figure no. 7: IR spectra of ketoprofen.

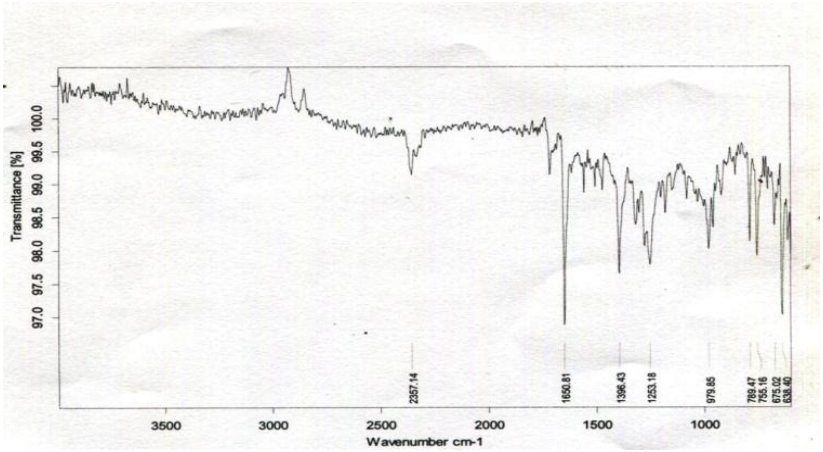

Figure no. 8: IR spectra of Physical mixtures of ketoprofen with gum damar.

DSC STUDIES

DSC thermograms of pure drug ketoprofen, damar gum, granules of ketoprofen with damar gum are shown in fig. 9, 10 and 11 respectively.

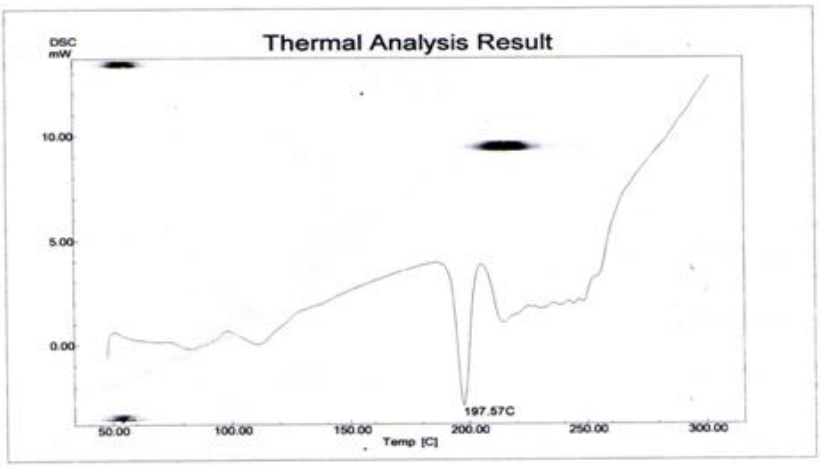

Figure no. 9: DSC thermogram of Ketoprofen

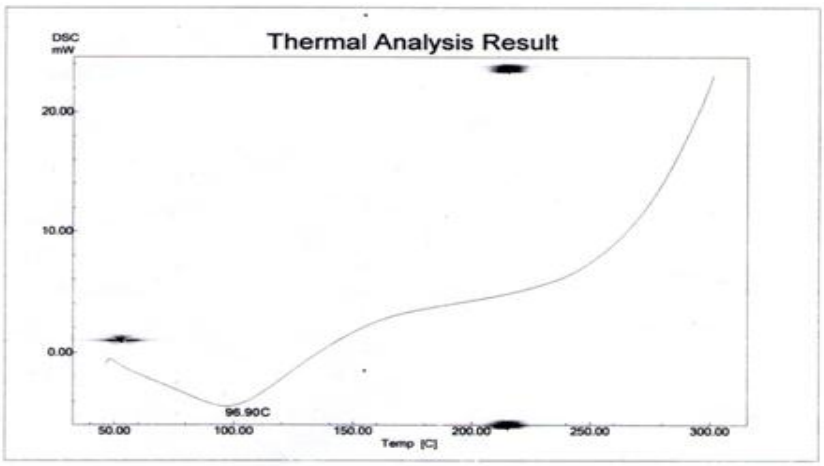

Figure no. 10: DSC thermogram of gum damar.

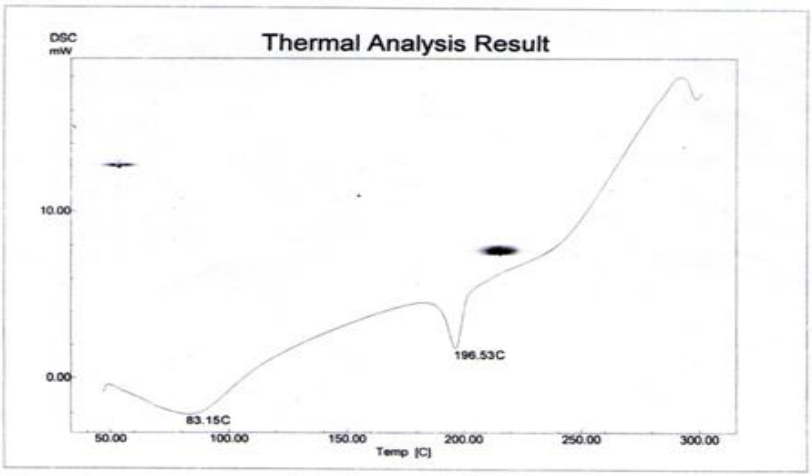

Figure no. 11: DSC thermogram of Ketoprofen with gum damar

DSC thermogram of ketoprofen shows sharp endothermic peak at 197.57°C, indicating the melting point of stable crystalline drug. However, the DSC thermo gram of granules of ketoprofen with damar gum shows sharp endothermic peak at 196.53°C. These thermograms indicated that no significant change in peak shape, area and no shift of peaks were found. Therefore this study revealed that there were no interaction between the drug and polymer.

CONCLUSION

The objective of the present work was to design, formulate and evaluate ketoprofen sustained release dosage form by incorporating it in a sustained release matrix made up of release retardant polymers. Which will prolong the drug release leading to minimize the peak and valley effect in the plasma and provide patient convenience. The compatibility of the drug, polymers and excipients was determined by I.R. spectroscopy and DSC studies. Results showed that the drugs are compatible with polymers and all excipients. The granules were subjected to pre-compression evaluation such as angle of repose, loose bulk density, tapped bulk density and compressibility index. It was concluded that granules exhibited good compressibility and flow property. Three formulations containing gum damar in different ratios were prepared. Three formulations containing 10% micro crystalline cellulose, DCP and lactose were prepared to see the effect of fillers excipients. The tablets were subjected to various evaluation parameters such as weight variation test, hardness test, friability test, and drug content uniformity test. The results for all above evaluation parameters indicate that the values are within the range. It was concluded from the *in-vitro* dissolution study that formulation F_2 from the first three formulations (combination of gum damar and drug with ratio 1:0.75) showed the best release profile. We concluded that the tablets containing DCP

showed lower drug release as compare to tablets containing lactose. All the formulations were subjected to model fitting analysis by treating the data according to various model equations. Formulations F_1 and F_2 followed Hixon crowell model while Formulation F_3 followed Higuchi model.

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