Original Article

Design and Development of Press Coated Pulsatile Release of Ketoprofen Tablets

Srujana Gandrathi[1], Padamatini Naveen kumar[1], Chandrasekhara Rao Baru[1], Sushma Desai[2], M. Shiroja[1], Raaga swetha[1]

From, [1]Assistant Professor, Department of Pharmaceutics, Chilkur Balaji college of Pharmacy, Moinabad Hyderabad, Telangana, India-500075, [2]Research Scholar, Gitam University, Rudraram, Patancheru, Hyderabad, Telangana, India- 502329

ABSTRACT

Ketoprofen pulsatile tablets were developed and evaluated in this work utilizing synthetic polymers grades Hydroxy propyl methyl cellulose (HPMC) E5, HPMCE15, and natural polymer xanthan gum. The angle of repose and compressibility index were determined to be within the acceptable range by pre-formulation investigations of core tablet granules, demonstrating excellent flow properties for compression. The core tablet underwent evaluation procedures that examined content homogeneity compliance, weight fluctuation within standard deviation (SD) ± 2%, hardness, and friability. Evaluations of the coated tablets showed that the weight fluctuation, hardness, and friability all fell within SD ± 2%. In vitro dissolving tests were conducted on formulations F1 through F9, and at the conclusion of the sixth hour, formulation 8 produced a pulsatile drug release. After the allotted period, the medication was released here at once. The stability study, which was conducted for two months for formulation 8 in accordance with International council of Harmonisation (ICH) requirements, was determined.

Key words: ketoprofen; Press-coated pulsatile release tablet; Xanthan gum

Technologies are evolving daily in the pharmaceutical industry, leading to the most effective dose form. In that regard, the most widely utilized and effective method of delivery has been oral for more design freedom for dose forms. Convenience and simplicity of administration [1-5]. Their pharmaceutics excellence and therapeutic advantages over quick release pharmaceutical medicines have been acknowledged more and more in regulatory approval for commercialization [6-11]. Modified-release oral dosage forms have given fresh life to medications that had lost commercial potential because of gastrointestinal problems, toxic effects associated with dose, and the need for frequent administration [12-16]. When it comes to treating conditions like peptic ulcer, asthma, cardiovascular disease, arthritis, diabetes, and hypercholesterolemia, the above regulated and sustained release medication delivery method has limitations because these conditions rely on biological rhythms [17,18]. Pulsatile release is the main rationale for its use when continuous drug release, also known as zero-order release, is desired. In this current project, it is hypothesized that pulsatile drug delivery with various polymers ketoprofen drug effectiveness can be improved [19-24].

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MATERIALS

Ketoprofen was purchased from Infinity Pharmaceuticals. Lactose Monohydrate was purchased from Biocon, Bangalore, India. Microcrystalline Cellulose was purchased from Sigachi Industries. Sodium Starch Glycolate was purchased from Maruthi Chemicals. PVP K 30 purchased from Nabhi chemicals, Thane, India. Isopropyl Alcohol was purchased from Rankem. Purified Talc was purchased from Gangotri Inorganics. Magnesium Stearate was purchased from Amishi Drugs and Chemicals. HPMC E5 & HPMC E15 was purchased from Jianxin Cellulose. Xanthan Gum purchased from Peer Chemical Industries, Hyderabad.

METHODOLOGY

Pre-formulation Studies

Standard graph preparation: Identifying the drug's lambda max: A 100 ml sample of ketoprofen was collected, diluted in 100 ml of 0.1N HCl (1000µg/ml), and then 1 ml of the concentrated sample was made up with 6.8 pH phosphate buffer solution to determine the drug's lambda max.

Calibration curve: To create the principal stock, 100 mg of precisely weighed medication was added to a 100 ml volumetric flask and topped off with 0.5N HCl (1000 mg/ml).

Correspondence to: Sushma Desai, Gitam University, Rudraram, Patancheru, Hyderabad, Telangana, India- 502329.

Email: d.sushmapharma@gmail.com

Serial dilutions of that solution (1, 2, 3, 4, 5) are prepared and scanned under a UV lamp at λ max 260 nm. This process was then repeated with a 6.8 pH phosphate buffer solution and UV scan at λ max 262 nm and menthol at λ max 257 nm.

The Fourier Transform Infra-Red Spectroscopic Study: For compatibility investigations Fourier Transform Infra-Red spectroscopic (FTIR) is used. For the pellet potassium bromide (KBr) was utilized. The ratio is (1:10). The empty medication was examined without any polymer as carrier, and in addition, drug combinations (1:1) were examined for formulation sample 1 mixture containing pure drug Ketoprofen and sample 2 containing Lactose + micro-cellulose phosphate (MCCP) + sodium starch glycollate (SSG) + polyvinyl pyrrolidone (PVP) + talc + magnesium stearate + ketoprofen. Sample 3 containing drug mixture with HPMC E5 and sample 4 containing drug mixture with HPMC E15 and sample 5 mixture containing pure drug ketoprofen with xanthan gum. Moreover, structural elucidation was done.

Solubility: The medicine ketoprofen has BCS (Biopharmaceutics classification system) Class II, which has a weak acid property, poor water solubility presents as (racemic) mixture and good solubility in certain organic solvents, according to a solubility study [25]. Using water, acetone, menthol, ethanol, 0.1N HCL, and 6.8 pH phosphate buffer, the sample was extracted and its solubility was examined. Drug purity assay: 100 mg of precisely weighed medication was added to a 100 ml volumetric flask and diluted with 6.8 pH phosphate buffer (1000 mg/ml). After extracting 1 milliliter of the sample from that solution, it was diluted in a 100-milliliter volumetric flask and examined under a UV lamp at λ max 262 nm. Additionally, the standard sample and this sample were contrasted (identified the difference between the sample and standard/reference sample).

Preparation of Ketoprofen tablet: To create a well-distributed mixture, the powdered ketoprofen, lactose, MCCP pH 102, and sodium starch glycolate were run through a 210µm sieve and then thoroughly combined using a pestle and mortar. With constant stirring, a PVP K 30 alcoholic solution should be added to the mixture dropwise. Lubricating should be followed by compacting the resulting powdery combinations. A conventional oven was used to dry the granules for six hours at 60ºC. Using a traditional single punch press, the dried granules with a size of 25–60 mesh were compacted into tablets after talc and magnesium stearate were added as a lubricant [7].

Pre-compression Studies

Angle of repose: After filling a funnel to overflowing, the produced grains were allowed to pass through the opening under the influence of gravity. The height (h) and the radius (r) of the pile was determined from the cone that formed on a graph sheet, which was used to estimate the pile's area [7].

Repose angle = tan-1 (h/r)

Bulk Density (BD): Twenty grams of precisely weighed grains were added to a 50 ml measuring cylinder. After the first volume (V_0) was measured and determined [12].

Density of bulk = M/V_0

Tapped Density (TD): The grains in the measurement cylinder were tapped 100 times. We measured and determined the cylinder's minimal volume (V_t). M/V_t is the tapped density. The Hausner's ratio. In order to determine Hanuser's ratio, bulk density and tapped density were used. Hausner's ratio = BD – TD [13].

Carr's index (CI) or compressibility index (CI): The tapped density and bulk density were used to calculate and assess the compressibility index [16].

CI=(TD-BD)/TD x 100

Ketoprofen pulsatile drug delivery tablet preparation: 400 mg of polymer (HPMC E5, HPMC E15, Xanthan Gum) and in combination {HPMC E5 and xanthan gum (1:1 and 3:1), HPMC E5 and HPMC E15 (1:1), HPMC E15. xanthan gum (1:1, 2:1, and 3:1)} were removed from the punched tablets, which were used as cores. Two phases were employed when using polymer: first, 200 mg of coating polymer was poured into the die, then cores were placed in the middle of the die and slightly pushed to secure the coatings under and around the core. Finally, the remaining coatings were filled and compressed [19].

Table 1: Formulation of ketoprofen tablets:

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoprofen	75mg	75mg	75mg	75mg	75mg	75mg	75mg	75mg	75mg
Lactose	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg
MCCP pH 102	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg
SSG	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg
PVP solution	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Talc	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg

Magnesium Stearate	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
HPMC E5	400mg	-	-	200mg	-	200mg	-	-	300mg
HPMC E15	-	400mg	-	-	200mg	200mg	250mg	300mg	-
Xanthan gum	-	-	400mg	200 mg	200mg	-	150mg	100mg	100mg

Post compression studies: From each formulation, ten tablets were chosen at random, and each tablet's thickness was measured with a vernier caliper. The standard deviation was also computed. Test of Friability: Using Tablet Friabilator test apparatus, the friability of tablets was assessed. Initially ten tablets were first weighed (W initial), they were put into a friabilator. The friabilator was run for four minutes at 25 rpm or until it reached 100 revolutions. Weighing the tablets after the friabilation as (W final). friability was then determined. Tablets with less than 1% friability are deemed acceptable [21].

In vitro studies: The drug release of ketoprofen from the produced pulsatile tablets was investigated using an eight-station dissolving rate testing device with a revolving paddle at 50 rpm and 25 cm depth in 0.1N HCl for two hours and in phosphate buffer pH 6.8 (900ml) for four hours. A constant temperature of 37.5ºC was maintained during the dissolving process. samples are taken out each at 1hr interval. Using a Ultra Violet (UV) visible spectrophotometer, the drawn samples are measured at 262 nm with 6.8 pH phosphate buffer as reference [21].

Stability Studies: optimized Formulation F8, underwent accelerated stability testing over a two-month period at 40℃ ± 2℃ and 75% ± 5% Relative Humidity (RH). Dissolution and content uniformity tests were also conducted [21].

RESULTS & DISCUSSION

Using various polymers (HPMC E5, HPMC E15, Xanthan gum) and a combination of synthetic and natural polymers (HPMC E5 and xanthan gum (1:1 and 3:1), HPMC E5 and HPMC E15 (1:1), HPMC E15 and xanthan gum (1:1, 2:1, and 3:1)), the current study aims to formulate and evaluate Ketoprofen pulsatile tablets.

Determination of lambda max:

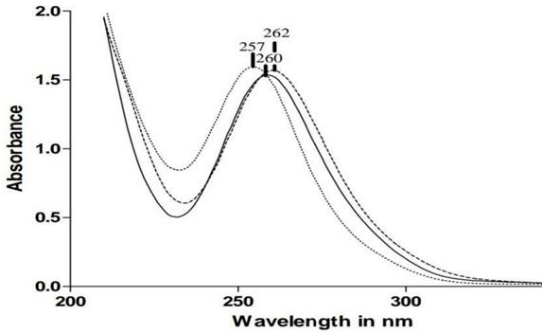


Fig 1: Determination of lambda max of Ketoprofen Drug

Construction of calibration curve:

Table 2: Construction of Calibration curve of Ketoprofen

S.no	Concentration	Absorbance in 0.1N Hcl	Absorbance in 6.8 pH Phosphate buffer
1	10	0.098	0.113
2	20	0.191	0.240
3	30	0.293	0.352
4	40	0.398	0.456
5	50	0.487	0.545

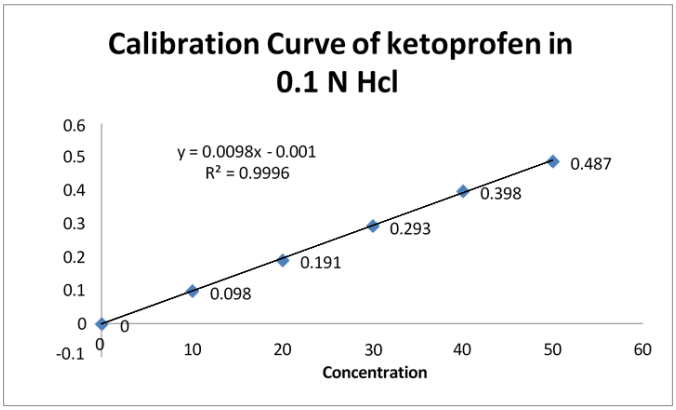


Fig 2: Calibration curve of Ketoprofen in 0.1N Hcl

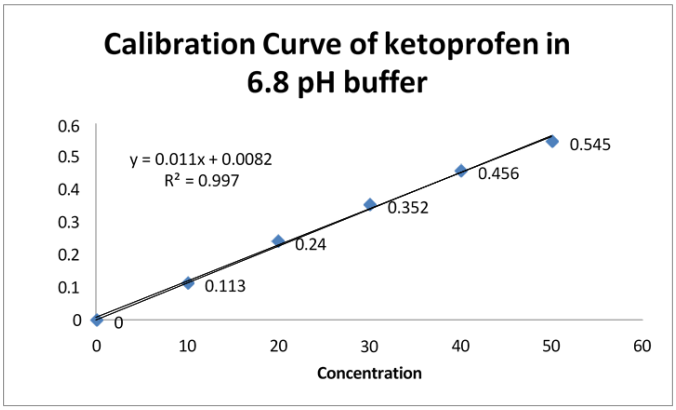


Fig 3: Calibration curve of Ketoprofen in 6.8 pH Phosphate buffer

Compatibility studies:

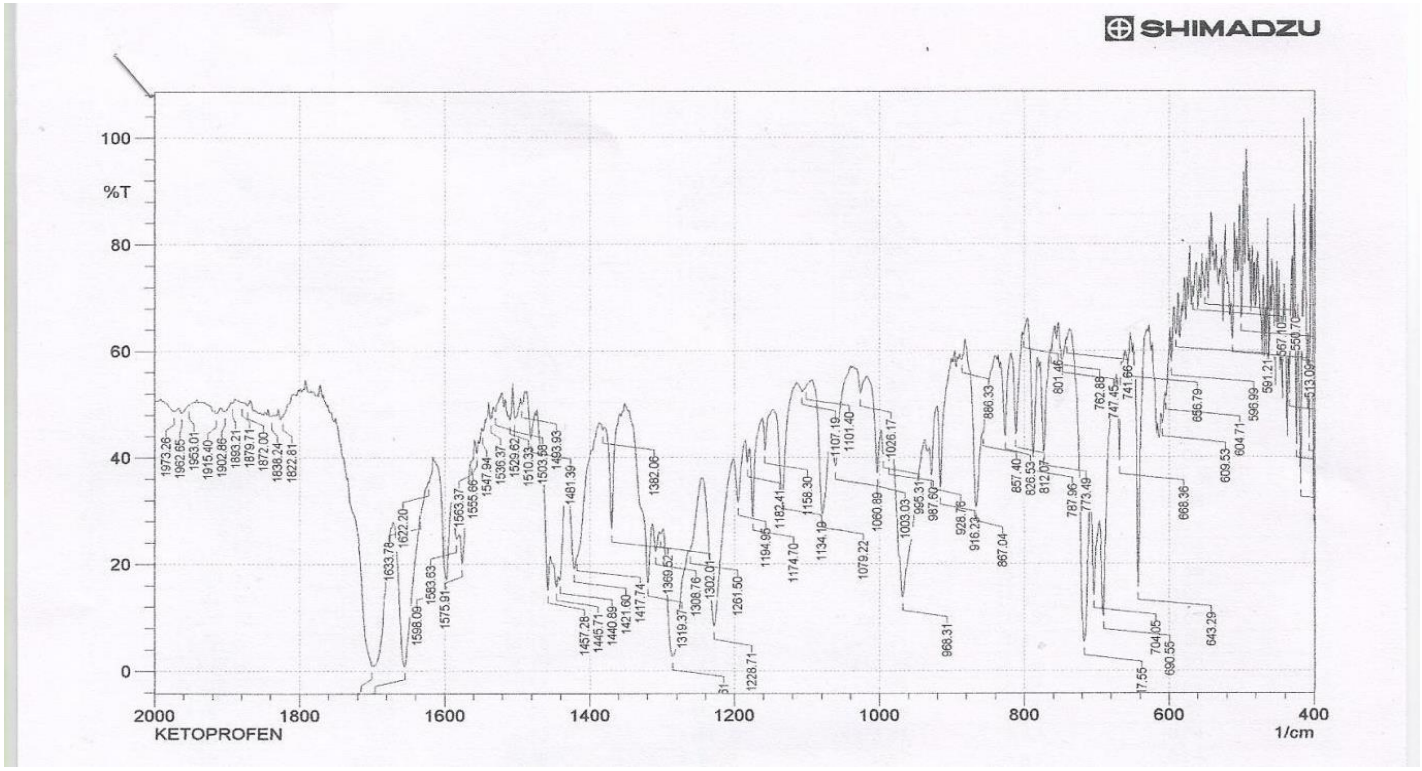


Fig 4: FT-IR of Ketoprofen

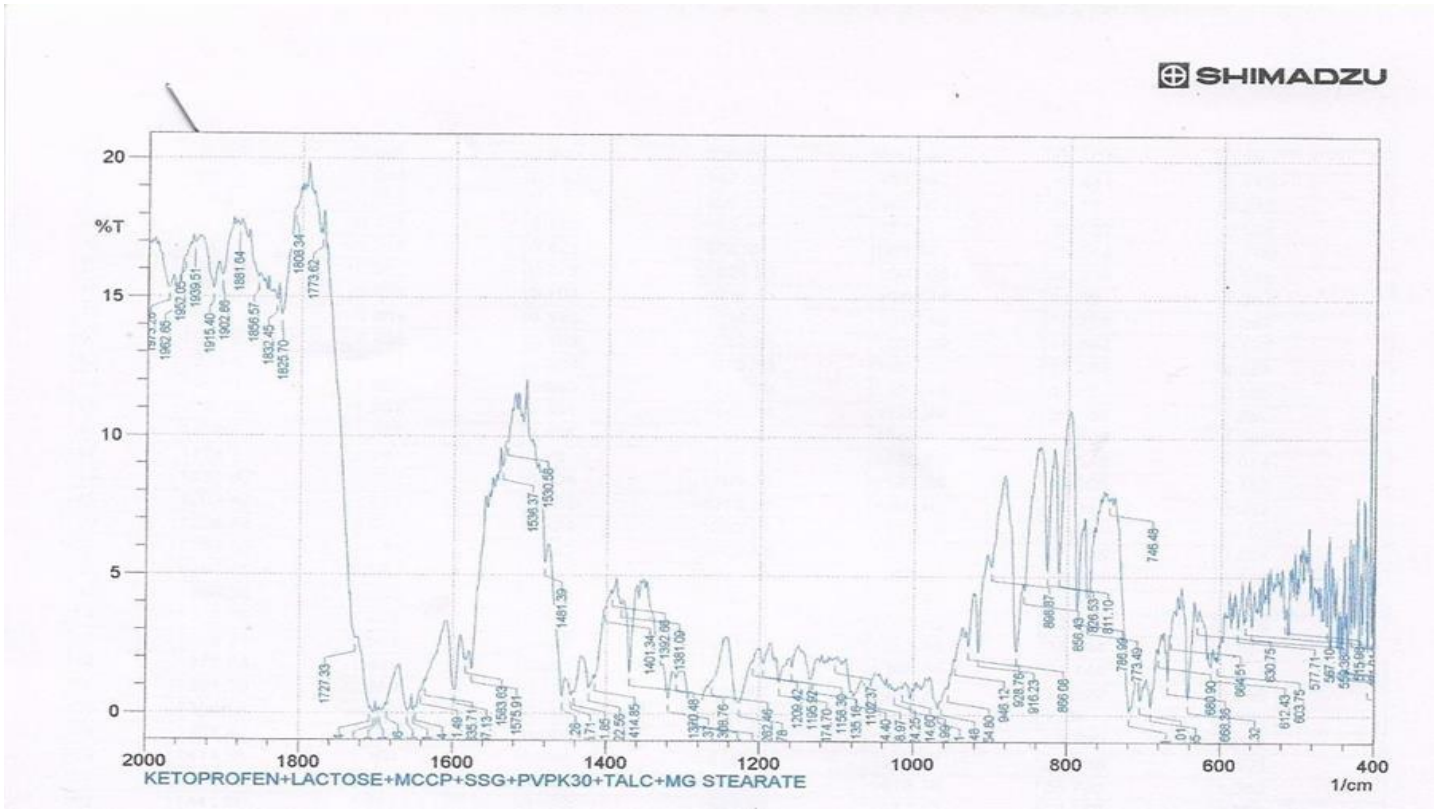


Fig 5: FT-IR of Ketoprofen+ Lactose+ MCCP+SSG+PVP K 30+ Talc + Mg stearate

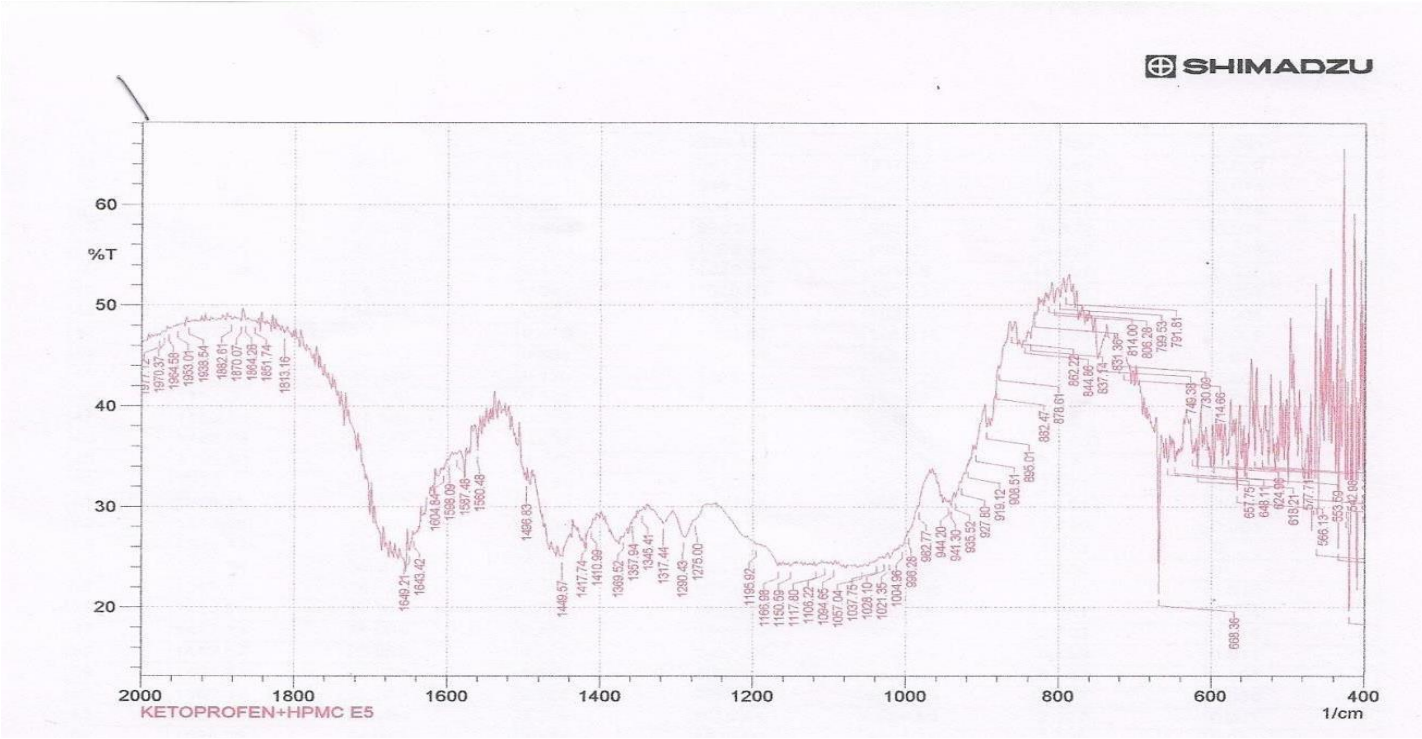


Fig 6: FT-IR of Ketoprofen +HPMC E5

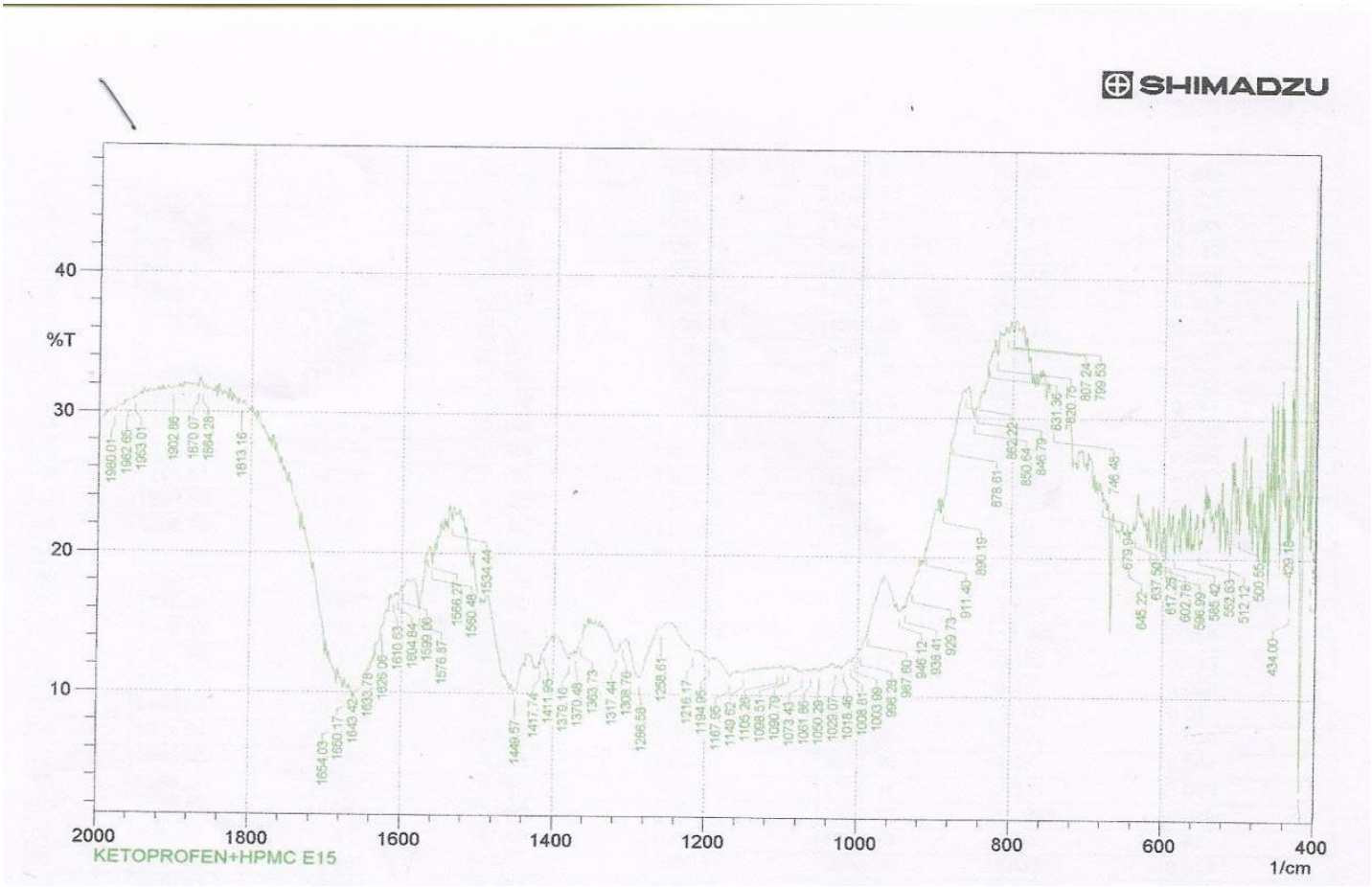


Fig 7: FT-IR of Ketoprofen +HPMC E15

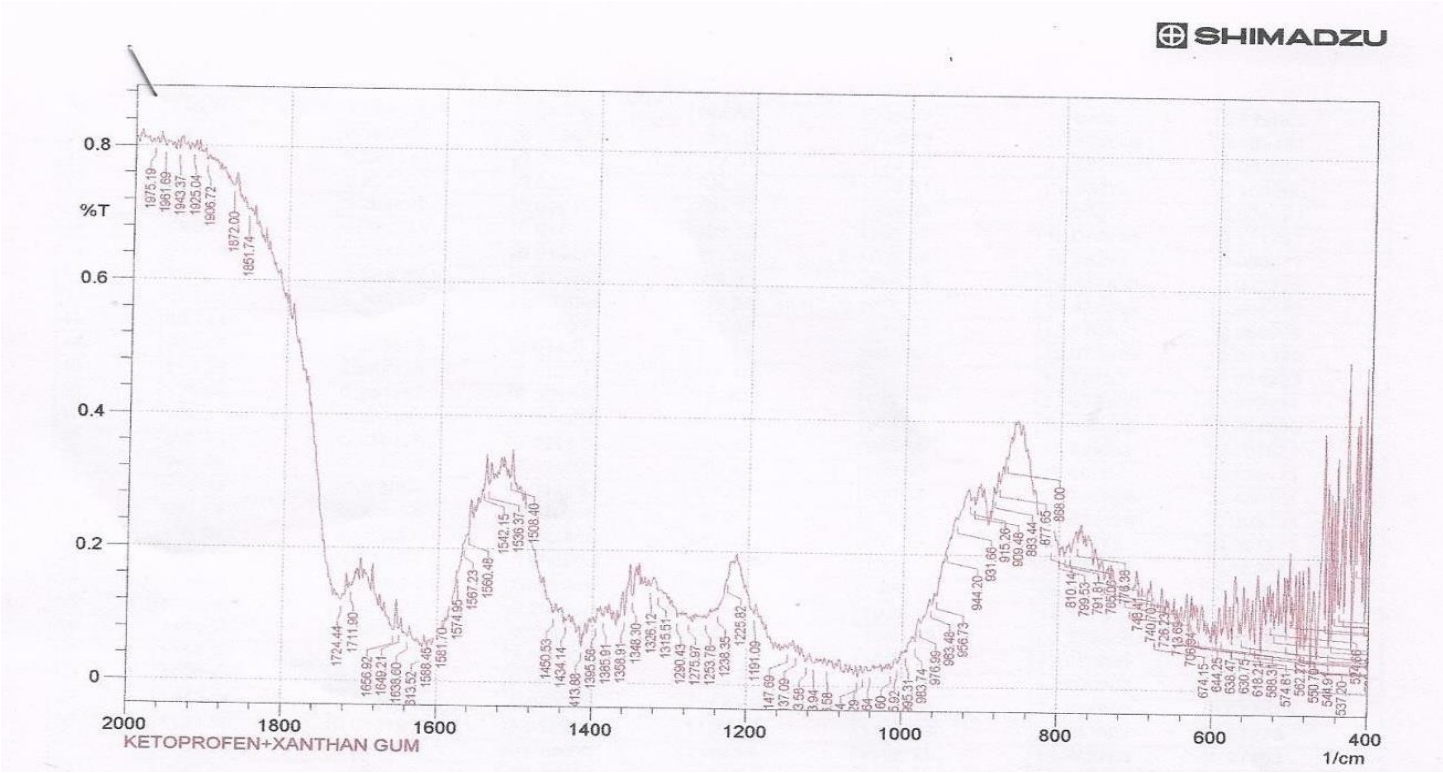


Fig 8: FT-IR of Ketoprofen + Xanthan gum

The FTIR analysis, which was conducted to identify and assess the compatibility of the drug and excipients, revealed no notable alterations in the powder combination of the drug and excipients. For the formulation development, the following excipients were chosen: lactose, MCCP, SSG, PVP, talc, magnesium stearate, and polymers: HPMC E5, HPMC E15, and xanthan gum.

Solubility studies:

Table 3: Solubility of Ketoprofen

SOLVENT	SOLUBILITY
Water	Practically insoluble
Acetone	Soluble
Methanol	Slightly soluble
Ethanol	Soluble
0.1N Hcl	Sparingly soluble
pH 6.8 phosphate buffer	Soluble

It was determined that the organoleptic characteristics and solubility of ketoprofen found highly soluble in acetone, ethanol.

Assay:

Table 4: Study the purity of drug

Method	1	2	3	Avg
Spectrophotometric method	99.96%	100.1%	99.98%	100.01%

Limits: ≤ 99 % - ≥100.5%

Pre-compression Studies

Table 5: Angle of Repose, Bulk density, Tapped Density, Hausner's ratio, Compressibility Index

S.no	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Compressibility Index (%)
1	24.680 ± 0.47	0.432 ± 0.004	0.480 ± 0.005	1.112 ± 0.0119	10.067 ± 0.97

All the values are expressed as mean ± SD n=3

Research on compatibility, solubility, and organoleptic characteristics was done and the results were satisfactory. Angle of repose and compressibility index were determined to be within the range by pre-formulation investigations of core tablet granules, demonstrating excellent flow properties for compression.

Post compression Studies

Table 6: Thickness, Diameter, Hardness, Friability and weight variation of optimized tablet

S.no	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)
1	3.013 ± 0.009	8.005 ± 0.007	9.9 ± 0.316	0.01	0.185 ± 0.003

All the values are expressed as mean ± SD. n=10 For thickness, diameter and weight variation.

Hence for hardness n=5, for friability n=1

Post compression studies of coated tablet

Table 7: Thickness, Diameter, Hardness, Friability, and weight variation

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)
F1	3.79 ± 0.03	12.86 ± 0.008	16.9 ± 0.31	0.02	594.6 ± 2.10
F2	3.81± 0.006	12.32± 0.006	17.0 ±0.3	0.01	595.2 ± 1.469
F3	3.87 ± 0.006	12.867 ± 0.04	6.1 ± 0.3	0.04	595.2 ± 2.18
F4	3.748 ± 0.007	12.931 ± 0.005	16.9 ± 0.3	0.03	595.4 ± 1.624
F5	3.815 ± 0.006	12.983 ± 0.006	14.1 ± 0.3	0.04	594.6 ± 1.854
F6	3.893 ± 0.007	12.883 ± 0.06	15.9 ± 0.3	0.04	594.8 ±1.939
F7	3.847 ± 0.006	12.963 ± 0.004	16.9 ± 0.3	0.02	596.2 ± 1.66
F8	3.863 ± 0.004	12.863 ± 0.004	16.9 ± 0.3	0.01	597.4 ± 1.113
F9	3.851 ± 0.005	12.944 ± 0.004	17.0 ± 0.3	0.01	593.3 ± 1.676

A powder mix was assessed for the pre-formulation investigations, which included Hausner's ratio (1.112 ±0.0119), compressibility index (10.067 ± 0.97), bulk density (0.432 ±0.004), taped density (0.480 ±0.005), and angle of repose (24.680 ± 0.47). The powder was then punched as tablets. The formulation core tablet's angle of repose and compressibility index (Carr's index) were determined to be within the range, demonstrating excellent compression flow properties. The core tablet underwent evaluation trials that included friability of 0.01%, hardness of 9.9 ± 0.316 kg/cm2, weight variation (mg) of -0.185 ± 0.003 falling within 2%, and content uniformity of 103.08 %, which conforms with not less than (NLT) 90.0% to not more than (NMT) 110.0% of the label claim. Following assessment tests of the core tablet, the tablet was press-coated utilizing coating materials HPMC E5, HPMC E15, and xanthan gum. Thus, evaluation tests for weight fluctuation, hardness, and friability of press-coated tablets were conducted and produced positive findings.

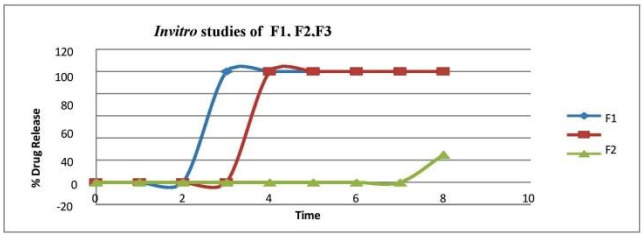


Fig: 9: Invitro studies graph of F1, F2, F3 formulations

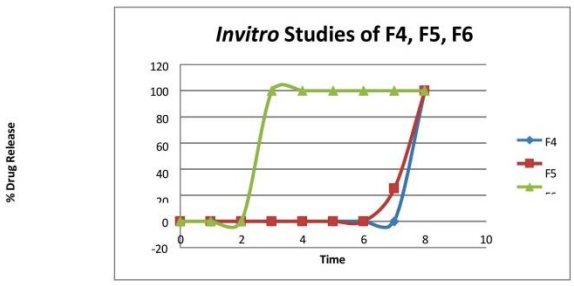


Fig10: In-vitro studies graph of F4, F5, F6 formulation

In vitro studies:

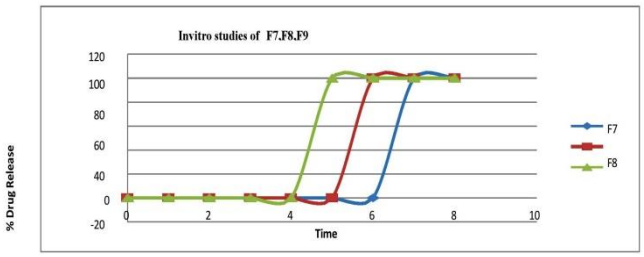


Fig 11: In-vitro studies graph of F7, F8, F9 formulations

In vitro dissolving tests were conducted on formulations F1 through F9, whereas formulation 8 provided a 6-hour pulsatile release of the medication. In this case, the medicine was released entirely after the allotted period, indicating that the formulation was deemed satisfactory. For stability investigations, F8 was chosen based on in vitro release tests.

Stability studies: For stability investigations, F8 was chosen based on in vitro release tests. The formulation 8 (F8), which has a 3:1 ratio of natural polymer (xanthan gum) to synthetic polymer (HPMC E15), exhibits a pulsatile drug release in 6 hours, according to drug release experiments and after two months of accelerated trials, the F8 formulation was discovered to be stable.

Accelerated studies: (40ºC ± 2ºC & 75%±5% RH)

Table 8: Stability studies data for the optimized formulation

S.no	Test parameters	Optimized formulation	
		1st month	2nd month
	Appearance	Almost white colour	Almost white colour
	Drug content	102.98%	102.91%
	Dissolution	At the end of 6th hr released completely	At the end of 6th hr released completely

The stability study was conducted for two months at 40°C ± 2°C and 75% relative humidity ± 5% ACS (Accelerated Stability Studies) in accordance with ICH recommendations. During the study time, tablets were assessed for assay and in vitro dissolving research, and no notable alterations were observed.

SUMMARY

Ketoprofen pulsatile tablets were developed and evaluated in this work utilizing a variety of polymers, including synthetic and natural polymers. The core tablet underwent evaluation procedures that examined content homogeneity compliance, weight fluctuation within SD±2%, hardness, and friability. Evaluations of coated tablets show that the weight fluctuation, hardness, and friability all fall within SD±2%. In vitro dissolving tests were conducted on formulations F1 through F9, and at the conclusion of the sixth hour, formulation 8 produced a pulsatile drug release. After the allotted period, the medication was released here at once. The stability study, which was conducted for two months for formulation 8 in accordance with ICH requirements, was determined to be stable.

CONCLUSION

Although controlled and sustained drug delivery systems have been widely used and successful in the medical field, pulsatile systems can be helpful for providing medications in line with the circadian behavior of diseases. There is always a need for new delivery systems to give patients additional therapeutic benefits. One such technique, pulsatile medicine administration, which administers medications at the appropriate time, place, and dose, has the potential to benefit patients with chronic illnesses such arthritis (rheumatoid arthritis) mostly affects women globally.

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