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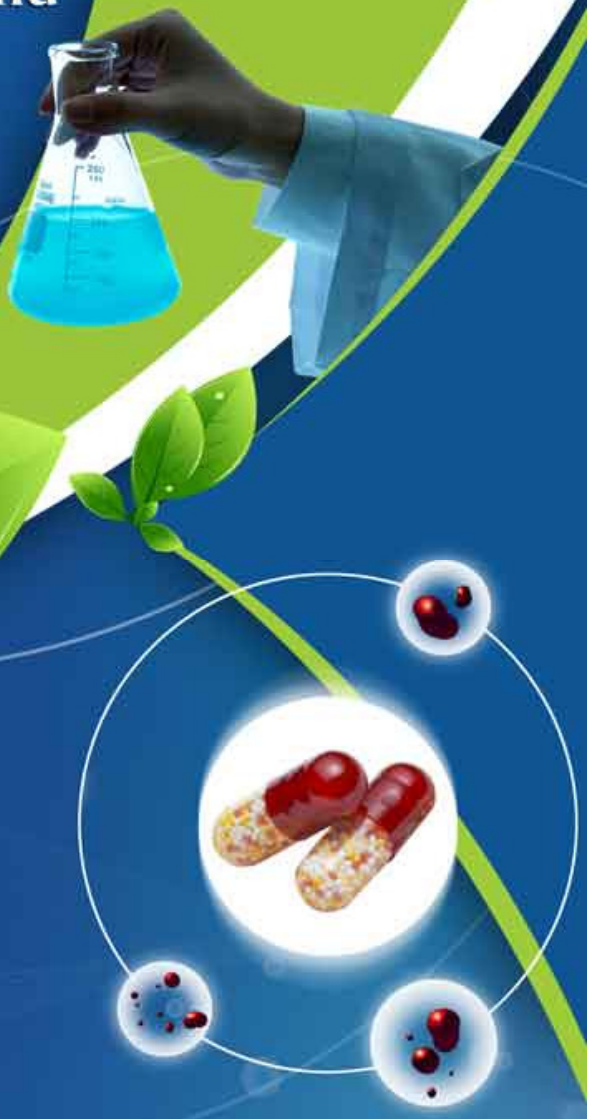

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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF KETOPROFEN

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ABSTRACT

In this study, investigation of pulsatile drug delivery system to achieve time and site specific release of Ketoprofen, based on chronopharmaceutical consideration. The rapid release core tablet contained drug Ketoprofen and superdisintegrant Sodium Starch Glycolate or Croscarmellose and a coating material Eudragit S100. The core tablets of Ketoprofen were prepared by direct compression method with superdisintegrants and other excipients. The pulsatile tablets prepared by using Eudragit S 100 in concentration of 1%, 2% and 3% coating solution. The formulated pulsatile tablets were evaluated for weight variation, hardness, % friability, % drug content and in-vitro drug release. The in-vitro drug release were carried out using pH 1.2 for first 2 hrs, then in pH 6.8 for 4 hrs and in pH 7.4 for period upto 8 hrs. At the end of 8 hr the drug release were 98.34±0.27, 96.44±0.41 and 95.84±0.23 in 1%, 2% and 3% respectively. From obtained results it was found that 1% coating of Eudragit S 100 showed more release than other concentration. The developed formulations showed uniform appearance, average weight, drug content and adequate hardness. It can be concluded from present research the optimized batch (1% Coating batch) beneficial for the pulsatile drug delivery system.

KEYWORDS: *Lag time, Pulsatile drug delivery system, Ketoprofen, Eudragit S 100, In vitro drug release*

INTRODUCTION

Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical R and D sector. Controlled drug delivery systems offer temporal or spatial control over the release of drug. These dosage forms offer many advantages such as

- Nearly constant drug level at the site of action,
- Prevention of peak-valley fluctuation,
- Reduction in dose of drug and reduced dosage frequency,
- Avoidance of side effects and improved patient compliance.

However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as “pulsatile release” [1]. The major bottleneck in the development of drug delivery systems that match circadian rhythms (Chronopharmaceutical Drug Delivery System: ChrDDS) may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases [2].

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Ketoprofen is a nonsteroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. The anti-inflammatory effects of Ketoprofen are due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Ketoprofen is a non-specific cyclooxygenase inhibitor. It is rapidly absorbed after oral administration and maximal concentration in plasma are achieved within 1-2 hrs; food reduces the rate but not extent of absorption. The drug is extensively bound to plasma proteins (60 to 90%) and it has half life in plasma of about 2 hrs; slightly longer half-lives are observed in elderly patients [3, 4, 5].

The core tablets of Ketoprofen were prepared by direct compression method with superdisintegrants and other excipients. The pulsatile tablets prepared by using Eudragit S 100 in concentration of 1%, 2% and 3% coating solution. The formulated pulsatile tablets were evaluated for weight variation, hardness, % friability, % drug content and *in-vitro* drug release. The *in-vitro* drug release were carried out using pH 1.2 for first 2 hrs, then in pH 6.8 for 4 hrs and in pH 7.4 for period upto 8 hrs [6, 7].

EXPERIMENTAL

Materials

Ketoprofen was gifted from Concept Pharma Ltd, Aurangabad. Sodium starch glycolate and Croscarmellose were obtained from JB chemicals Pvt. Ltd. Mumbai. Eudragit S 100 was obtained from Evonik Pvt. Ltd. Mumbai. All other chemicals used were of analytical grade and were used without further purification.

Methods

Drug-excipient compatibility

The infrared spectra of pure Ketoprofen, binary mixture of drug and polymer (1:1), and optimized formulation were recorded between 600 and 4000 cm-1 by FT-IR spectrometer using KBr pellet technique. [8]

Preparation of core tablet F1 to F6 batches

The core tablets were prepared as per given in Table 1 with selected excipients by direct compression on single punch tablet compression machine. Accurately weighed quantities of drug and other ingredients like sodium starch glycolate or Cros carmellose, magnesium stearate, talc were mixed by triturating in glass mortal-pestle. The blend was directly compressed at weight of 200 mg using 8 mm diameter punch. The compositions of the formulation batches containing different ratios of polymers chosen on trial and error basis. Due to slightly solubility of Ketoprofen, solid dispersion of physical mixture of Ketoprofen with HP-β CD in the ratio 1:1 was prepared (Table 2).

Table 1: Preparation of core tablet F1 to F6 batches

Ingredient (mg)	*F1 (4%)*	*F2 (6%)*	*F3 (8%)*	*F4 (3%)*	*F5 (4%)*	*F6 (5%)*
Ketoprofen	50	50	50	50	50	50
SSG	08	12	16	-	-	-
Cross Carmellose	-	-	-	06	08	10
Avicel	128	124	120	130	128	126
Talc	10	10	10	10	10	10
Magnesium stearate	04	04	04	04	04	04
Total (mg)	**200**	**200**	**200**	**200**	**200**	**200**

Table 2: Formulation of solid dispersion core tablet (F7)

Ingredient	*Quantity*
Ketoprofen SD	100
SSG	16
Avicel	120
Talc	10
Magnesium stearate	04
Total	250

Table 3: Formulation of coating solution

Coating material	*Concentration*		
	1 %	*3 %*	*5 %*
1. Eudragit S 100 (gm)	0.5	1.5	2.5
2. Acetone (ml)	10	30	50
3. Castor oil (gm)	0.2	0.6	1
4. Titanium dioxide	q.s	q.s	q.s
5. Talc (gm)	0.5	1.5	2.5

The coating solution prepared as Eudragit S 100 dissolved in the acetone. This organic solution stirred well on the magnetic stirrer for 30 min. During stirring add castor oil, titanium dioxide and talc in that solution. Eudragit S 100 was used as coating material. Castor oil was used as plasticizer to make the coating more flexible. Titanium dioxide was used as opacifier and talc used as antiadherent.

Evaluation of core and coated Ketoprofen Tablets [10, 11, 12]

The core and coated tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (thickness), weight variation, hardness, friability, drug content and in-vitro dissolution profile.

Organoleptic Properties

The prepared tablets were evaluated visually for cracks, depressions, pinholes, colour and polish.

Thickness

Thickness permits accurate measurements and provide information on the variation between tablets. Each core and coated ten tablets were taken and the thickness was measured using a vernier-caliper. The tablet thickness should be controlled within ±5% variation of a standard value.

Hardness

For each formulation, the hardness of each core ten tablets were measured using the

Monsanto hardness tester and mean value and standard deviation was calculated.

Weight variation:

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and the percentage deviation in weight was calculated.

Friability Test:

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by;

$$\% F = Winitial - Wfinal / Winitial \times 100$$

Content of uniformity:

Drug content was determined by dissolving equivalent to 50 mg of drug in methanol kept in ultasonicator for 20 min. Volume was adjusted to 100 ml. Then solution was filtered through whatman filter. Then solution was suitably diluted and absorbance was measured at 259 nm (Thermofisher UV1650). Each sample was analysed in triplicate.

Disintegration test [13]:

Disintegration test was carried out as described under procedure for uncoated tablets in USP. One tablet each was placed in each of six tubes of the basket of the assembly. Apparatus was operated using water, maintained at 37 ± 20 C as the immersion fluid. The time required for complete disintegration was noted for each tablet is as shown in Table 32.

***In-Vitro* dissolution study for core tablets [14]:**

The *In-Vitro* dissolution studies of the pulsatile tablet formulation of Ketoprofen were carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900 ml of standard buffer of pH 7.4 for 1hr. The temperature of the medium was maintained at 37±0.50C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 1 ml were withdrawn after every 5 minutes for a total of 1 hr. These samples were diluted to make up the volume of 10ml with pH 7.4. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form was measured by U.V. visible spectrophotometer, by measuring the absorbance for the samples solutions at 260 nm for Ketoprofen.

***In-Vitro* dissolution study coated tablet [15, 16]:**

The *In-Vitro* dissolution studies of the pulsatile tablet formulation of Ketoprofen were carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900 ml of standard buffer of pH 1.2 for the first 2 hours, in between 4-6 hours followed by pH 6.8 and for the remaining time period up to 6 to 8 hours. The temperature of the medium was maintained at 37±0.5o C. The speed of rotation of the basket was kept at 75 rpm. Aliquots of 1 ml were withdrawn after every half and hrs for a total of 10 hrs. These samples were diluted to make up the volume of 10ml with pH 1.2 buffer for first 2 hours and then by pH 6.8 and 7.4 buffer. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by U.V. visible spectrophotometer, by measuring the absorbance for the samples solutions at 260 nm for Ketoprofen.

Table 4: Data of dissolution study

Apparatus	*USP type II Dissolution apparatus*
Temperature	37 ± 0.5° C
Initial Volume	900ml
Speed	100 rpm
Drawn volume	1 ml
Running Time	2 hrs in pH 1.2, 4-6 hrs in pH 6.8, 8-10 hrs in pH 7.4
Medium Replacement	Media refilling at 2 hrs

***Stability study* [17, 18, 19]**

Accelerated Stability study

Stability studies were carried out as per ICH guidelines. During the stability studies, the product is exposed to normal conditions of temperature and humidity. The optimized Ketoprofen formulations were subjected for stability studies.

Stability protocol

- **Packaging material:** The tablets were wrapped in aluminum foils.
- **Storage condition:** The tablets were subjected to stability as per ICH guidelines at the following conditions. Samples were kept in a stability chamber (Thermo lab, TH 200S).
- **Stability storage conditions**

Table 5: Stability storage conditions

Description	*Storage conditions*
Accelerated testing	40° C / 75 % RH
Room temperature	25° C-30° C

Sampling points

The optimized formulations were subjected to stability for a period of three months. The formulations were subjected to evaluate for the Physico-chemical parameters, for every one month intervals up to three months.

RESULTS AND DISCUSSIONS

FT-IR studies for drug-polymer compatibility

The IR spectra of Ketorofen (Figure 1) exhibited Principal peaks at wavenumbers 1695cm−1 (C=O streching for acid), 1655cm−1 (C=O streching of ketone), 3010cm−1 (C-H streching for aromatic ring), 2968 cm−1 (C-H streching for aliphatic). Thermal analysis of drug was carried out using DSC. The DSC curve of Ketoprofen (Figure 2) showed a sharp endothermic peak at 95.83o C corresponding to its melting point and indicating purity of sample.

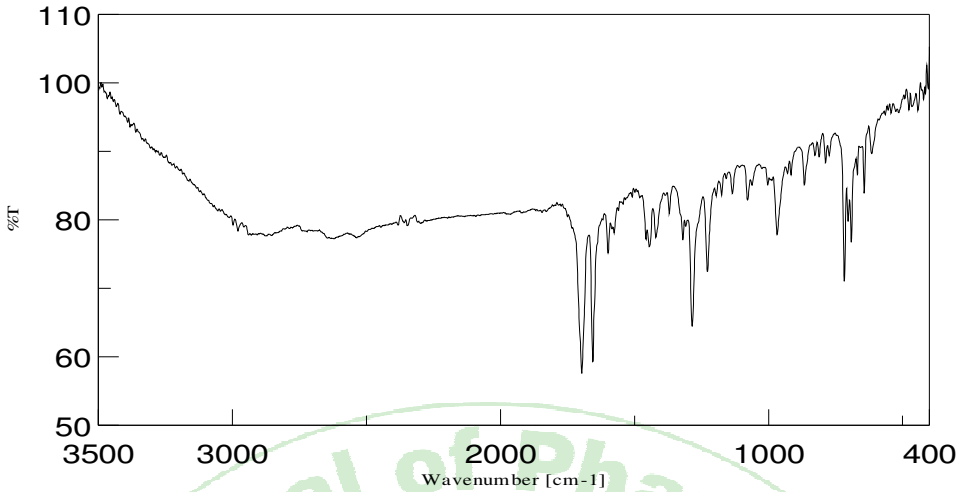

Figure 1: FTIR spectrum of Ketoprofen

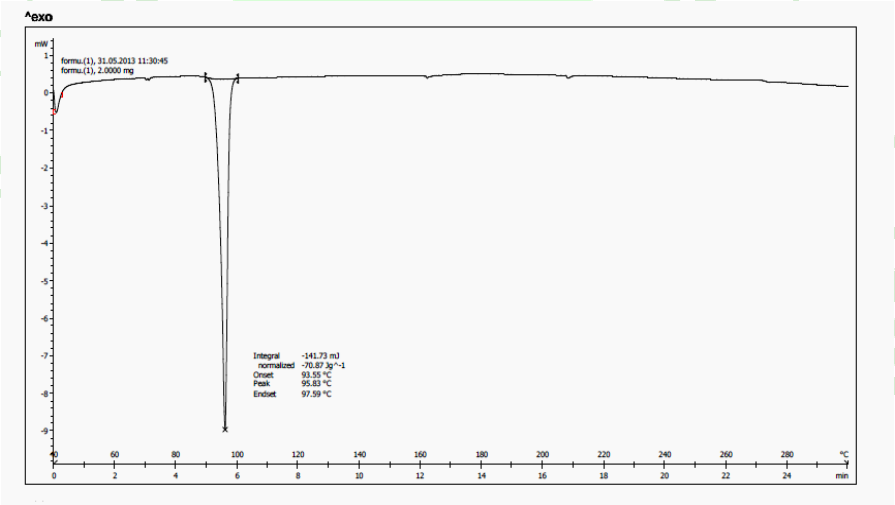

Figure 2: DSC thermogram of Ketoprofen

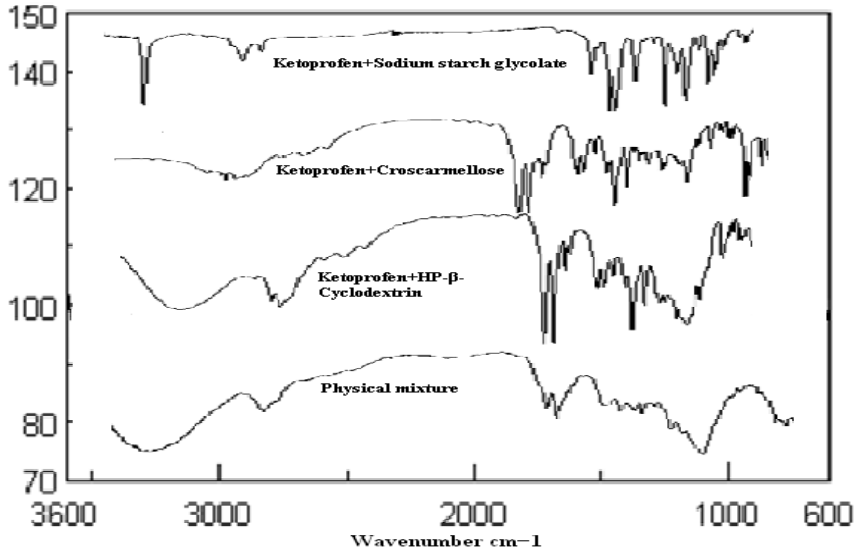

Figure 3: FT-IR spectrum of binary mixture

The IR spectra of binary mixture of Ketoprofen+Sodium starch glycolate, Ketoprofen+Croscrmellose, Ketoprofen+HP β- Cyclodxtrin (1:1) and physical mixture did not show any changes. The principle peaks obtained for the combinations were almost same as that of pure drug. Since there is no change in the position and nature of the bands in the formulation, it is concluded that the drug maintains its identity without any chemical interaction with polymer and excipient used. So all compounds were compatible with each other. The FT-IR spectra of Ketoprofen, binary mixture (1:1) of Ketoprofen with polymers are shown in Fig. 1 and 3 respectively.

Precompression parameters

All the formulations of Ketoprofen showed good flow property as shown in table 3. Angle of repose observed in the ranged of 26.11 to 28.29, Bulk density and tapped density observed in the ranged of 0.42 to 0.51 and 0.47 to 0.5 respectively. While % compressibility index ranged from 7.54 to 10.63%. Hausner's ratio ranged from 1.11 to 1.07. (Table 3)

Table 6: Powder blend properties

Formulation	*Angle of repose*	*Bulk Density (g/cm2)*	*Tapped Density (g/cm2)*	*% Compressibility*	*Hausner's ratio*
F1	26.11±0.04	0.42±0.06	0.47±0.03	7.54±0.03	1.11±0.06
F2	26.88±0.03	0.48±0.06	0.51±0.05	6.12±0.04	1.06±0.02
F3	28.45±0.03	0.47±0.04	0.48±0.03	8.92±0.03	1.02±0.04
F4	28.67±0.02	0.51±0.05	0.58±0.06	7.94±0.05	1.13±0.05
F5	27.02±0.03	0.43±0.06	0.57±0.06	9.09±0.03	1.32±0.06
F6	27.78±0.03	0.52±0.04	0.54±0.05	11.11±0.05	1.03±0.04
F7 (SD)	28.29±0.04	0.51±0.04	0.55±0.03	10.63±0.07	1.07±0.05

[Note- All values are given as mean ± SD, n=3]

Evaluation of core tablets (F1-F7) batch

Hardness and Friability test

The hardness of prepared Ketoprofen tablets was found to be in the range of 4.8 to 4.9 kg/cm2 and friability of tablets was found in the range of 0.6 to 0.5 (< 1%) as shown in Table 4.

Thickness and Weight variation

All the prepared tablets were evaluated for thickness and weight variation and results are shown in Table 4. The percent deviation from the average weight was found to be within the official limits.

Drug content

The drug content uniformity studies revealed that drug content between 97.47 ± 0.22% and 100.51±0.13 is acceptable. (Table 4)

Disintegration test

The disintegration time of all formulation batches were found to be 42-63 sec.

Table 7: Evaluation of tablets parameters

Formulation	*Thickness (mm)*	*Hardness (Kg/cm2)*	*Weight Variation*	*% Friability*	*Content uniformity*	*Disintegration Time (sec)*
F1	2.1±0.15	4.8	200.18±0.49	0.6	97.47±0.22	63
F2	2.2±0.05	4.9	200.94±0.69	0.5	96.37±0.24	55
F3	2.4±0.15	4.8	201.84±0.63	0.6	100.31±0.13	42
F4	2.3±0.15	4.6	201.46±0.54	0.4	97.47±0.23	69
F5	2.1±0.05	4.8	204.5±0.59	0.6	96.28±0.17	61
F6	2.1±0.1	4.5	200.53±0.52	0.6	97.55±0.15	58
F7 SD	2.5±0.15	4.9	250.54±0.59	0.5	100.51±0.13	45

[Note- All values are given as mean ± SD, n=3]

Evaluation of coated tablets (CT1-CT3) batch

Hardness and Friability test

The tablets showed hardness values ranging from 5.4 to 6 kg/cm2. Friability of coated batch was found in the range of 0.3 to 0.6 (< 1%) as shown in Table 5.

Thickness

All coated batches showed thickness values in the range of 2.62±0.020 to 3.20±0.35mm.

Weight variation

The pharmacopoeial limits for deviation for tablets of more than 250 mg are ± 7.5%. The values are found between 255.18±0.035 to 285.53±0.031 for CT 1 to CT 2 batch shown in Table 5. The average percentage deviation for all tablet formulations was found to be within the specified limits. Hence all formulations complied with weight variation test.

Table 8: Evaluation of Coated tablets (CT1-CT3)

Formulation	*Hardness (kg/cm²)*	*Thickness (mm)*	*Weight Variation (mg)*	*Friability (%)*
CT 1	5.4	2.62 ± 0.020	255 ± 0.035	0.3
CT 2	5.2	2.78 ± 0.026	270 ± 0.027	0.4
CT 3	6.0	3.20 ±0.035	285 ± 0.031	0.6

[Note- All values are given as mean ± SD, n=3]

Table 9: *In vitro* drug release study for F1-F7 batch

Time (min)	*F1 (%)*	*F2 (%)*	*F3 (%)*	*F4 (%)*	*F5 (%)*	*F6 (%)*	*F7 SD (%)*
5	30.21±0.27	32.39±0.36	36.22±0.36	33.49±0.23	34.89±0.23	35.67±0.27	17.41±0.27
10	42.08±0.49	35.07±0.23	38.45±0.13	36.17±0.13	37.97±0.36	39.15±0.27	28.81±0.23
15	43.33±0.27	45.80±0.23	42.02±0.27	37.39±0.23	39.90±0.14	42.33±0.23	47.17±0.36
20	49.11±0.35	49.65±0.27	45.53±0.27	44.23±0.27	45.82±0.23	48.89±0.24	62.02±0.35
25	53.21±0.27	54.91±0.36	48.67±0.41	48.99±0.14	51.38±0.36	52.43±0.41	75.32±0.24
30	59.74±0.36	61.77±0.13	51.35±0.35	51.53±0.13	54.08±0.23	56.31±0.36	80.26±0.35
35	67.17±0.36	68.12±0.36	54.91±0.36	55.32±0.27	58.43±0.36	59.97±0.27	83.43±0.23
40	68.39±0.27	71.30±0.36	59.11±0.23	61.24±0.13	63.43±0.13	65.68±0.13	90.68±0.24
45	70.09±0.49	74.65±0.24	69.49±0.23	64.53±0.24	66.74±0.23	69.24±0.28	93.59±0.36
50	75.93±0.24	79.11±0.27	73.85±0.24	69.64±0.35	72.48±0.24	74.06±0.14	94.32±0.49
55	79.69±0.36	81.95±0.27	78.23±0.27	73.22±0.23	75.14±0.27	77.89±0.46	96.36±0.6
60	83.32±0.27	85.51±0.24	88.40±0.24	78.76±0.23	80.30±0.23	82.52±0.23	98.01±0.24

[Note- All values are given as mean ± SD, n=3]

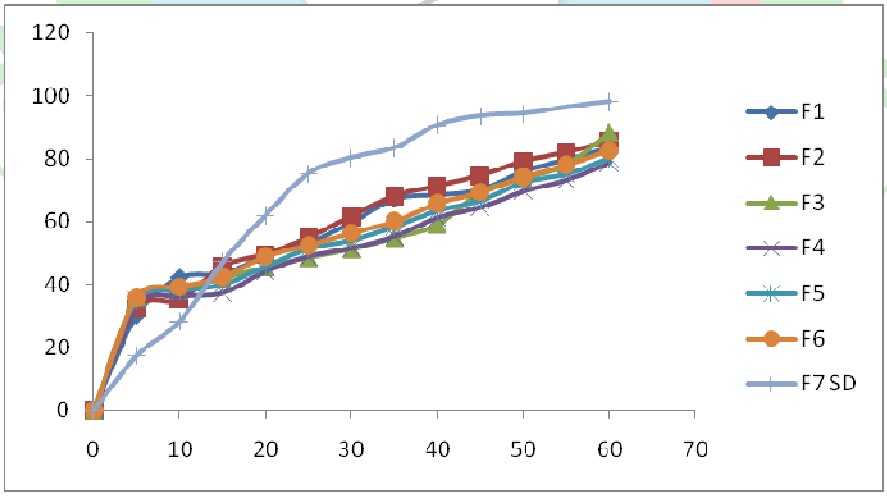

Figure 4: Dissolution profile of core tablets (F1-F7) batch

The *in vitro* dissolution study of F1-F3 batch showed the drug release from 83.32±0.27 to 88.40±0.24. From this data it concludes that F3 batch shown more drug release because it contain 8% of sodium starch glycolate. The *in vitro* dissolution study of F4-F6 batch showed the drug release from 78.76±0.23 to 82.52±0.23. The *in vitro* dissolution study of F7 solid dispersion batch shows the drug release from 98.01±0.24. From this data it concludes that F7 batch shows more drug release from all batches.

Table 10: *In vitro* drug release study for CT 1 – CT 3 batch

Time (hrs)	*CT 1*	*CT 2*	*CT 3*
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	98.11± 0.25	96.11±0.36	95.32±0.12
8	98.34± 0.27	96.44± 0.41	95.84± 0.23

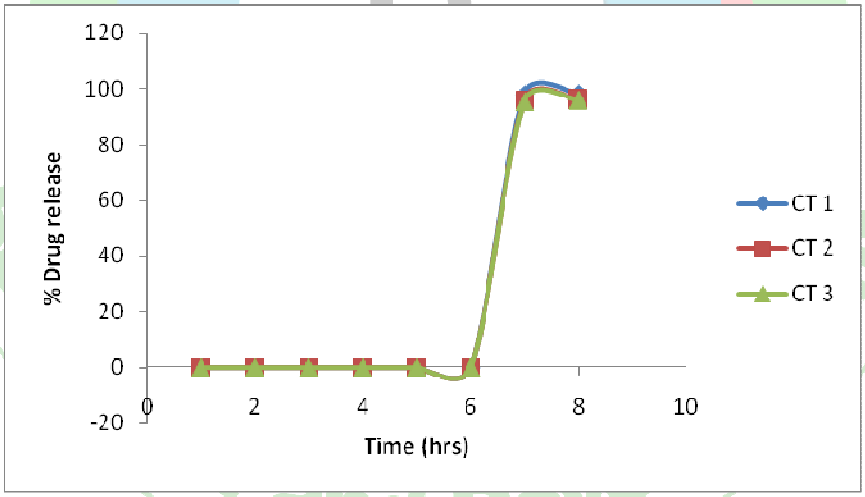

Figure 5: Dissolution profile of coated tablets (CT1-CT3) batch

As the pH dependent coating of Eudragit S 100 was given to CT1-CT3 batch. The dissolution data of batches CT 1-CT 3 revealed that no drug release upto 6 hrs. The *in vitro* dissolution study of CT1, CT2 and CT3 batch showed the drug release 98.34± 0.27, 96.44± 0.41 and 95.84± 0.23 respectively. Batch CT 1 i.e. optimized batch showed more drug release than batch CT 2 and CT 3.

Evaluation of Optimized batch

IR spectrum and DSC thermogram of Optimized batch

FTIR spectra retained the characteristic principal peaks of Ketoprofen shown in Fig.6. The IR spectra of Optimized batch exhibited Principal peaks at wavenumbers 1695cm−1 (C=O streching for acid), 1651cm−1 (C=O streching of ketone), 2968 cm−1 (C-H streching for aliphatic), 1140cm−1 (Ester). The presence of absorption bands corresponding to

the functional groups in the structure of Ketoprofen indicating that there was no interaction between drug and polymer. Thermal analysis of drug was carried out using DSC. The DSC curve of Optimized batch showed a sharp endothermic peak at 96.55o C. The shift in melting point as compared to pure Ketoprofen was observed to due to entrapment of drug within the polymers.

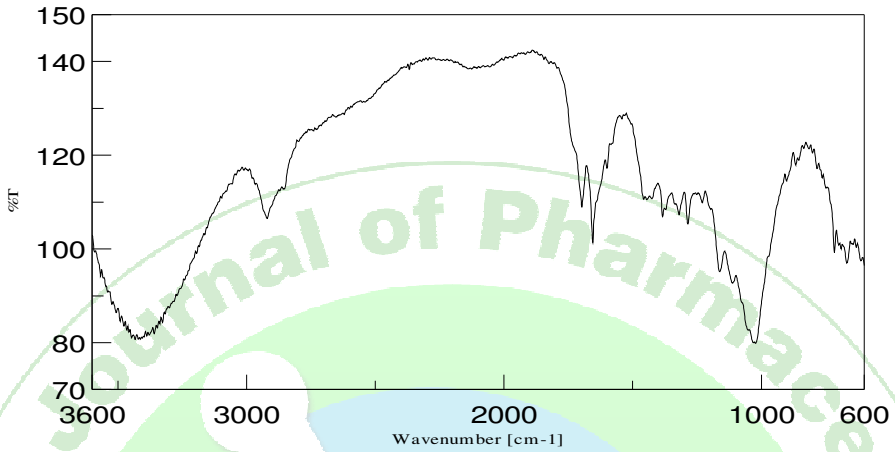

Figure 6: IR spectrum of Optimized Batch (CT 1)

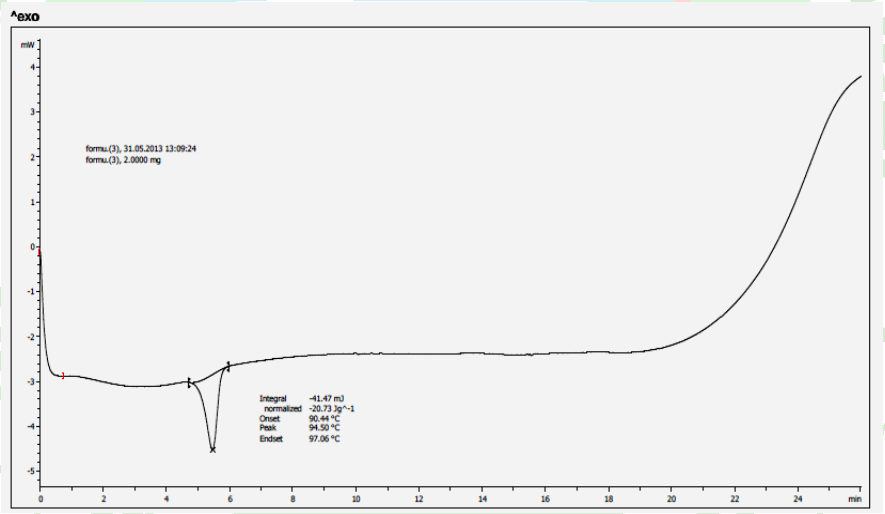

Figure 7: DSC thermogram of Optimized Batch (CT 1)

Stability Studies

The stability studies were carried out on the optimized formulations (CT 1) at two different conditions, as per ICH guidelines for a period of three months. In 3 month stability study there was no significant change in visual appearance, % drug content and % drug release. There wasn't any significant change in drug release profile. The evaluations for 3 month stability are depicated in following Table 8 and 9.

Table 11: Evaluation parameters for stability studies at 40C°±20 /75%±5% RH

Sr. No.	*Evaluation Parameter*	*After 1 month*	*After 2 month*	*After 3 month*
1.	Visual appearance	No change	No change	No change
2.	% Drug content (98.51%)	97.79%	97.63%	97.68%
3.	% Drug release (98.34%)	98.25%	98.19%	98.09%

Table 12: Evaluation parameters for stability studies at 25C°-30C°

Sr. No.	*Evaluation Parameter*	*After 1 month*	*After 2 month*	*After 3 month*
1.	Visual appearance	No change	No change	No change
2.	% Drug content (98.51%)	97.34%	97.25%	97.38%
3.	% Drug release (98.34%)	98.01%	98.88%	98.35%

Thus it was found that the formulation remained stable even after exposing to high temperature and moisture conditions i.e. accelerated condition of temperature and humidity. So it may possess longer shelf life at normal room temperature.

CONCLUSION

From obtained results it was conclude that 1% (CT1 batch) coating of Eudragit S 100 showed more release than other 2% (CT2 batch) and 3% (CT3 batch). The developed formulations showed uniform appearance, average weight, drug content and adequate hardness. The lag time was observed with an appropriate concentration in Eudragit S100 concentration and appropriate concentration of superdisintegrant. It can be concluded from the outcome of the present research that optimized 1% coating of Eudragit S 100 can prove to be best suitable for developing the pulsatile drug delivery system. The outcome of the present study indicated that superdisintegrant like *sodium starch glycolate* exhibits excellent disintegrating property. The lag time was observed with an appropriate concentration in Eudragit S100 concentration and appropriate concentration of superdisintegrant.

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