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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF LORNOXICAM BY DIRECT COMPRESSION METHOD

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ABSTRACT

The aim of the present work was to develop sustained release Lornoxicam matrix tablets with polymers like HPMC K15M, Ethyl cellulose, and Crospovidone as carriers in varying quantities. Direct compression was used to make matrix tablets. Various assessment parameters, such as hardness, friability, thickness, percent drug content, weight variation, and so on, were applied to the prepared formulations. *In vitro* dissolution studies were carried out for 24 hrs. The tablets were subjected to in-vitro drug release in (pH 1.2) for first 2 hrs. Then followed by (pH 6.8) phosphate buffer for next 22 hrs. And the results showed that among the six formulations FL3 showed good dissolution profile to control the drug release respectively. The drug and polymer compatibility were tested using FT-IR spectroscopy, which revealed that the drug was compatible with all polymers. It is also required to design an appropriate prolonged release formulation for Lornoxicam in order to maintain the drug's release. Hence by using the compatible polymers sustained release tablets were formulated and subjected for various types of evaluation parameters like friability, hardness, drug content and dissolution behaviour. Finally, the findings reveal that the prepared sustained release matrix tablets of lornoxicam have improved efficacy and patient compliance.

Keywords: Lornoxicam, HPMC, Ethyl cellulose, Crospovidone, Sustained release, Matrix tablets.

INTRODUCTION

Lornoxicam is a Non-Steroidal anti-inflammatory drug which is mainly used in treatment of "Arthritis" means joint Inflammation. Lornoxicam drug belongs to class of oxicam which inhibits the production of prostaglandins by inhibiting the action of cyclooxygenase enzyme which regulates the conversion of arachidonic acid to prostaglandins pathway. Lornoxicam drug is absorbed rapidly and completely from gastro- intestinal tract after oral administration route[1]. The absolute bioavailability of Lornoxicam drug is 90-100% the inhibition of cyclooxygenase enzyme is thought to be primarily responsible for the anti-inflammatory effect and analgesic effect of Lornoxicam drug [2, 3].

The main objectives of present investigation are to confirm the drug by various analytical techniques, to study the drug excipients compatibility, to avoid the dose as well as the frequency of the dosage form and to perform the stability[4-7] . Jadi PM *et al* 2015 worked on development of extended-release matrix type tablets of lornoxicam drug using HPMC K15M, Crospovidone, Ethyl cellulose, and polymer as carrier's substance in various concentrations. Their study showed to improve biological efficiency of drug and better type patient compliance[8].

Any medication delivery method that provides slow drug release over a long period of time is classified as a sustained release system. A controlled-release system is one that is successful in maintaining consistent medication levels in the blood or target tissue. If it fails to achieve this but nevertheless extends the duration of action beyond that of conventional delivery, it is considered as a prolonged release system [9].

MATERIALS AND METHODS

Chemicals: Lornoxicam, Hydroxypropylmethyl cellulose (HPMC K15M), Ethyl cellulose, Crospovidone, Microcrystalline Cellulose, Magnesium stearate And Talc.

Instruments: Electronic Balance, UV Spectrophotometer, FTIR Spectrophotometer, DSC, Sonicator, Stability Chamber, Tablet Dissolution Testing Apparatus, Rimek Mini Tablet Press 2, Monsanto Hardness Tester, Rotatory Flask Shaker.

UV Spectra: Accurately weighed about 100 mg of Lornoxicam drug and dissolved in phosphate buffer solution (pH 6.8). To dilute the solution to 100 mL, phosphate buffer was used (pH 6.8). Further 10 ml of this solution type was diluted to 100 ml with phosphate buffer solution (pH 6.8). The resultant solution of the drug was scanned for absorption maxima (λmax) spectrophotometrically between 200nm and 400nm range. The maximum absorption of the drug solution was observed at 376nm.

Fourier Transform Infrared Spectroscopy: The formulations were subjected to FT-IR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FTIR analysis of the pure drug and optimized formulation was carried out using an FTIR spectrophotometer (Bruker FT-IR - USA).

Preparation of sustained release Lornoxicam tablet

Using the direct compression technique, 8mg of Lornoxicam was mixed with excipients (Magnesium stearate, microcrystalline cellulose, and talc). Desired amount of blend was directly compressed into tablets using rotary with various polymers such as HPMC K15M, Ethyl cellulose, Crospovidone and other tablet

compression machine (Multi punch machine). Magnesium stearate was used to lubricate the surface of the die and punch before compression. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 5.5-6.5 kg/cm2. All of the preparations were kept at room temperature in an airtight container for future research.

Evaluation of Pre-compression Parameters

Angle of repose

The angle of repose of the powder blend was determined by using the funnel method. The accurately weighed or quantity of the powder was taken in a funnel. The height of the funnel which was more adjusted in such a way that the tip of the funnel is just touched the apex of the heap of the powder material. The diameter of the powder material cone formed was measured and the angle of repose was calculated by using the below formula.

$$\text{Tan } \theta = h/r$$

Where: θ = is angle of repose. h = is height of the heap of pile and r = is radius of base of pile

Bulk Density and Tapped Density

They were able to determine both the loose bulk density (LBD) and the tapped bulk density (TBD). An amount of the powder blend was introduced in a 100 ml measuring cylinder then the weight of powder blend was determined tarred type method. The cylinder was allowed to fall onto a hard surface or plate from a height of 2.5 cm at 2 sec intervals. The tapping on the tab densitometer was continued until no volume change in the cylinder was observed. The formulas below were used to calculate LBD and TBD.

LBD=weight of the powder/ volume before tapping

TBD= weight of the powder/ tapped volume of the packing

Carr's Compressibility Index

A significant measure that can be simple obtained from the bulk density determinations is percent (%) compressibility C, % Carr's Index parameter can be basically calculated by using the following formula.

Carr's index percentage = tapped bulk density (TBD) –loose bulk density (LBD)/tapped bulk density (TBD) x 10

Hausner's ratio

Hausner ratio is an indirect type index for measuring the powder flow character. It is widely used for calculated by this following formula.

Hausner ratio's ratio = tapped density (TD)/ bulk density (BD).

Evaluation Post compression studies of Lornoxicam sustained release matrix table:

Thickness

Vernier callipers were used to measure the thickness of the tablets. Ten tablets from each batch were used and thickness values are reported in millimetres Mean and SD values were also calculated.

Hardness

Tablet requires certain amount of mechanical strength or stress or hardness which was measured by Monsanto Hardness Tester. During manufacturing ten tablets were randomly selected from each formulation of the drug batch and evaluated for hardness, which was expressed in Kg/cm^2. For each single batch five tablets were used.

Weight variation

Using Thirty pills were chosen at random from each formulation type and weighed individually to assess for weight variance. The average weight was computed and compared to the weight of each individual pill. The US Pharmacopoeia allows for very minor variations in tablet formulation weight. The following formula is used.

Weight Variation = (IW - AW)/AW X 100%

Where: IW: Individual weight, AW: Average weight

Drug content uniformity

Twenty tablets were weighed accurately and crushed into a fine powder. Lornoxicam tablet powder weighing 25 mg equivalent weight was accurately weighed and transferred to a 100 ml volumetric flask. After shaking for 10 minutes, 50 ml of phosphate buffer (pH6.8) was added. Then, the volume was made up to 100 with phosphate buffer. The solution in volumetric flask was filtered, diluted suitably and analysed spectrophotometrically at 376 nm. The amount of drug was estimated by using standard calibration. The percentage drug content was calculated.[10]

Friability[11]

The Friability was performed by using Roche Friabilator. Twenty lornoxicam formulation tablets were weighed (Initial weight-W) and placed in the friabilator plastic chamber. The machine was then turned 100 times at 25 rpm for 4 minutes. Tablets were dropped from a distance of six inches with each revolution of friabilator. Tablets were deducted and reweighted (final weight-Wt). Friability of the tablets of lornoxicam formulation should be less than 1%.

$$\text{Friability} = [1 - (Wt/W)] \times 100$$

In-vitro dissolution studies[12]

In-vitro dissolution studies were carried out using the USP XXIII dissolution apparatus type II at 50 rpm using 0.1N HCl (pH 1.2) solution (900 ml) as a dissolution medium at 37 ± 0. 5ºC for the first 2 hr interval and phosphate buffer (pH 6.8) solution (900 ml) for the rest of the time period. 5 ml of drug sample was withdrawn at the predetermined time interval of 1 hr up to 24 hr and replaced with the same volume of fresh dissolution medium. The withdrawn drug samples were filtered and analysed by UV spectrophotometer at 376 nm using pH 6.8 solution as a blank. The Percentage cumulative drug release was calculated.

RESULTS AND DISCUSSION

All batch tablets F1-F6 were successfully prepared using the direct compression process.

All the formulations were prepared by direct compression process to improve the solubility of drug and to mask the bitter taste of the drug, which is vital for preparation of oral Sustained release matrix tablets.

Preformulation studies Lornoxicam were carried out by determination melting point, solubility and λmax. The obtained results complied with IP standards, thus indicating the purity of drug.

FTIR and DSC study revealed that there was no chemical interaction between the drug (Lornoxicam) and other excipients when they are combined together.

The λmax of Lornoxicam were measured at 376nm respectively, and the calibration curve was built using concentration ranges of 0-10 ppm. Equation was found to be y = 0.032X - 0.007 and the regression coefficient R2 = 0.999. Spectra and calibration curve were showed in Fig 2.

FTIR spectra of Lornoxicam and the optimized formulations are shown in Figures 6 and 7. The FTIR spectrum of Lornoxicam exhibited at 3588cm-1 , 3091cm-1 , 1386cm-1 , 1643cm-1 , 750 cm-1 , 1150cm-1, 1772cm-1. (OH group, NH group, S=O Stretching, C=N Stretching, C-Cl Stretching C-N bending, C=O group,). Band at 3090cm-1 , 3067cm-1 , 1487cm-1 , 1597cm-1 , 740cm-1 , 1225cm-1,1643m-1.(OH group, NH group, S=O Stretching, C=N Stretching, C-Cl Stretching C-N bending, C=O group,). All of these distinct bands were retained in formulations, indicating that there is no interaction between the drug and the polymers.

Figures 4 show DSC thermograms of Lornoxicam and Lornoxicam exhibited a strong endothermic peak at 240.18°C, which corresponded to its melting point.

The DSC curve of drug and polymers (physical mixture) shows sharp endothermic peak at 102.32°C and 182.53°C respectively. The drug does not undergo decomposition following its melting. This indicates that no chemical interaction between the drug and excipients mixture is likely. Thermograms is as shown in Figure 5.

The powder blends were prepared by mixing of various ingredients mentioned in Table 1 and used for characterization of various flow properties of powder. Table 4 reports the values for Compressibility Index (CI) and Hausner's ratio (HR) for all prepared batches. According to the literature, powders with CI values below 15% are suitable for producing the tablets and those with a Hausner's ratio values below 1.25 and angle of repose values in between 20-40˚ indicate good flow properties of powders. The results are shown in Table 5.

Tablets were evaluated for hardness, thickness, friability, contents of active matter, and weight variation, as procedure mention in method. The results were within the specified limits. All the studies were performed in triplicate, and results are expressed as mean ± SD. The results are shown in Table 6.

The in-vitro release of drug (Lornoxicam) from sustained release matrix tablets was found to vary according to the type and concentration of disintegrants used. The drug release was increased, due to the higher concentrations of (Ethyl cellulose and crospovidone) which enhance the tablets and improves dissolution. Among all the formulation, the F3 showed significantly higher drug release than other formulations.

In-vitro dissolution studies of SR matrix tablets were within limit and drug release profile was found to be 96.63 % in 24 hrs. Which shown in Table 7.

Stability studies were carried out with selected formulation i.e. F3 and the results of studies indicated the formulation was stable at 400C / 75%RH as presented in Table 8.

Table 1: Composition for sustained release matrix tablet of Lornoxicam formulation design

Ingredients (in mg)	FL1	FL2	FL3	FL4	FL5	FL6
Lornoxicam	8	8	8	8	8	8
HPMC K15M	10	10	10	10	10	10
Ethyl cellulose	8	16	24	-	-	-
Crospovidone	-	-	-	8	16	24
Magnesium Stearate	6	6	6	6	6	6
Microcrystalline cellulose	64	56	48	64	56	48
Talc	4	4	4	4	4	4
Total	100	100	100	100	100	100

Table 2: Angle of Repose I.P. limits

Angle of Repose (◦)	Type of Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Table 3: Compressibility Index (%) and Hausner's Ratio I.P. limits

Compressibility Index (%)	Flow property	Hausner's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59

Table 4: Standard of Weight variation

Average weight of tablet	% deviation
≤ 80mg	±10
>80 mg – 250 mg	±7.5
≥ 250 mg	±5

Table 5: Micromeritic properties for lornoxicam sustained release matrix tablets

Parameters	FL1	FL2	FL3	FL4	FL5	FL6
Angle of repose (Θ)	25.33	25.12	25.30	25.41	24.16	25.52
Loose bulk density (LBD) g/ml	0.400	0.372	0.384	0.332	0.337	0.254
Tapped density (TBD) g/ml	0.464	0.453	0.373	0.392	0.398	0.284
Carr's index	13.96	14.60	10.15	13.56	14.51	11.52
Hausner ratio	1.15	1.16	1.10	1.14	1.11	1.16

Table 6: Post formulation parameters of Lornoxicam sustained release matrix tablets

Parameters	FL1	FL2	FL3	FL4	FL5	FL6
Thickness ±S.D. mm(n=10)	2.43±0.02	2.51±0.04	2.54±0.02	2.51±0.03	2.46±0.05	2.55±0.03
Hardness S.D. (kg/cm2)	5.7±0.2	6.1±0.4	6.2±0.2	5.9±0.2	6.5±0.2	5.8±0.3
Average Weight variation (n=20) mg	101.4±1.50	102.62±1.67	101.51±1.42	100.35±1.34	100.27±1.59	101.22±1.60
Drug Content (%)	100.65±1.20	98.51±1.47	97.25±1.59	98.70±0.94	99.66±2.16	98.81±0.56
Friability (% w/w)	0.37±0.04	0.41±0.05	0.35±0.03	0.45±0.04	0.39±0.08	0.30±0.03

Table 7: Cumulative % drug release

Time (hrs.)	% CDR					
	FL1	FL2	FL3	FL4	FL5	FL6
0.5	16.36	10.9	4.09	34.09	31.36	6.81
1	24.65	24.61	10.93	42.5	43.84	8.22
2	28.9	30.23	19.19	52.32	49.59	11.01
3	31.93	31.87	26.16	54.26	54.21	24.76
4	33.35	35.11	31.91	59.44	60.73	34.61
5	41.28	40.25	53.41	67.1	64.69	43.39
6	46.36	47.8	62.81	75.6	67.88	57.74
12	51.41	51.63	72.72	77.36	70.09	66.54
18	60.35	68.93	84.05	80.96	76.41	78.83
24	68.55	79.85	96.63	87.22	84.08	82.51

Table 8: Physicochemical evaluation for stability study

Parameters	Drug content (%)	Hardness ± S.D. (kg/cm2)	Friability ± S.D. (% w/w)	Weight variation (N=20) mg	In-vitro drug release	
					At 10hr.	At 24hr.
Initial	99.48±0.91	5.1±0.3	0.36±0.08	100.40±2.81	48.59	96.85
After one month	99.26±0.44	5.0±0.4	0.36±0.08	100.38±1.34	48.06	96.83
After two months	99.25±0.41	5.0±0.4	0.36±0.02	100.38±1.12	48.02	96.42

Table 9: Characteristic peaks of pure drug lornoxicam and optimized formulation

Functional Group	Pure drug lornoxicam (Wave no. cm^{-1})	Optimized formulation (Wave no. cm^{-1})
OH	3588	3090
NH	3091	3067
S=O	1386	1487
C=N	1643	1597
C-Cl	750	740
C-N	1150	1225
C=O	1772	1643

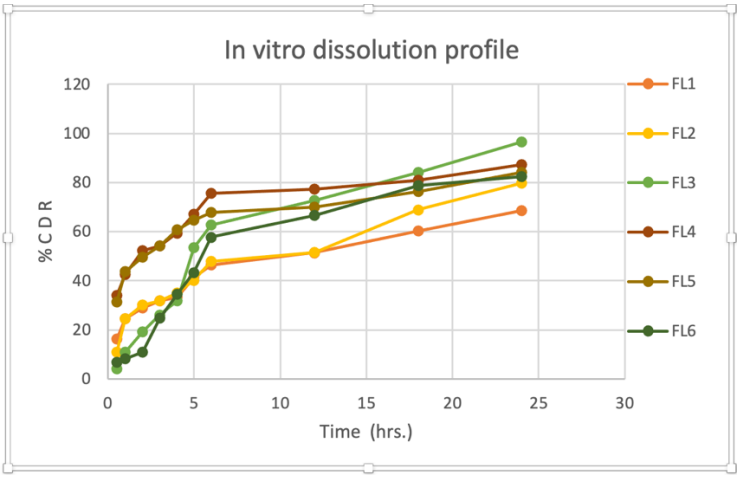

Fig 1: *In vitro* dissolution profile

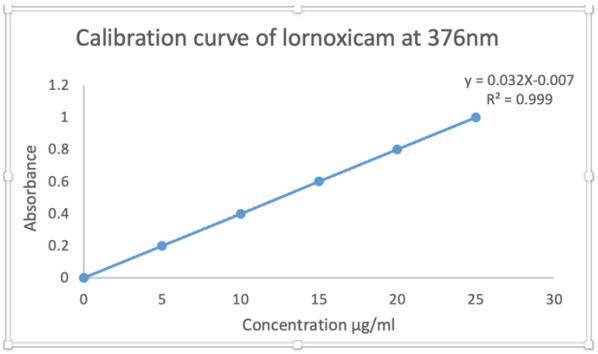

Fig 2: Standard calibration curve of lornoxicam

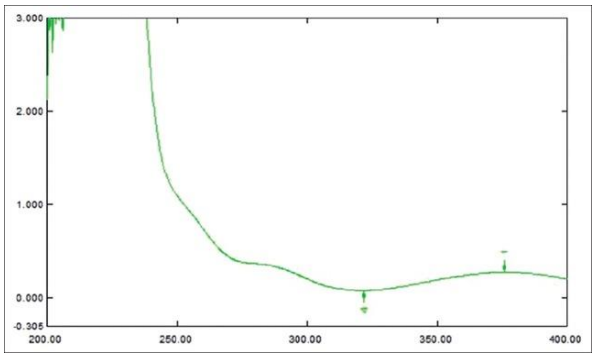

Fig 3: Determination λ max of lornoxicam

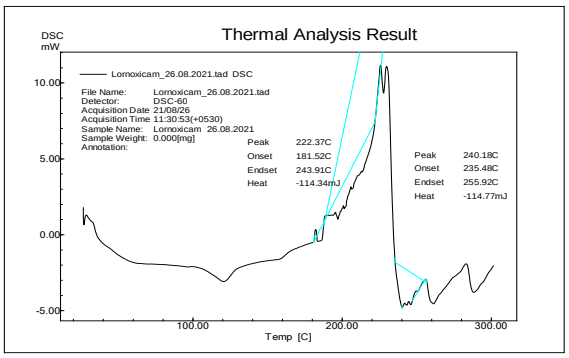

Fig 4: DSC of lornoxicam

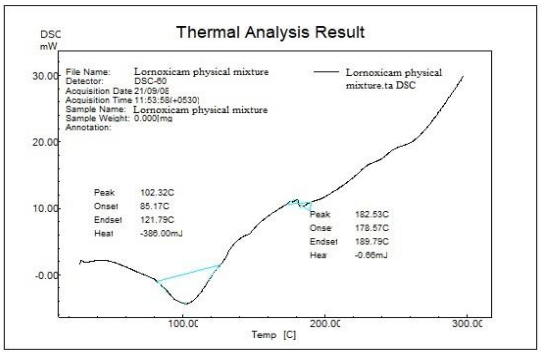

Fig 5: DSC of physical mixture

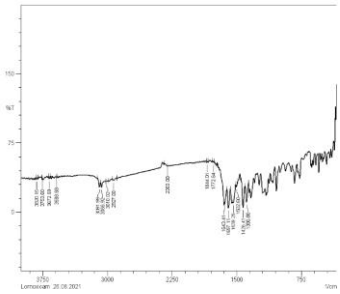

Fig 6: FTIR Spectrum of lornoxicam pure drug

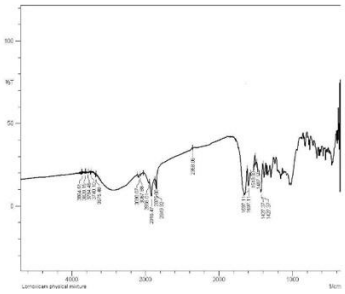

Fig 7: FTIR Spectrum of lornoxicam pure drug

CONCLUSION

According to the findings of sustained release study, hydrophilic and hydrophobic polymers may be successfully mixed to make Lornoxicam sustained release matrix tablets. The drug release was effectively sustained for 24 hours using an optimized formulation including HPMC K 15M and Ethyl cellulose at the optimal ratio. In vitro drug release was seen in matrix tablets from an improved batch. By examining various preformulation parameters, it was discovered that the optimal matrix tablets of the optimized batch have a better flow property. And Matrix tablets of batch FL3 had good in vitro drug substance release. FL3 was selected as more optimized formulation and was further subjected or evaluated for stability study. The formulation FL3, which contained HPMC K15M and Ethyl cellulose polymer in a 3:1 ratio, had a maximum drug substance release of 96.63 percent after 24 hours. Thus sustained release matrix tablets of Lornoxicam using biocompatible polymers were successfully formulated. And SR matrix tablets were evaluated and determined to be good candidates for prolonging the drug's release from matrix tablets.

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