Original Article

FABRICATION AND DEVELOPMENT OF ONCE-DAILY LORNOXICAM BI-LAYER MATRIX TABLETS: FOR THE EFFECTIVE TREATMENT OF ARTHRITIS

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ABSTRACT

The aim of this study was to prepare bi-layer tablet of Lornoxicam (LOR) for the effective treatment of arthiritis. LOR was formulated as immediate release layer and sustained release layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K15M]). The effect of concentration of hydrophilic matrix (HPMC K15M), binder (polyvinyl- pyrollidone [PVP K30]) and dissolution study of sustained release layer showed that an increasing amount of HPMC or PVP K30 results in reduced Lor release. The most successful formulation of the study, exhibited satisfactory drug release in the initial hours, and the total release pattern was very close to the theoretical release profile. All the formulations exhibited diffusion-dominated drug release.

Key words: Lornoxicam, Bi-Layer Tablet, Arthiritis, HPMCK-15M

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INTRODUCTION

Many strategies are available for the design and development of modified release drug delivery formulation. The primary purpose of the drug delivery devices is to improve the state of disease management by modifying the pharmokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Conventional oral dosage forms often produce fluctuation of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level, this effect is usually

totally dependent on particular agents, biological half-life, frequency of administration, and release rate. It is recognized that many patient can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range (Hamdy A.2007) [1].The most commonly used method of modulating drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance (Abraham MA.1997)[2].

Lornoxicam is a member of the oxycam group of non-steroidal anti-inflammatory drugs (NSAID) with extremely potent anti-inflammatory and analgesic activity. It is widely used for the symptomatic treatment of pain and inflammation in patient with osteo arthritis and rheumatoid arthritis. Moreover, it showed great efficacy in various clinical trials in the management of pre-operative and post-operative pain associated with gynecological, orthopedic, abdominal, and dental surgeries. However, Lornoxicam usefulness is limited due to its short half-life that ranges from 3 to 5 hours. Added to that, Lornoxicam shows a distinct pH dependent solubility characterized by very poor solubility in acidic condition present in the stomach (Balfour JA.1996)[3].

The layered tablet concept has been utilized to develop controlled- release formulation (K. R. Reddy. 2003)[14]. Multi- layered tablet concept has long been utilized to develop sustained-release formulation (Lordi GN 1987)[6]. Such a tablet has a fast releasing layer and may contain bi or triple layers, to sustain the drug release. Generally conventional controlled-release doses form delay the release of drugs and do not provide rapid onset of action after oral administration. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug released from the sustained release layer. This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained- release

phase to avoid repeated drug administration. It is reported that the NSAID drugs are suitable candidate drugs for this type of administration (Hamid A. M. 2006) [6].

Hence, in the present research work, an attempt was to develop sustained release bi-layer matrix tablets of Lornoxicam using hydrophilic matrix material such as hydroxypropyl methyl cellulose (HPMC K15).

MATERIALS AND METHOD

Lornoxicam was obtained as a gift sample from Hetro lab limited (Hyderabad, India) and PVP K30 was obtained from Wockhardt Research Centre (Aurangabad, India). HPMC K15M was obtained as a gift from Colorcon (Mumbai, India). Magnesium stearate and talk were purchased from SD Fines Chemicals (Mumbai, India). All other reagents used in this experiment were analytical grades.

Preparation and characterization of bilayer tablets:

The bilayer tablets of Lornoxicam were prepared by the wet granulation method. The drug and polymers for both fast release and sustaining layer were passed through an 80-μm sieve before their use in the formulation.

Calculation of Theoretical Release Profile of Lornoxicam from Sustained-Release Formulations:

The total dose of Lornoxicam for a once-daily sustained release formulation was calculated by the following available pharmacokinetic data (Rawlins EA.1977)[7], (Shobha R 200)[8].

Volume of distribution (V_d) = 0.2 Liter per kg

By taking average body weight of 60 kg

Then,

V_d = 0.2×60=12 liter

C_{max} = maximum plasma concentration

= 270μg per liter

= 0.270 mg per liter

Therefore, loading dose (D_L) can be calculated by-

D_L = $C_{max} \times V_d$

D_L = 0.270×12

=   3.24 mg

Calculation of maintenance dose:

Dt   = $D_L (1 + 0.693 \times t/t_{1/2})$

Where

D_t =   total dose

D_L =   loading dose

$t_{1/2}$ =   half life of drug

t   =   time during which sustained release is desired

D_t = $3.24 (1 + (0.693 \times 24)$

=   14.07 mg is total dose

D_L =   3.24(Loading dose)

D_m =   10.75 (Maintenance dose)

Hence, the formulation should release 3.25mg in 1 hour like conventional tablets, and 0.467 mg per hour up to 24 hours thereafter.

Fourier Transform Infrared Spectroscopy:

The FTIR spectrum of lornoxicam showed (Figure 2) a characteristic peak at 3396, 3354 and 2924 cm−1 corresponding to −NH stretches vibration. Intense absorption peak was found at 1,642 cm−1 due to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1639 1465, 1440 and 1422 cm−1 and were assigned to bending vibrations of the N–H group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1332, 1337 and 1309 and cm−1. Other prominent peaks appeared at 831.94 cm−1 corresponding to −CH aromatic ring bending and heteroaromatics and at 781.20 cm−1 due to the C–Cl bending vibration. All these

prominent peaks of Lor were present in mix of Lor with Sodium alginate (figure 3). It clearly indicates that the drug has retained its cutity without loosing its characteristics.

Formulation of the fast release layer

The dose in the formulation for fast release was 3.25 mg, the maintenance dose or sustained dose (10.75 mg) of Lornoxicam was calculated as per the reported method (7,8). The fast release granules were prepared by direct compression technique the granules were mixed with talc and magnesium stearate.

Formulation of sustaining layer:

Granules for sustaining layer were prepared by mixing maintenance dose of drug with matrix materials. The powders were mixed with sufficient quantity of 4% w/v of PVP in alcohol until a wet mass formed. The cohesive mass obtained was passed through sieve no. 12 and the granules were dried in an oven at 45 °C for half an hour. The dried granules were again sieved by passing through sieve no. 16. The granules were mixed with required quantities of talc and magnesium stearate. The required amount of granules for sustained release layer was compressed into tablets on a single punch tablet machine (Remark, India) using 8 mm round and convex punches. Over this compressed layer, required quantity of fast release layer granules was placed and compressed lightly to form a bi-layered tablet.

Evaluation of Granules

Angle of Repose

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

$\tan \theta = h/r$

Where h and r are the height and radius of the powder cone

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted.

LBD and TBD were calculated using the following formulas6:

LBD = weight of the powder/volume of the packing

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

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility

index:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space,V)

(%) = Vbulk – V/V bulk × 100

Drug Content

An accurately weighed amount of Lornoxicam tablets (20 tablets) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, New Delhi, India). The absorbance was measured at 376 nm after suitable dilution.

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX- 100, Arvada, Colorado), and the test was performed according to the official method.9

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively(I.P. 1996)[9].

In Vitro Release Studies

The in vitro dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 50rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 6.8 from 3 to 24 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer at 376 nm (I.P. 1996)[9].

RESULTS AND DISCUSSION

The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, (**Table 2**). The results of angle of repose and compressibility index (%) ranged from 21.20 ± 0.02 to 24.50 ± 0.02, and 11.09 ± 0.02 to 15.33 ± 0.04, respectively. The results of LBD and TBD ranged from 0.481 ± 0.04 to 0.550 ± 0.04 and 0.541 ± 0.03 to 0.650 ± 0.02, respectively.

The drug content of all formulations ranged from 98.76 ± 0.82 to $99.94 \pm 0.52\%$. The thickness of the tablets ranged from 7.81 ± 0.06 to 8.01 ± 0.04 mm. The average percentage deviation of 20 tablets of each formula was less than $\pm 5\%$ (**Table 3**). The results of dissolution studies of formulations F-I-FV composed of HPMC, Ethanol alone as granulating agent, are shown in **Figure 1**. Tablets F-I, F-II, F-III FIV and FV released 29.62%, 28.21, 24.38% 23.45% and 29.42% of Lornoxicam at the end of 2 hours; and 99.21%, 99.15%, 99.45%, 99.905 and 99.68% of drug at the end of 8 hours, 11 hours, 15 hours, 21 hours and 24 hours respectively. Formulations F-VI, and F-VII released 23.63%, and 20.15% of Lornoxicam at the end of 2 hours and 69.09% and 59.67% at the end of 24 hours, respectively ((**Figure 2**), among all the formulations, formulation F-V showed the best result. The hardness, friability, weight variation, thickness, layer separation, assay and content uniformity were found to be within the limits.

Table1. Formulation of the fast release layer

Ingredient (mg/tab)	Quantity for a single tablet
Lornoxicam	3.25
Lactose	45.25
Magnesium stearate	0.5
Talc	0.5

Table 2 Formulation of the sustained release layer

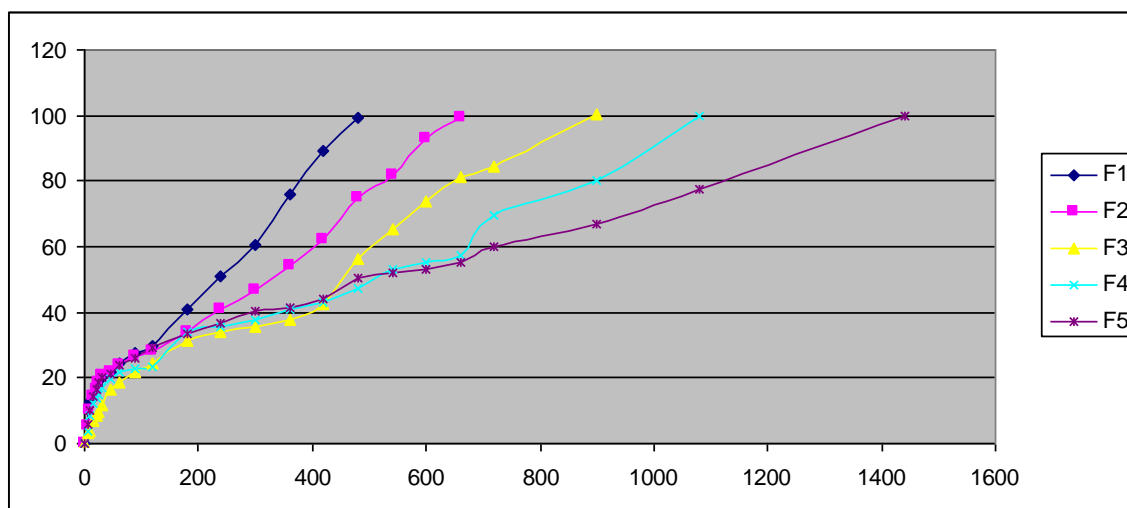| Ingredient (Mg/Tab)	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Lornoxicam	10.75	10.75	10.75	10.75	10.75	10.75	10.75
HPMC (K15-M)	30	45	60	75	90	105	120
Lactose	100.25	85.25	70.25	55.25	40.25	25.25	10.25
PVP K-30	6	6	6	6	6	12	12
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Figure 1 : *In vitro* **drug release profile of formulation F1, F2, F3, F4, and F5**
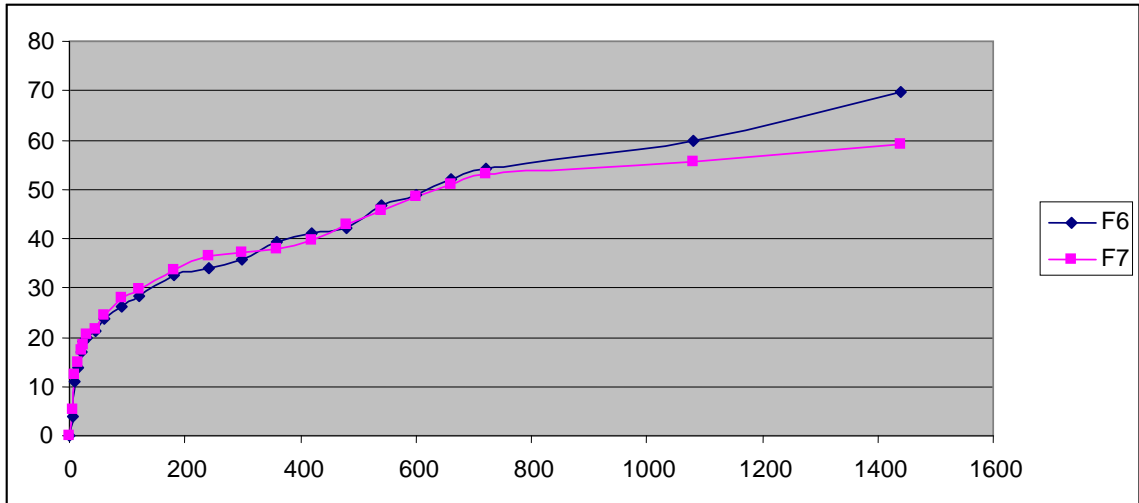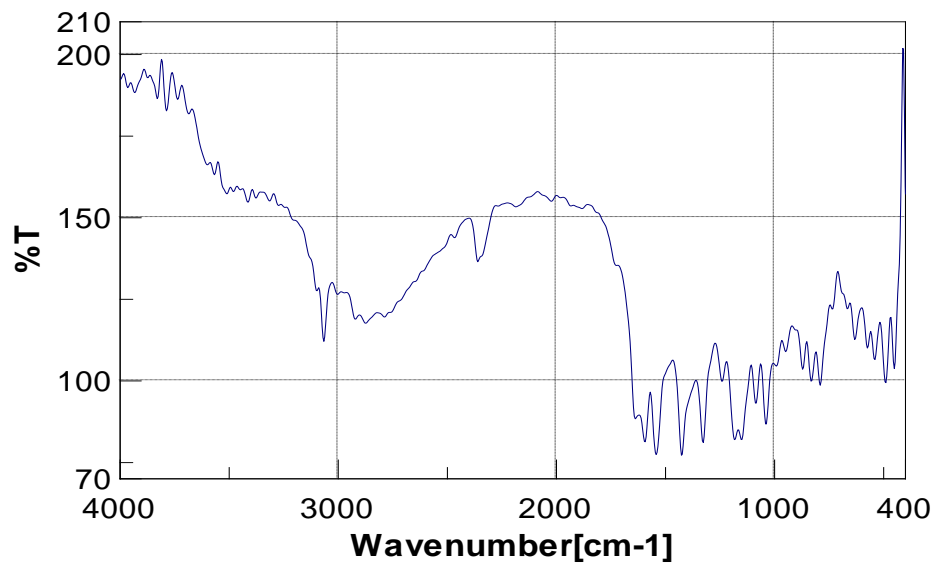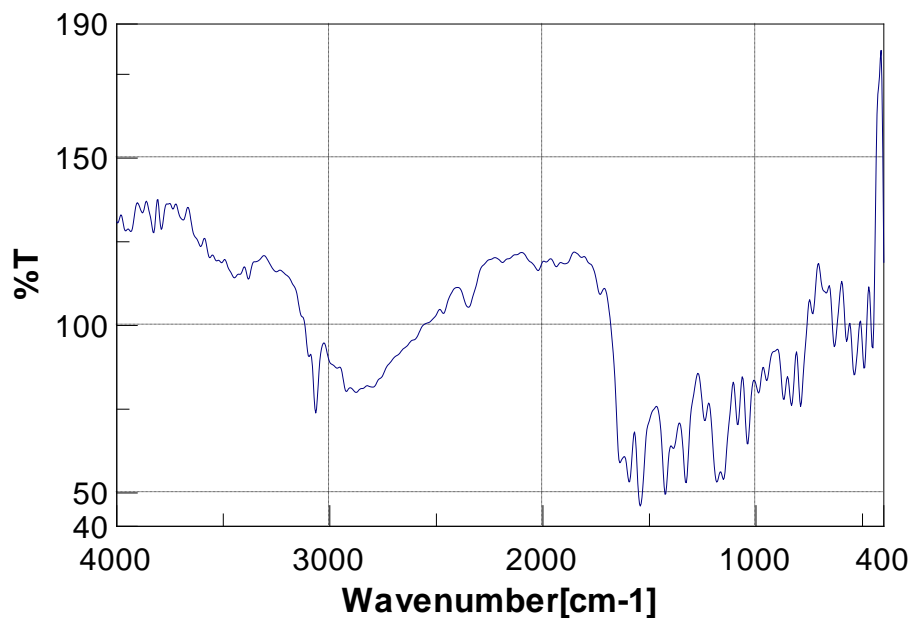
Figure 2: In *vitro* drug release profile of formulation F6 and F7

Figure 3: FTIR spectrum of Lornoxicam pure drug.

Figure 3: FTIR spectrum of Lornoxicam pure drug with HPMC

Table 3: Pre Compressional Studies

Formulations	Angle of Repose	Loose Bulk Density (g/mL)	Tapped Bulk Density (g/mL)	Compressibility Index (%)
F1	24.50 ± 0.02	0.520±0.007	0.600 ± 0.003	13.33± 0.04
F2	21.20 ± 0.02	0.550 ± 0.04	0.650 ± 0.02	15.33± 0.04
F3	22.10 ± 0.01	0.506 ± 0 .02	0.582 ± 0.04	13.08 ± 0.02
F4	23.95 ± 0.01	0.493 ± 0.03	0.555 ± 0.03	11.25 ± 0.03
F5	23.42 ± 0.02	0.512 ± 0.04	0.581 ± 0.02	11.82 ± 0.03
F6	22.32 ± 0.02	0.501±0.003	0.581±0.004	13.76±0.01
F7	23.56±0.03	0.481±0.005	0.541±0.003	11.09±0.002

Table 4: Post Compressional Studies

Formulations	Hardness (kg)	Friability (%)	Thickness (mm)	Weight (mg)	Drug Content (%)
F1	6.51 ±0.67	0.15	7.86 ±0.05	200 ±0.98	99.94 ± 0.52
F2	6.53 ±0.70	0.14	7.87 ±0.07	202 ±1.88	98.76± 0.82
F3	6.55 ±0.66	0.18	8.01 ±0.08	199 ±1.09	99.44± 0.64
F4	6.50 ±0.66	0.16	7.81 ±0.06	200 ±1.65	99.43 ± 0.55
F5	6.52±0.65	0.19	7.85±0.07	199.66±1.80	99.21±0.67
F6	6.50±0.69	0.16	7.83±0.08	199.54±1.90	99.73±0.73
F7	6.66±0.67	0.18	7.87±0.09	200.15±1.50	98.89±0.80

CONCLUSION

The hydrophilic matrix of HPMC could control the Lornoxicam release effectively for 24 hours. It is evident from the results that a matrix tablets prepared with HPMC and binding agent (PVP, 4% wt/vol) is a better system for once-daily sustained release of a highly water-insoluble drug like Lornoxicam.

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