Formulation and Evaluation of Compression Coated Tablets of Lornoxicam for Targeting Early Morning Peak Symptoms of Rheumatoid Arthritis

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ABSTRACT: In the present research work, we have designed a pulsatile formulation of lornoxicam to treat rheumatoid arthritis as per the chronotherapeutic pattern of the disease. Core tablets were prepared by incorporating different concentration of disintegrants and were compressed in between different concentration and combination of hydrophobic and hydrophilic polymers. The core and compression coated tablets were subjected to pre-formulation, physicochemical, *in-vitro* drug release and stability studies. FTIR and DSC studies revealed that there was not any chemical reaction between pure drug lornoxicam and polymers. The pre and post-compressional parameters of tablets were also found to be within limits. The core tablets which were incorporated with 10% of crospovidone were found to be as most fastly disintegrating. Our optimized formulation F-5 releases lornoxicam after a lag time of 5.5±0.7 hours and 99.81±0.81% upto 8 hours. Stability was also found for the optimized formulation according to ICH guidelines.

Key words: Pulsatile formulation, Lornoxicam, Rheumatoid arthritis, Chronotherapeutic pattern, Compression coated tablets.

INTRODUCTION

Rheumatoid arthritis is a chronic disease and it destroys the joints intergrity. In patients of rheumatoid arthritis, symptoms such as pain in the joints and functional disability mainly persists in the early morning time after awakening.[1] It has been recommended to treat rheumatoid arthritis by using the concept of chronopharmacotherapy to ensure that the highest blood levels of the drug should be available to treat the peak pain and stiffness. A pulsatile drug delivery system which can be administered at night i.e. before sleep but releases the drug during early morning time would be a promising chronopharmaceutic system.[2,3] These type of delivery systems deliver the drug at the time when the symptoms of the disease are at its peak within a period of 24 hours. They rapidly release the drug after a lag time (i.e. a period of no drug release).[4]

Drug targeting to the colon has been found as a useful approach for delaying the drug absorption, and it usually requires for the treatment of diseases that are having symptoms in the early morning time like rheumatoid arthritis.[5,6] Compression coated tablets are one such delivery systems through which drugs can be easily targeted to the colon. [7]

Lornoxicam belongs to the class of NSAIDs and is more effective for treating the pain and inflammation of rheumatoid arthritis.[8,9]

By keeping in view to target lornoxicam during the time of its greatest need in rheumatoid arthritis,

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we have developed compression coated tablets of lornoxicam as a pulsatile drug delivery system.

MATERIALS AND METHODS

Materials. Lornoxicam and L-hpc were received as a gift sample from Spectrum Pharma Training Institute, Hyderabad, India. Ethyl cellulose, HPMC K4M and PVP K30 were obtained from FMC Biopolymers. Sodium carboxy methyl cellulose, Lactose, Avicel PH 102 and Aerosil was purchased from SD Fine Chemicals, Mumbai. Magnesium stearate was purchased from Himedia Chem Lab, Mumbai. The remaining ingredients were of analytical grade.

Preformulation studies

Fourier Transform Infrared (FTIR) spectral analysis.[10] Compatibility studies were carried out between pure drug lornoxicam and polymers used in the formulation. We used 2 mg of sample in 200 mg of potassium bromide pellets (Perkin Elmer, Spectrum-100, Japan). The range of scanning was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

DSC studies.[10] DSC thermograms of pure drug lornoxicam and physical mixture of drug and polymers used in the formulation were recorded using Diffraction scanning calorimeter (Shimadzu, Japan). We performed the measurement between 30 and 350ºC at heating rate of 10ºC/min.

Experimental methods

Preparation of core tablets of lornoxicam.[11] Direct compression technique was used to prepare the core tablets of lornoxicam. As per the quantity mentioned in Table 1, lornoxicam, crospovidone, lactose and PVP K30 were weighed and passed through a sieve of 60 mesh size. This mixture after thoroughly blending in a mortar was lubricated with magnesium stearate and aerosil and further blended for 10 minutes. This prepared blend was finally punched into core tablets using 8 mm flat faced punches on a rotary tablet press (Rimek minipress, Karnavathi engineering, Ahmedabad).

Table 1. Formulation of core tablets.

Ingredients	Quantity (mg)			
	LCT-1	LCT-2	LCT-3	LCT-4
Lornoxicam	8	8	8	8
Crospovidone	0	2.5	5	10
PVP K30	5	5	5	5
Lactose	85.4	82.9	80.4	75.4
Aerosil	0.8	0.8	0.8	0.8
Magnesium stearate	0.8	0.8	0.8	0.8
Total weight	100	100	100	100

LCT: Lornoxicam core tablets

Preparation of compression-coated tablets.[11] The prepared core tablets of lornoxicam were further compression coated with polymers of different weight ratios as shown in Table 2. First, a powder bed at the bottom of the die cavity was made by

Table 2. Formulations of compression coated tablets of lornoxicam.

Ingredients	F-1 (mg)	F-2 (mg)	F-3 (mg)	F-4 (mg)	F-5 (mg)	F-6 (mg)	F-7 (mg)	F-8 (mg)	F-9 (mg)	F-10 (mg)	F-11 (mg)	F-12 (mg)
Lornoxicam core tablet (LCT-4)	100	100	100	100	100	100	100	100	100	100	100	100
Composition of Barrier layers												
HPMC K4M	150	200	225	240	--	--	--	--	--	--	--	--
L-hpc	--	--	--	--	150	200	225	240	--	--	--	--
NaCMC	--	--	--	--	--	--	--	--	150	200	225	240
EC (18-22 cps)	150	100	75	60	150	100	75	60	150	100	75	60
Total coating weight	300	300	300	300	300	300	300	300	300	300	300	300
Final compression coated tablets weight	400	400	400	400	400	400	400	400	400	400	400	400

HPMC- Hydroxypropylmethyl cellulose**; L-hpc**- Low substituted hydroxypropyl cellulose**; NaCMC:** Sodium carboxymethyl cellulose; **EC**- Ethyl cellulose.

filling the half quantity of coating polymer blend. Then, the previously prepared core tablets of lornoxicam was placed in the centre of the above powder bed and filled with the remaining half quantity of coating polymer blend in the upper portion of the die. Finally, the whole content was compressed using 11 mm concave punches.

Evaluation parameters

Pre-compression parameters.[12] The prepared powder blend for core tablets was evaluated for various pre-compression parameters like angle of repose, bulk and tapped density, Carr's compressibility index and Hausner's ratio.

Post-compression parameters.[12] The prepared core tablets and compression coated tablets were evaluated for post-compression parameters such as hardness, thickness, weight variation, friability etc.

***In vitro* disintegration time.**[13] The *in-vitro* disintegration of the core tablets were determined using disintegration test apparatus as per I.P specifications. One core tablet was placed into each of the six tubes of the basket. The disc was added to each tube and run the apparatus using 900 ml of pH 6.8 phosphate buffer as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute maintained at 37ºC. The time in seconds for complete disintegration of the core tablets with no palable mass remaining in the apparatus was measured and recorded.

Drug Content Uniformity.[10] 10 core tablets of lornoxicam were crushed into a fine powder in mortar, and the weighed powder equivalent to 8 mg of lornoxicam was extracted in pH 6.8 phosphate buffer. Then filter the solution through a millpore filter of 0.45 pore size. Finally, drug content was determined by UV-spectrophotometer (UV-1700, Shimadzu corporation, Japan) at a λ_{max} 375 nm after suitable dilution.

***In vitro* dissolution testing of core tablets and compression coated tablets of lornoxicam.**[10] We performed the dissolution studies using USP XXIII dissolution test apparatus paddle type (Electrolab USP, India) by maintaining a rotation speed of 100 rpm at 37 ± 0.5°C. First, core tablets of lornoxicam were subjected to dissolution testing in order to assess the effect of disintigrant. This study was carried out by using 900 ml of pH 6.8 phosphate buffer. Then, the compression coated tablets of lornoxicam were also subjected to dissolution testing in order to assess the effect of different weight ratios of coating polymer blend. This study was carried out by using 750 ml of pH 1.2 buffer for 2 hours and further continued with 900 ml of pH 6.8 phosphate buffer for remaining subsequent hours. At equal intervals of time, 5 ml of sample was withdrawn from the dissolution medium and was replaced with equal volume of pH 1.2 and pH 6.8 buffers respectively. After filtering the samples through Whatman filter paper the amount of lornoxicam released was analyzed using a shimadzu UV-Spectrophotometer at a λ_{max} 376 and 375 nm for samples tested in pH 1.2 and pH 6.8 buffers, respectively.

Stability studies.[14] The stability studies were performed by packing the optimized formulation in an amber colored glass container which was closed tightly with a screw cap. Then the container was exposed to 40°C ± 2°C / 75% ± 5% RH in a stability chamber according to ICH guidelines for a period of 6 months. The containers were removed at regular intervals of time and the tablets were again subjected to evaluation of parameters like appearance, drug content, hardness and dissolution profile.

Statistical analysis. Statistical analysis was expressed as mean±standard deviation and the experimental tests were performed for a repeated number of times which control the experimental wise error at rate α=0.05 which was used to determine significance among all possible pairs of formulations and interactions. The level of statistical significance was chosen as $p \leq 0.05$.

RESULTS AND DISCUSSION

In this research work**,** our main was to target lornoxicam as per the circadian rhythm of rheumatoid arthritis. As the symptoms of this disease mainly persists in the early morning hours, by keeping this

fact in view we aimed to design a pulsatile dosage form. The desired lornoxicam release profile was targeted in such a way that when the formulation is taken before going to bed, then maximum portion of the drug should be released in the early morning hours so that, maximum portion of the drug will be available for targeting early morning peak symptoms of rheumatoid arthritis.

In our research work, the designed tablet device is based on time dependent drug delivery approach. The device was formulated into two steps: First lornoxicam was prepared as fast dissolving core tablets; second these was core tablets of lornoxicam pressed on a bigger die in between the coating polymer blend.

FTIR studies. Spectra of pure drug Lornoxicam, polymers and physical mixture of both drug and polymer in compression coated tablets was recorded in between 400 to 4000 cm^{-1}.

The following results were obtained after FTIR spectral analysis:

Lornoxicam. Ar-CH: 3100 cm^{-1}, –NH: 3066 cm^{-1}, -C=O: 1647 cm^{-1}, -CONH-: 1594 cm^{-1}, $-SO_2$: 1327 cm^{-1}, C-Cl: 790 cm^{-1}.

Low substituted hydroxyl propyl cellulose. -OH: 3418 cm^{-1}, CH: 2886 cm^{-1}, C-O: 1317 cm^{-1}.

Ethyl cellulose: OH: 3318 cm^{-1}, CH: 2911 cm^{-1}.

Lornoxicam + Low substituted hydroxyl propyl cellulose + ethyl cellulose. OH: 3400 cm^{-1}, –NH: 3288 cm^{-1}, Ar-CH: 2972 cm^{-1}, CH: 2902 cm^{-1}, -C=O: 1749 cm^{-1}, -CONH-: 1647 cm^{-1}, -SO2: 1387 cm^{-1}, C-O: 1080 cm^{-1}, C-Cl: 785 cm^{-1}.

The recorded spectra (as shown in figure 1) reveal that all the peaks which are present in drug and polymers remained intact in their physical mixture.

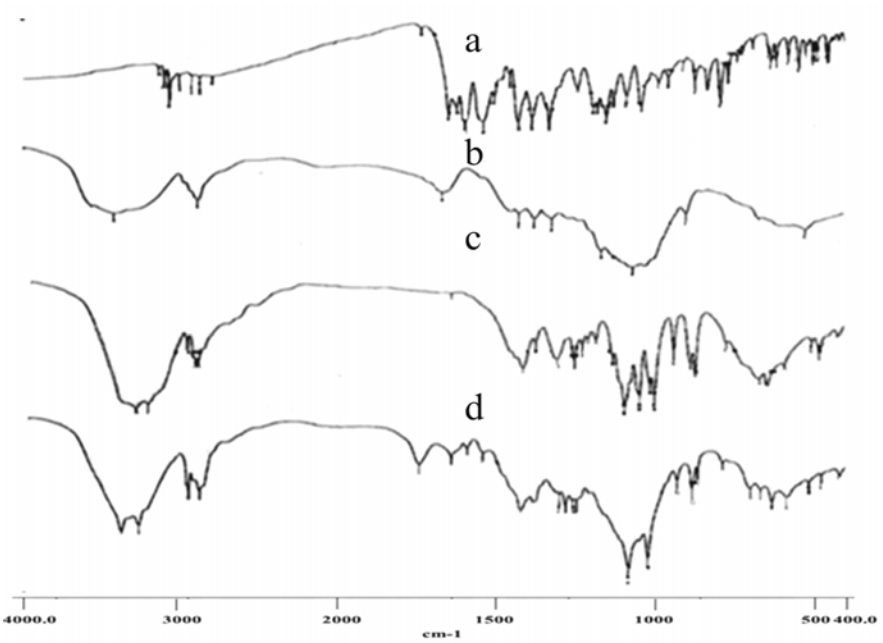

Figure 1. FTIR spectra of a) Pure drug lornoxicam b) Low substituted hydroxyl propyl cellulose (L-hpc) c) Ethyl cellulose d) Lornoxicam + L-hpc + ethyl cellulose.

DSC studies. Along with FTIR studies, DSC thermograms were also taken to study the compatibility between drug and polymers. The DSC thermograms of drug, and physical mixture of drug and polymers is shown in Figure 2. DSC thermograms of lornoxicam due to its melting process shown a sharp endothermic peak at 218.74ºC. The peak for physical mixture of lornoxicam, low substituted hydroxyl propyl cellulose and ethyl cellulose in Formulation F-5 was found at 219.79 ^{0}C.

The same range of drug melting peak is present even in the physical mixture of formulations. Thus, both the FTIR and DSC studies confirms that there was no possible chemical interaction between pure drug lornoxicam and polymers which are present in the optimized formulation F-5.

Evaluation of powder blend. The angle of repose values for all the core tablets was found to range between 22 º.15' ± 0.13 to 24º.40' ± 0.10, which were less than 30 and hence indicates good flow properties of the powder. The compressibility index values for all the core tablets was found to range between 13.23 ± 0.86 to 14.49 ± 0.94, which were less than 15% and hence results in good to excellent flow properties. The Hausner's ratio values were also lesser than 1.25 which indicates good flow properties. Thus, the prepared powder blend for all the core tablets was exhibiting good flow properties as evident from Table 3.

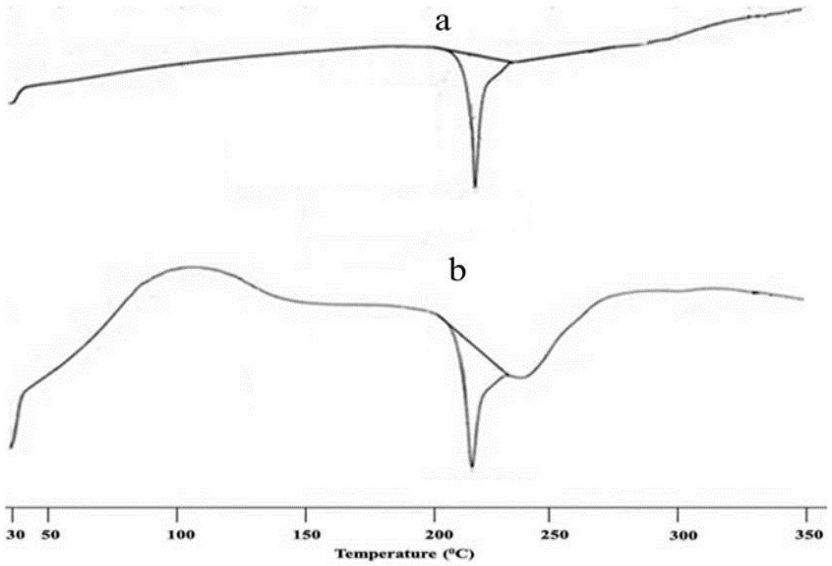

Figure 2. DSC spectra of a) Pure drug lornoxicam b) Lornoxicam + Low substituted hydroxyl propyl cellulose + Ethylcellulose.

Table 3. Results of physical evaluation of Pre-compression Blend.

Batches	Angle of repose (°) ± SD, n=3	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's ratio ± SD, n=3
LCT-1	24 º.40'±0.14	0.59 ± 0.02	0.69 ± 0.02	14.49 ± 0.94	1.16 ± 0.02
LCT-2	22 º.48'±0.09	0.57 ± 0.02	0.66± 0.02	13.63±0.81	1.15± 0.01
LCT-3	23 º.36'±0.10	0.58 ± 0.01	0.67 ± 0.02	13.43± 0.90	1.15± 0.02
LCT-4	22 º.15'±0.13	0.59 ± 0.03	0.68 ± 0.03	13.23±0.86	1.15± 0.03

Evaluation of prepared core tablets. The physical evaluation results of core-tablets are given in Table 4. The hardness of all the core tablet batches was found to range between 3.69±0.10 to 3.77±0.16 kg/cm^2. Friability values were also found to be less than 1. Thus, the results of hardness and friability values have shown that core tablets have got sufficient strength. The thickness was found to range between 2.14 ± 0.01 to 2.16 ± 0.01 mm. The results of weight variation values were found to range between 98.0 ± 0.26 to 100.6 ± 0.16. The weight variation of the entire core tablet batches were also found to be in pharmacopoeial limit i.e. 130 mg or less is ± 10 %. The drug content was found to range between 97.63 ± 0.02 to 98.22 ± 0.04. This indicates that in all the core tablets batches drug content more than 95 % and thus confirms that drug was uniformly distributed. When the lornoxicam core tablets were

subjected to disintegration studies it was found that as the concentration of crospovidone was increasing the disintegration time was decreased. The disintegration time was found to range between 1.52±0.47 to 12.44 ±0.35 and LCT-4 batch was found to be the most fast disintegrating core tablets.

***In vitro* dissolution testing of core tablets tablets of lornoxicam.** The results of *In-vitro* dissolution testing for LCT-1, LCT-2, LCT-3 and LCT-4 core tablets showed that they released 53.66±0.91, 62.01±1.05, 69.16±0.84 and 99.93±0.81 % of lornoxicam at the end of 30 minutes. From the results we found, as the concentration of crospovidone in core tablets was increasing, the release of lornoxicam was also increased in 30 minutes period of time as shown in Figure 3. Hence, we considered LCT-4 batch core tablets to be the most suitable for incorporation in compression coated tablets.

Table 4. Evaluation of core tablets of lornoxicam.

Core-tablets batch	Weight variation(mg) (±SD), n=20	Hardness (kg/cm^2) (±SD), n=6	Thickness (mm) (±SD), n=10	Friability (%) (±SD), n=6	% Drug content (±SD), n=3	Disintegration time (min) (±SD), n=3
LCT-1	99.4±0.22	3.89±0.10	2.14 ± 0.01	0.16 ± 0.04	97.63± 0.02	12.44 ±0.35
LCT-2	100.6±0.16	3.94±0.32	2.16 ± 0.01	0.24 ± 0.07	99.12 ± 0.04	6.74±0.27
LCT-3	98.0±0.26	3.90±0.29	2.15 ± 0.01	0.19 ± 0.02	98.10 ± 0.03	4.96±0.33
LCT-4	99.8±0.17	3.97±0.16	2.16 ± 0.02	0.11 ± 0.04	98.22 ± 0.02	1.52±0.47

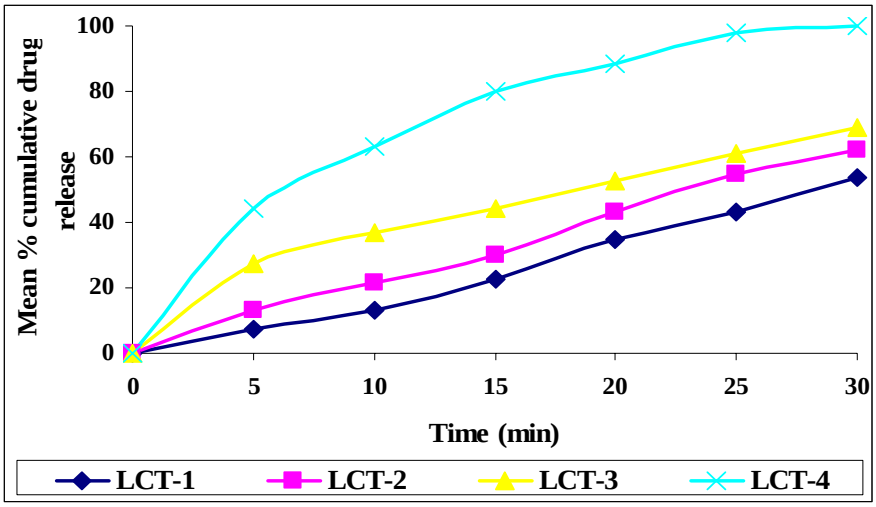

Figure 3, *In-vitro* release profile of lornoxicam core tablets.

Evaluation of press-coated tablets of lornoxicam. The physical evaluation results of all the press-coated tablets are shown in Table 5. The hardness of all the press coated tablet formulations was found to range between 11.25±0.18 to 11.69±0.28 kg/cm^2. Friability values were also found to be less than 1. Thus, the results of hardness and friability values have shown that all the compression coated tablet formulations have got sufficient strength. The thickness was found to range between 4.27 ± 0.01 to 4.30 ± 0.02. The results of weight variation was found to range between 396 ± 0.20 to 404 ± 0.18. The weight variation between the compression coated tablets were also found to be in pharmacopoeial limit i.e. 324 mg or more is ± 5 %.

***In vitro* dissolution testing of compression coated tablets of lornoxicam.** The prepared compression coated tablets of lornoxicam with different combinations and concentrations of HPMC-K4M, ethylcellulose and L-HPC, ethylcellulose were

also subjected to *in vitro* dissolution testing. Our main aim in the dissolution test was to identify a suitable formulation which could release the drug after a lag time of at least 5 hours and almost all portion of the drug till 8 hours. The results of *in vitro* dissolution testing profile is shown in figure 4.

When formulations F-1, F-2, F-3 and F-4 prepared with varying concentrations of HPMC-K4M and ethyl cellulose were evaluated it was found that they released lornoxicam after a lag time of 10.5 ± 0.78, 8 ± 0.65, 7 ± 0.93, 5.5 ± 0.82 hours and 98.38 ± 0.98, 98.26 ± 1.06, 99.10 ± 1.02, 99.34 ± 0.80% at the end of 14, 12, 11, 9 hours respectively. From these results, it was found that as the concentration of HPMC K4M polymer was increasing or ethylcellulose concentration was decreasing the lag time and dissolution rate of lornoxicam was decreased. This is due to the hydrophilic nature of HPMC K4M polymer. Its rate of hydration has increased due to its increased concentration resulting in increased dissolution rate. All these four formulations do not meet our desired criteria to release lornoxicam.

Table 5. Evaluation of compression coated tablets of lornoxicam.

Compression-coated tablets formulations	Weight variation (mg) (±SD), n=20	Hardness (kg/cm^2) (±SD), n=6	Thickness (mm) (±SD), n=10	Friability (%) (±SD), n=6
F-1	396±0.20	11.57±0.12	4.27 ± 0.01	0.25 ± 0.05
F-2	397±0.16	11.68±0.00	4.31 ± 0.02	0.18 ± 0.02
F-3	401±0.19	11.65±0.32	4.29 ± 0.03	0.33 ± 0.06
F-4	398±0.33	11.69±0.28	4.28 ± 0.01	0.18 ± 0.03
F-5	397±0.31	11.25±0.18	4.30 ± 0.02	0.49 ± 0.05
F-6	403±0.29	11.37±0.00	4.29 ± 0.01	0.52 ± 0.04
F-7	399±0.34	11.41±0.20	4.29 ± 0.02	0.38 ± 0.03
F-8	404±0.18	11.39±0.12	4.28 ± 0.01	0.27 ± 0.04
F-9	399±0.20	11.45±0.26	4.29 ± 0.02	0.38 ± 0.05
F-10	398±0.15	11.42±0.32	4.30 ± 0.02	0.36 ± 0.04
F-11	402±0.36	11.38±0.00	4.28 ± 0.02	0.44 ± 0.03
F-12	399±0.19	11.47±0.22	4.29 ± 0.01	0.32 ± 0.04

When formulations F-5, F-6, F-7 and F-8 prepared with varying concentrations of L-hpc and ethyl cellulose were evaluated it was found that they released lornoxicam after a lag time of 5.5 ± 0.7, 4 ± 0.89, 3 ± 0.76, 1.5 ± 0.88 hours and 99.81 ± 0.81, 99.58 ± 0.75, 99.22 ± 0.93, 99.46 ± 0.98 % at the end of 8, 7, 6, 4 hours, respectively. From these results, it was found that as the concentration of L-hpc polymer was increasing or ethyl cellulose concentration was decreasing the lag time and dissolution rate of lornoxicam was decreased. It is due to the reason that L-HPC is hydrophilic in nature and it acts as a disintegrant too. In our formulations as the concentration of L-HPC was increased it leads to the increased wetting and disintegrating tendency of tablet due to its hydrophilic and disintegrant properties and decreases the dissolution time. Similarly, when the concentration of ethylcellulose was more it retarded the wetting of L-HPC polymer due to its hydrophobic tendency and thus decreased the dissolution time.

When formulations F-9, F-10, F-11 and F-12 prepared with varying concentrations of NaCMC and ethyl cellulose were evaluated it was found that they released lornoxicam after a lag time of 4±0.88, 3 ± 0.95, 2 ± 0.82, 1.5±0.91 hours and 99.81±0.77, 99.69 ± 0.83, 99.93 ± 0.69, 99.46 ± 0.97 % at the end of 7, 6, 5, 4 hours, respectively. From these results, it was found that as the concentration of NaCMC polymer was increasing the lag time and dissolution time of lornoxicam was decreased. Because, as we increased NaCMC concentration similarly hydrophobic polymer i.e. ethyl cellulose concentration was decreased. It was also found that, while compared to HPMC-K4M and L-HPC polymers this polymer showed a minimal lag time and dissolution time. Therefore, these formulations i.e. from F-8 to F-12 released lornoxicam within a short period of time.

From all the observations of these formulations, it was found that the order of extending the lag time for polymers was found as HPMC-K4M > L-HPC >NaCMC. Also, it was found that formulation F-5 was the most suitable formulation as it was satisfying our desired criteria. Hence, it was considered as the best formulation.

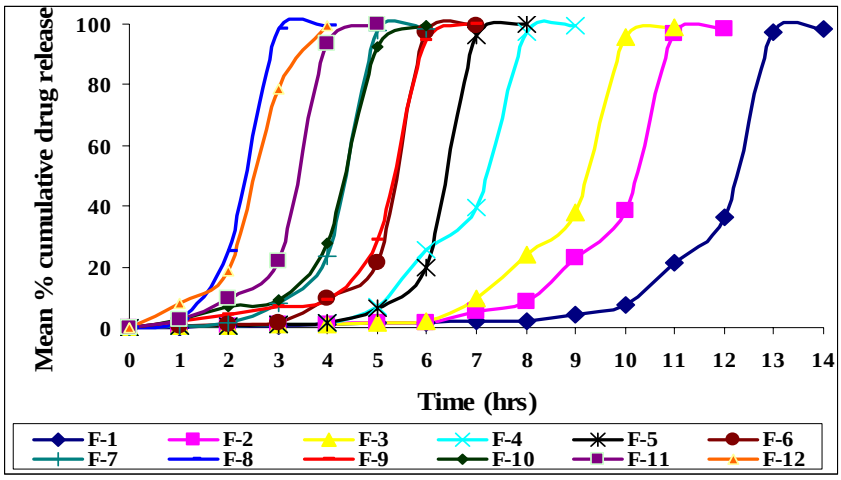

Figure 4. *In-vitro* release profile of compression coated tablets of lornoxicam.

Stability studies. When optimized compression coated tablets formulation F-5 was subjected for evaluation, it was found that there was no change in appearance and the hardness was also found to be uniform. When performing the stability studies for drug content, it was found that the drug was reduced by 0.87 % (i.e. less than 1 %) in a period of 6 months indicating the stability of drug. When stability studies were performed for dissolution testing it was observed that there was very small variation (i.e less than 1 %) in both lag time and drug release profile. The results of *in-vitro* drug release profile after stability studies were found as 8.27±1.15 and 98.93±1.08 at the end of 5.5 and 8 hours, respectively. Hence, by the above mentioned results it was confirmed that our optimized formulation was stable for a period of 6 months i.e. according to ICH guidelines.

CONCLUSION

As we have mentioned in the introduction that our aim was to target lornoxicam in the early morning hours i.e. as per chronotherapy. By keeping this concept in view we have successfully developed a pulsatile dosage form by compression coating of lornoxicam core tablets by combination of L-hpc and ethycellulose polymers. Formulation F-5 was considered as the best formulation as it releases 9.13 ± 0.79 and 99.81 ± 0.81% of lornoxicam at the end of 5.5 and 8 hours, respectively. This release profile is based on the assumption that if the patient takes this optimized formulation at 10:00 A.M (i.e. before going to bed) then the drug starts releasing after a lag time 5.5 hours and almost all portion of the drug will be released in between 4-6 A.M. Thus, maximum drug will be available for targeting early morning peak symptoms of rheumatoid arthritis.

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