

FORMULATION AND EVALUATION OF LORNOXICAM TABLET BY PRESS COATING METHOD FOR PULSATILE DRUG DELIVERY SYSTEM

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ABSTARCT

In the present research work pulsatile drug delivery system of Lornoxicam tablets were formulated by employing compression coating technology. Initially the core tablets were prepared by using various concentrations of super disintegrates, the formulated core tablets were coated with the polymers by using compression coating technology. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. In vitro release of Lornoxicam of core

tablet formulations F1-F3, F1 showed faster drug release after 20 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric coated formulations C1, C2 showed maximum drug release after 4 hour. C3 and C7 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C7 with 99.9%.

KEYWORDS: Lornoxicam, Super disintegrates, Ethyl cellulose, Pulsatile tablets.

INTRODUCTION

The pulsatile release tablets that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 hr in the intestine. The system consists of a core, a swelling agent of cross-linked PVP and a coating film of ethyl cellulose / Eudragit L. But Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. So Penetration of water molecules from the surroundings through the

pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of the coating film can control the lag time.

Site specific pulsatile drug delivery system

Generally, the aim of site specific and receptor release system refers to targeting of the drug directly to a certain biological location that means the drug must release at targeted site with sufficient amount to maintain peak plasma concentration for the desired time period. Environmental factors like pH or enzymes present in the intestinal tract and also transit time control the release of a site-controlled system where as the drug release from time-controlled systems is controlled primarily by the delivery system and not by the environment. Over the past two decades the major challenge for scientist is to target the drugs especially to the colonic region of GIT. Previously colon was considered as a innocuous organ that responsible for the water absorption, electrolytes and stool storage but it's accepted as important site for the delivery of drugs.

Inflammation induced pulsatile drug delivery system

Any physical or chemical stress like-injury, fracture etc. which acts as a stimulus in the case of inflammation due to hydroxyl radicals produced from inflammation responsive cells. Yui et al., (1992), designed and prepared stimuli based inflammation responsive chronotropic system which responded to hydroxyl radicals and degraded in a limited manner. Basically with the system utilized hyaluronic acid (HA) which is specifically hydrolyzed by hyaluronidase or free radicals that present at inflammatory site. Degradation of HA via the hyaluronidase is very low in a normal state of health. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery system.

MATERIALS AND METHODS

Lornoxicam was purchased from zopinax pharma Ltd(Ahemadabad), Methocel k100 purchased from Lab Press Pharma, Polyplasdone purchased from calendula pharma ltd., Tulson purchased from Elixir pharma ltd, Talc and Magnesium stearate purchased from Lab press pharma, Micro Crystalline cellulose, Ethyl Cellulose N 50, Sodium hydroxide, Hydrochloride purchased from Sartourious Lab, sodium bicarbonate purchased from Sarco

chemical ltd.

METHOD

Formulation of core tablets by direct compression: The inner core tablets were prepared by using direct compression method as shown in the table no6.3. Powder mixtures of Lornoxicam, microcrystalline cellulose, polyplasdone XL, talc, ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 50mg of resultant powder blend was manually compressed using, Lab press with a 5mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions containing Ethyl cellulose N 50, methocel k100, magnesium stearate, talc, pvpk-30 and microcrystalline cellulose. Different compositions were weighed dry blended at about 10 min. and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets: The core tablets were press-coated with 200 mg of mixed blend as given in Table.No6.4. 100mg of barrier layer material was weighed and transferred into a 10mm die then the core tablet was placed manually at the center. The remaining 100mg of the barrier layer material was added into the die and compressed by using Lab press Limited, India

EVALUATION OF PRESS COATED TABLET

Disintegration time of core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Servewell Instruments pvt. Ltd., Electrolab ED-2L, India) specified in indian pharmacopoeia. Distilled water at 37 ± 0.5 °C was used as the disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining on the screen was measured in seconds.

In vitro drug release of pulsatile Lornoxicam core tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. Distilled water was used as dissolution medium. Release pattern was studied visually by taking sample of 5 mL at the specific time intervals. Also the sample was analyzed at 271 nm for 0.1N HCL and 270nm for 6.8 phosphate buffer using a UV

spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F = K_0 t$$

Where, 'F' is the drug release at time 't', and 'K₀' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log} (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k t^{1/2}$$

Where, 'k' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

Present study was done on pulsatile tablets with different formulations C1 to C8. Formulations had weight ratio of polymers like Ethyl cellulose, Tulson, polypladone, Explotab along with various excipients. Ethyl cellulose is an insoluble. Aim of the formulation was to get effect of drug in inflammatory and anti pyritic action. This section gives detailed description of the results and discussion on pulsatile Lornoxicam tablets.

PREFORMULATION STUDIES**Determination of λ max of Lornoxicam**

The λ max of Lornoxicam was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 271 nm and the same was selected for Lornoxicam.

Standardization method for estimation of Lornoxicam

Standard curves of Lornoxicam were prepared in 0.1N HCl, and phosphate buffer (pH 6.8).

Standard graph of Lornoxicamin 0.1N HCl

Lornoxicam showed maximum absorbance in 0.1N HCl at 271 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 μ g / mL to 10 μ g / mL with regression coefficient of 0.996. Standard curve of Lornoxicam prepared in 0.1N HCl is shown below in Table 1 and Figure 1.

Table 1: Calibration data of Lornoxicamin 0.1N HCl.

Sl.No.	Conc [mg/l]	Abs
0	0	0
1	5	0.223
2	10	0.335
3	15	0.516
4	20	0.643
5	25	0.778

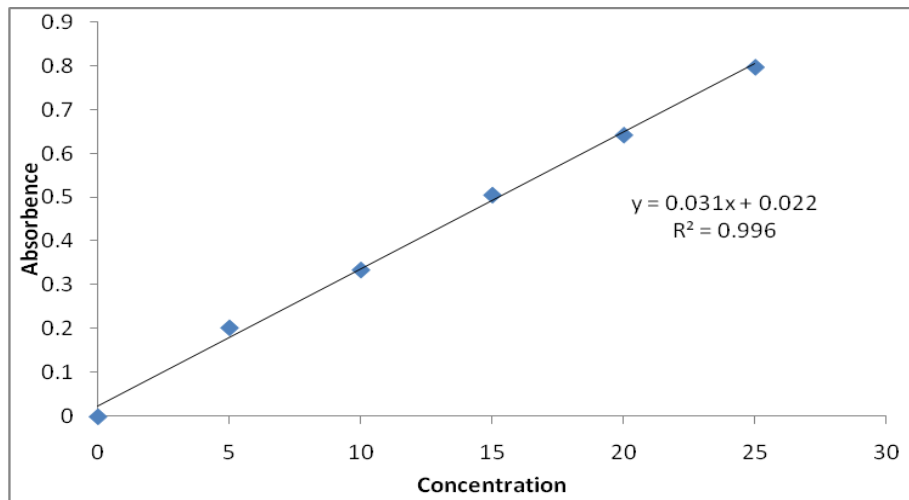


Fig 1: Standard Graph of Lornoxicamin 0.1N Hcl.

Standard graph of Lornoxicam in phosphate buffer (pH 6.8)

Lornoxicam showed maximum absorbance in phosphate buffer (pH 6.8) at 270 nm. The solution obeyed Beer-Lambert's law for concentration range of 1 to 10 $\mu\text{g} / \text{mL}$ with regression coefficient of 0.998. Standard curve of prepared Lornoxicamin phosphate buffer pH 6.8 is shown below.

Table 2: Calibration data of Lornoxicam in pH 6.8 phosphate buffer.

Sl.No.	Conc [mg/l]	Abs
0	0	0
1	5	0.215
2	10	0.372
3	15	0.560
4	20	0.714
5	25	0.910

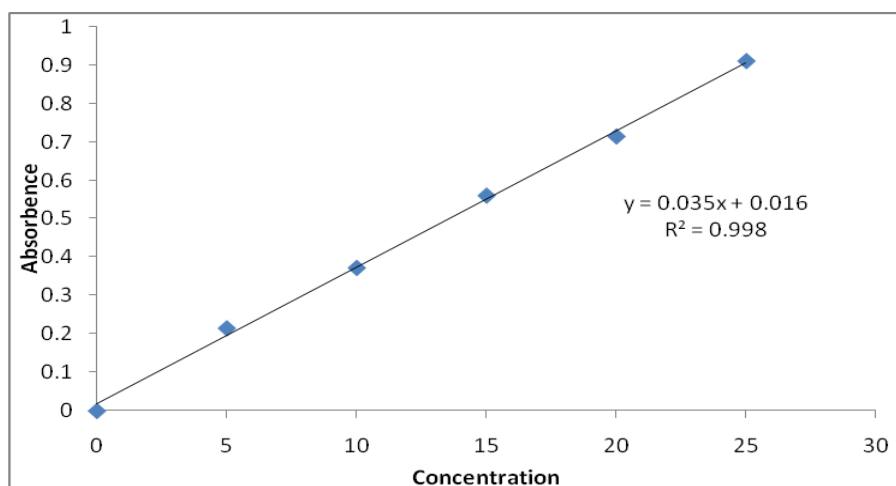


Fig 2: Standard Graph of Lornoxicam in pH 6.8 phosphate buffer

Drugs Polymer Interaction Study by FTIR spectrophotometer

In order to investigate the possible interaction between drug and selected polymers, FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks. The studies suggest that there is no incompatibility between drug and polymer.

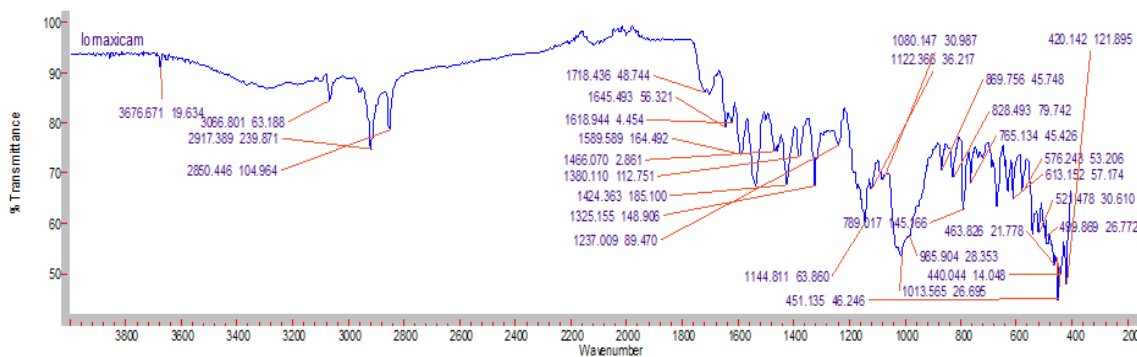


Fig 3: FTIR Spectrum of Lornoxicam pure drug.

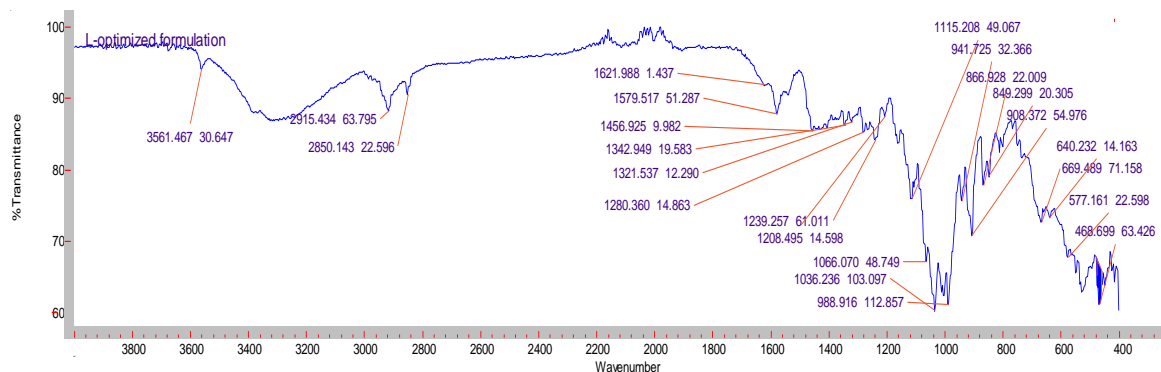


Fig 4: FTIR spectrum of Optimized formulation.

Table 3: Pre compression parameters of Lornoxicam core tablets

Formulation code	Angle of repose (o) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.8	0.49	0.56	12.56	1.14
F2	25.6	0.52	0.59	11.86	1.13
F3	29.8	0.48	0.55	12.7	1.15

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.52 (gm/cm³) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.55 to 0.59 showing the powder has good flow properties. The compressibility

index of all the formulations was found to be ranging between 11 to 13 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Table 4: Post compression parameters of Core tablet.

Formulation codes	Weight variation (mg)	Hardness(kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	47.2	2.5	0.45	4.2	98.5
F2	52.6	2.4	0.51	4.3	99.5
F3	48.96	2.4	0.43	4.5	102.2

7.5. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 5: Pre compression Parameters of Lornoxicam coated Tablets.

Formulation code	Angle of repose (°) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	27.01	0.51	0.56	16.21	1.09
C2	25.8	0.55	0.63	16.87	1.14
C3	26.74	0.56	0.68	17.1	1.21
C4	25.33	0.55	0.65	17.67	1.18
C5	24.24	0.56	0.68	16.92	1.21
C6	23.12	0.54	0.61	17.65	1.12
C7	22.08	0.49	0.58	16.43	1.18
C8	24.12	0.51	0.56	17.97	1.09

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.56 (gm/cm³) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Table 6: Post compression parameters of Coated tablet.

Formulation codes	Weight variation (mg)	Hardness (kg/cm ²)	Friability	Thickness	Drug content (%)
C1	255.5	4.1	0.53	4.7	99.76
C2	246.4	4.2	0.55	4.8	99.45
C3	251.6	4.0	0.59	4.9	99.34
C4	248.6	4.3	0.56	4.6	99.87
C5	247.4	4.5	0.57	4.8	99.14
C6	246.7	4.4	0.49	4.4	98.56
C7	253.3	4.3	0.57	4.7	98.42
C8	246.2	4.4	0.51	4.8	99.65

***In-Vitro* Drug Release Studies of Lornoxicam core tablet**

In vitro dissolution studies of Lornoxicam core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation F1-F3 Lornoxicam core tablets, F1 showed faster drug release after 20 mins than the other formulations. Faster drug release can be correlated with the high disintegration and friability observed in this study. So, F1 Lornoxicam core tablet formulation was selected as best formulation for further press coating and enteric coating formulations. *In vitro* drug release profiles of all Lornoxicam core tablets were shown in Table 7 and Figure.5.

Table no 7: Dissolution data of core tablets.

Time(min)	F1	F2	F3
0	0	0	0
5	54.6	29.50	37.5
10	71.6	41.5	48.5
15	88.5	54.6	56.7
20	98.5	69.2	57.81
30		72.4	70.6
45		89.6	88.2
60		91.5	98.5

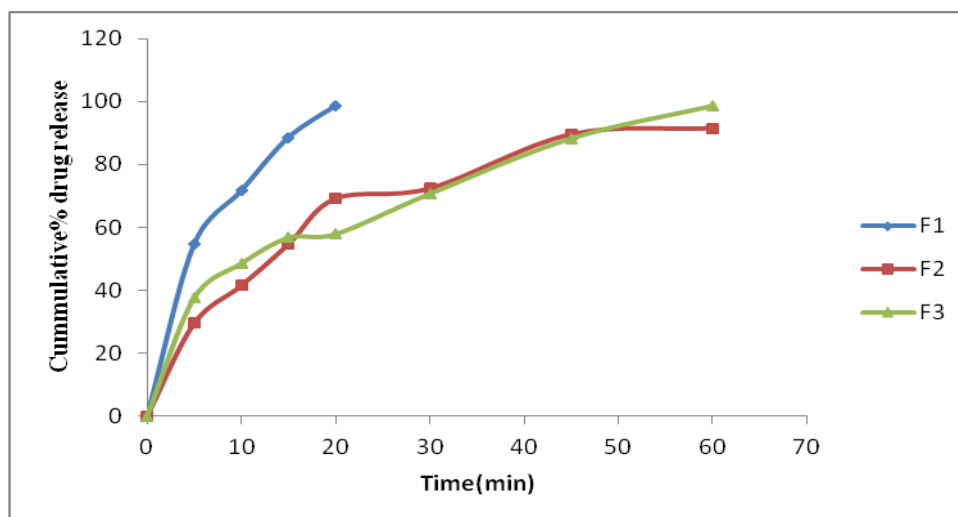


Fig 5: Cumulative % drug release of Lornoxicam core tablets.

***In vitro* drug release study of Lornoxicam pulsatile tablets**

Based on the above characters formulation F1 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the Lornoxicam from enteric coated tablets. This enteric coat has enabled us to achieve definite non release lag phase for 8 hours. The formulations C1, C2, and C3 showed maximum drug release after 3th hour. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C8 with 90.1% and 99.9% drug release which meets demand of chronotherapeutic drug delivery. The formulations containing M and Ethylecellulose N 50, Methocel k 100 in 40 mg and 60 mg respectively were found to be optimum as enteric coating polymers. The data were shown below.

Table 8: Cummulative Percentage Release Of Coated Lornoxicam Tablets.

Sl.No	Time(min)	C1	C2	C3	C4	C5	C6	C7	C8
0	0	0	0	0	0	0	0	0	0
1	0.5	0.12	0.14	0.28	0.10	0.28	0.13	0.10	0.13
2	1.0	18.54	0.20	04.56	0.95	2.43	2.17	0.14	0.28
3	2.0	30.34	5.43	08.18	18.50	6.56	3.95	5.27	0.35
4	3.0	96.37	13.68	14.56	20.34	12.54	4.12	15.25	0.30
5	4.0		56.32	20.30	32.12	15.68	10.23	56.9	2.38
6	5.0		98.62	65.17	75.34	20.34	15.8	96.5	9.39
7	6.0			80.61	88.66	46.56	50.6		25.59
8	7.0			99.8	90.5	62.12	87.9		53.30
9	8.0				91.5	88.37	99.9		62.12

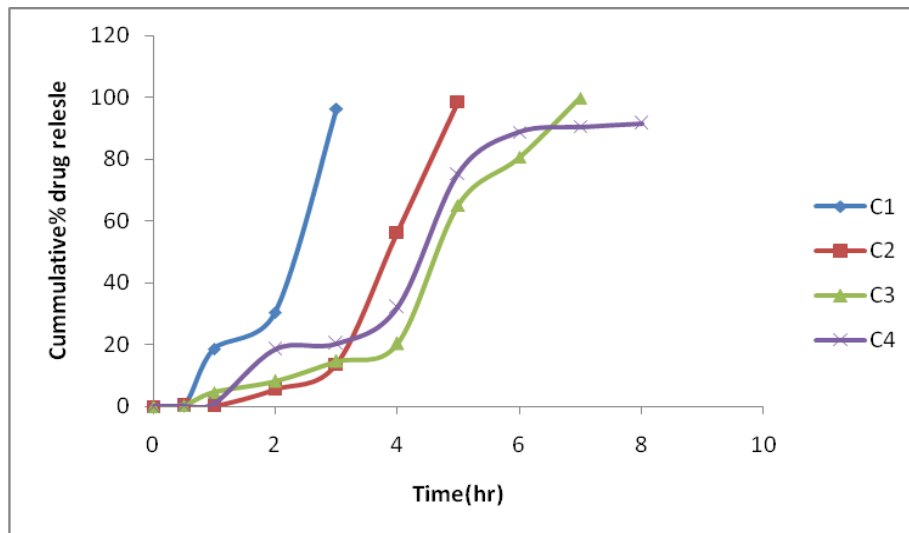


Fig 6: *Cumulative % release study of Lornoxicam pulsatile tablets using ethyl cellulose.*

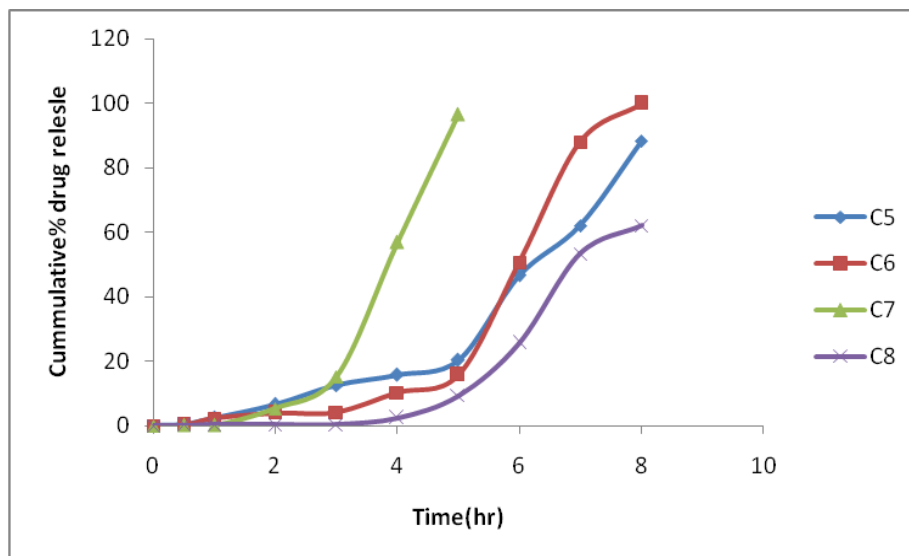


Fig 7: *Cumulative % release study of Lornoxicam pulsatile tablets methocel k 100.*

CONCLUSION

Pulsatile drug delivery system is characterized by a lag time that is interval of no drug release followed by rapid drug release. It is useful in body functions that follow circadian, drugs have extensive first pass metabolism, biological tolerance and interact with other drugs. A pulsatile dosage form taken at bedtime with a programmed start of drug release in the early morning hours, can prevent a sharp increase in the incidence of inflammation during the early morning hours, a time when the risk of inflammation is the greatest. In the present study, an attempt was made to design and characterize pulsatile drug delivery system in order to release the drug after 5-6 hr in the intestine, and intentionally delaying the drug absorption from therapeutic point of view in the treatment of inflammation, where

peak symptoms are observed in the early morning.

Standard plots of Lornoxicam in 0.1N HCl, phosphate buffer (pH 6.8) were prepared by UV Spectrophotometry which showed good correlation coefficient (R^2) values. The drug-polymer interaction studies were performed by FTIR Spectrophotometry and it was found that there was no interaction between the drug and various polymers used in the formulation. The coated tablets were prepared by direct compression method.

The pulsatile tablet of Lornoxicam tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated with swellable hydrophobic polymer (SSG) and hydrophobic polymer (ethyl cellulose) alone and / or in different weight ratio. An enteric coating layer.

The formulation mixtures of powders for core tablets (F1-F3) prior to the compression step have been evaluated for pre-compression parameters namely angle of repose, bulk density, tapped density and Carr's Index for the flow ability nature was determined. All the formulation mixtures showed good to excellent compressibility.

All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. All the formulations showed favourable drug loading with uniformity of drug content in the tablets and disintegration time. Based on the friability and disintegration time, formulation A1 was selected as best formulation and press coated and enteric coated for further evaluations studies. All the formulations of press coated tablets showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (C1-C8) like thickness, friability, hardness and drug content ranged lies within pharmacopoeia limits.

In vitro release of Lornoxicam of core tablet formulations F1-F3, F3 showed faster drug release after 20 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric coated formulations C1, C2, and C3 showed maximum drug release after 5 hour. C7 showed maximum drug release after 8th hr about 99.9%.

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