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Research Article

Design Development And Evaluation Of Floating Drug Delivery System For Lornoxicam NSAID Drug

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ABSTRACT

Lornoxicam is one of the drugs used for the management of arthritic pain. The site of absorption of Lornoxicam is in the GIT and it has a short half life of 3-4 h. Therefore, the present investigation was concerned with the development of the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time and thus, improve the bioavailability of the drug as well as its half life. Lornoxicam showed maximum absorption at wavelength at 374 nm in 0.1 N HCl. Drug-Polymer compatibility studies by FTIR gave conformation about their purity and showed no interaction between drug and selected polymers. Various formulations were developed by using release rate controlling gel forming polymers like HPMC (K-4 M, K-15 M & K-100 M) in a single by direct compression method with the incorporation of NaHCO3 as a gas generating agent. All the formulation had floating lag time below 55 seconds and constantly floated on dissolution medium for more than 24 hours. Swelling studies indicated significant water uptake and contributed in drug release. From among all the developed formulations, as formulation F-3 prolonged the drug release for longer period of time and it had less floating lag time as compared to other formulations. So, it was selected as the best formulation. It was concluded that the drug release followed Zero order kinetics, as the correlation coefficient (R2 value) was higher for Zero order release, so the drug release followed controlled release mechanism. The best formulation was found to be stable during the stability studies for two months. Thus, the best formulation satisfied physicochemical parameters, floating properties, swelling index and in vitro drug release profile requirements for a floating drug delivery system.

INTRODUCTION

ARTHRITIS

The term arthritis literally means "joint inflammation",but it is generally used to describe

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inflammatory and degenerative conditions of the joints. Contrary to popular misconception arthritis is not diseases,which is inevitable with old age .It can effect anyone to any age also there are a hundred different types of arthritis. The most common type of which is the osteoarthritis,rheumatoid arthritis (RA) and gout. Arthritis is a condition where the joints can undergoes degenerative changes leading to pain, stiffness, swelling with limitation of joint movements.

OSTEOARTHRITIS

Osteoarthritis can affect the cartilage. Cartilage is tough material that covers and protects ends of bones and acts as cushioning material between two bones. In osteoarthritis bits of cartilage may break off and cause pain swelling in between the joints over a period of time. Cartilage may wear away entirely and bones will rub together causing pain. The cause of this disorder entirely not known it is commonly related to naturally attribute to age related natural disintegration. It is most relevant form of arthritis.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is auto immune disease in which the immune system attacks our own body tissues. RA is one of the serious and mostly effecting disease in the women.

GOUT

It is result of defect in our body chemistry. This condition attacks small joints,especiallythe big toe. Gout can be controlled within the medication.

ALKYLOSING SPONDYLITIS:

It is type of arthritis that affects the spine as a result of inflammation,bones of spine grow together.

JUVENILE ARTHRITIS:

It is general term for all types of arthritis that occur in children.

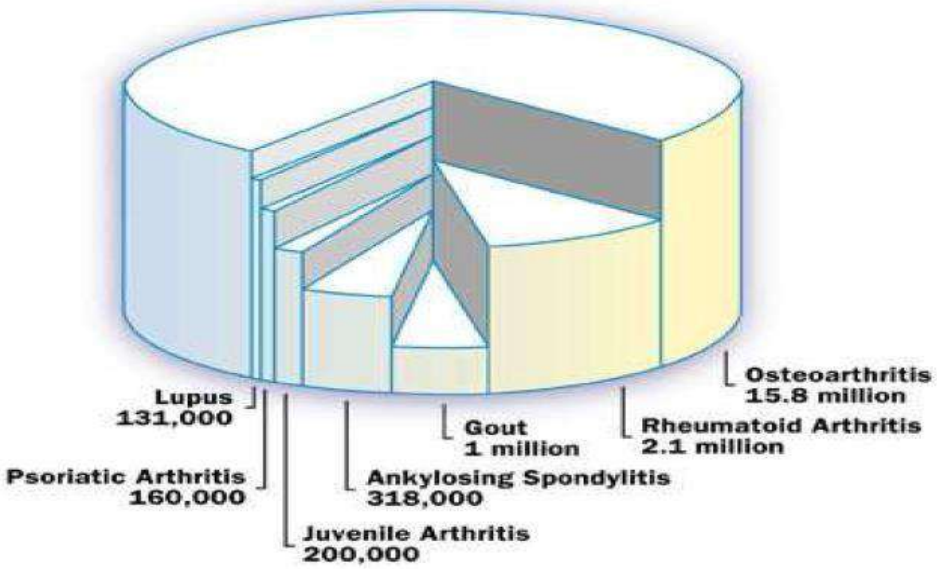

Figure 1: Survey Of Arthritis In Human Population

Lornaxicam is an orally active molecule which belongs to the oxicam family. It is also named as 5-chloro tenoxicam. It was introduced in 2005 and is a cyclo-oxygenase II (COX II) inhibitor which is used in the management of arthritis. Lornaxicam is marketed in the conventional dosage form of tablet in usual strength of 4-8mg. The bioavailability of Lornaxicam is 70-90% and its half-life is approximately 3-4hrs.

OBJECTIVES

The objective of the present study is to formulate the GRDFs containing Lornoxicam, which would

remain in stomach and/or upper part of GIT for prolonged period of time in views to improve bioavailability of the drug as well as its half-life and to release the drug in physiological environment of stomach with controlled rate.

The specific objectives of research include:

1. To carry out preformulation studies for possible drug-polymer interactions by FTIR.
2. To develop and formulate controlled release floating tablets (gastro-retentive) for Lornoxicam.
3. To evaluate the formulated dosage forms based on

- Physicochemical parameters like…
- Weight variation
- Thickness
- Hardness
- Friability
- Uniformity of drug content
- Floating lag time
- Floating time
- In vitro release studies.

4. To carry out short term stability studies of the most satisfactory formulation as per ICH guidelines for two months.

METHODOLOGY

Table 1: List of equipment's

Equipment's	Model/ Company
UV Visible Spectrophotometer	UV-1700, Shimadzu
Electronic Balance	AUX220, Shimadzu
Rotary Tablet Punch Machine	Rimek, Mini Press-I, Karnavati
Vernier Calipers	Ultra Science Aids
Hot Air Oven	Servwell
Roche tablet Friabilator	EF-2/ Electrolab
Tablet Dissolution Tester	DS 8000/ Labindia
Tablet Hardness Tester	Pfizer
FT-IR	Tensor 27, Bruker
Automated Tap Density Tester	ETD-1020/Electrolab
pH – meter	Eutech instruments

PREFORMULATION STUDY

Preformulation study is one of the important prerequisite in development of any drug delivery system. Thus, a preformulation study was carried out to check the compatibility between drug and selected polymers and development of analytical method of drug.

DRUG POLYMER COMPATIBILITY STUDIES:

- Drug polymer compatibility studies were carried out using FTIR.
- Infrared spectrum of pure drug was seen in between 600 to 3800 cm-1.
- The study was carried out on individual pure drug and its physical mixture with the selected polymers under study.

UV SPECTRUM ANALYSIS OF LORNOXICAM:

The solution was scanned in the range of 200 to 400 nm to fix the maximum wavelength and UV spectrum was obtained.

PREPARATION OF STANDARD CURVE:

Standard stock solution of Lornoxicam in simulated gastric fluid pH (1.2):

Accurately weighed 10 mg of Lornoxicamwas made to dissolve in 10 ml of 0.1 N NaoH and the solution was made upto 100 ml with 0.1 N HCl.

Calibration curve of Lornoxicam:

From standard stock solution, 30 ml was withdrawn and transferred into 100 ml volumetric flask, the volume was made with 0.1 N HCl in order to get standard stock solution containing 30µg/ml. from this aliquots series of dilutions of 1, 2, 3, 4, 5 and 6 ml were taken in 6 different 10 ml volumetric flasks and the volume was made up with 0.1 N HCl. Absorbance of these solutions was measured against blank of 0.1 N HCl at 374 nm for Lornoxicam.

METHOD OF PREPARATION OF FLOATING MATRIX TABLETS

Lornoxicam, HPMC K4M, HPMC K15M, and HPMC K100M; and filler like microcrystalline cellulose (MCC). Sodium bicarbonate was

selected as gas generating agent. Talc and megnisium stearate were used as lubricants. Lornoxicam, selected polymers (various grades of hydroxy propyl methyl cellulose), sodium bi carbonate and MCC were taken in required quanties. In dry state, drug was mixed with other ingredients for the period of 10 min in mortar to get uniform mixture. Powder was lubricated with magnesium stearate and talc. Lubricated powder was compressed to tablets in 8 mm concave die cavity of tablet punching machine (Mini press-I, Rimek, Karnavati).

EVALUATION OF PREFORMULATION PARAMETERS:-

i. **Micromeritic properties**

a. Angle of repose :-

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

$$tan\theta = \frac{h}{r}$$

Therefore θ= tan-1h/r.

Where, θ = angle of repose, h = height of the pile,r = radius of the pile base.

Table 2: Angle of repose values

Flow Property	Angle of Repose (º)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

b. Bulk and Tapped density:-

Both loose bulk density (LBD) or bulk density and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 100 ml measuring cylinder of tap density tester. 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 1 min. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula:

$$\text{Bulk density} = \frac{Weight of the Powder}{volume\ of\ Powder}\ \text{Bulk}$$

$$\text{Tapped density} = \frac{Weight of the Powder}{Tapped volume of the Powder}$$

c. Carr's Index :-

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. Compressibility index determined by measuring both the bulk volume and the tapped volume of a powder

$$\text{Compressibility Index}(\%) = \frac{[(TBD - LBD) \times 100]}{TBD}$$

Where, LBD = weight of the powder/volume of the packing TBD = weight of the powder/tapped volume of the packing.

Table 3: Scale of Flowability

Compressibility Index (%)	Flow Character
10	Excellent
11–15	Good
16–20	Fair

21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very, very poor

ii. Compatibility studies

In the tablets, drug is in intimate contact with one or more excipients, which could affect the stability of the drug. The knowledge of drug excipients interactions is therefore essential for selecting appropriate excipients. This was studied using FTIR spectrophotometry.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra for pure drug, Polymers and drug loaded microparticles were obtained using a FTIR spectrophotometer type Bruker Optic, Tensor 27, USA.

iii. Physicochemical parameters

a. Tablet hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

b. Tablet thickness

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using Vernier calipers on 3 randomly selected samples

c. Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 min dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were re-weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{Initial wt. of tablets - Final wt. of tablets}{Initial wt. of tablets}$$

d. Weight variation:

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table 7) and none deviates by more than twice that percentage.

Table 4: IP standards of percentage of weight variation

Average weight of tablet (mg)	% deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 or more	5

e. Uniformity of drug content

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder weight equivalent to 8 mg drug was dissolved in 0.1 N NaoH and the volume was made upto 100 ml with 0.1 N HCl (Stock-1). The solution was shaken for 1 h and kept for 24 h. From the stock solution, 1 ml solution was taken in 10 ml volumetric flask and the volume was made with 0.1 N HCl, absorbance was measured spectrophotometrically at 374 nm against 0.1 HCl N as a blank.

Amount of drug present in one tablet was calculated.

f. Floating lag time

The floating lag time was carried out in a beaker containing 100 ml of simulated gastric fluid as a testing medium maintained at 37 °C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

g. Floating time:

Floating time was the time, during which the tablet floats in simulated gastric fluid dissolution medium (including floating lag time).

h. Swelling characteristics

The swelling properties of floating matrix tablets containing drug were determined by placing the tablet matrices in the USP dissolution testing apparatus II, in 900 ml of simulated gastric fluid at 37 ± 0.5 °C without enzyme, rotated at 75 rpm. The tablets were removed periodically from dissolution medium, blotted / to remove excess water and weighed. Swelling characteristics were expressed in terms of percentage water uptake (WU %).

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the tablet}} \times 100$$

i. Dissolution studies

The release rate of Lornoxicam from floating matrix tablets were determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of SGF (0.1 N HCl, 0.2% NaCl) without enzyme at 37 ± 0.5 °C and 75 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 24 h and the samples were replaced with fresh dissolution medium. The withdrawn samples were made up to 10ml using methanol. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

Details of dissolution test:

1. Apparatus : USP type II
2. Volume of medium : 900 ml
3. Temperature : 37 ± 0.5 °C
4. Paddle speed : 50 rpm
5. Dissolution medium used : Simulated gastric fluid (0.1 N HCl 0.2% NaCl) 6. Aliquot taken at each time interval: 10 ml

OPTIMIZATION STUDY

The runs or formulations, which are designed, based on simplex lattice design are evaluated for the response. The response values are subjected to the multiple regression analysis to find out the relationship between the factors used and the response values obtained. The response values subjected for this analysis are

- Hardness (kg/cm2)
- Floating lag time (sec)
- Drug release for 1 h (%)
- Drug release for 2 h (%)
- Drug release for 8 h (%)
- Drug release for 24 h (%)

KINETICS MODELING OF DRUG DISSOLUTION PROFILES

The dissolution profile of most satisfactory formulation was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas models to ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model.

1. Zero order Kinetics

The zero order rate Eq. describe the systems where the drug release rate is independent of its concentration. The plot of % cumulative drug released vs. time is the linear.

$$C = K_0 t \quad \text{---------- (1)}$$

Where, K0 = Zero-order rate constant,

t = Time

2. First order kinetics

The first order Eq. describes the release from the systems where release rate is concentration dependent. A plot of log of % drug remaining verses time is the linear.

$$\log C = \log C_0 - Kt / 2.303 \quad \text{---------- (2)}$$

Where, C0 = initial concentration of drug K = First order constant.

3. Higuchi model

Higuchi model was developed on the basis of Fick's law and it describes the fraction of drug release from a matrix is proportional to square root of time. A plot of % drug released versus square root of time is linear.

Q = K t1/ 2 ---------- (3)

Where, K= Constant t = Time.

4. Korsmeyer-Peppas model

It describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

Mt/M∞= Ktn ---------- (4)

Where, Mt / M∞= Fraction of drug released at time t, K = Rate constant, n = Release exponent. where Mt/M∞ corresponds to the amount of drug released at time 't' and after an infinite time, 'K' is a constant comprising the structural and geometric characteristics of the tablet and the release exponent 'n' is a parameter that depends on the release mechanism. Peppas used this 'n' value in order to characterize different release mechanisms. If the 'n' value is 0.5 or less, the release mechanism follows Fickian diffusion, and higher values 0.5 < n < 1 for mass transfer follow a Non-Fickian model (anomalous transport). The drug release follows zero-order and case-II transport if the 'n' value is 1. For the values of 'n' higher than 1, the mechanism of drug release is regarded as super case-II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomena was involved. The 'n' value could be obtained from the slope of a plot of log Mt/M∞ versus log time.

STABILITY STUDIES FOR THE MOST SATISFACTORY FORMULATION

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines.

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5 % RH for two months. At the end of studies, samples were analyzed for the drug content, in vitro dissolution, floating behavior and other physicochemical parameters.

RESULTS

PREFORMULATION STUDIES

DEVELOPMENT OF STANDERD CALIBRATION CURVE

Table 5: Standard calibration curve of Lornoxicam in simulated gastric fluid

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	3	0.178 ± 0.005
3	6	0.345 ± 0.0097
4	9	0.509 ± 0.013
5	12	0.691 ± 0.009
6	15	0.861± 0.017
7	18	0.997±0.026

STANDARD CALIBRATION CURVE OF LORNOXICAM

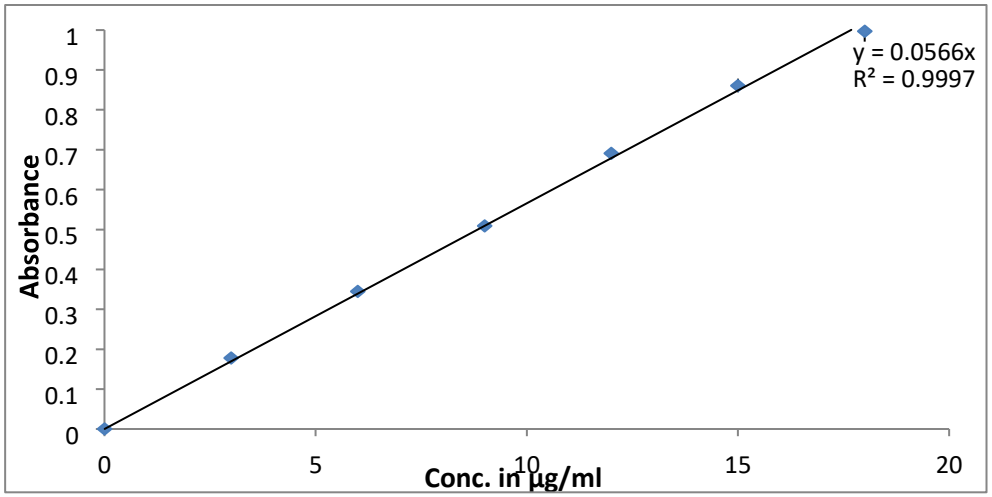

Figure 2: Standard Calibration Curve of Lornoxicam

FT-IR of pure drug and polymer mixture

Table 6: Characteristic peaks of lornoxicam in FT-IR spectra in cm-1

Pure drug	Pure drug + HPMC K-4M	Pure drug + HPMC K-15M	Pure drug + HPMC K-100M	Description
3061	3062	3062	3063	-NH stretch
1636	1636	1636	1637	Primary amide (CONH) present
1592, 1534	1592, 1535	1593, 1534	1593, 1535	Secondary amide present
1143, 1323, 1377	1142, 1324, 1377	1142, 1323, 1377	1142, 1324, 1378	R-SO_2-R present
829	830	829	830	C-H Aromatic ring bending
785	786	785	786	C-X present

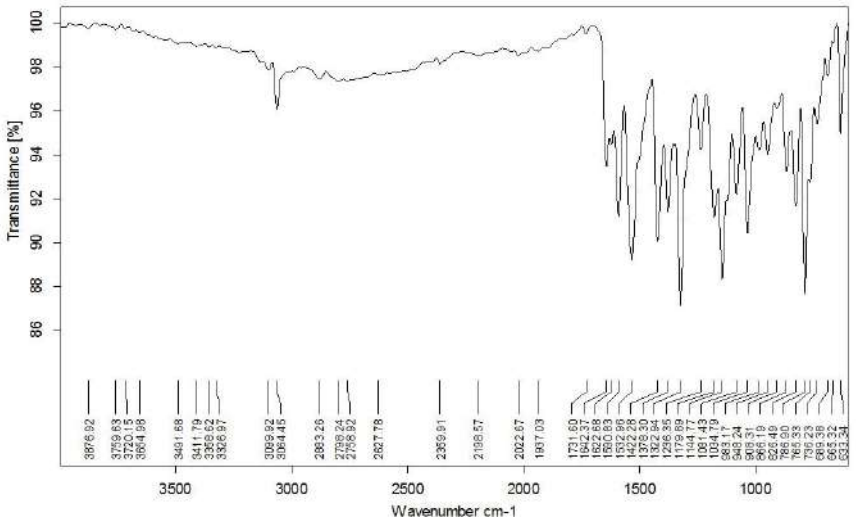

Figure 3: FT-IR spectra of pure drug Lornoxicam

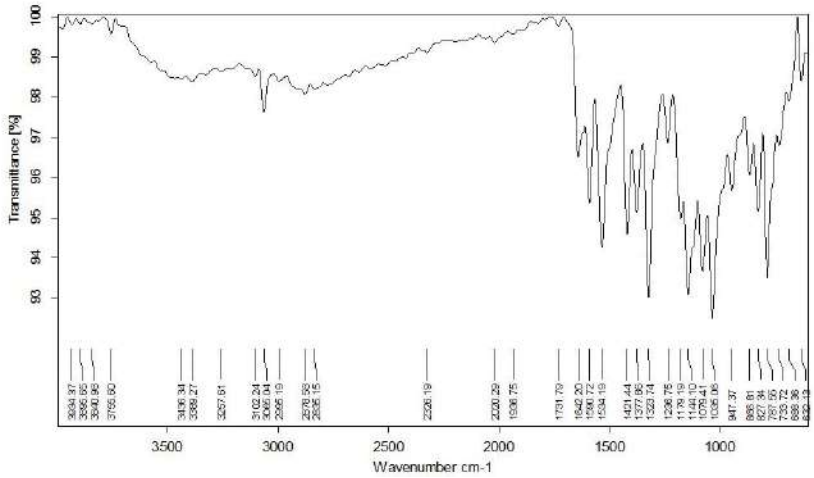

Figure 4: FT-IR spectra of physical mixturw of Lornoxicam with HPMC K-4M

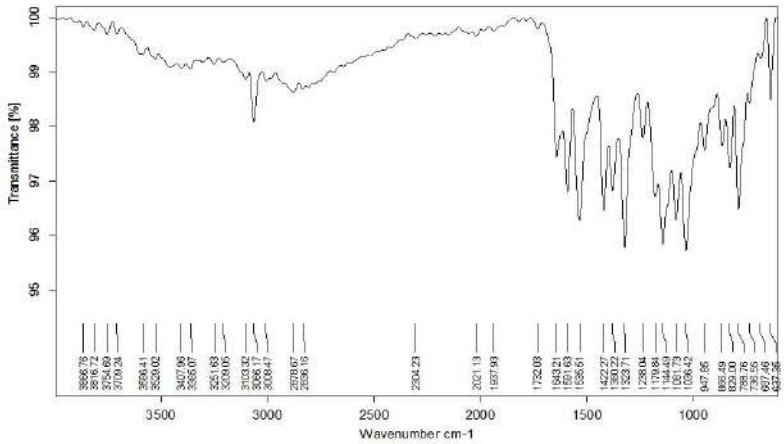

Figure 5: FT-IR spectra of physical mixture of Lornoxicam with HPMC K-15M

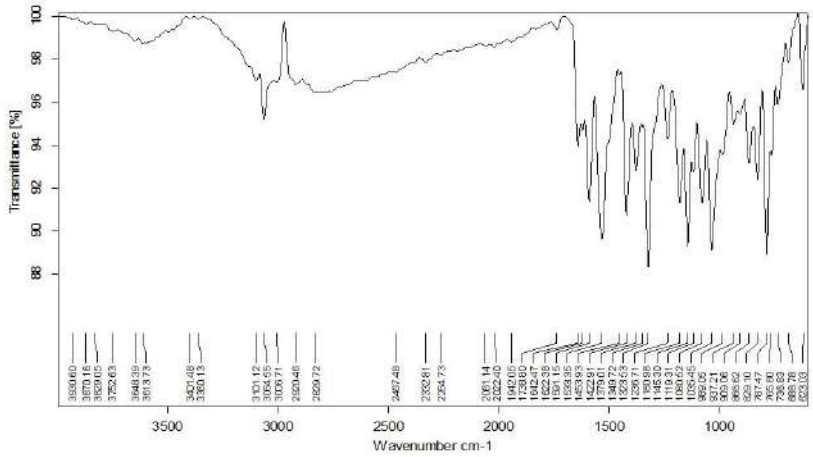

Figure 6: FT-IR spectra of physical mixture of Lornoxicam with HPMC K-100M

Table no 7

Formulation code	Ingredients							
	Lornoxicam (Mg)	HPMC K4M (Mg)	HPMC K-15 M (mg)	HPMC KM 100 mg	NaHCO3 mg	MCC (mg)	Magnesium stearate (mg)	Talc (mg)
F1	8	8	-	-	50	79	2.5	2.5
F2	8	16	-	-	50	71	2.5	2.5
F3	8	24	-	-	50	63	2.5	2.5
F4	8	32	-	-	45	60	2.5	2.5
F5	8	40	-	-	45	52	2.5	2.5
F6	8	-	8	-	50	79	2.5	2.5
F7	8	-	16	-	50	71	2.5	2.5
F8	8	-	24	-	50	63	2.5	2.5
F9	8	-	32	-	45	60	2.5	2.5
F10	8	-	40	-	45	52	2.5	2.5
F11	8	-	-	8	50	79	2.5	2.5
F12	8	-	-	16	50	71	2.5	2.5
F13	8	-	-	24	50	63	2.5	2.5
F14	8	-	-	32	45	60	2.5	2.5
F15	8	-	-	40	45	52	2.5	2.5

Total weight of the tablet is 150 mg.

EVALUATION OF PREFORMULATION PARAMETERS

Table 8: Micromeritic properties of Lornoxicam floating matrix tablets

Formulation code	Angle of repose* (°) ± S.D.	Bulk density* (gm/ml) ± S.D.	Tapped density* (gm/ml) ± S.D.	Carr's index* (%) ± S.D.
F1	29.47±6.32	0.388±0.019	0.444±0.014	12.44±9.05
F2	29.24±5.1	0.348±0.028	0.395±0.021	11.72±6.21
F3	27.95±2.47	0.32±0.011	0.3938±0.023	15.5±1.55
F4	28.95±8.14	0.31±0.039	0.35±0.04	11.4±3.36
F5	30.47±4.89	0.324±0.013	0.373±0.014	13.06±5.51
F6	33.82±3.22	0.311±0.022	0.361±0.019	13.8±3.29
F7	34.24±5.35	0.352±0.051	0.399±0.028	11.78±4.28
F8	28.95±6.49	0.331±0.017	0.397±0.031	16.62±7.04
F9	32.9±1.05	0.352±0.023	0.3939±0.049	10.57±2.67
F10	29.24±2.96	0.378±0.035	0.45±0.020	15.95±1.5
F-11	32.12±8.03	0.325±0.006	0.393±0.044	17.38±3.66
F-12	33.21±4.451	0.362±0.013	0.413±0.056	12.34±3.29
F-13	29.73±3.331	0.338±0.037	0.392±0.027	13.77±5.67
F-14	30.9±2.41	0.34±0.041	0.384±0.051	11.41±3.32
F-15	30.98±6.9	0.346±0.044	0.392±0.060	11.73±6.44

*Average of 3 determination ± standard deviation

EVALUATION OF PHYSICO-CHEMICAL PARAMETERS OF PREPARED TABLETS OF FLOATING MATRIX TABLETS

Table 9: Characterization of floating matrix tablets of Lornoxicam

Formulation code	Hardness* ± S.D. Kg/cm ^{2}) (	Friability (%)	Weight variation* mg (	Estimation of drug content % (	Thickness* ± S.D. mm (	Floating Lag Time sec /	Floating Time sec (
F1	7.0± 0.41	0.325	150.8±1.69	94.7±2.05	2.76±0.08	47	>24
F2	5.0± 0.33	0.465	150.33±2.55	96.71±1.2	2.69±0.06	54	>24
F3	5.6± 0.56	0.54	149.88±0.61	94.07±0.77	2.69± 0.048	37	>24
F4	5.0± 0.18	0.458	150.22±1.85	98.68±0.52	2.68±0.02	51	>24
F5	5.2± 0.78	0.355	150.11±1.9	92.76±0.52	2.715±0.034	40	>24
F6	5.0± 0.14	0.398	149.67±2.39	100.9±4.24	2.659±0.032	45	>24
F7	6.0± 0.77	0.444	149.88±2.37	100.2±3.23	2.68±0.03	50	>24
F8	5.2± 0.61	0.387	150.89±2.26	98.46±0.99	2.703±0.045	45	>24
F9	5.6± 0.39	0.34	150.33±2.07	93.85±0.51	2.758±0.062	35	>24
F10	6.8±0.7	0.38	150.67±1.8	95.6±0.59	2.753±0.028	50	>24
F-11	5.2± 0.58	0.67	150.63±1.51	98.90±1.91	2.657±0.033	45	>24
F-12	7.0± 0.93	0.338	150.5±2.1	102.4±2.91	2.665±0.063	45	>24
F-13	4.8± 0.47	0.45	149±1.69	94.09±4.07	2.698±0.103	55	>24
F-14	4.8±0.6	0.378	150.13±2.47	92.32±0.23	2.73±0.11	40	>24
F-15	6.2± 0.41	0.331	148.87±1.73	92.33±2.32	2.73±0.11	45	>24

*Average of 3 determination ± standard deviation

Table 10: Swelling Characteristics of Lornoxicam Floating Matrix Tablets

Swelling Index (%) Using HPMC K-4M				
Formulation	**Time (hr)**			
	1	**4**	**8**	**12**
F-1	23.1±4.73	43.5±4.023	79.4±4.11	104.3±6.55
F-2	29.33±4.58	47.1±1.46	81.2±0.926	109.2±3.68
F-3	35.1±1.61	49.1±6.54	81.6±2.178	114.72±1.54
F-4	39.4±6.36	56.7±4.92	89.9±6.54	119.6±2.48
Swelling Index (%) using HPMC K-15M				
Formulation	**Time (hr)**			
	1	**4**	**8**	**12**
F-6	29.4±1.828	49.8±3.37	81.7±6.26	116.4±5.25
F-7	33.8±2.59	59.4±3.79	88.93±2.13	124.89±2.86
F-8	46.92±4.05	64.75±3.47	90.45±6.35	132.11±1.98
F-9	51.8±3.32	77.81±2.99	96.84±2.6	133.95±2.11
Swelling Index (%) using HPMC K-100M				
Formulation	**Time (hr)**			
	1	**4**	**8**	**12**
F-11	33.9±0.31	54.5±1.18	89.4±0.59	121.67±1.11
F-12	34.7±3.36	64.92±3.97	92.7±0.73	130.56±5.17
F-13	49.5±2.28	75.89±4.79	97.6±4.79	135.8±1.125
F-14	61.93±0.95	82.11±4.77	99.45±0.35	136.91±1.7

F-15	74.6±0.403	88.36±4.13	111.43±2.37	149.99±1.39

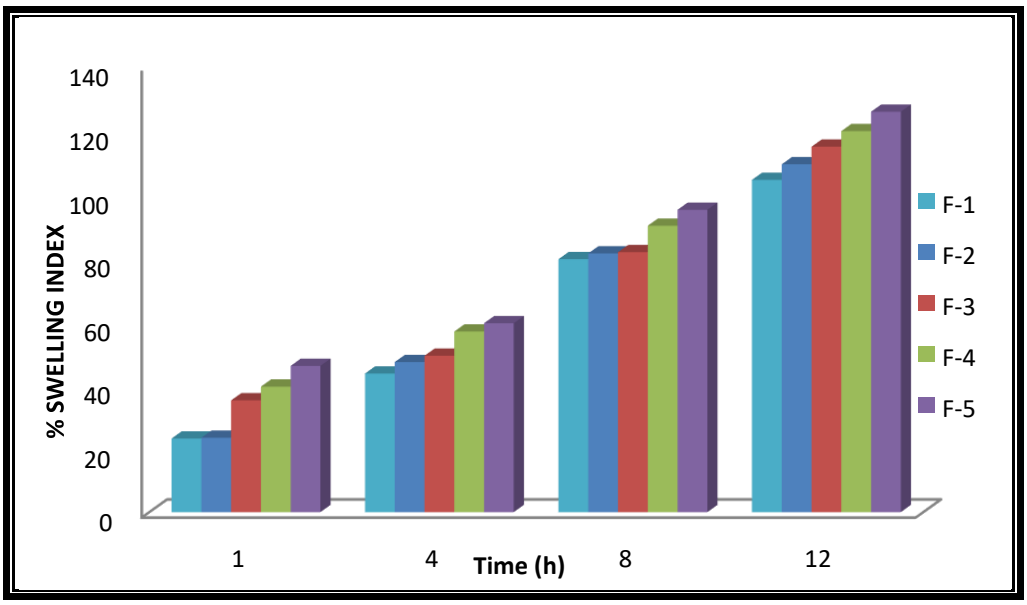

Figure 7: Swelling Index of HPMC K-4M based Floating matrix tablets

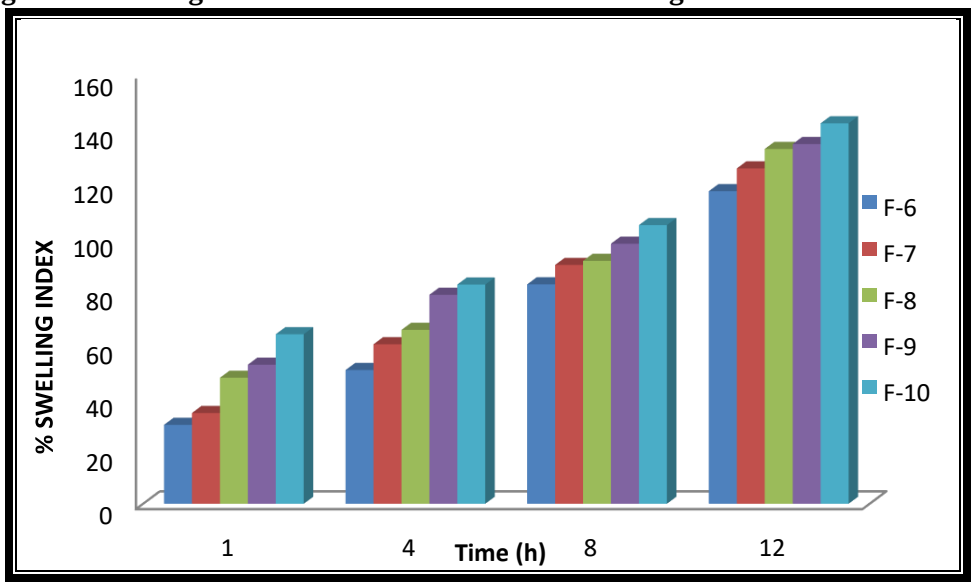

Figure 8: Swelling Index of HPMC K-15M based Floating matrix tablets

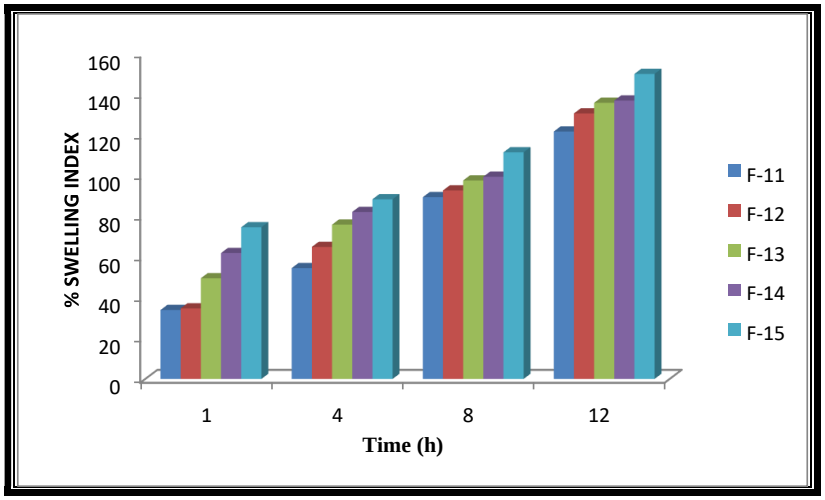

Figure 9: Swelling Index of HPMC K-100M based Floating matrix tablets

IN VITRO DRUG RELEASE STUDY

Table 11: Cumulative Drug Release of HPMC K-4M based Floating Matrix Tablets

Time (h)	F-1 (%)	F-2 (%)	F-3 (%)	F-4 (%)	F-5 (%)
1	13.83±1.7	12.32±2.91	5.97±2.21	5.84±0.698	6.05±2.88
2	21.1±1.23	17.75±2.78	8.16±1.15	10.31±0.83	7.92±2.17
3	25.18±1.5	26.21±2.99	13.27±1.6	13.27±1.56	10.26±3.2
4	31.85±2.34	32.82±4.55	18.17±2.84	17.61±1.71	14.56±3.6
5	38.18±2.65	36.96±6.14	22.23±1.72	22.05±0.71	17.91±2.11
6	44.37±3.07	42.81±7.62	26.52±1.93	25.29±1.58	21.43±2.44
7	53.36±2.28	50.72±9.13	31.54±1.12	28.61±0.66	24.98±1.66
8	60.85±2.03	57.32±9.61	36.65±1.62	32.64±0.75	30.10±1.87
9	68.47±3.36	66.23±8.83	41.04±1.99	37.85±2.05	35.48±1.07
10	79.77±2.42	75.91±6.87	46.92±1.46	41.77±1.89	39.18±1.24
11	89.18±2.22	84.09±4.67	50.94±2.58	46.46±1.01	43.52±1.23
12	97.56±0.67	91.02±3.91	56.13±1.81	51.67±1.14	47.5±0.97
24	-	-	97.02±1.08	88.26±1.63	84.18±1.8

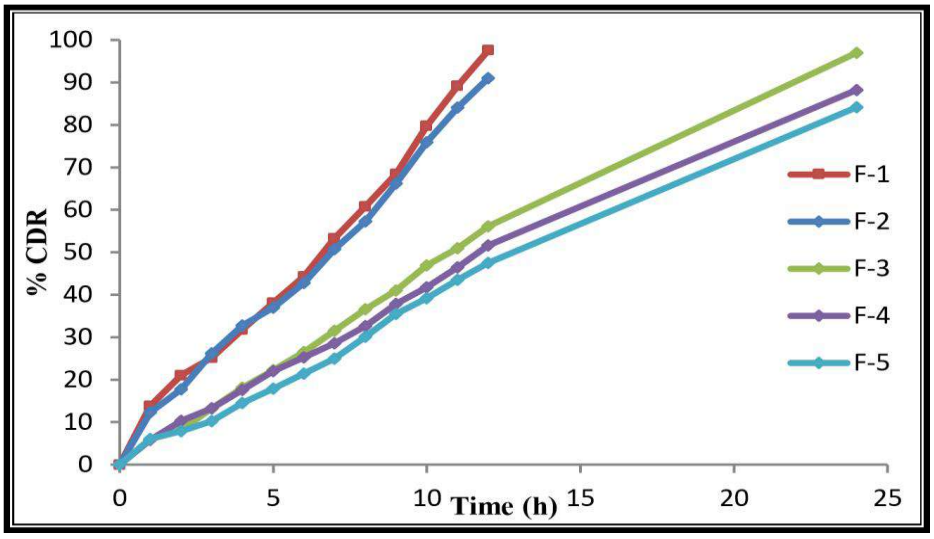

Figure 10: Drug release profile of HPMC K-4M based floating matrix tablets

Table 12: Cumulative Drug Release of HPMC K-15M based Floating Matrix Tablets

Time (h)	F-6 (%)	F-7 (%)	F-8 (%)	F-9 (%)	F-10 (%)
1	15.45±5.50	7.051±3.62	5.91±0.81	5.24±2.61	5.18±2.77
2	20.8±6.96	14.71±3.69	9.24±1.24	6.78±2.11	3.16±2.18
3	26.08±8.23	19.72±4.14	12.53±1.93	10.24±1.98	11.66±1.65
4	33.48±7.92	25.06±3.77	16.47±2.52	13.48±1.46	13.38±2.37
5	38.9±6.41	32.25±4.22	21.16±4.28	18.21±3.46	16.05±2.61
6	45±4.78	38.98±4.76	25.78±4.57	22.27±3.01	20.08±3.73
7	53.56±2.61	45.85±4.67	29.38±4.6	26.09±2.84	23.56±3.14
8	58.85±3.22	52.85±4.37	35.02±4.63	30.17±2.26	24.2±6.86
9	65.07±2.84	59.87±4.09	39.78±2.79	35.27±2.68	31.48±2.81
10	70.8±2.16	66.88±4.16	44.92±3.57	40.44±2.45	37.2±3.69
11	79.25±3.68	74.71±2.57	50.33±1.97	44.71±5.26	40.92±5.16
12	88.78±2.39	83.6±1.37	54.49±2.64	50.46±4.19	47.13±5.05
24	-	-	92.78±1.76	87.54±3.93	81.52±5.01

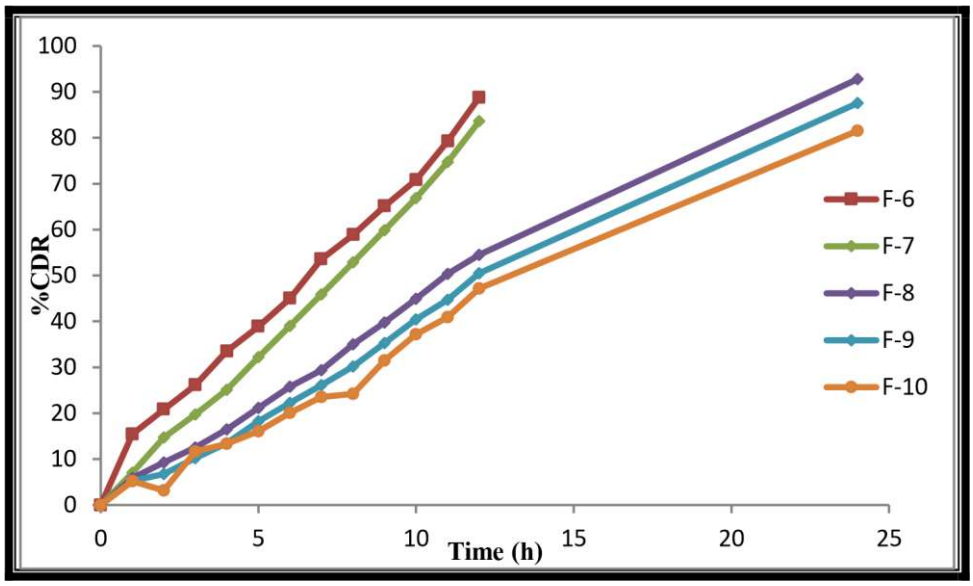

Figure 11: Drug release profile of HPMC K-15M based floating matrix tablets

Table 13: Cumulative Drug Release of HPMC K-100M based Floating Matrix Tablets

Time (h)	F-11 (%)	F-12 (%)	F-13 (%)	F-14 (%)	F-15 (%)
1	7.84±1.74	8.51±1.52	5.71±1.47	6.16±2.13	2.79±0.72
2	14.25±4.68	12.19±3.54	8.57±1.11	8±2.47	5.01±0.92
3	22.05±6.58	15.2±3.85	12.72±0.94	10.92±3.53	7.5±2.65
4	27.88±3.94	20.34±4.84	16.85±0.69	15.58±4.57	11.74±3.94
5	33.97±4.01	25.95±4.64	20.56±0.91	19.74±5.13	15.32±3.6
6	40.79±3.61	31.42±4.42	24.11±1.49	22.95±5.36	19.41±3.59
7	46.88±3.05	39.53±3.94	28.89±3.31	27.97±5.74	22.81±1.59
8	53.83±3.79	46.87±4.65	33.85±4.22	31.96±5.67	25.98±1.27
9	61.11±3.53	55.95±3.9	39.13±3.67	35.39±5.73	29.12±1.21
10	69.02±4.16	64.13±3.55	43.07±3.35	40.03±4.97	33.08±2.04
11	75.75±2.78	73.45±3.45	46.65±3.84	43.17±4.79	37.69±2.28
12	85.82±2.69	80.94±3.68	53.88±4.85	47.73±5.61	42.94±1.49
24	-	-	83.94±3.11	81.02±5.79	74.62±3.43

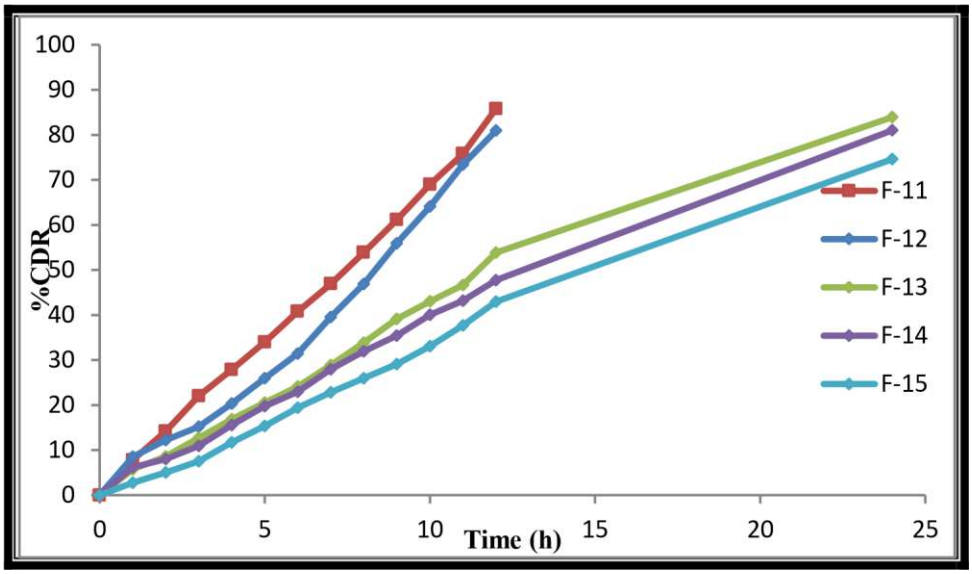

Figure 12: Drug release profile of HPMC K-100M based floating matrix tablets

KINETICS MODELING OF DRUG DISSOLUTION PROFILES

Table 15: Correlation coefficients of drug release curves for floating matrix tablets of batch F-3 based on three kinetic models

Model	R^2 (Correlation coefficient)
	F-3
Zero order	0.990
First order	0.777
Higuchi	0.826
Mechanism	Controlled

The in vitro release data obtained were fitted in to various kinetic models. Correlation coefficients of formulation F-3 batch showed higher correlation with zero order plots. So, predominant drug release mechanism is controlled release.

STABILITY STUDIES

Table 14: Drug release profile of the most satisfactory formulation during stability studies

Time	After 30 Days		After 60 days	
	A	B	C	D
	F-3 (%)	F-3 (%)	F-3 (%)	F-3 (%)
1	5.18±2.02	4.19±1.61	4.39±2.4	3.99±1.16
2	7.64±2.34	5.43±1.44	6.24±2.21	5.83±2.32
3	9.51±2.12	8.49±2.13	8.89±1.1	9.88±1.12
4	13.21±2.11	13.37±2.91	12.39±1.4	13.78±4.12
5	18.35±2.09	17.11±1.73	17.71±3.33	16.92±2.51
6	24.93±1.32	22.27±2.95	23.88±2.15	22.89±2.74
7	28.99±0.09	27.51±1.81	27.14±1.39	26.94±1.29
8	33.69±1.41	31.99±4.87	31.22±3.09	32.81±1.46
9	37.64±0.91	35.72±1.99	35.94±3.12	35.35±2.32
10	44.62±1.61	41.49±1.17	42.31±1.27	41.91±2.65
11	48.88±3.55	45.52±3.22	46.54±3.04	46.94±1.9
12	54.58±0.78	51.38±1.57	52.42±1.01	52.23±0.23
24	95.46±0.09	94.42±1.43	95.07±2.13	93.98±1.82

A, C = 30± 2 °C / 65 ± 5 % RH B, D = 40 ± 2 °C / 75 ± 5 % RH

All regarding are mean of 2 reading ± standard deviation

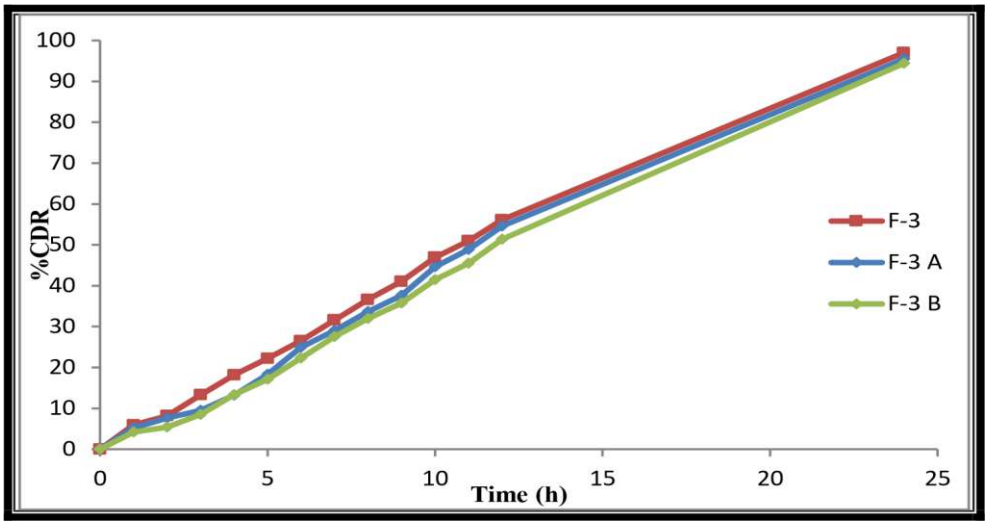

Figure 13: Drug release profile of Formulation F-3 during stability studies

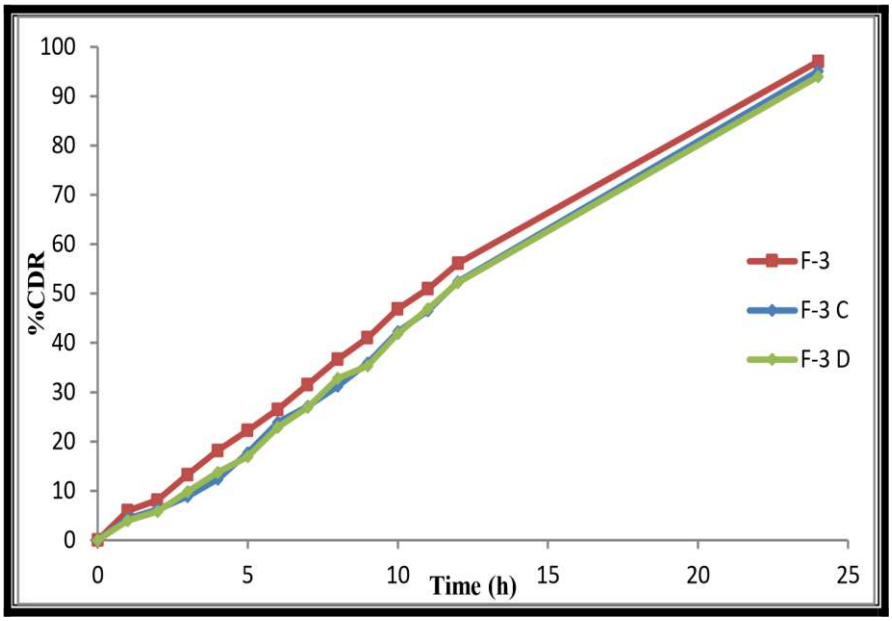

Figure 14: Drug release profile of formulation F-3 during stability studies

DISCUSSION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system. Floating drug delivery system belongs to oral controlled drug delivery system group, which is capable of floating in the stomach for prolonged period of time. Lornoxicam, a highly potent non-steroidal anti-inflammatory drug (NSAIDs), a cyclooxygenase-II (COX-II) inhibitor is used in management of different types of Arthritis. The bioavailability of Lornoxicam is 70-90 %, its half life is 3-4 h. So, in the present study, an attempt was made to formulate floating matrix tablets of Lornoxicam in order to increase residence time in stomach for better absorption. In the present study, Lornoxicam floating matrix tablets were prepared by using HPMC (K-4M, K-15M, K-100M) as a drug retardant polymer and sodium bicarbonate as a gas generating agent. A total number of fifteen formulations were prepared by direct compression technique. The preformulation studies such as bulk density, tapped density, angle of repose and Carr's index were evaluated and were found to be within prescribed limits and

indicated good free flowing property. The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content, floating properties, swelling studies and in vitro drug dissolution gave satisfactory results.

PREFORMULATION STUDIES

1. Any formulation development work has to be proceeded by preformulation studies. This preformulation study includes drug polymer compatibility study and analytical investigation of drug.
2. FTIR study showed that there is no interaction between drug and polymer. So, the drug and polymer are compatible.
3. Estimation of Lornoxicam was carried out by SHIMADZU-1700 UV spectrophotometer at λmax374 nm in simulated gastric fluid. The linear coefficients of each were found to be closer to
4. By using the regression coefficient equation the assay and % CDR were calculated.

UV SPECTRUM ANALYSIS OF LORNOXICAM

At the outset, a method for the drug was developed. Lornoxicam showed maximum absorption at wavelength 374 nm in 0.1 N HCl. Standard calibrated curve obeyed beer's law at given concentration range of 0.5 µg/ml and when subjected to regression analysis, the value of regression coefficient was found to be 0.999, which showed linear relationship between concentration and absorbance.

MICROMERETIC PROPERTIES

ANGLE OF REPOSE

The results of angle of repose were ranged between 27.95 ± 2.47 to 34.24 ± 5.35 which indicates good to average flow properties of powder.

CARR'S INDEX

The Carr's index values were found to be in the range of 10.57 ± 2.67 % to 17.38 ± 3.66 %. These findings indicated that the powder mixture of all batches of formulation exhibited good flow properties and hence, were suitable for direct compression into floating matrix tablets.

FORMULATION STUDIES

FORMULATION DEVELOPMENT

Various formulations of floating matrix tablets were developed for Lornoxicam using selected polymers like HPMC K-4M, HPMC K-15M, HPMC K-100M; and filler like micro crystalline cellulose. Sodium bicarbonate was selected as gas generating agent. Talc and magnesium stearate were used as glidant and lubricants. Various formulations of floating matrix tablets were prepared by direct compression technique using 8 mm flat punches to an average weight of 150 mg.

EVALUTION OF PHYSICOCHEMICAL PARAMETERS

TABLET THICKNESS

Thickness of the developed formulations F-1 to F-15 varied from 2.657 ± 0.033 mm to 2.76 ± 0.08 mm. each sample was analyzed in triplicate (n=3).

TABLET HARDNESS

Hardness of the developed formulations F-1 to F-15 varied from 4.8 ± 0.47 kg/cm2 to 7.0 ± 0.93 kg/cm2.

FRIABILITY

Friability of the developed formulations varied from 0.325 % to 0.67 % loss which was less than 1 % as per official requirement of I.P.

WEIGHT VARIATION

The average weight of twenty tablets was calculated for each formulations which varied from 149 ± 1.69 mg to 150.89 ± 2.26 mg as well as % deviation i.e. ± 7.5 % complied the official requirement as per I.P.

UNIFORMITY OF DRUG CONTENT

The drug content varied from 92.32 ± 0.23 % to 102.4 ± 2.91 % which was within the required limits.

FLOATING LAG TIME

The buoyancy lag time of tablets depends upon the type and the amount of polymers used. For floating system, the ideal matrix forming polymer should be highly permeable to dissolution media in order to initiate rapid generation of CO2and should be permeable for CO2 to promote floating properties. In the present study, based on the preliminary studies, quantity of sodium bicarbonate varied from 40 mg, and 35 mg in all the developed formulations. All the formulations F-1 to F-15 showed floating lag time, which varied from 35 sec to 55 sec. formulation F9 showed the lowest floating lag time. Sodium bicarbonate is used widely as gas generating agent in the formulation to make the tablets to float. Floating time was found to depend on typed of polymers and their concentrations, swelling property, degree of gelling and their gel strength. All the developed matrix tablets showed a floating time up to 12 and 24 h.

SWELLING CHARACTERISTICS

The percentage water uptake (%WU) of the formulations F-1 to F-15 varied from 23.1 ± 4.73 % to 149.99 ± 1.54 %. The percentage water uptake was found to improve by increasing the concentration of HPMC in formulations. Formulation F3 had maximum swelling index of 114.72 ± 1.54 %. The highest degree of hydration was achieved by HPMC K-4M based formulations. The swelling index of HPMC K-4M based formulations F-1 to F-15 was lower as compared to that of HPMC K-15M and HPMC K-100M tablets. The swelling index of HPMC K-15M based formulations F-6 to F-10 was low compared to that of HPMC K-100M. The swelling index of HPMC K-100M based formulations F-11 to F-15 was high compared to that of HPMC K-4M and HPMC K-15M.

IN VITRO DRUG RELEASE STUDIES

The release of Lornoxicam from floating matrix tablets varied according to the type and proportion of matrix forming polymers.

HPMC K-4M based formulations

The progressive decrease in the amount of drug release from formulations F-1 to F-5 may be attributed to a gradual increase in HPMC K-4M content. It can be concluded that an increased in the proportion of matrix forming polymer HPMC K-4M, increases the viscosity of gel and also it retards, the drug release which leads to better control of polymers on the release of Lornoxicam. The duration of drug release was slower with formulation F-5 which was about only 84.18 ± 1.58 % in 24 h from among the formulations F-1 to F-5.

HPMC K-15M based formulations

The progressive decrease in the amount of drug release from formulations F-6 to F-10 attributed to a gradual increase in HPMC K-15M content. The duration of drug release was slower with formulation F-10 which was about only 81.52 ± 5.01 % in 24 h from among the formulations F-6 to F-10.

HPMC K-100M based formulations

The progressive decrease in the amount of drug release from formulations F-11 to F-15 attributed to a gradual increase in HPMC K-100M content. The duration of drug release was slower with formulation F-15 which was about only 74.62 ± 3.43 % in 24 h from among the formulations F11 to F-15. The order of drug release from the selected polymers were found to decrease in the following order HPMC K-100M > HPMC K-15M > HPMC K-4M Among the three grades of HPMC polymer used, the tablets prepared with lower viscosity grade i.e. HPMC K-4M has shown drug release rate 84.18 ± 1.58 % to 97.02 ± 1.08 %. The higher grade viscosity polymers i.e. HPMC K-15M has shown drug release rate 81.52 ±5.01 % to 92.78 ± 1.76 % and HPMC K-100M has shown drug release rate 74.62 ± 3.43 % to 83.94 ± 3.11 %.

KINETICS MODELING OF DRUG DISSOLUTION PROFILES

The in vitro release data obtained were fitted in to various kinetic models. Correlation coefficients of formulation F-3 batch showed higher correlation with zero order plots than higuchi and first order. So, predominant drug release mechanism is controlled release.

STABILITY STUDIES

Stability studies were carried out of the most satisfactory formulations F-3 at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5 % RH for two months to assess their long term stability as per ICH guidelines. At various time intervals of 30 days and 60 days, samples were evaluated. There was no major change in the various physicochemical parameters evaluated like hardness, drug content and floating properties, in vitro dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies.

CONCLUSION

- Lornoxicam is one of the short half life oxicams, which is used for the management of different types of Arthritis. Moreover, the site of absorption of Lornoxicam is in the stomach. The half-life of Lornoxicam was found to be 3-4 h. therefore, the present investigation was concerned with the development of floating matrix tablets, which after oral administration were designed to prolong the gastric residence time and thus, it improves the bioavailability of the drug as well as its half-life.
- A suitable method of analysis of drug by UV spectophotometry was developed. Lornoxicam showed maximum absorption at wavelength 374 nm in 0.1 N HCl. The value of correlation coefficient was found to be 0.999, which showed linear relationship between concentration and absorbance. Preformulation study for drug-polymer compatibility by FT-IR gave conformation about their purity and showed no interaction between drug and selected polymers.
- Various formulations were developed by using release rate controlling and gel forming polymers like HPMC (K-4M, K-15M, K-100M) separately by direct compression method with the incorporation of sodium bicarbonate as gas generating agent.
- Developed floating matrix tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content, swelling index and floating properties. All the developed floating matrix tablets floated up to 12 to 24 h.
- Swelling studies indicated significant water uptake and contributed in drug release and gastro-retention. The higher viscosity polymer had been seen to inhibit the initial burst release of Lornoxicam from the FDDS. From among the all the developed formulations, formulation F-3 prolonged the drug release for longer period of time of beyond 24 h and it had minimum floating lag time as compared to other formulations. So, it was selected as the best formulation.
- The most satisfactory formulation had showed no significant change in physicochemical properties, drug content, floating properties or in vitro dissolution pattern after storage at 30 ± 2 °C / 65 ± 5 % RH and at 40 ± 2 °C / 75 ± 5 % RH during stability studies for two months.
- Therefore, it was concluded that the most satisfactory formulation satisfied the physicochemical parameters, floating properties, drug content requirements. thus, the objective of the present work is to formulate a floating dosage form for Lornoxicam by using different proportions and grades of HPMC.

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