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Preparation and evaluation of controlled release tablets containing lornoxicam

K. Sowmya Sri, Dr. Y. Krishna Reddy, Juveria Tasleem

Department of Pharmaceutics, Nalanda College of Pharmacy, Charlapally, Nalgonda, Telangana, India.
***Corresponding Author: K. Sowmya Sri**
Email: juveriatasleem@gmail.com

ABSTRACT

The aim of study was to prepare controlled release tablets of Lornoxicam using HPC 2M, HEC 2M and HPMC K 15M polymer. Tablets were formulated by direct compression technology employing the polymer in different concentrations (4, 8, 12 and 16). The prepared batches were evaluated for drug weight variation, thickness, hardness and subjected to *in vitro* drug release studies. Among all the formulations F10 formulation showed maximum % drug release i.e., 98.41 % in 12 hours hence it is considered as optimized formulation F10 which contains HPMC K 15M (8mg). Whereas the formulations with HPMC K 15M showed more retarding with increasing concentration of polymer. *In vitro* drug release data were fitted in various release kinetic models for studying the mechanism of drug release. The drug release from the matrix tablets was found to follow peppas models.

Keywords: Lornoxicam, HPC 2M, HEC 2M and HPMC K 15M, Controlled Tablets.

INTRODUCTION

Lornoxicam is chemically4-hydroxy-2-methyl-N- (5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide. It has a molecular formula of$C_{14}H_{13}N_3O_4S_2$ and molecular weight of 351.403 g/mol. And it has a bioavailability of 89 % and half-life up to 3-5 hrs, it Is 99.4% protein bind drug. And it is used as Nonsteroidal anti-inflammatory drug (NSAID)

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. So, controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Controlled release dosage forms provide better control of plasma drug levels, less dosage

frequency, less side effect, increased efficacy and constant delivery. [1]

The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration. [2, 3] The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time. [4] Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now a days the technology of sustained release is also being applied to veterinary products also. [5]

Controlled release formulation

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal Controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systematically, for a specific period of time. [6]

Repeat action preparations

A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose [7]

Table 1: List of Materials

NAME OF THE MATERIAL	SOURCE
Lornoxicam	Procured FromGlenmark generics Ltd, Mumbai, India. Provided by **SURA LABS, Dilsukhnagar, Hyderabad.**
HPC 2M	Signet, Mumbai, India.
HEC 2M	International Specialty Products, Mumbai, Maharashtra, India
HPMC K 15M	Signet, Mumbai, India
MCC	Dow Chemicals Asia Pvt. Ltd., Mumbai, India.
Aerosil	Merck Specialities Pvt Ltd, Mumbai, India
Magnesium Stearate	S. D. Fine Chemicals Ltd., Mumbai, India

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Lornoxicampure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VI Sspectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Lornoxicam pure drug was dissolved in 100ml of Methanol (stock solution)10ml of

above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10,20,30,40 and 50µg/ml of Lornoxicamper ml of solution. The absorbance of the above dilutions was measured at 380 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia. Angle of repose, bulk density, tapped density, Measures of powder compressibility. [8]

Formulation development of tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 2. The tablets were prepared as per the procedure given below and aim is to prolong the release of Lornoxicam Total weight of the tablet was considered as 100mg.

Procedure

1 Lornoxicam and all other ingredients were individually passed through sieve no ≠ 60.
2 All the ingredients were mixed thoroughly by triturating up to 15 min.
3 The powder mixture was lubricated with talc.
4 The tablets were prepared by using direct compression method.

Table 2: Formulation composition for tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lornoxicam	4	4	4	4	4	4	4	4	4	4	4	4
HPC 2M	4	8	12	16	-	-	-	-	-	-	-	-
HEC 2M	-	-	-	-	4	8	12	16	-	-	-	-
HPMC K 15M	-	-	-	-	-	-	-	-	4	8	12	16
MCC	85	81	77	73	85	81	77	73	85	81	77	73
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100

All the quantities were in mg

Evaluation of post compression parameters for prepared tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content. [8]

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Dissolution parameters

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCL, p H 6.8 Phophate buffer
RPM -- 50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c ± 0.5°c

Procedure

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 380 and 384nm using 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.

Drug – excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1}. The resultant spectrum was compared for any spectrum changes.

RESULTS AND DISCUSSION

Standard calibration curve of lornoxicam

Table 3: Concentration and absorbance obtained for calibration curve of Lornoxicam in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 380 nm)
1	0	0
2	10	0.145
3	20	0.311
4	30	0.441
5	40	0.579
6	50	0.697

It was found that the estimation of Lornoxicam by UV spectrophotometric method at λ_{max}380.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10-50µg/ml.

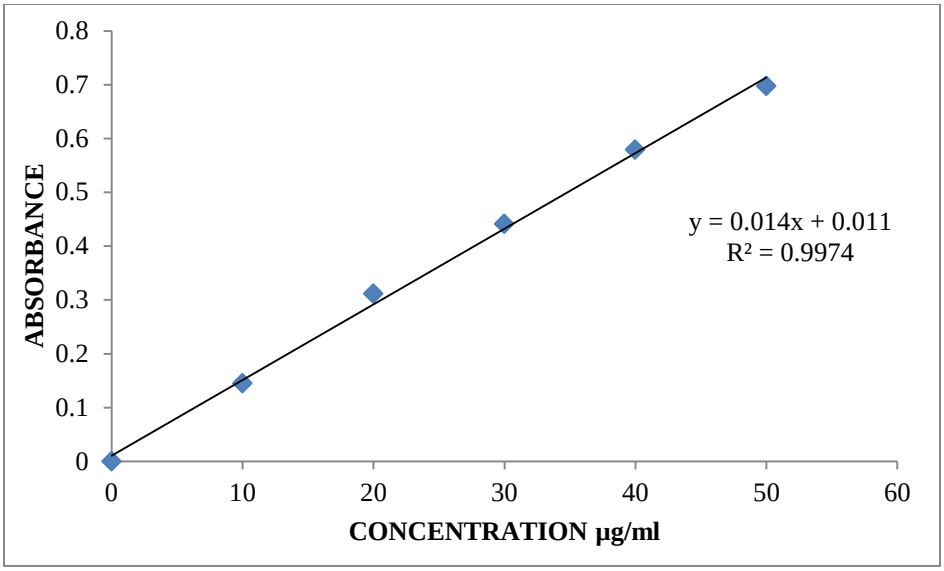

Fig 1: Standard graph of Lornoxicam in 0.1 N HCL

Table 4: Concentration and absorbance obtained for calibration curve of Lornoxicam in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 384 nm)
1	0	0
2	10	0.114
3	20	0.221
4	30	0.332
5	40	0.426
6	50	0.542

It was found that the estimation of Lornoxicam by UV spectrophotometric method at λ_{max}284.0 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10-50µg/ml.

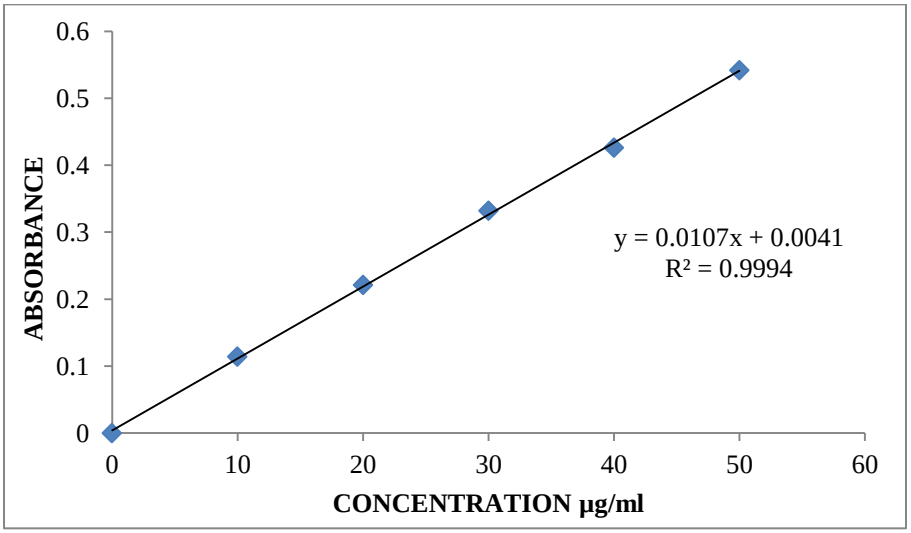

Fig 2: Standard graph of Lornoxicam in pH 6.8 Phosphate buffer

Evaluation parameters for sustained release tablets of lornoxicam

Pre-compression parameters

The data's were shown in Table 5. The values for angle of repose were found in the range of 30.48±0.02 -39.23±0.01. Bulk densities and tapped densities of various formulations were found to be in the range of 0.515±1.47 to 0.527±0.45 (gm/cc) and 0.610±0.01 to 0.623±0.02 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 14.56±0.20 % to 16.53±1.6 %. The Hausner's ration fall in range of 1.17±0.02 to 1.198±0.21. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 5: Pre-compression parameters

Formulations	Bulk Density(gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner's ratio	Angle Of Repose (Ɵ)
F_1	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07	35.24±0.07
F_2	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06	36.27±0.06
F_3	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13	34.65±0.08
F_4	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02	33.54±0.04
F_5	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03	32.21±0.01
F_6	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21	39.23±0.01
F_7	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01	31.10±0.02
F_8	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03	32.19±0.02
F_9	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15	33.28±0.01
F10	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01	30.86±0.03
F11	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02	31.24±0.04
F12	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01	30.48±0.02

Post compression parameters

Average weight

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 6. The average weight of the tablet is approximately in range of 95.15 to 100.0 mg, so the permissible limit is ±5% (.100 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 6. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 6. The result showed that thickness of the tablet is raging from 2.11 to 2.91 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 6. The average friability of all the formulations lies in the range of 0.15 to 0.75 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 95.72 -100.2 %.

Table 6: post compression parameter

Formulation Code(F)	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	98.24	4.1	2.64	0.15	98.61
F_2	99.36	4.6	2.91	0.62	97.15
F_3	95.15	4.8	2.48	0.39	99.47
F_4	99.12	4.9	2.75	0.48	95.72
F_5	97.95	4.7	2.67	0.75	99.16
F_6	98.64	4.8	2.11	0.68	97.29
F_7	99.45	4.2	2.86	0.49	98.64
F_8	98.14	4.6	2.74	0.35	99.16
F_9	98.67	4.5	2.15	0.28	100.2
F_{10}	97.19	4.1	2.48	0.19	98.52
F_{11}	100.0	4.3	2.11	0.68	99.14
F_{12}	99.89	4.2	2.64	0.58	97.95

In Vitro Dissolution studies

In-Vitro dissolution studies were carried out by using 900ml of 0.1 N HCL in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 7.

Table 7: *In vitro* dissolution data

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	14.17	16.21	19.42	9.99	8.33	11.2	21.98	17.61	14.87	25.07	16.63	12.43
2	21.67	23.93	23.36	14.34	12.34	16.2	27.62	23.93	18.91	31.29	22.82	16.95
3	28.19	31.68	28.58	19.46	18.41	23.3	35.35	31.48	25.37	46.17	28.39	23.13
4	34.41	39.77	35.32	21.38	20.34	26.4	41.75	35.36	30.81	52.43	32.12	26.71
5	50.37	44.51	43.39	26.47	23.49	29.3	48.94	43.69	34.65	55.17	39.56	35.24
6	69.32	52.97	51.64	29.62	26.67	32.5	55.41	47.41	43.91	62.71	46.91	38.17
7	74.31	59.84	58.41	33.32	34.94	38.8	61.35	58.24	49.43	68.92	53.49	47.22
8	79.47	65.81	64.22	38.64	39.56	46.4	68.23	64.71	56.38	74.52	59.31	51.36
9	83.61	70.91	73.37	43.85	44.78	59.5	77.11	71.52	61.72	81.17	64.64	54.69
10	86.58	78.29	77.56	54.66	54.32	65.15	83.42	76.31	64.25	89.64	71.21	62.58
11	96.51	83.94	81.55	65.32	66.81	79.36	91.74	84.67	72.61	96.35	76.12	68.35
12		89.88	76.11	72.21	78.14	86.46	95.52	91.12	76.32	98.41	81.26	72.16

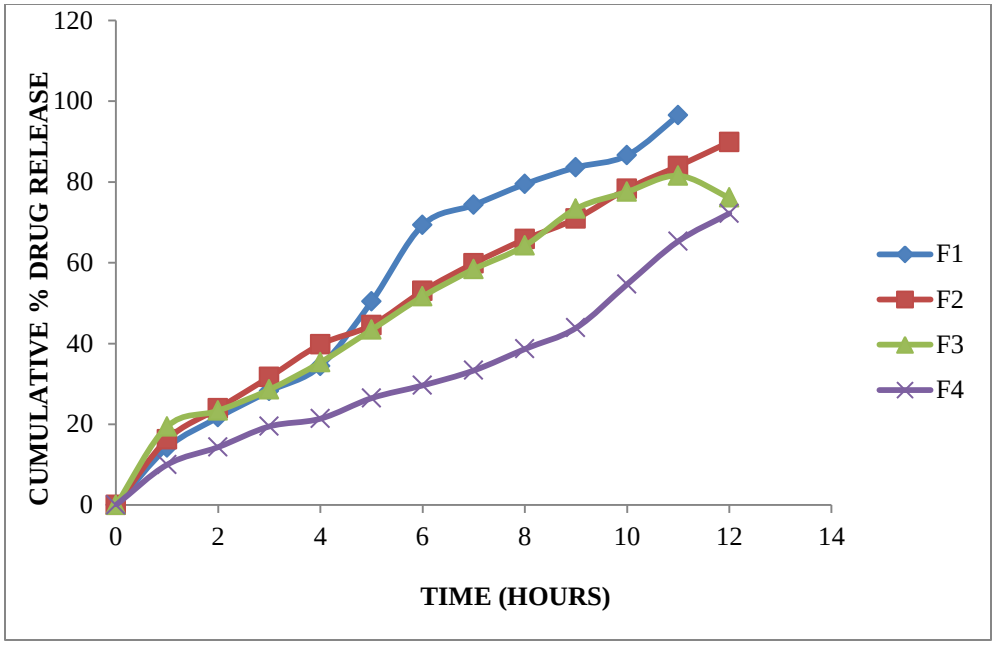

Fig 3: Dissolution profile of formulations prepared with HPC 2M polymer

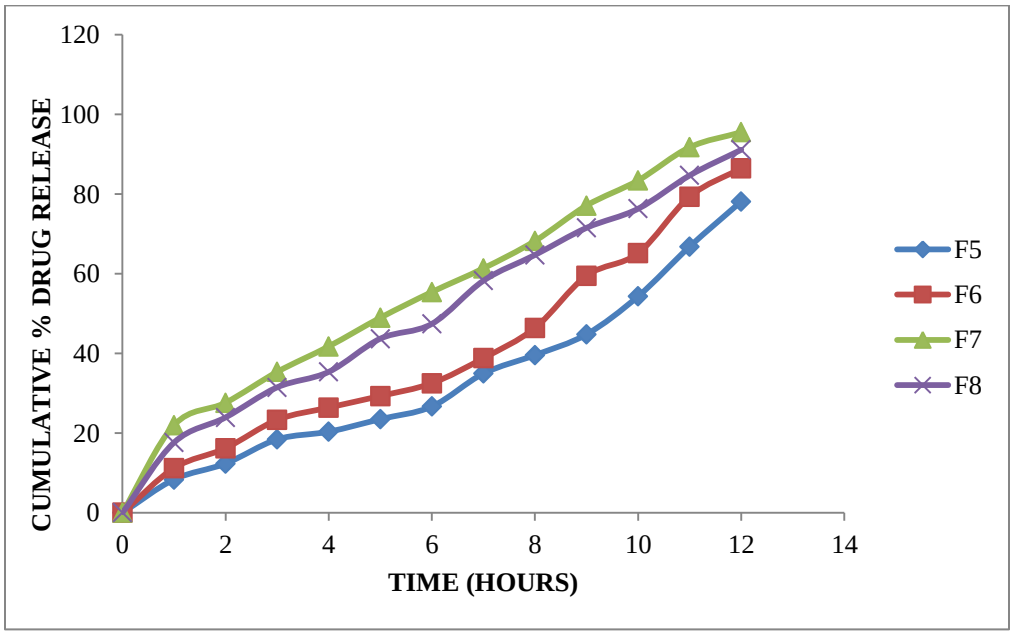

Fig 4: Dissolution profile of formulations prepared with HEC 2M polymer

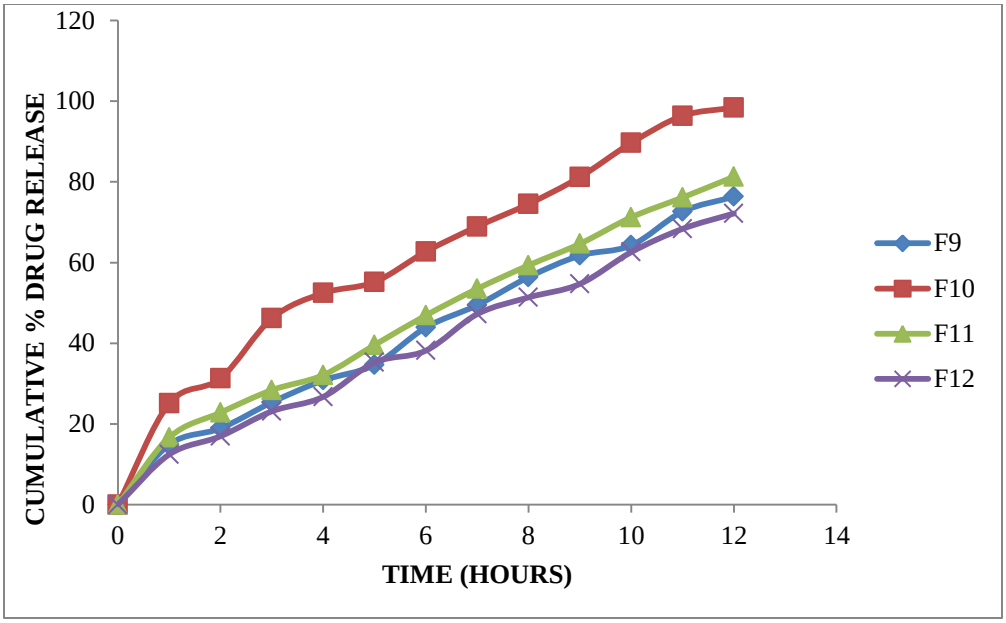

Fig 5: Dissolution profile of formulations prepared with HPMC K 15M as polymer

From the table 5 it was evident that the formulations prepared with HPC 2M as retarding polymer in low concentrations the polymer was able to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also decreased. HPC 2M in the concentration of 8 mg showed good % drug release i.e., 89.88 in 12 hours.

Where as in case of formulations prepared with HEC 2M as retarding polymer, the formulations with 12 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature increased. The Formulation Containing HEC 2M in 12 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 95.52 %.

Where as in case formulations prepared with HPMC K 15M as retarding polymer, as the concentration of polymer increases the retarding nature was also decreased.

From the above results it was evident that the formulation F10 is best formulation with desired drug release pattern extended up to 12 hours.

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 mode

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q0 1/3	Qt 1/3	Q0 1/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
25.07	1	1.000	1.399	0.000	1.875	25.070	0.0399	-0.601	74.93	4.642	4.216	0.426

31.29	2	1.414	1.495	0.301	1.837	15.645	0.0320	-0.505	68.71	4.642	4.096	0.546
46.17	3	1.732	1.664	0.477	1.731	15.390	0.0217	-0.336	53.83	4.642	3.776	0.866
52.43	4	2.000	1.720	0.602	1.677	13.108	0.0191	-0.280	47.57	4.642	3.623	1.018
55.17	5	2.236	1.742	0.699	1.652	11.034	0.0181	-0.258	44.83	4.642	3.552	1.089
62.71	6	2.449	1.797	0.778	1.572	10.452	0.0159	-0.203	37.29	4.642	3.341	1.301
68.92	7	2.646	1.838	0.845	1.492	9.846	0.0145	-0.162	31.08	4.642	3.144	1.498
74.52	8	2.828	1.872	0.903	1.406	9.315	0.0134	-0.128	25.48	4.642	2.943	1.699
81.17	9	3.000	1.909	0.954	1.275	9.019	0.0123	-0.091	18.83	4.642	2.660	1.981
89.64	10	3.162	1.953	1.000	1.015	8.964	0.0112	-0.047	10.36	4.642	2.180	2.462
96.35	11	3.317	1.984	1.041	0.562	8.759	0.0104	-0.016	3.65	4.642	1.540	3.102
98.41	12	3.464	1.993	1.079	0.201	8.201	0.0102	-0.007	1.59	4.642	1.167	3.474

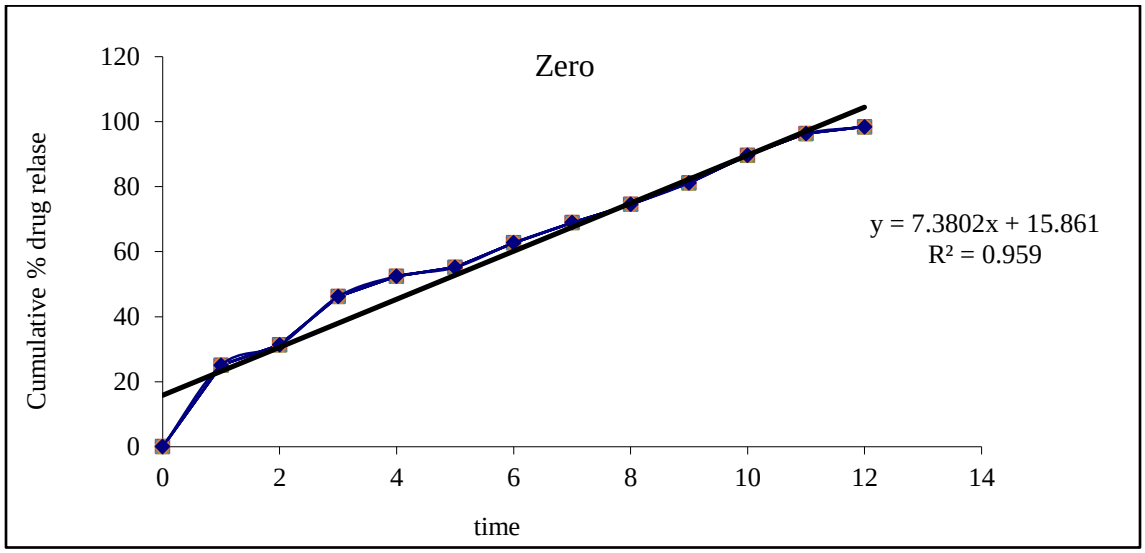

Fig 6 : Zero order release kinetics graph

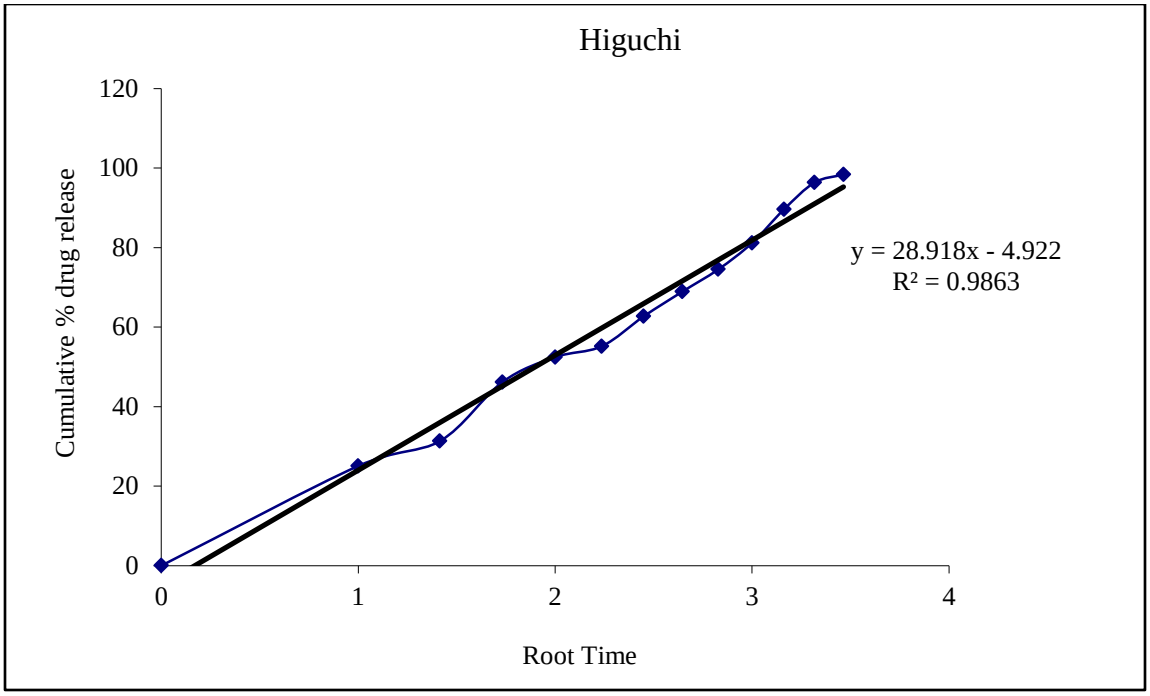

Fig 7 : Higuchi release kinetics graph

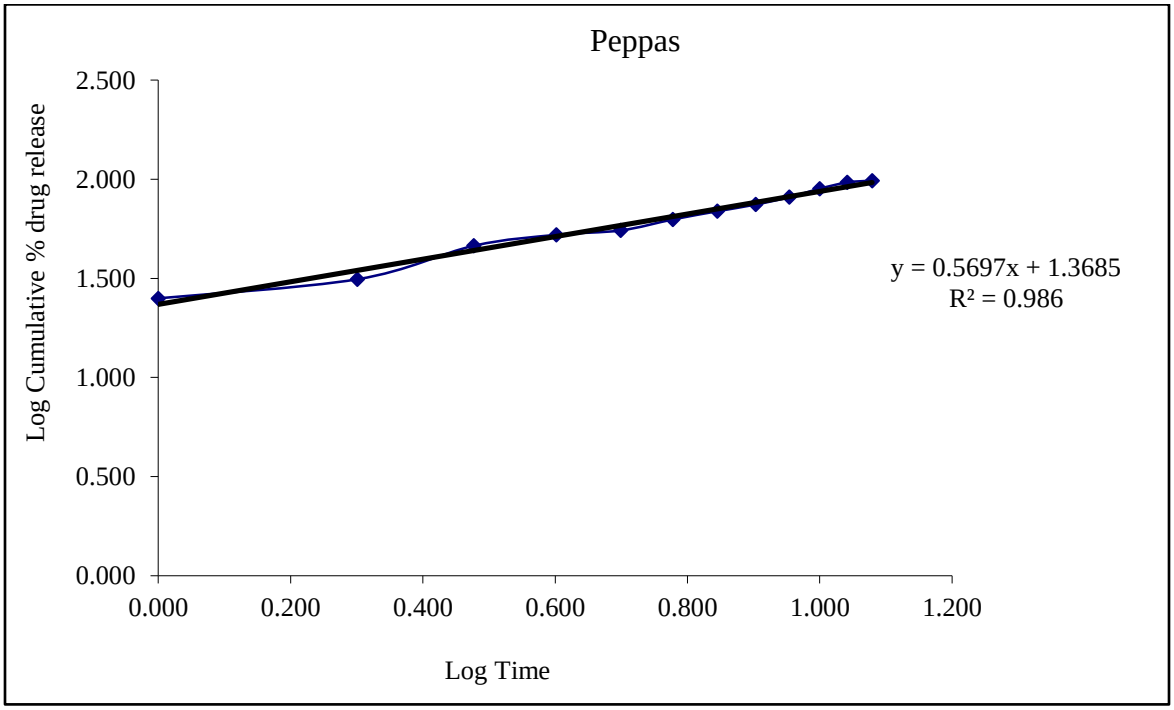

Fig 8: Kars mayer peppas graph

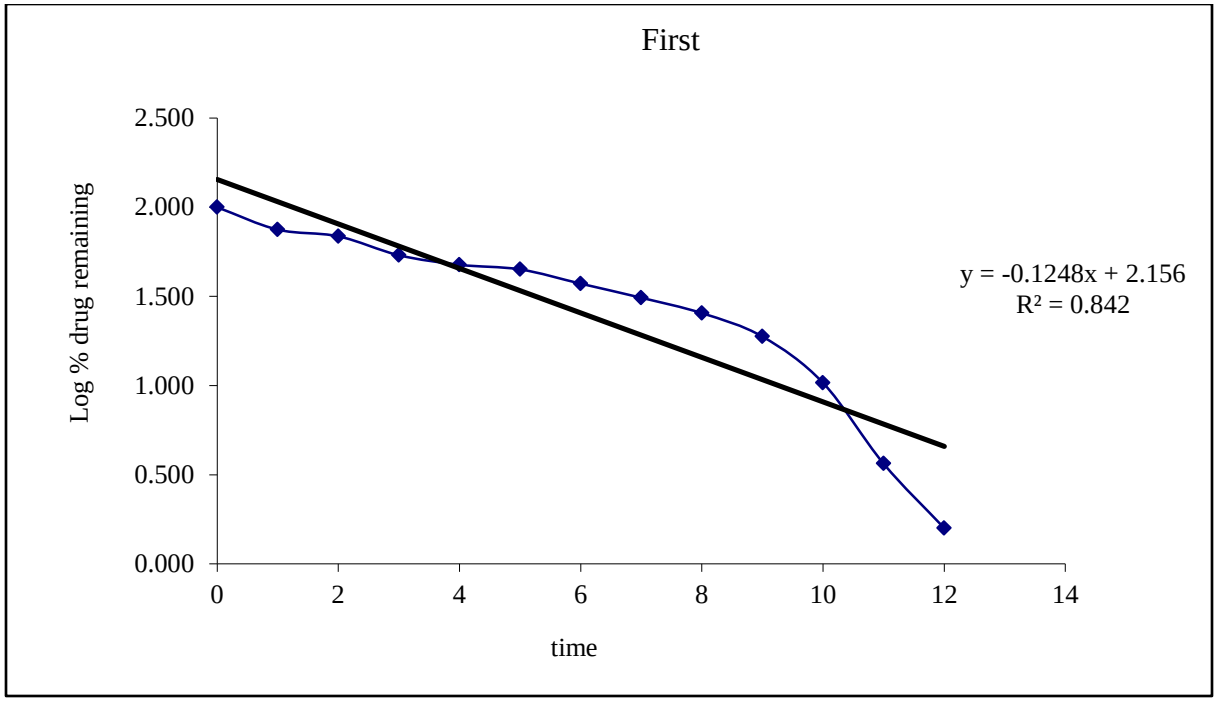

Fig 9: First order release kinetics graph

From the above graphs it was evident that the formulation F10 was followed peppas release mechanism.

FTIR

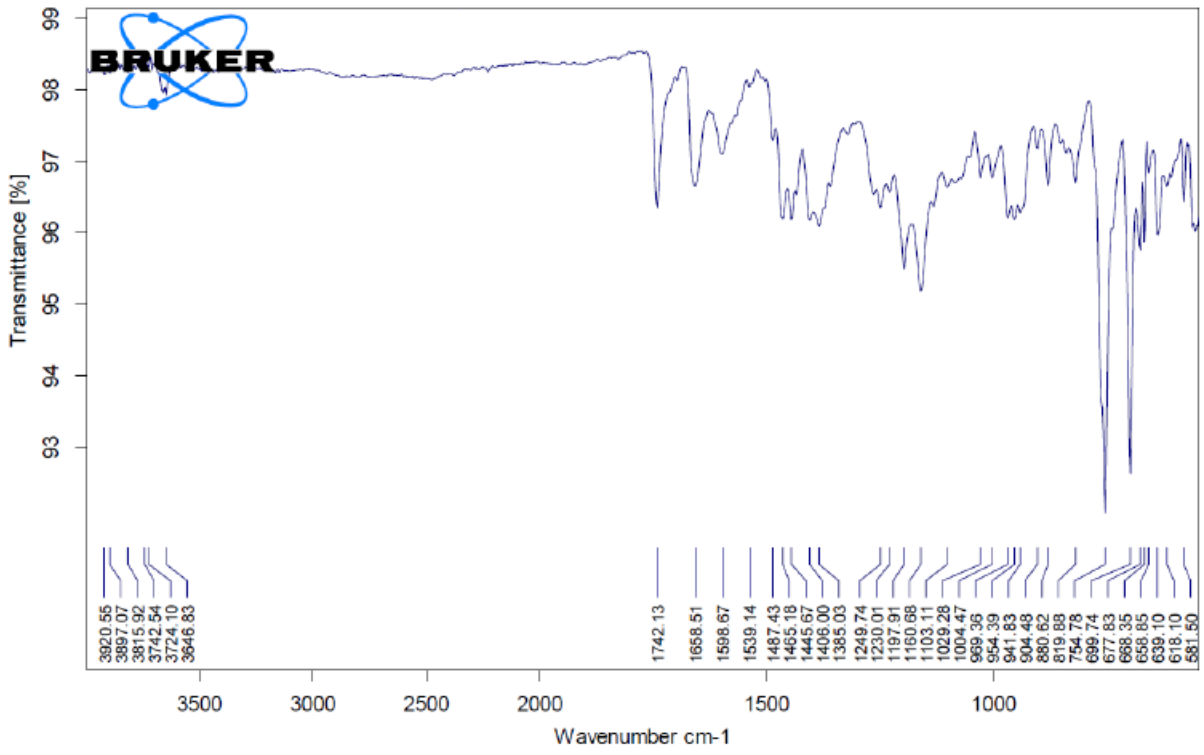

Fig 10: FT-TR Spectrum of Lornoxicam pure drug

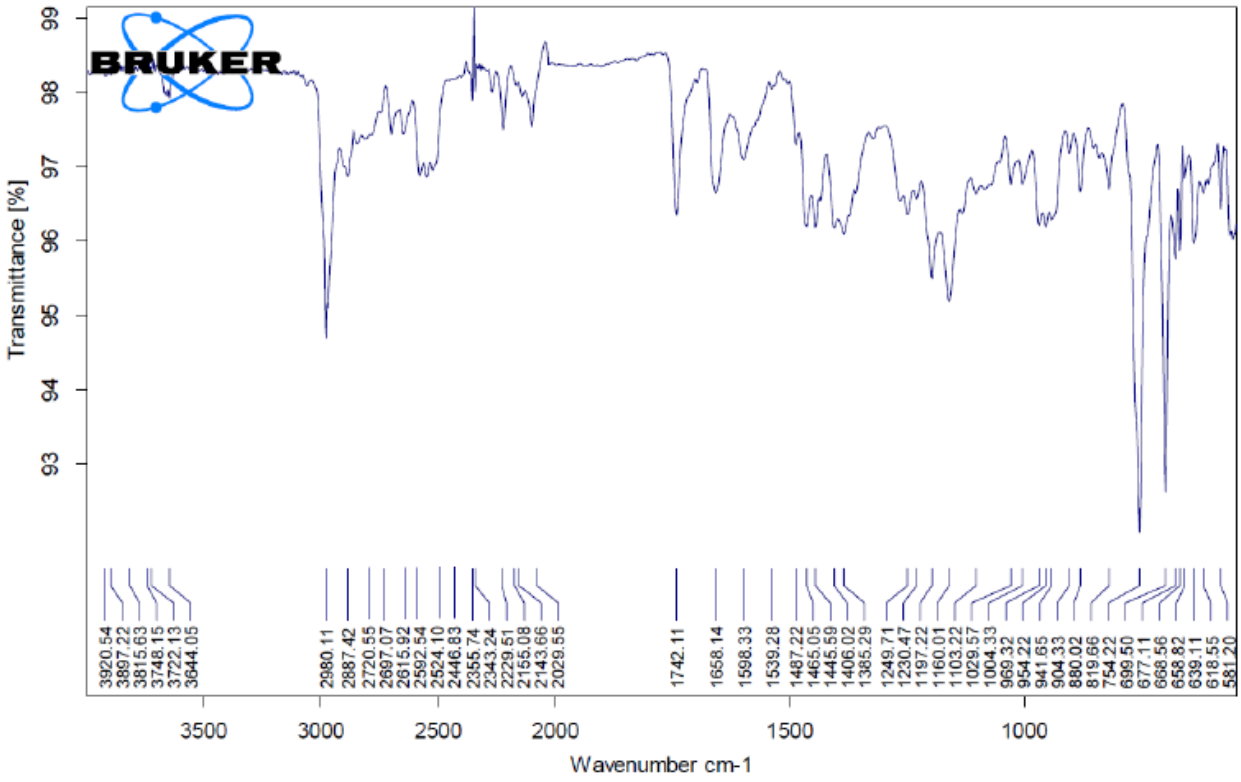

Fig 11: FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimized formulation.

CONCLUSION

In this study matrix tablet of Lornoxicam were prepared by direct compression method, using HPC 2M, HEC 2M and HPMC K 15M polymers as retardant. The drug-polymer ratio was found to influence the release of drug from the formulations. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release were evaluated. Based on these results formulation F-10 was found to be the most promising formulations. The results suggest that the developed controlled-release tablets of Lornoxicam could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved.

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