International Journal of Current Research and Applied Studies, (IJCRAS)

ISSN: 2583-6781

available at https://ijcras.com/

Volume 4 Issue 1 Jan-Feb 2025, Page 63-80

To cite this article: Prince Joshi Bollam, Munija Pancheddula, K. Durga Mounika, B. Shailaja and Srujana Raparti* (2025). FORMULATION AND EVALUATION OF LORNOXICAM EXTENDED-RELEASE TABLETS, International Journal of Current Research and Applied Studies (IJCRAS) 4 (1): Article No. 110, Sub Id 185

FORMULATION AND EVALUATION OF LORNOXICAM EXTENDED-RELEASE TABLETS

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DOI: https://doi.org/10.61646/IJCRAS.vol.4.issue1.110

ABSTRACT

The aim of the present study was to develop Extended-release formulation of Lornoxicam to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K100M, HPMC (K4M) and Carbopol 71 G were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 98.85% in 12 hours. It contains the HPMC (K4M) as Extended-release material. It followed Peppas release kinetics mechanism.

Keywords: Lornoxicam, HPMC (K4M), HPMC K100M, Carbopol 71 G, Extended-release system.

1. INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes1,2. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose3,4. Extended release formulations make the drug available over extended time period after oral administration. The extended-release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hours into one tablet/capsule from which the drug is released slowly5,6. This formulation helps to avoid the side effects associated with low and high concentrations7,8,9,10. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations[11-17.]

2. MATERIALS AND METHODS

Lornoxicam HPMC (K4M) Carbopol 71 G, PVP K 30, MCC 102, Magnesium stearate was used for formulation. All the formulations were prepared by using direct compression method. The compositions of different formulations are given in Table 1, the tablets were prepared as per the procedure given below and the aim is to prolong the release of mirabegron. The total weight of the tablet was considered 200mg

METHODOLOGY

2.1. Drug-excipient compatibility studies

2.1.1. Fourier Transform Infrared (FTIR) Spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR GERMANY (Alpha T). The solid powder sample was directly placed on a yellow crystal which was made up of Zn Se. The spectra were recorded over the wave number of 4000cm–1 to 400cm–

2.2 Analytical method development:

a) Determination of absorption maxima:

100mg of Lornoxicam pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Lornoxicam pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1) 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 0.2, 0.4, 0.6, 0.8 and 1 ml of solution and make up to 10ml with 0.1N Hcl to obtain 10, 20, 30, 40 and 50 µg/ml of Lornoxicam per ml of solution. The absorbance of the above dilutions was measured at 376 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 (R2) which determined by least-square linear regression
analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

2.3. Preparation of Lornoxicam Extended-release tablets

Lornoxicam and all ingredients were individually passed through sieve no. 60. All the ingredients were mixed thoroughly by triturating up to 15min and the powder mixture was lubricated with talc. The tablets were prepared by using the direct compression method [6-8]

Table 1: Formulation of Extended-release tablets

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam	2	2	2	2	2	2	2	2	2
HPMC K100M	4	8	12	-	-	-	-	-	-
HPMC (K4M)	-	-	-	4	8	12	-	-	-
Carbopol 71 G	-	-	-	-	-	-	4	8	12
PVP K 30	10	10	10	10	10	10	10	10	10
MCC102	76	72	68	76	72	68	76	72	68
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	100	100	100	100	100	100	100	100	100

2.4 Evaluation Parameters

2.4.1 Pre-Compression parameters

Bulk density (D_B) Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

Bulk density (D_B) = W /V_0

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume.

Tapped Density (DT)Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (Vf). The tapped density was calculated by using the formula.

Tapped density = mass of the powder/ tapped volume

Tapped density (D_T)=W/V_f

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

Hausner's $\text{Hausner ratio} = \frac{Dt}{Db}$**ratio = D_T/D_B**

Where, D_T is the tapped density

D_B is the bulk density

Compressibility index

Compressibility index (C_I) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

% Compressibility index = V_o - V/V_o x 100

Angle of repose

Angle of repose was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane. The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose
h= is the height in cm r = is the radius in cm
Flow property.

Table 2: The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

2.4.2 Post Compression parameters

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Table 3: IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss(F) was calculated by the following formula.

$F = 100 (W0-W)/W0$

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

***In vitro* drug release studies**

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl, p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 12
Temperature	--	37°c $\pm$ 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media 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. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued upto 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at wavelength of drug using UV-spectrophotometer.

7.4 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 ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'Ko' 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

$$Log (100-F) = kt$$

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.

$$F = k\ t1/2$$

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 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.

3.RESULTS AND DISCUSSION

3.1. Drug excipients compatibility studies

3.1.1. Fourier Transform-Infrared Spectroscopy

No change in the peaks of the graph is seen which indicates no interaction of drug and excipients

FTIR study

Fig 1: Ftir Graph of Pure Drug of Lornoxicam

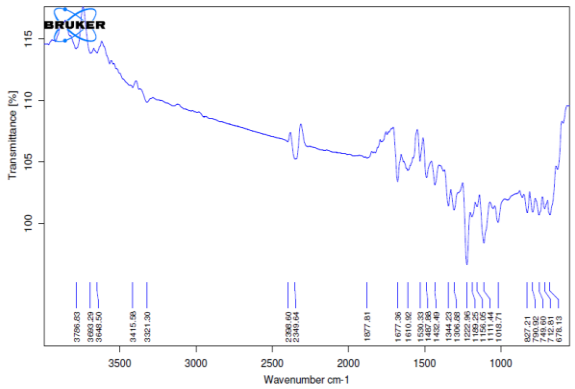
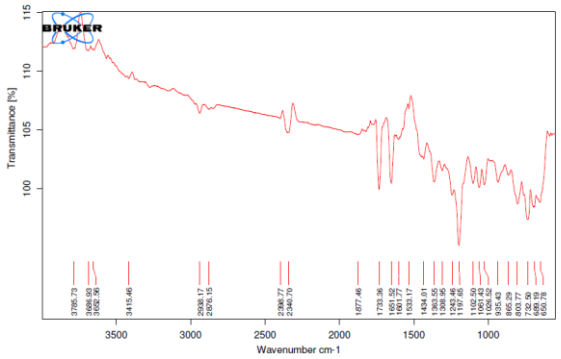


Fig 2: Ftir Graph of Pure Drug of Lornoxicam Optimized Graph



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

3.2 Standard graph of Lornoxicam in 0.1N HCl:

The scanning of the 10µg/ml solution of Lornoxicam in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 376 nm. The standard concentrations of Lornoxicam (10-50 µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of
0.999, which suggests that it obeys the Beer-Lamberts law.

Table 4: Standard curve of Lornoxicam in 0.1N HCl

Concentration (µg/ mL)	Absorbance
0	0
10	0.119
20	0.234
30	0.345
40	0.461
50	0.572

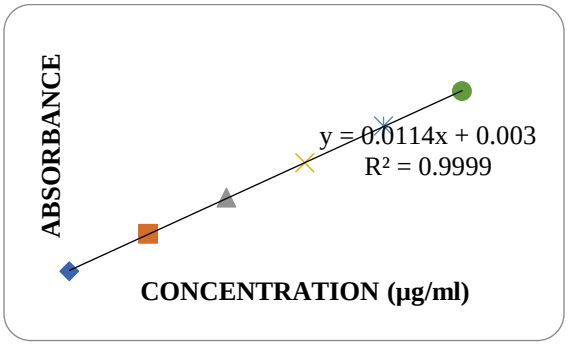


Fig. 3: Calibration curve of Lornoxicam in 0.1 N HCl at 376 nm

3.3 EVALUATION PARAMETERS

3.3.1 Pre-compression parameters

Table 5 pre-compression Parameters of power blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)	Hausner's Ratio
F1	25.01	0. 59	0.57	14.03	1.16
F2	26.8	0. 46	0.67	16.41	1.19
F3	27.7	0. 32	0. 54	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	25.24	0.52	0.65	18.46	1.22
F6	28.12	0. 46	0. 56	15.15	1.17

F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.67	15.78	1.18
F9	26.45	0.54	0.65	16.92	1.25

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25.01 to 28.12; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.32-0.59 (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 0.54-0.69 showing the powder has good flow properties.

The compressibility index of all the formulations was found to be ranging from 14.03 to 18.75 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 1.16 to 1.25 indicating the powder has good flow properties.

3.3.2 Post Compression Parameters For tablets

Table 6: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.62	5.9	0.52	3.16	96.35
F2	96.35	**5.1**	0.34	3.56	99.61
F3	99.21	5.6	0.62	3.41	98.52
F4	97.49	5.2	0.41	3.22	97.42
F5	95.32	5.8	0.26	3.61	97.12
F6	99.58	5.1	0.39	3.25	99.33
F7	97.96	5.7	0.65	3.42	98.64
F8	99.67	5.9	0.73	3.13	95.78
F9	98.32	5.5	0.15	3.24	96.41

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.4. The average tablet weight of all the formulations was found to be between 95.32 to 99.67. The maximum allowed percentage weight variation for tablets weighing >100.5 mg is 1.5% and no formulations are not exceeding this limit. Thus, all the

formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.13 to 3.61.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 8.4. The average hardness for all the formulations was found to be between (5.1 to 5.9) Kg/cm2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 8.4. The average percentage friability for all the formulations was between 0.15 and 0.73, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7.4. The drug content values for all the formulations were found to be in the range of (95.78 to 99.61). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

In *Vitro* Drug Release Studies

The formulations prepared with different natural polymers by wet granulation method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 7: Dissolution Data of Lornoxicam Tablets Prepared with HPMC K100M In Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG RELEASED**		
	F1	**F2**	**F3**
0	0	0	0
0.5	25.32	20.04	18.63
1	34.53	27.56	21.63
2	49.90	34.35	28.52
3	54.96	43.52	31.31
4	59.14	48.75	38.25
5	62.85	52.54	45.78

6	73.92	59.26	50.17
7	80.41	65.95	57.79
8	89.61	70.14	62.27
9	93.17	73.45	69.64
10	96.33	81.57	74.87
11		98.18	84.10
12			98.64

Table 8: Dissolution Data of Lornoxicam tablets Prepared with HPMC (K4M) in Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG RELEASED**		
	F4	**F5**	**F6**
0	0	0	0
0.5	15.17	13.90	10.49
1	22.12	19.45	16.63
2	36.64	25.02	27.55
3	42.20	31.31	33.21
4	48.56	37.82	40.96
5	55.43	43.47	45.11
6	58.01	50.74	55.28
7	67.57	54.05	61.71
8	73.91	57.93	67.34
9	79.41	63.26	74.98
10	83.72	75.45	80.74
11	86.02	80.36	86.12
12	90.14	95.47	98.85

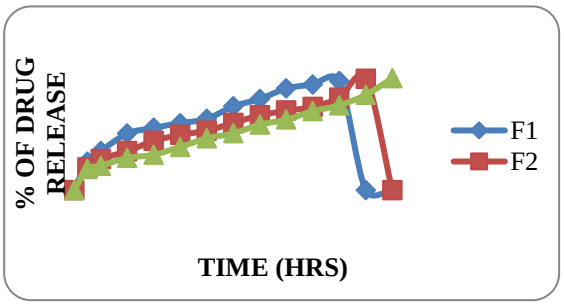


Figure 4: Dissolution study of Lornoxicam extended tablets (F1 to F3)

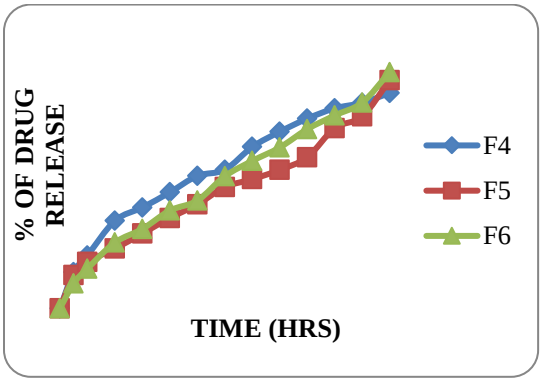


Figure 5: Dissolution study of Lornoxicam tablets (F4 to F6)

Table 9: Dissolution Data of Lornoxicam tablets Prepared with Carbopol 71 G in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	**F8**	**F9**
0	0	0	0
0.5	20.56	17.58	10.62
1	26.45	23.20	15.28
2	31.23	27.35	20.95
3	40.54	34.14	25.51
4	49.73	39.75	29.32
5	56.46	43.09	33.96
6	58.12	46.16	39.78

7	62.59	55.75	44.35
8	71.41	60.11	50.62
9	78.98	64.67	56.43
10	83.24	68.34	60.02
11	89.72	76.40	64.10
12	90.14	85.18	70.16

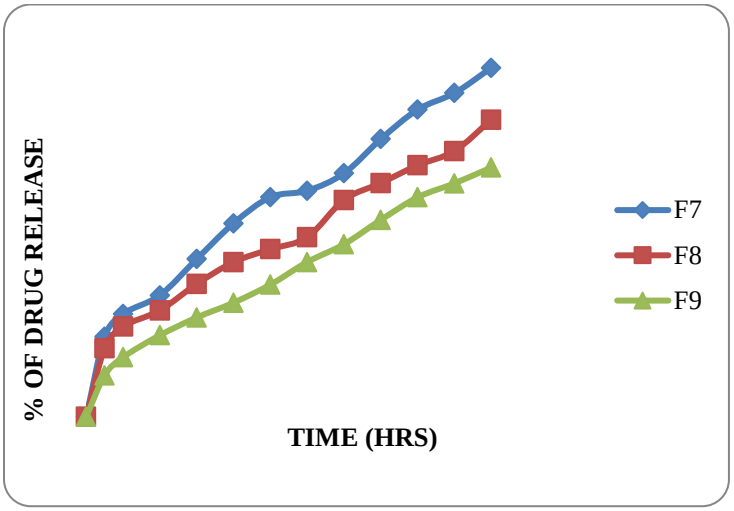


Figure 6: Dissolution study of Lornoxicam tablets (F7 to F9)

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer were retarded the drug release more than 12 hours.

Whereas the formulations prepared with higher concentration of HPMC (K4M) retarded the drug release up to 12 hours in the concentration 12 mg. In lower concentrations the polymer was unable to retard the drug release.

The formulations prepared with Carbopol 71 G showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that F6 formulation was considered as optimised formulation because good drug release (98.85%) in 12 hours.

3.4 Application of Release Rate Kinetics to Dissolution Data

Data of in vitro release studies of formulations which were showing better drug release were fit into

different equations to explain the release kinetics of Lornoxicam release from Extended tablets. The data was fitted into various kinetic models such as Zero, first order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table

Table 10: Release kinetics data for optimised formulation (F6)

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	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
10.49	**0.5**	0.707	1.021	-0.301	1.952	20.980	0.0953	-0.979	89.51	4.642	4.473	0.168
16.63	**1**	1.000	1.221	0.000	1.921	16.630	0.0601	-0.779	83.37	4.642	4.369	0.273
27.55	**2**	1.414	1.440	0.301	1.860	13.775	0.0363	-0.560	72.45	4.642	4.169	0.473
33.21	**3**	1.732	1.521	0.477	1.825	11.070	0.0301	-0.479	66.79	4.642	4.057	0.584
40.96	**4**	2.000	1.612	0.602	1.771	10.240	0.0244	-0.388	59.04	4.642	3.894	0.748
45.11	**5**	2.236	1.654	0.699	1.739	9.022	0.0222	-0.346	54.89	4.642	3.800	0.841
55.28	**6**	2.449	1.743	0.778	1.651	9.213	0.0181	-0.257	44.72	4.642	3.550	1.092
61.71	**7**	2.646	1.790	0.845	1.583	8.816	0.0162	-0.210	38.29	4.642	3.371	1.271
67.34	**8**	2.828	1.828	0.903	1.514	8.418	0.0149	-0.172	32.66	4.642	3.196	1.445
74.98	**9**	3.000	1.875	0.954	1.398	8.331	0.0133	-0.125	25.02	4.642	2.925	1.717
80.74	**10**	3.162	1.907	1.000	1.285	8.074	0.0124	-0.093	19.26	4.642	2.681	1.961
86.12	**11**	3.317	1.935	1.041	1.142	7.829	0.0116	-0.065	13.88	4.642	2.403	2.238
98.85	**12**	3.464	1.995	1.079	0.061	8.238	0.0101	-0.005	1.15	4.642	1.048	3.594

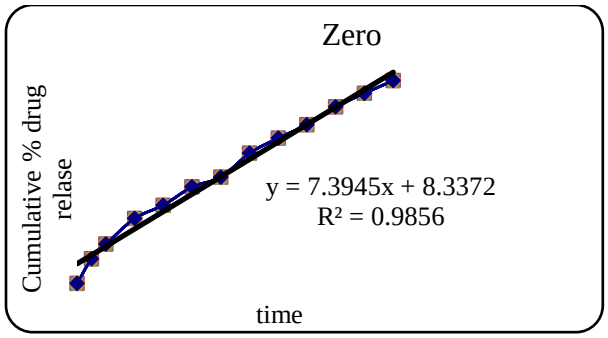


Figure 7: Graph of zero order kinetics

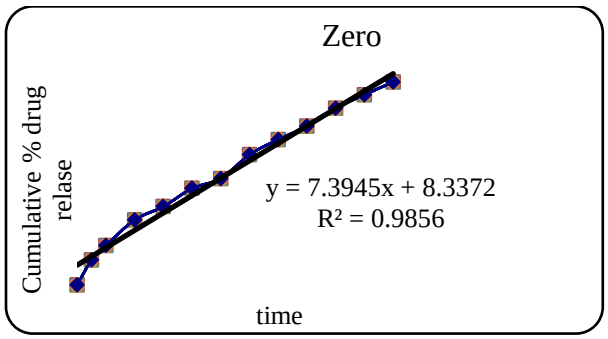


Figure 8: Graph of Higuchi release kinetics

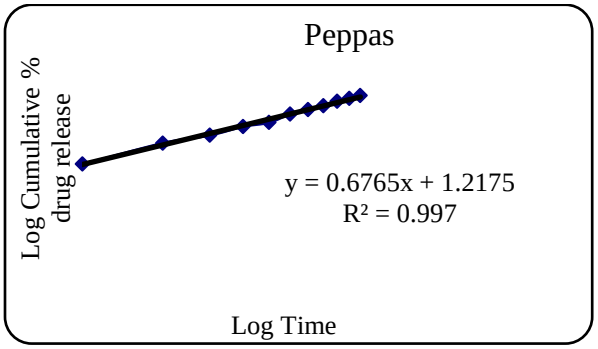
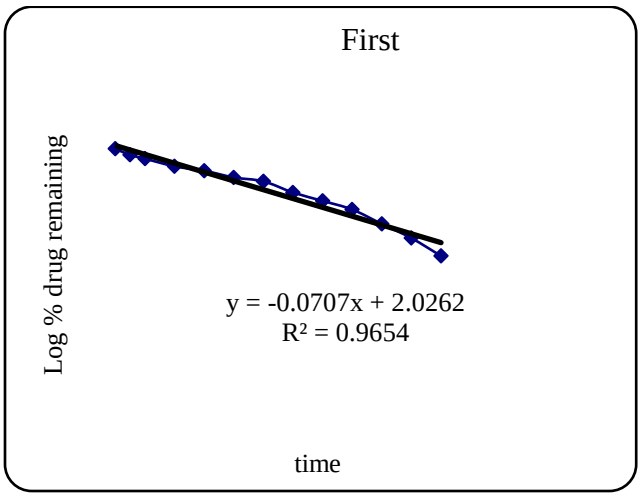


Figure 9: Graph of peppas release kinetics



Optimised formulation F6 was kept for release kinetic studies. From the above graphs it was evident that the formulation F6 was followed peppas release

CONCLUSION

The present study concludes that Extended drug delivery of Lornoxicam tablets can be a good way to

prolong duration of action of drug by reducing the frequency of dosing of Lornoxicam. Present study concludes that extended drug delivery system should be a suitable method for Lornoxicam administration. The optimised formulation was found to be F6 formulation.

ACKNOWLEDGEMENT

We sincerely thank Management, Vision College of pharmaceutical science & Research, for the encouragement, support &Facilities which served as strength to our research work.

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