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FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS OF LORNOXICAM

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ABSTRACT

The aim of the present study was to prepare sustained release matrix tablets of lornoxicam to make drug in sustained form so as to prolong its elimination time for the effective treatment of rheumatoid arthritis, and also in the management of ankylosing spondylitis, acute sciatica and low back pain. The present investigation demonstrates that, use of hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of Lornoxicam. Optimized formulation containing HPMC K100M and Ethyl cellulose at optimum ratio had successfully sustained the drug release for 24 h. Matrix tablets of optimized batch had in vitro drug release. It was observed that the optimized matrix tablets of optimized batch shows better flow property by studying various pre-compression parameters. Thus, sustained release matrix tablets of Lornoxicam using biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

Keywords: Lornoxicam, HPMC, Sustained release, matrix tablets

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INTRODUCTION

A sustained-release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug" [1]. Development of oral sustained release (SR) tablets of highly water soluble drugs or bioactives has always been a challenge and therefore, opportunity for formulation scientist. Most of these drugs if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic levels and hence will lead to toxic side effects. Sustained delivery of such drugs ensures improved drug delivery and patient compliance, greater safety and efficacy, desired release kinetics and helps in maintaining the plasma drug concentration within the therapeutic window for extended period of time [2, 3].

Several techniques including melt granulation [4], melt pelletization [5], hot melt coating [6], Wet granulation [7, 8, 9], hot melt extrusion [10] and direct compression [11, 12] have been used to obtain sustained release matrix dosage forms.

The tablet can be developed with the combination of HPMC K 100M and Ethyl Cellulose as a matrix former. Lornoxicam is NSAID that has numerous functions in the body. It can be absorbed rapidly and completely from gastrointestinal track after the oral administration. Absolute bioavailability of Lornoxicam is 90-100%. No first pass effect is observed. It is found in the plasma in the unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity. CYP_2C_3 has been shown to be the primary enzyme responsible for the biotransformation of Lornoxicam. Approximately 2/3 part of Lornoxicam is eliminated via the liver and 1/3 via the kidneys as inactive substance. Lornoxicam inhibits the production of prostaglandins by inhibiting

the action of cyclooxygenase, which regulates the conversion of Arachidonic Acid to Prostaglandins. Lornoxicam mainly prescribed in the treatment of osteoarthritis and rheumatoid arthritis, and also in the management of ankylosing spondylitis, acute sciatica and low back pain[13, 14, 15, 16].

The main objectives of present investigation are to confirm the drug by various analytical techniques, to study the drug excipients compatibility, to avoid the dose as well as the frequency of the dosage form and to perform the **stability**[13, 14, 15, 16].

MATERIALS AND METHODS

Chemicals: Lornoxicam, HPMC K 100M, Ethyl Cellulose, PVP K- 30, Microcrystalline Cellulose, Lactose, Talc, Magnesiun Stearate, Potassium Dihydrogen Phosphate, Potassium Chloride, Potassium Bromide

Instruments: Electronic Balance, Hot Air Oven, UV Spectrophotometer, FTIR Spectrophotometer, DSC, Sonicator, Stability Chamber, Tablet Dissolution Testing Apparatus, Rimek Mini Tablet Press 2, Monsanto Hardness Tester, Rotatory Flask Shaker.

Preformulation work

Identification of drug was done by FTIR Spectrophotometer and all the drug excipients compatibility study was performed. All the ingredients were mixed well in a double cone blender. Lornoxicam was first mixed with the polymer, PVP K30 and directly compressible lactose for 10 min to obtain uniform mixture. Then the mixture was passed through 60#. Finally the mixture was blended with the talc and magnesium stearate. 100 mg tablets were punched by compression machine.

In-process evaluation study[17, 18]

Pre-compression parameters

To find out physiochemical properties and release characteristics of the granular blend, all formulations are subjected to pre-formulation studies like bulk density, tapped density, Angle of repose, compressibility index and Hausner's ratio.

Preparation of matrix tablet:

Tablets are prepared by direct compression technique [11, 12, 19]

Table 1: Composition for sustained release matrix tablet of Lornoxicam formulation design

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam	16	16	16	16	16	16	16	16	16
HPMC K100M	16	32	48	-	-	-	24	16	08
Ethyl cellulose	-	-	-	16	32	48	08	16	24
PVP K 30	10	10	10	10	10	10	10	10	10
Lactose	40	28	16	56	24	16	32	40	24
Micro crystalline cellulose	16	12	08	-	16	08	08	-	16
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100

Evaluation of compressed tablets

The tablets prepared were evaluated for weight variation, disintegration test, dissolution test, thickness, hardness of individual dose and friability.

Weight variation

The weight variation was performed by weighing 20 tablets individually, then individual weight of tablet is compared with average weight of 20 tablets.

Hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

Friability

The friability was determined by first weighing 10 tablets before placing in friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the remaining weight of tablet was determined.

Thickness

The thickness of tablet was determined by vernier caliper.

Disintegration[17, 18]

The test was performed by introducing one tablet in each tube and adds a disc to each tube. Suspend the assembly in the beaker containing purified water and operate the apparatus until the tablet completely disintegrates.

In Vitro Dissolution test[17, 18]

In-vitro dissolution studies were carried out using USP XXIII dissolution apparatus type II at 50 rpm. Dissolution test was carried out for a total period of 24 hr using 0.1N HCl (pH 1.2) solution (900 ml) as a dissolution medium at 37 ± 0. 5°C for first 2 hr and phosphate buffer (pH 6.8) solution (900 ml) solution for the rest of the period.5 ml of sample was withdrawn at predetermined time interval of 1 hr up to 24 hr and replaced with same volume of fresh dissolution medium. The withdrawn samples were filtered and analyzed by UV spectrophotometer at 376 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

RESULTS AND DISCUSSION

Pre-compression parameters

Table 2: Evaluation parameters of powder blend

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loose bulk density (LBD) g/ml	0.400	0.385	0.324	0.331	0.338	0.254	0.305	0.317	0.302
Tapped density (TBD) g/ml	0.465	0.451	0.371	0.383	0.399	0.284	0.365	0.379	0.348
Consolidation index	13.97	14.63	12.66	13.57	15.28	10.56	14.43	16.35	13.21
Hausner ratio	1.16	1.17	1.14	1.15	1.18	1.11	1.19	1.19	1.16
Angle of repose (Θ)	25.54	25.25	25.18	25.22	24.87	24.85	24.28	26.95	26.11

Post-compression parameters

Table 3: Evaluation of sustain release matrix tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness ±S.D. mm(n=10)	2.44 ± 0.02	2.50 ± 0.04	2.55 ± 0.03	2.52 ± 0.02	2.45 ± 0.05	2.56 ± 0.03	2.61 ± 0.02	2.62 ± 0.03	2.40 ± 0.04
Hardness S.D. (kg/cm^2)	6.8 ± 0.3	7.1 ± 0.5	7.2 ± 0.2	5.48 ± 0.2	5.48 ± 0.2	5.7 ± 0.3	5.1 ± 0.5	5.75 ± 0.5	5.64 ± 0.2
Average Weight variation (n=20) mg	101.4 ± 1.51	102.63 ± 1.69	101.50 ± 1.41	100.39 ± 1.35	101.26± 1.58	102.23 ± 1.60	100.41 ± 1.80	102.47 ± 1.20	101.51 ± 1.40
Drug Content (%)	100.65 ± 1.20	98.50 ± 1.46	97.25 ± 1.56	98.70 ± 0.92	99.65 ± 2.12	98.80 ± 0.55	99.50 ± 0.92	97.21 ± 0.83	101.25 ± 1.31
Friability (% w/w)	0.38 ± 0.04	0.42 ± 0.06	0.35 ± 0.02	0.45 ± 0.04	0.38 ± 0.08	0.29 ± 0.03	0.36 ± 0.06	0.29 ± 0.09	0.33 ± 0.03

In-vitro dissolution studies

In-vitro dissolution studies were carried out using USP XXIII dissolution apparatus type II at 50 rpm. Dissolution test was carried out for a total period of 24 hr using 0.1N HCl (pH 1.2) solution (900 ml) as a dissolution medium at 37 ± 0. 5°C for first 2 hr and phosphate buffer (pH 6.8) solution (900 ml) solution for the rest of the period.5 ml of sample was withdrawn at predetermined time interval of 1 hr up to 24 hr and replaced with same volume of fresh dissolution medium. The withdrawn samples were filtered and analyzed by UV spectrophotometer at 376 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

Table 4: Cumulative % drug release

Time (hrs.)	% CDR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.6	3.51	3.62	5.09	3.99	3.65	6.8	2.63	2.63
2	14.41	9.63	8.01	6.91	5.41	4.57	12.46	8.07	5.45
3	20.11	15.7	12.12	31.75	13.37	13.92	18.16	20.43	7.72
4	43.78	20.89	15.56	49.29	19.57	17.83	21.63	24.04	10.38
5	47.71	26.45	19.33	67.12	26.37	21.64	24.4	26.3	13.25
6	55.72	31.69	22.56	79.98	36.36	26.56	27.68	30.31	17.2
7	59.83	36.61	26.36	92.17	39.03	31.34	29.91	33.6	23.29
8	65.47	40.85	29.51	94.11	44.56	35.87	36.76	37.35	29.91
9	70.31	44.94	32.79	96.49	54.61	38.95	39.78	40.67	38.01
10	74.95	48.53	36.9	98.47	61.55	42.48	43.87	44.58	46.66
24	99.81	96.26	67.66	97.36	96.38	82.93	96.97	97.38	97.35

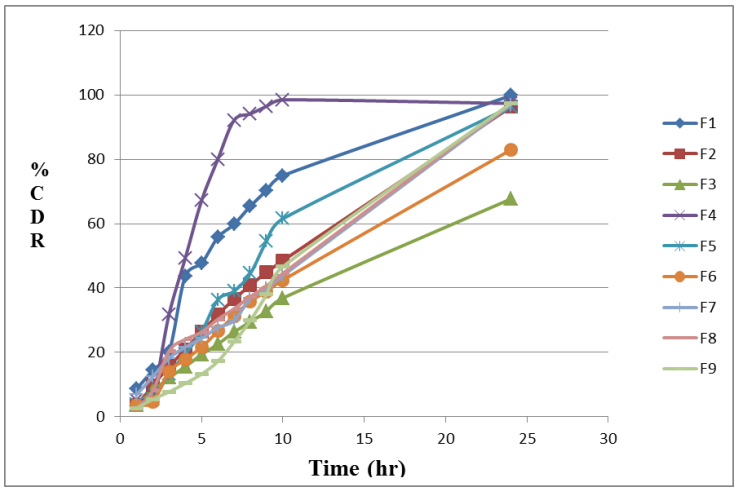

Figure 1: *In-vitro* dissolution profile

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of various environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and self-lives to be established.

ICH specifies the length (duration) of study and storage conditions

Accelerated stability studies are testing at 40 °C ± 2 °C / 75 % RH ±.5 % for a specific time period up to 3 months and long term stability studies are testing at 25 °C ± 2 °C / 60 % RH ±5 % for a specific time period up to 12 months. Stability studies were carried out at 40 ± 2°C / 75 % RH for a specific time period up to 90 days.

Table 5: Physicochemical evaluation for stability study

Parameters	Drug content (%)	Hardness ± S.D. (kg/cm^2)	Friability ± S.D. (% w/w)	Weight variation (N=20) mg	*In-vitro* drug release	
					At 10 hr.	At 24 hr.
Initial	99.50 ± 0.92	5.1 ± 0.5	0.36 ± 0.06	100.41 ± 2.80	48.58	96.26
After one month	99.27 ± 0.45	5.0 ± 0.6	0.36 ± 0.09	100.39 ± 1.35	48.07	96.84
After two months	99.28 ± 0.42	5.0 ± 0.6	0.36 ± 0.02	100.40 ± 1.12	48.00	96.43
After three months	99.29 ± 0.68	5.0 ± 0.6	0.36 ± 0.04	100.38 ± 1.24	48.18	96.25

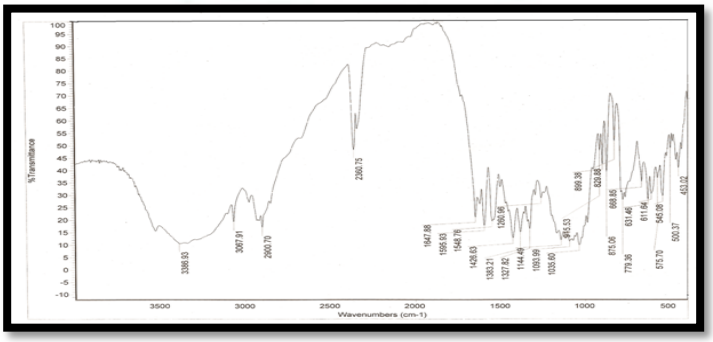

Figure 2: FTIR Spectra of F7 after 3 months stability study

Table 6: position of main functional group bands after three months stability study

Sample No.	-NH Stretching	C=O Stretching	N-H Bending		O=S=O Stretching			C-H (Bend) Aromatic	C-Cl Bending
After 3 month	3067.91	1647.88	1595.93	1548.76	1144.49	1383.21	1327.82	829.88	779.36

CONCLUSION

The present investigation demonstrates that, use of hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of Lornoxicam. Optimized formulation containing HPMC K100M and Ethyl cellulose at optimum ratio had successfully sustained the drug release for 24 h. Matrix tablets of optimized batch had in vitro drug release. It was observed that the optimized matrix tablets of optimized batch shows better flow property by studying various pre-compression parameters. Thus, sustained release matrix tablets of Lornoxicam using biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

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