ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Lornoxicam Sustained Release Tablets: Formulation, In-Vitro Evaluation and Comparison with Marketed Lofecam SR.

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ABSTRACT

Lornoxicam (chlortenoxicam) is a non-steroidal anti-inflammatory drug (NSAID) belonging to chemical class of oxicam derivatives having analgesic, anti-inflammatory and antipyretic properties. In the present investigation, sustained release tablet of Lornoxicam was prepared by wet granulation technique using various hydrophilic polymers like Polyox N303 (F1), Polyox N750 (F2), Polyox N80 (F3), HPMC K4M (F4), HPMC K15M (F5) and HPMC K100M (F6).Formulations having different ratios of drug: polymers were evaluated to get similar release rate with the marketed product i.e. Lofecam SR of Sun Pharmaceuticals. The compatibility study of Lornoxicam with different polymers was described i.e. FTIR studies was done on 1:1 ratio of drug to polymers. The result showed that there was no interaction between the drug and polymers. XRD study of pure drug showed high intensity peaks which indicate the nature to be crystalline. The tablets were evaluated for physical parameters like hardness, thickness, friability, weight variation along with % drug content. All the tests were found to be within the range for all the formulations and the results were found to be satisfactory. The % drug release of all the prepared formulations were found out to be approximately similar to the % drug release of the marketed product. All the prepared formulations were following zero order release kinetics. The results of stability study indicated that there is no significant change in hardness, friability, and percentage of drug content after storage at different temperatures and relative humidity conditions for four weeks.

Keywords: Lornoxicam, SR (Sustained release tablet).

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ISSN: 0975-8585

INTRODUCTION

Lornoxicam, also known as chlortenoxicam [1] is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs) with extremely potent anti-inflammatory and analgesic activities [2]. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis. [3].Generally, conventional controlled release dosage forms provide delayed release of drug from the dosage form which leads to delay in attaining maximum therapeutic plasma levels immediately. To modify the release of the drug from these systems, the surface area exposed to a fluid can be restricted by the addition of barrier layers to one or both sides of the tablet.[4]The basic rationale of a sustained drug delivery system is to optimize the biopharmaceutic, and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route.[5] The mode of action of lornoxicam is partly based on inhibition of prostaglandin synthesis (inhibition of the cyclo-oxygenase enzyme). Furthermore, it has a short elimination half-life of 4 hrs, which makes it a suitable candidate to be delivered at a controlled rate.[6]Formulation of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval.[7,8] The bioavailability of Lornoxicam is 90% – 100%. Because of its relatively short plasma half-life (3-5 hr), it is prescribed to take lornoxicam in divided daily doses either twice or thrice daily in order to maintain the therapeutic plasma concentration. These characteristics make lornoxicam a suitable candidate for developing into sustained release tablet or a microsphere.[9] During ulceration even high concentration of Lornoxicam doesn't produce gastro intestinal tract (GIT) as compared to other NSAID's . Due to its short half life and acidic nature, sustained release of Lornoxicam occurs in lower part of GIT that results in prolonged release and therapeutic action [10,11]. Hydrophilic matrix systems are usually preferred for oral delivery particularly HPMC based systems. HPMC has good compressibility nature, wide range of compatibility, non-toxic, gel forming capability and its availability in various viscosity grades. Polymeric chain relaxations occur due to contact with water. [12,13]

In the present investigation, we made an attempt to prepare sustained release tablet of Lornoxicam by wet granulation technique using various hydrophilic polymers like Polyox N303 (F1), Polyox N750 (F2), Polyox N80 (F3), HPMC K4M (F4), HPMC K15M (F5) and HPMC K100M (F6).Formulations having different ratios of drug: polymers were evaluated to get similar release rate with the marketed product i.e. Lofecam SR of Sun Pharmaceuticals.The compatibility study of Lornoxicam with different polymers done using FTIR and XRD studies.

MATERIALS AND METHODS

Lornoxicam was received as a gift sample from Alkem Laboratories Limited, India. Polymers (Polyox N303, Polyox N750, Polyox N80, from Central drug house (P) Ltd, New Delhi, India. HPMC K4M, HPMC K15M and HPMC K100M),Avicel ,PVP K30, from Himedia Laboratories Limited, Mumbai. Potassium dihydrogen phosphate procured from Finar chemical Ltd Ahemedabad India.Sodium Hydroxide from Merck Ltd Mumbai.

PREFORMULATION STUDIES OF PURE DRUG:

Micromeritics study

Bulk density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by $D_b = M/ V_b$, Where M is the mass of powder V_b is the bulk volume of the powder.

Tapped density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times (Macro scientific works, India) and the tapped volume was noted. Tapping was continued until the difference between successive volumes was less than 2%.

ISSN: 0975-8585

It is expressed in gm/ml and is given by $D_t = M / V_t$, Where, M is the mass of powder, V_t is the tapped volume of the powder.

Angle of repose (θ): The frictional forces in a loose powder blend were measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

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

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

The powder blend was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

Carr's index (I)% compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = [(D_t - D_b)/D_t] \times 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = D_t/D_b$$

Where, D_t is the tapped density, D_b is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).[Table1]

Table-1.MICROMIRITICS STUDIES

Parameters	Results
Bulk density	0.298 gm/cm^3
Tapped density	0.425gm/cm^3
Carr's index	31.87
Hausner's ratio	1.45
Angle of repose	39^0

pH Dependent Solubility: Solubity studies of pure drug was done using the following solvents:
pH 1.2 (0.1 N HCl)
pH 6.8 Phosphate buffer
pH 7.4 Phosphate buffer [Table2]

Table-2. pH DEPENDENT SOLUBILITY

Sl.No	Solvent	Solubility(mg/ml)	Quantity/250ml(mg)
1	Water	0.1	26.0
2	pH 1.2 (0.1 N HCl)	0.15	38.5
3	pH 6.8 Phosphate buffer	0.2	51.0
4	pH 7.4 Phosphate buffer	0.25	62.5

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Dissolution Study of Pure Drug:

In vitro dissolution study of various formulations were carried out with 7.4 phosphate buffer (Type II, Electro lab, India).900ml of 7.4 phosphate buffer was placed in the vessel and temperature was maintained at 37±0.5° C. Lornoxicam (100mg) was added to dissolution medium at 100rpm. 2 ml sample was taken from the dissolution medium at regular time interval. After each sampling of 2ml, 7.4 Phosphate buffer was added to maintain sink condition. Further the sample were analyzed for the drug content at 409 nm using U.V. visible spectrophotometer using 7.4 Phosphate buffer as blank. [Table3]

Table-3. DISSOLUTION STUDY OF PURE DRUG:

Time(mins)	%DR
0	0
5	14.5609
15	46.6475
30	61.1885
45	70.1538
60	72.3824
75	74.9831
90	75.7293
105	78.3511
120	79.8424

Drug Excipient Compatibility Study:

The drug excipient compatibility study was performed by subjecting the drug excipient blend to FT-IR analysis (Elico SL-159)[Fig1]and XRD.[Fig 2]

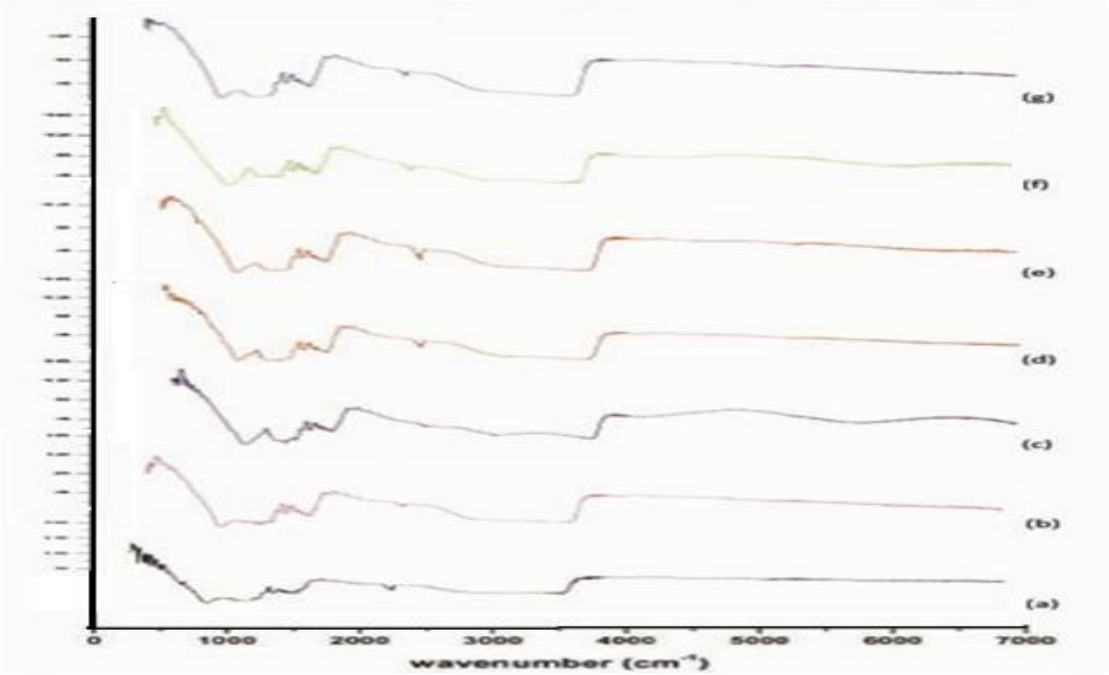

Fig. 1- FTIR Graphs

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Fig.2- XRD Graphs

FORMULATION OF SUSTAINED RELEASE TABLETS:

Weighed amount of Lornoxicam , Polymers (Polyox N303, Polyox N750, Polyox N80, HPMC K4M, HPMC K15M and HPMC K100M), Avicel, PVP K30, Talc were taken and passed through the sieve no-44.Lornoxicam, Avicel, and 70% of the polymer were mixed properly. Granulation of above mixture was done by using isopropyl alcohol (IPA) containing PVP K30. Then the dough mass was shifted through sieve #10 and dried. Then dried granule was passed through sieve #16.Then rest 30% of the polymer was mixed in a poly pack. Magnesium stearate was mixed which was passed previously through sieve #60.Finally talc was mixed. After mixing all the ingredients, the granules were subjected to compression by Cadmach Single Punch Machine using 6 mm round biconcave punch. [Table 4]

Table-4. FORMULATION OF SUSTAINED RELEASE TABLETS OF LORNOXICAM

Ingredients	F1	F2	F3	F4	F5	F6
Lornoxicam	16	16	16	16	16	16
Polyox N303	35					
Polyox N750		65				
Polyox N80			70			
HPMC K4M				20		
HPMC K15M					15	
HPMC K100M						10
Avicel	37.5	7.5	2.5	57.5	62.5	67.5
PVP30	10	10	10	10	10	10
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1	1
Total	100	100	100	100	100	100

EVALUATION OF GRANNULE WITH PURE DRUG AND FORMULATED LORNOXICAM SR TABLETS:

Diameter (Size) and Thickness:

Tablets from each formulation were selected and their diameter and crown thickness was measured. Individual tablets are measured by sliding caliper scale. Weight Variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

Hardness:

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. The Monsanto hardness tester was used for above said parameter.

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Friability:

Tablets were tested for friability using Roche friabilator to know the mechanical strength of the tablet while handling. Ten tablets were weighed initially and transferred to the friabilator. The instrument was set at 25 rpm for four minutes. The resulting tablets were reweighed and percentage loss was calculated using the formula:

(Initial weight –Final weight)/ Initial weight X 100

The percentage loss should be within the limits of 0.1%-0.9%.

Drug content: Content uniformity test was done to assure uniform potency of tablets.20 tablets were weighed and powdered. A quantity equivalent to 100mg of lornoxicam was transferred to the 10ml volumetric flask and volume made up-to 10ml with methanol and filtered. 0.5ml of the above filtrate was transferred into 25ml volumetric flask and made up-to 25mlwith 7.4 Phosphate buffer. The samples were analyzed for the drug content at 409 nm using U.V. Visible Spectrophotometer (Jasco, Japan) against 7.4 phosphate buffer blank. [Table 5, 6]

Table-5.EVALUATION OF GRANNULE WITH PURE DRUG (MICROMIRITICS STUDY)

Parameters	Results						
	Lornoxicam	Lornoxicam Grannule \+ Polyox N303	Lornoxicam Grannule + Polyox N750	Lornoxicam Grannule + Polyox N80	Lornoxicam Grannule + HPMC K4M	Lornoxicam Grannule + HPMC K15M	Lornoxicam Grannule + HPMC K100M
Bulk density	0.287gm /cm^3	0.5 gm/ml	0.281gm/ml	0.262 gm/ml	0.301 gm/ml	0.321 gm/ml	0.271 gm/ml
Tapped density	0.415 gm/cm^3	0.543 gm/ml	0.34 gm/ml	0.321 gm/ml	0.384 gm/ml	0.402 gm/ml	0.332 gm/ml
Carr's index	30.67	7.56	20	18.74	24	21	18.19
Hausner's ratio	1.45	1.09	1.25	1.23	1.32	1.25	1.21
Angle of repose	39^0	26^0	28^0	29^0	30^0	26^0	22^0

Table-6. EVALUATION OF FORMULATED LORNOXICAM SR TABLETS

Formulation Code	Thickness (cm)	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
MKT	0.4±0	97±4.618	6.1±0.353	0.773±0.095	90.12±1.72
F1	0.3±0	99±2	6.0±0	0.601±0.095	92.62±1.56
F2	0.3±0	98±0.707	5.3±0.288	0.506±0.005	90.54±0.96
F3	0.3±0	97±1.264	5.0±0	0.434±0.048	91.48±1.69
F4	0.3±0	99±0.707	6.1±0.288	0.504±0.048	92.97±1.58
F5	0.3±0	98±1.951	5.6±0.288	0.602±0.095	94.22±1.51
F6	0.3±0	100±0	6.1±0.288	0.504±0.040	98.35±1.05

ISSN: 0975-8585

COMPARATIVE DISSOLUTION PROFILE OF MARKETED SR TABLET AND FORMULATED LORNOXICAM SR TABLETS:

By using the Dissolution apparatus, drug release for Marketed SR Tablets of Lofecam (Sun Pharma) and prepared formulations of Lornoxicam SR Tablets (F1-F6) were compared. [Table7][Fig3]

Table-7. COMPARATIVE DISSOLUTION PROFILE OF MARKETED SUSTAINED RELEASE TABLET AND FORMULATED LORNOXICAM SR TABLETS

Time (min)	% DR of MKT	% DR of F1	% DR of F2	% DR of F3	% DR of F4	% DR of F5	% DR of F6
0	0	0	0	0	0	0	0
30	12.125	8.509	10.636	12.527	21.037	14.655	16.309
60	18.188	12.527	19.619	19.146	25.76	19.382	26.47
120	31.713	23.164	27.655	30.25	31.910	26.94	37.110
240	62.02	51.293	45.147	54.60	48.45	45.85	50.111
360	75.319	75.87	58.38	71.385	71.385	70.912	68.312
480	93.68	94.24	95.89	97.31	95.42	94.95	96.59

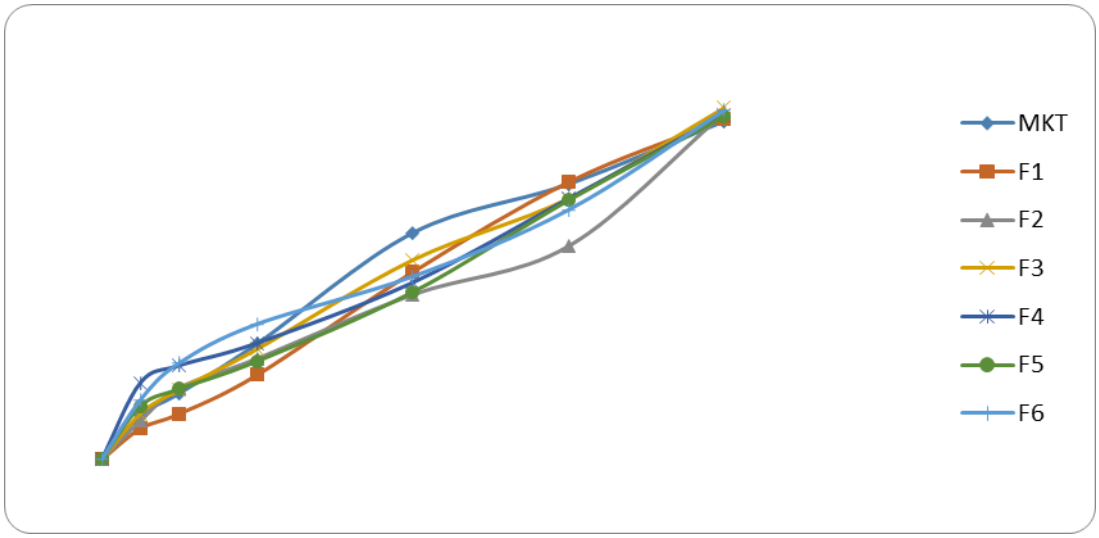

Fig.3- DISSOLUTION PROFILE GRAPH OF MARKETED SR TABLET AND FORMULATED SR TABLETS

STABILITY STUDY: Stability study of formulated sustained release tablets was carried out by storing it for 1 month. The samples were withdrawn at weekly intervals. The tablets were dissolved in 7.4 phosphate buffers, diluted appropriately and estimated for the drug content spectrophotometrically at 407 nm using UV-visible spectrophotometer. No significant differences in the drug contents were observed for four weeks indicating that the formulations were stable. [Table8]

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Table-8. STABILITY STUDY

Name of the sample	Drug Content (%)				
	0 week	1st week	2nd week	3rd week	4th week
F1	92.62±1.56	92.23±1.13	92.17±0.93	92.20±0.96	92.38±1.03
F2	90.54±0.96	90.96±0.99	91.62±0.82	91.92±0.99	91.99±0.81
F3	91.48±1.69	91.44±1.09	91.47±1.09	91.61±1.07	91.38±1.21
F4	92.97±1.58	93.58±1.33	92.32±1.62	91.79±1.67	90.83±1.18
F5	95.22±1.51	95.08±0.85	94.41±1.49	93.99±1.68	93.55±1.30
F6	98.35±1.05	99.15±0.82	98.81±0.90	98.43±1.40	98.35±1.06

RESULTS AND DISCUSSIONS

Organoleptic characteristics of pure drug i.e. Lornoxicam was observed and the result showed that the drug was yellow in color, bitter in taste and crystalline in nature. In the spectroscopic study using UV-Visible spectrophotometer of pure drug with medium 7.4 phosphate buffer, maximum wavelength was found out to be 407 nm. The compatibility study of Lornoxicam with different polymers was described i.e. FTIR studies was done on 1:1 ratio of drug to polymers. The result showed that there was no interaction between the drug and polymers.XRD showed high intensity peaks which indicate the nature to be crystalline. Formulations having different ratios of drug: polymers were evaluated to get similar release rate and physical characteristics with the marketed tablets (MKT) i.e. Lofecam SR of Sun Pharmaceuticals. Weight variation and thickness of tablets were within the IP limits**.**Hardness was found to be satisfactory as per IP specifications. All the formulations had satisfactory friability. Drug content of all the formulation had satisfactory results. Dissolution study of the formulations showed that the % drug release was found to be 94.24 %, 95.89 %, 97.31 % 95.42 %, 94.95 % and 96.59 % in 8 hr for formulation F1 to F6 respectively as compared to 93.68% for MKT. All the formulations showed approximately similar %DR to the marketed tablet.Study showed that all the formulations follows zero order release kinetics.The results of stability study indicated that there is no significant change in hardness, friability and percentage of drug content after storage at a constant temperatures and relative humidity conditions for four weeks.

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