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Formulation development and evaluation of Bilayer tablets of Lornoxicam

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Abstract

The objective of the present study was to develop bi-layer tablets of lornoxicam, a highly potent nonsteroidal anti-inflammatory drug with short half-life, that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect.

Immediate release layer prepared by using dry granulation method in which ac-di sol used as a disintigrant for immediate release of drug, roll compaction of drug with sodium citrate which act as buffering agent and create basic micro-environmental pH inside the tablets favorable to drug release in acidic conditions. Sustained release layer formulated by using HPMC as release retardant, two grades of HPMC that are HPMC K4M and HPMC K100M used to get sustained release profile for 24 hr. various trial batches are taken to get desired release profile. Batch F8 formulate as bilayer tablet in which drug as to sodium citrate ratio taken 1:5 show maximum drug release 24.67 % for 1 hr in immediate release layer and drug release 98 % for 24 hr in sustained release layer is selected as optimized batch of bilayer tablet formulation. All the prepared bilayer tablets showed acceptable physical properties before and after storage.

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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)] Lornoxicam is commercially available in the form of conventional immediate-release tablets (4 and 8 mg), rapid-release tablets (8 mg), and parenteral

formulations (4 mg/ml) for intravenous and intramuscular use [2]. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis [3]. Moreover, it showed great efficacy in various clinical trials in the management of perioperative and postoperative pain associated with gynecological, orthopedic, abdominal, and dental surgeries [2]. However, lornoxicam's usefulness is limited due to its short half-life that ranges from 3 to 5 h [4, 5]. Added to that, lornoxicam shows a distinct pH-dependent solubility characterized by very poor solubility in acidic conditions present in the stomach [5]. Thus, it remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration [6].The layered tablet concept has been utilized to develop controlled-release formulations [7–12]. Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fast-release layer combined with single [7– 10] or double sustained-release layers [11,12]. Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration [13, 14]. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled- release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained-release layer [14]. This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained-release phase to avoid repeated drug administration. It is reported that the NSAIDs are suitable candidate drugs for this type of administration [13, 14].

MATERIAL AND METHODS

Lornoxicam and HPMC were obtained as a gift sample from Glenmark generics Ltd, Mumbai, India.MCC, Povidone, Sodium Citrate, and Crosscarmellose sodium, Talk, Magnesium Sterate were purchased from local authorized dealer.

Method

Preformulation Study

Confirmation of Drug

Confirmation of drug was carried out by using infrared spectroscopy, differential scanning calorimetry (DSC) and UV spectroscopy.

FTIR Spectra

The IR absorption spectrum of the pure drug was taken in the range of 4000-450 cm- using KBr pellet method .The major peaks were reported for evaluation of purity. Observed peaks are similar to reported peaks of Lornoxicam.

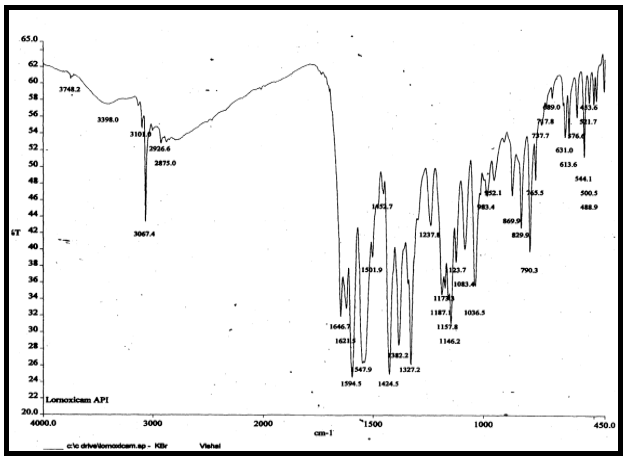

Figure. 1. Infrared spectrum of Lornoxicam.

Table 1: Peak and chemical group present in IR spectrum of Lornoxicam

Wave number (cm-1)	Characteristic absorption
3067 cm-1	-NH Stretching
1646 cm-1	C=O Group
1597 cm-1, 1559 cm-1	N-H Group
1157 cm-1,1146 cm-1,1173 cm-1	O=S=O Group
829 cm-1	CH Stretching
765 cm-1	C-Cl bending vibration.

DSC

Lornoxicam was confirmed by differential scanning calorimetry at scan rate of 10oC/min it exhibits a

sharp melting endotherm with onset temperature 236°C and peak temperature 237°C.

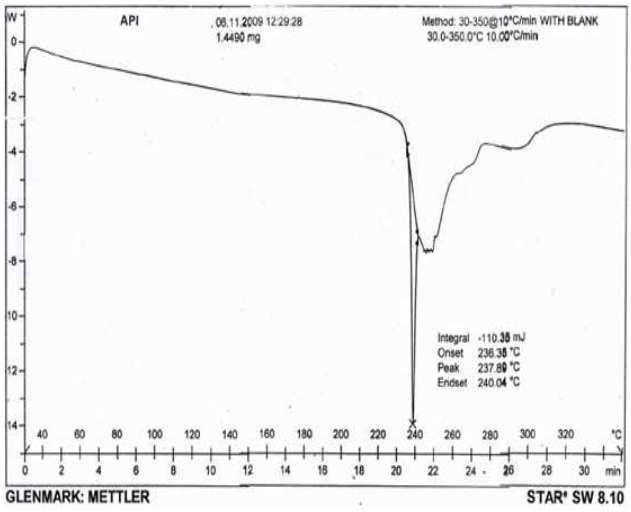

Figure 2. DSC thermogram of pure Lornoxicam

UV Spectroscopy

Lornoxicam solution was scanned at 400 nm to 200 nm, two maximas are observed at 288 nm and 379.35 nm**.** This was confirmed with reported UV spectrum of drug.

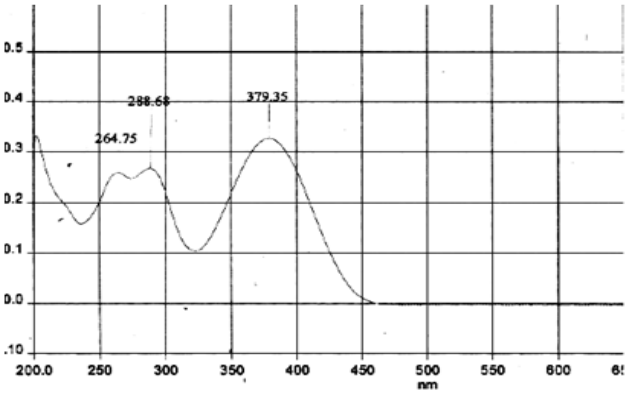

Figure 3.UV spectrum of Lornoxicam solution in 7.4 pH buffer

Moisture Content

Moisture content determination of API was carried in "METTLER TOLEDO HR73 Halogen Moisture Analyzer" for 5min at 105°C.

Table 2: Moisture Content of drug.

Sr. No	I	II	III	Average
Weight	1.5	1.5	1.5	1.5
Loss on drying	0.23	0.24	0.23	0.23

Analysis of Particle Size

Particle size distribution was carried out in "Malvern Particle Size Analyzer" model-Mastersizer-2000. The Dry method is preferred for determination of particle size. A uniform Particle size distribution curve is obtained and geometric mean diameter (d) was calculated from graph.

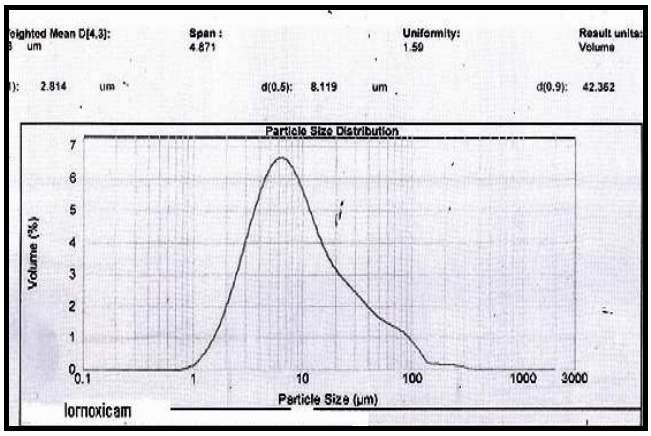

Figure 4: Particle size distribution of lornoxicam

Discussion .Particle size (geometric mean diameter) range d (0.1)-2.814µm, d (0.5)-8.119 µm and d (0.9)-42.362 µm.

Solubility

Solubility is a useful parameter mainly for poorly soluble drugs. Bioavailability problems are often present, when the solubility of a drug is less than 10 mg/ml over the pH range 1-8. Drug solubility was determined by preparing saturated drug solutions in various buffer medium, maintained at 37°C ± 0.5°C in a water bath and continually shaken in to mechanical shaker up to 24 hrs. Withdrawn samples were filtered through a filter paper, and assayed by UV spectrophotometer.

Table: 3 The solubility of Lornoxicam as a function of pH

Medium	Mean Drug Solubility(mg/ml)
0.1N HCL (PH 1.2)	0.003
Demonized Water (PH 5.1)	0.021
Phosphate Buffer (PH 6.8)	0.705
Phosphate Buffer (PH 7.4)	0.905

Physical Properties of Drug.

Drug was characterized for their physical properties such as angle of repose, density, compressibility, Hausner's ratio.

Angle of repose, density, compressibility, and Hausner's ratio. Results are shown in Table 4

Table 4: Physical parameters of drug.

Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Compressibility Index (%)
33	0.37	0.50	1.35	26.00

Calculation of Dose

The loading dose & mainataineence dose of Lornoxicam Bilayer tablet was calculated by following equation using available pharmacokinetic data. Dt= Dose (1 +0.693 x t/t1/2) Where, Dt= Total dose of drug; Dose = dose of immediate release part (4 mg); t=time (hours) during which the sustained release is desired (24 hours); t1/2= half-life of drug (4.2) Dt= 4 (1 + 0.693 x 24/4.2) = 16 mg Hence formulation should contain total dose 16 mg with 4mg as loading dose, dose of immediate release part and 12mg is mainataineence dose, dose of sustained release part.[15]

Formulation of bi-layer tablet of Lornoxicam

Formulation and development of Lornoxicam Bilayer tablet involves two steps. Step one formulation of immediate release layer, immediate release layer formed by ac-disol as a super disintegrant, Avicel-112 as a diluent, Sodium citrate used as an alkaline agent to produces Buffering action to release drug in acidic environment and Magnesium sterate used as a lubricant in optimum concentration per tablet. FDC Red No.40 was used as color for the formulation to identify the mixing of two blends during compression. The Immediate release layer was formed by roll-compaction method (Dry Granulation Method), to improve the dissolution of drug in order to get an immediate drug loading effect. Step two is formulation of Sustained release layer HPMC K4M, HPMC K100M selected as polymer; Binder plays a major role in a formulation. As Lornoxicam was supposed to be granulated with water then the hydrophilic binder selected for study. Kollidon K30 (PVP) was a versatile binder, used in the study. Magnesium sterate used as lubricant.

Table 5: Composition of different batches of Bi-Layer tablets of Lornoxicam.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Immediate Release Layer								
Lornoxicam	4	4	4	4	4	4	4	4
Ac- di sol	18	18	18	18	18	18	18	18
MCC	155	151	147	143	135	131	135	135
Sodium Citrate	-	4	8	12	20	24	20	20
FDC RED NO 30	1	1	1	1	1	1	1	1
Magnesium Sterate	2	2	2	2	2	2	2	2
Sustained Release Layer								
Intragranular								
Lornoxicam	12	12	12	12	12	12	12	12
MCC	159	154	164	169	174	174	169	174
HPMC K4M	100	100	85	70	60	50	50	50
Granulation								
PVP K30	5	10	15	15	15	15	15	15
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extragranular								
HPMC K100M	-	-	-	10	15	25	30	25
Mg.Sterate	4	4	4	4	4	4	4	4
Total	460	460	460	460	460	460	460	460

The Immediate release layer was formed by Roll-Compaction method, Lornoxicam, Ac-di-sol, Sodium Citrate and Microcrystalline Cellulose were co-sieved by 60 no sieve, this mixture passed through roll compactor, in 3 RPM and 200lb/cm3 pressure and slugs are produced, Slugs produced in roll compaction were milled in Multi mill 1.5mm mesh. Granules are passed through 40 no sieve, and blended for 10min. Magnesium sterate was passed through sieve no 80 and Lubricated for 5min in bin blender. The Sustained release layer was formed by Wet granulation method; Lornoxicam, HPMC K4M, and microcrystalline cellulose were accurately weighed and co-sieved through 60 no sieve. Dry mix

above material in rapid mixture granulator for 5min. polyvinyl pyrollidone was dissolved in sufficient quantity of water to form a clear solution; the binding solution was added solely and uniformly to the content in mixture in rapid mixture granulator for 1 min. Then it was mixed thoroughly to obtain coherent mass for 10 min. The Granules was dried in FBD for 20 min.Check loss on drying it should not be less than 2 %, dried granules passed through 40 no sieve, dried granules and HPMC $K_{100}M$ co-sieved thro 60 no sieve. The blending of granule was done in Bin blender at 12 RPM for 10 min. Magnesium sterate was passed through 80 no sieve and Lubricate with granules for 5 min. Bilayer tablets were prepared by using immediate and sustained release layer. Various batches of bilayer tablets were prepared by method according to formula Table no1, and compression by using 10.5 mm round punch on Bilayer rotary tablet machine (jaguar, India).

Evaluation of formulated tablets:

Weight Variation Test

According to the official test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation.

Friability and Hardness [16]

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. In The Roche friabilator the weight of tablets was noted initially (W1) and placed in a friabilator for 4 min/ 100 rpm. The tablets were reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage.

$$\% \text{ friability} = \left[1 - \frac{\text{weight of tablets after test}}{\text{weight of tablets before test}}\right] \times 100$$

The mean ± SD of 6 tablets were calculated.

Thickness

The thickness of the tablets was determined using a vernier caliper. 20 tablets from each batch were used and mean ± SD was calculated.

Drug content

Ten Tablets were weighed individually, crushed, and the drug was extracted in phosphate buffer ph 7.4. The solution was filled through a 0.45 um Millipore filter and drug content was determined by UV spectroscopy after a suitable dilution with reference to calibration curve.

Table 6: Evaluation of Bi-Layer tablets of Lornoxicam.

SR. No.	Weight Variation (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)	Drug Content (%)
F1	460±1.3	7.0±0.03	5.0±0.60	1.12±1.1	92.0±1.1
F2	461±2.1	5.4±0.04	6.5±0.50	1.00±0.9	97.0±1.2
F3	459±1.3	6.1±0.09	9.12±1.20	0.1±0.12	95.0±1.1
F4	460±1.1	5.7±1.8	9.3±0.89	0.12±0.1	99.0±1.1
F5	462±1.1	6.0±1.1	9.5±0.55	0.13±0.2	98.0±1.3
F6	460±1	5.9±1.4	9.4±0.98	0.14±0.1	99.0±0.4
F7	460±2.7	6.0±1.8	9.3±1.20	0.12±0.3	99.0±1.0
F8	459±2.0	6.1±1.8	9.1±1.12	0.12±0.2	99.0±0.9

In-Vitro dissolution Studies

Apparatus- USP apparatus type II, equipped with Perkin-Elimer Dissolution Software

Glass fiber filter- Whatman GF/F

Dissolution medium-750 ml of dissolution medium 1, After 1 hour the medium is changed to 900 ml of dissolution medium 2.Number of revolutions speed-50 rpm Stirrer- Paddle ,Temperature of dissolution medium- 37° C± 0.5° C.

Table 7: Dissolution of Bi-Layer tablets of Lornoxicam.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	6.5	11.5	9.89	16.0	24.67	17.21	21.12	24.10
2	11.7	24	27.0	29.0	28.0	29.0	28.0	29.0
4	17.59	38.8	39.2	41.0	39.0	41.6	39.0	41.6
6	26.49	53.0	51.0	57.0	56.0	51.0	47.0	51.0
8	39.2	61	55.0	58.9	60.10	60.9	54.2	60.0
12	45.4	69.0	58.0	66.1	63.0	70.0	69.0	70.0
16	53.72	70.4	61	71	79	81	78	81
24	66.4	71.1	74.0	83.1	89.0	97.5	91.0	98.51

RESULTS AND DISCUSSION:

Formulate immediate release layer and sustained release layer individually by dry granulation and wet granulation method. Both Layers passes the Precompression tests that are Angle of repose, density, compressibility, and Hausner's ratio. Precompression parameters like angle of repose, loose bulk density, tapped bulk density, compressibility index, and hausner's ratio of all batches of lornoxicam was represented in Table 5. From the results of precompression parameter of lornoxicam tablet granules study, it was found that all the batches have good compressibility. Flow properties also found to be good for all batches (angle of repose between 28-30 indicates good flow). Hausner's ratio (less than 1.25) for all batches which indicate good flow properties.

Post compression parameter of bi-layer tablet like weight variation, thickness, hardness, friability, and drug content uniformity were represented in **Table 6**. Weight variation of bi-layer tablet was found within limit (460 ± 5%). Friability of bi-layer tablet 0.1 % was found less than 1% except in batch F1 & F2 due to less binder. Hardness was found 9.0-9.5, in batch F1 & F2 hardness is less (5.0-6.5) and thickness variation was found less than 5% variation. Content uniformity of lornoxicam in bi-layer tablet was found between 92 -99 % respectively.

Immediate release layer ac-di sol disintigrant selected for immediate release of drug, drug has less solubility in acid media, its solubility increase by addition of sodium citrate as buffering agent. Roll compaction of drug with sodium citrate at 1:1, 1:2 and 1:3, 1:5, 1:6 ratio show significant increases in drug release foe 1 hr. Drug: In trial batch F5 Sodium citrate ratio1:5 show drug release 24.67 % is maximum for 1 hr selected as batch for preparation of immediate release layer in bilayer tablet preparation.

Sustained release layer formulated by using HPMC as release retardant, two grades of HPMC that are HPMC K4M and HPMC K100M selected, PVP-K30 Selected As Binder. Batch F1 and F2 Increases the Binder Concentration to Increase Hardness and pass the friability test. Various trial batches are taken to get sustained release profile for 24 hr by addition of HPMC K4M and HPMC K100M extra granular to intragranular ratio. Batch F6 give maximum release 97.7% in 24 hr is selected as batch in formulation of bilayer tablet. Batch F8 formulate as bilayer tablet which shows 24.10 % of drug release in 1 hr in immediate release layer and 98 % drug release in 24 hr is selected as optimized batch of bilayer tablet formulation.

CONCLUSION:

The Experiment relates to formulation and development of oral pharmaceutical bilayer tablet of lornoxicam for administration of therapeutically and prophylactically effective amount of non-steroid anti-inflammatory drug substance to obtained both a relatively fast or quick onset of therapeutic effect and mainatainence of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from pain and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

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