Research Article

Design, Development and Evaluation of Trilayer Swelling Gastro Retentive Tablets of Lornoxicam for Biphasic release and Lansoprazole for Immediate release for the treatment of Arthritis

***D Jaison[1], K Elango[1], V Sundar Raj[1], K Dhunmati[2], M Kousalya[3]**

1. Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai – 03, Tamil Nadu, India.
2. Department of Pharmaceutical Chemistry, C. L. Baid Metha College of Pharmacy, Thooraipakkam, Chennai, Tamil Nadu, India.
3. Department of Pharmacology, Jaya College of Pharmacy, Thiruninravur – 602024, Tamil Nadu, India.

ABSTRACT

The objective of this present investigation is to design and evaluate Trilayer Swelling Gastro Retentive Tablets (TSGRT) containing Lornoxicam for biphasic release and Lansoprazole for immediate release using Buffer technology for the treatment of Arthritis. The buffer layer containing Trisodium phosphate and Magnesium Oxide is employed in the formulation for making the Gastric pH alkaline, suitable for the immediate release of an acid labile drug Lansoprazole and a less soluble drug Lornoxicam. The objective of this combination is to provide relief in Arthritis and to effectively prevent the NSAID induced ulcer thus improving patients' compliance. To achieve the desired therapeutic effect, Lornoxicam is employed as biphasic delivery. The immediate release layer is prepared using different super disintegrants like SSG, CCS, Cross Povidone. Sodium bicarbonate is employed for the stability of drugs. The swellable gastro retentive layer containing Lornoxicam was prepared using HPMC K4 M or Ethyl Cellulose in combination with Xanthan Gum and Psyllium Husk for release retardation and Gastro retention. The TSGRT was evaluated for physical parameters such as weight uniformity, hardness, friability, drug content and swelling index. From the investigation it was observed that swelling of tablets lasted for up to 24 hours for optimized TSGRT. FT-IR peaks assured the compatibility of the drug with excipients and confirmed the presence of pure drug in the formulation. It was supported by the *in-vitro* release dissolution studies; and the dissolution data was subjected to various release kinetic models to understand the mechanism of drug release.

Keywords: Buffer technology, Psyllium Husk, Trilayer Swelling Gastro Retentive Tablets, Xanthan Gum

Received 20 April 2015 Received in revised form 4 May 2015 Accepted 6 May 2015

***Address for correspondence:**
D Jaison,
Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai – 03, Tamil Nadu, India.
E-mail: jaipharma17@gmail.com

INTRODUCTION

Arthritis is an inflammatory disease that causes pain, swelling, stiffness and loss of function in the joints. Approximately 1 to 2 % of world population was affected by Rheumatoid Arthritis [1]. Lornoxicam, a member of oxicam group of NSAIDs is found to possess potent anti-inflammatory and analgesic activities. Lornoxicam is widely recommended for symptomatic treatment of pain and inflammation in patients with osteoarthritis and rheumatoid arthritis. The absolute bioavailability of Lornoxicam is 90 – 100 %. As Lornoxicam has half -life of 3 to 4 hours and poor solubility in acidic conditions, it is an ideal candidate for swelling gastro retentive sustained release dosage forms [2].

25% of Chronic NSAID users develop Ulcer disease and 2 to 4 % bleed or perforate [3]. Lansoprazole is an antiulcer drug belonging to the class of Proton Pump Inhibitor (PPI) is recommended by the FDA for the treatment and prevention of NSAIDs induced ulcer. Lansoprazole is a benzimidazoles sulfoxide derivative and produces long lasting inhibition of gastric acid secretion, thus effective in the prevention of NSAIDs induced ulcer [4].

Oral route is the most often used route for administration of drug. Tablets are the most convenient oral dosage form and preferred by patient and physicians. The chronic disease conditions require long term treatment. Conventional formulations are required to be administered in multiple doses and thus have several limitations. The development of sustained release dosage forms have been found to improve therapeutic efficiency by maintaining steady state plasma concentration of drug [5].

Oral sustained release dosage forms have been the field of focus for the past three decades. Limitations of unsuitability and reduced bioavailability in sustained release dosage forms are tackled and overcome by gastro retentive dosage forms [6].

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Swellable systems are retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form in the stomach will withstand gastric transit if it is bigger than pyloric sphincter. The use of polymers in controlling the drug release and increasing gastric residence time has become an important tool in the formulation of swelling gastro retentive dosage forms [7].

The combination of water soluble buffer (Trisodium Phosphate) and water insoluble buffer (Magnesium oxide) gives an initial rise in pH above 6 and upon addition of excess acid for a period of 1 hour, the pH gradually increases and maintains stable at pH between 7.0 – 8.0, which proved that this combination as a suitable one to alter the Gastric pH [8]. The present investigation was attempted to develop trilayer swelling gastro retentive tablets comprising Buffer layer, Lornoxicam and Lansoprazole immediate release layer and Lornoxicam sustained release layer. The change in gastric pH is effected by the use of buffer layer and creates a suitable environment for the release of acid labile drug Lansoprazole. The rationale of the study is to provide the effective treatment of Arthritis, minimizing the side effects of Lornoxicam. In this work physicochemical characterization, formulation and *in-vitro* evaluation of formulated trilayer swelling gastro retentive tablets were carried out.

MATERIALS AND METHODS:

Materials:

Lornoxicam and Lansoprazole were obtained as a gift sample from Glenmark Generics (Mumbai) and Orchid Healthcare (Chennai) respectively. HPMC K4 M, Ethyl Cellulose, Xanthan gum were provided by Kniss Laboratories (Chennai) as gift samples. Psyllium Husk was obtained from Organics India Pvt. Ltd. (Mumbai).

Methods:

Formulation of Trilayer Swelling Gastro Retentive Tablets (TSGRT):

All the ingredients for buffer layer were dispensed accurately, sifted and the Buffer granules were prepared by wet granulation method using PVP and isopropyl alcohol. Buffer layer was kept constant for all batches. The immediate release layer was prepared by slugging method using various disintegrants (SSG, CCS, Cros povidone) in various concentrations. Dry mixing was done for 10 minutes before processing it into slugs. The Swelling sustained release layer was prepared by direct compression technique by varying the concentration of the polymers. Preformulation parameters were evaluated for all blends and then compressed into trilayer tablets by 10 station single punching machine (Model: Rimek, Karnavati Engineering Ltd, Gujarat, India) using 9 mm punch in three stages i.e. 1) transfer of sustained release layer and manual compaction, 2) transfer of immediate release layer above the compacted sustained release layer and compressed into bilayer tablets, 3) the buffer layer was transferred above the bilayer tablet which were placed into the die and compressed to yield Trilayer Swelling Gastro retentive tablets. The formulated tablets were stored in air tight container at room temperature for further evaluation of the tablet parameters. The table 1 and 2 shows the formulations of immediate release trilayer tablets and biphasic release TSGRT respectively.

Evaluation of preformulation parameters [6, 9]

Fourier Transform infra-red spectroscopy (FT-IR)

The powdered samples of the tablets were mixed thoroughly with previously dried potassium bromide (IR grade) and compressed so as to form transparent pellets. The samples were scanned from 4000 to 400 cm-1 at ambient temperature.

Angle of Repose

The angle of repose of granules or powder blend of each layer of each formulation was determined by fixed funnel method. The granules or blends were poured through funnel separately until the apex of pile so formed just touches the tip of the funnel. The angle of repose was measured using the formula,

$\tan\theta = h/r$: h – height of pile ; r = radius of pile

Bulk density

Bulk density was determined by placing the powder blend in a measuring cylinder and the total volume was measured and total weight of powder was measured. Bulk density was calculated by using the formula,

Bulk density (BD) = Weight of powder/Bulk volume

Tapped Density

The tapped density was obtained by dropping the cylinder onto a hard wooden surface. The tapping was continued until no further change in volume was noted it was calculated by using the formula

Tapped density (TD) = Weight of powder/Tapped volume

Carr's Compressibility index

Carr's Compressibility index (CCI) was calculated by using the formula,

% CCI = [(TD – BD)* 100] / TD

Table 1: Formulation of immediate release trilayer tablets

INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6
BUFFER LAYER						
Tri Sodium Phosphate	250	250	250	250	250	250
Magnesium Oxide	100	100	100	100	100	100
Sucrose	20	20	20	20	20	20
Cros Carmellose Sodium	8	8	8	8	8	8
PVP K30	12	12	12	12	12	12
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
IMMEDIATE RELEASE LAYER						
Lornoxicam	4	4	4	4	4	4
Lansoprazole	30	30	30	30	30	30
Sucrose	10	10	10	10	10	10
Sodium Bicarbonate	25	25	25	25	25	25
Sodium Starch Glycolate	2	4	-	-	-	-
Cros Carmellose Sodium	-	-	1	2	-	-
Cros Povidone	-	-	-	-	2	5
Microcrystalline Cellulose	21.5	19.5	22.5	21.5	21.5	18.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5
BACKING LAYER						
HPMC K4 M	45	45	45	45	45	45
Xanthan Gum	30	30	30	30	30	30
Psyllium Husk	15	15	15	15	15	15
Sodium Bicarbonate	30	30	30	30	30	30
PVP K 30	4	4	4	4	4	4
Microcrystalline Cellulose	23	23	23	23	23	23
Magnesium Stearate	3	3	3	3	3	3

Total weight of Tablets = 650 mg

Table 2: Formulation of Biphasic Release TSGRT

INGREDIENTS	FS_1	FS_2	FS_3	FS_4	FS_5	FS_6	FS_7	FS_8
BUFFER LAYER								
Tri Sodium Phosphate	250	250	250	250	250	250	250	250
Magnesium Oxide	100	100	100	100	100	100	100	100
Sucrose	20	20	20	20	20	20	20	20
Cros Carmellose Sodium	8	8	8	8	8	8	8	8
PVP K30	12	12	12	12	12	12	12	12
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
IMMEDIATE RELEASE LAYER								
Lornoxicam	4	4	4	4	4	4	4	4
Lansoprazole	-	-	-	-	-	-	-	-
Sucrose	10	10	10	10	10	10	10	10
Sodium Bicarbonate	25	25	25	25	25	25	25	25
Cros Carmellose Sodium	2	2	2	2	2	2	2	2
Microcrystalline Cellulose	51.5	51.5	51.5	51.5	51.5	51.5	51.5	51.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5
SWELLING GASTRO RETENTIVE LAYER								
Lornoxicam	12	12	12	12	12	12	12	12
HPMC K4 M	15	30	45	60	75	-	-	-
Ethyl Cellulose	-	-	-	-	-	-	45	15
Xanthan Gum	60	45	30	15	-	75	30	60
Psyllium Husk	15	15	15	15	15	15	15	15
Sodium Bicarbonate	30	30	30	30	30	30	30	30
PVP K 30	4	4	4	4	4	4	4	4
Microcrystalline Cellulose	11	11	11	11	11	11	11	11
Magnesium Stearate	3	3	3	3	3	3	3	3

Total weight of Tablets = 650 mg

Hausner's Ratio

Hausner's ratio is a number that is correlated to the flowability of powder and powder blend. It was calculated using the formula,

Hausner's ratio = TD / BD

Evaluation of Trilayer Swelling Gastro Retentive Tablets [10, 11]

Thickness

The thickness of the tablet was measured using Vernier Caliper. A total of 5 tablets were randomly selected and thickness was measured.

Weight Variation test

20 tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were individually weighed and the weight variation was determined as per specifications.

Hardness

The resistance of the tablets to break under conditions of storage, transportation and handling before usage depends on hardness of tablets which was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability

Tablets pre-weighed were placed in Roche Friabilator and rotated for 4 minutes at 25 rpm. Percentage friability was determined by the formula,

% Friability = [(initial weight – final weight) / initial weight] * 100

Drug Content

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to average weight were taken in a 100 ml standard flask and dissolved with 20 ml of ethanol and made upto 100 ml with phosphate buffer pH 7.4. The solution was filtered and the absorbance of the resulting solution containing Lornoxicam and Lansoprazole was measured spectrophotometrically at 376 nm and 285 nm respectively using phosphate buffer pH 7.4 as blank. The absorbance of the standard concentration of Pure Lornoxicam and Lansoprazole measured. The drug content was estimated using simultaneous

equation method [12]. The mean percent drug content was calculated as an average of three determinations.

***In-vitro* drug release study**

In-vitro dissolution study of trilayer swelling gastro retentive tablets of Lornoxicam and Lansoprazole immediate release were determined using USP type II (paddle) dissolution studies under sink conditions at 100 rpm. The dissolution medium used was 250 ml of Simulated Gastric fluid (pH 1.2) and the temperature was maintained at 37±0.5ºC [8]. The Aliquots of dissolution medium were withdrawn for one hour with 10 minutes interval and replaced immediately with equal volume of fresh medium. The samples were filtered; Lornoxicam and Lansoprazole were analyzed spectrophotometrically at 376 nm and 285 nm respectively using simultaneous equation method.

The sustained release of Lornoxicam was estimated at 376 nm. The Aliquots of dissolution medium were withdrawn for one 24 hours with specific time interval and replaced immediately with equal volume of fresh medium. Drug concentration was calculated and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Swelling Studies

The swelling property of TSGRT was determined by placing the tablet in the dissolution test apparatus containing 250 ml of Simulated Gastric fluid (pH 1.2) and maintained at 37±0.5ºC. At periodic intervals, the tablets were taken out and the weight gain in each tablet was checked using electronic weighing balance. The swelling characteristics were expressed in terms of the percentage water uptake according to the equation [6],

SI = [(Weight of tablet at time t – Weight of tablet at time 0) / Weight of tablet at time 0]* 100

Curve fitting analysis

Zero order, First order, Korsemeyer Peppas, Higuchi and Hixson Crowel were applied to the observed release profile data to analyze the rate, mechanism and pattern of the drug release [13].

RESULTS AND DISCUSSION

Fourier Transform Infra-Red Spectroscopy of Lornoxicam, Lansoprazole and formulation

The IR spectrum of Lornoxicam exhibited distinctive peaks at 3409.90 cm^{-1} owing to N-H stretching of the Secondary amide and at 788.90 cm^{-1} because of C-Cl stretching as shown in Fig.1. The IR spectrum of Lansoprazole exhibited distinctive peaks at 3402.18 cm^{-1} owing to N-H stretching and at 1450.36 cm^{-1} because of C-F stretching as shown in Fig.2. The formulation containing the Lornoxicam and Lansoprazole do not interact with each other and with that of excipients present was shown in (**Fig. 3**).

Preformulation studies

The pure Lornoxicam and Lansoprazole were studied for flow properties and found that these drugs have poor flowability. To formulate immediate release (IR) the Lornoxicam and Lansoprazole were mixed with the excipients to be used and found that flow was poor. Dry compression technique was applied. For sustained release layer the flow was satisfactory thus direct compression technique was used. In case of buffer layer the flow is excellent but still has poor adhesion properties thus wet granulation technique was used.

Immediate Release Trilayer tablets

Preformulation study of Lornoxicam and Lansoprazole IR trilayer tablets

The bulk density and tapped density of the formulation ranged from 0.5405 – 0.7407 g/ml, 0.6896 – 0.9523 g/ml respectively. The compressibility index and Hausner ratio ranged from 21.62 – 25.00 % and 1.2758 – 1.333 respectively signifying satisfactory flow property which was further confirmed by the angle of repose values ranging from 33.63°- 34.81° as shown in (**Table 3**) [9].

Characterization of Lornoxicam and Lansoprazole IR trilayer tablets

The average weight of tablets ranged from 0.6402 to 0.6527 g for all the formulations which compiled with the monograph specification limit of ± 5%. As a measure of mechanical strength, these formulations exhibited satisfactory hardness of 5 to 5.8 kg/cm^2 and the same fact was further supported by friability of less than 1 %. The Drug content of all formulations containing Lornoxicam ranged between 95.10 to 99.06

% and Lansoprazole ranged from 96.03 to 102.53 % which was within the standard limits are shown in (**Table 4**) [11].

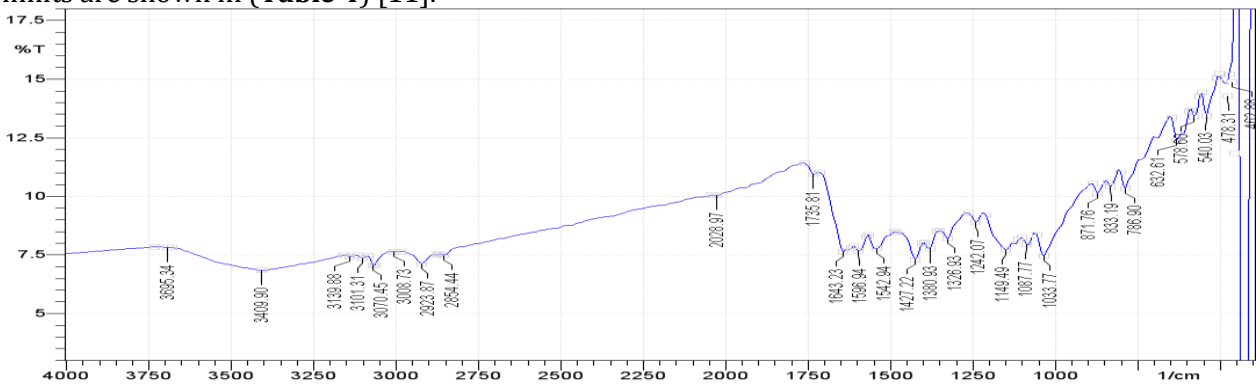

Figure 1: FTIR graph of Lornoxicam

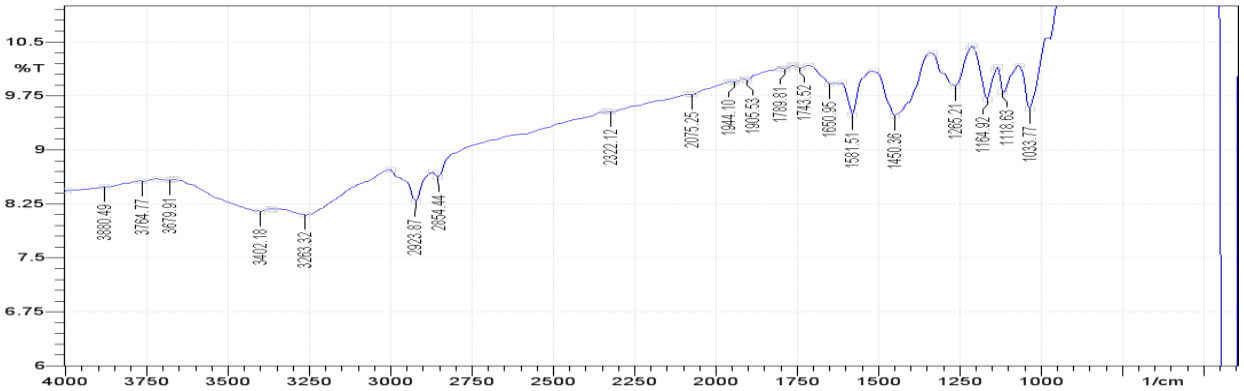

Figure 2: FTIR graph of Lansoprazole

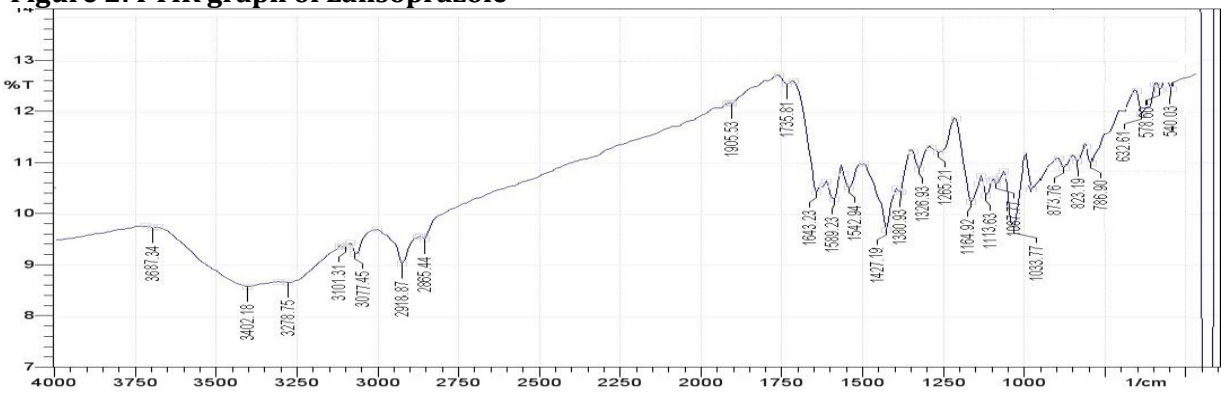

Figure 3: FT-IR graph of formulation containing Lornoxicam and Lansoprazole

Table 3: Micrometric properties of Lornoxicam and Lansoprazole IR trilayer tablets

Formulation Code	Bulk Density* g/cm³	Tapped density* g/cm³	Carr's Index (%)*	Hausner Ratio*	Angle of Repose (degree)
Buffer Layer	1.3157±0.013	1.3888±0.013	5.26±0.029	1.055±0.015	31.70°
F_1	0.7142±0.021	0.9523±0.027	25.00±0.078	1.33±0.029	34.81°
F_2	0.7407±0.029	0.9523±0.016	22.21±0.056	1.2857±0.051	33.71°
F_3	0.7407±0.026	0.9523±0.017	22.21±0.069	1.2857±0.062	33.63°
F_4	0.7407±0.021	0.9523±0.011	22.21±0.051	1.2857±0.078	33.95°
F_5	0.7142±0.012	0.9090±0.018	21.43±0.021	1.272±0.090	33.70°
F_6	0.5405±0.023	0.6896±0.043	21.62±0.017	1.275±0.086	33.95°
Swelling Layer	0.7407±0.016	0.9090±0.019	18.51±0.021	1.227±0.029	31.28°

***Mean ± SD (n=3)**

Table 4: Post compression parameters of Lornoxicam and Lansoprazole IR trilayer tablets

Formulation code	Thickness (mm) [a]	Hardness (kg/cm²) [a]	Friability (%) [b]	Weight Uniformity (g) [b]	% Drug content [b]	
					Lornoxicam	Lansoprazole
F_1	5±0.0023	5.6±0.489	0.15 ± 0.023	0.6402 ± 0.0105	97.15 ± 0.431	99.46± 0.367
F_2	5±0.0034	5.4±0.489	0.189 ± 0.018	0.6438 ± 0.0090	96.23± 0.361	96.03± 0.298
F_3	5±0.0021	5.8±0.4	0.208 ± 0.021	0.6478 ± 0.0087	95.10± 0.580	101.26± 0.613
F_4	5±0.0014	5.2±0.373	0.218 ± 0.012	0.6515 ± 0.0085	98.89± 0.291	102.53± 312
F_5	5±0.0019	5.8±0.4	0.265 ± 0.016	0.6487 ± 0.0092	99.06± 0.326	99.43± 0.365
F_6	5±0.0017	5±0.42	0.264 ± 0.012	0.6527 ± 0.0091	96.89± 0.379	97.96± 0.396

Mean ± SD ([a]n=5, [b]n=3)

In-vitro Dissolution Studies

In-vitro dissolution data showed that 4 % concentration of CCS was found to be optimum for immediate release of Lornoxicam (LOR) and Lansoprazole (LAN) which showed 99.82 % and 99.45 % at the end of 60 minutes and it is given in the (**Table 5**).

Table 5: Cumulative % drug release of Lornoxicam and Lansoprazole IR trilayer tablets

Time in Minutes	Cumulative % drug release											
	F_1		F_2		F_3		F_4		F_5		F_6	
	LOR	LAN	LOR	LAN	LOR	LAN	LOR	LAN	LOR	LAN	LOR	LAN
5	4.01	2.92	8.59	3.48	8.07	8.62	11.59	7.152	5.27	5.76	9.50	7.06
10	6.90	3.74	16.28	5.54	18.35	19.02	22.37	19.58	12.38	18.43	25.15	23.48
15	9.78	5.17	31.93	14.11	33.23	36.06	34.81	39.93	28.23	37.88	36.84	39.36
20	9.89	5.22	59.80	36.78	52.90	47.12	56.48	52.22	53.44	42.14	54.33	50.26
25	15.1	8.07	64.56	41.72	62.34	59.68	63.54	61.04	57.67	49.12	60.81	60.36
30	31.23	12.71	67.57	48.84	73.34	65.91	73.11	65.45	67.56	61.53	70.96	67.79
35	51.16	24.51	72.14	51.29	76.98	71.62	77.65	71.59	69.09	63.47	78.57	72.14
40	54.37	35.71	74.65	54.10	81.29	73.94	83.19	78.98	77.39	69.77	86.28	79.00
45	55.39	37.68	77.47	61.19	84.70	79.36	87.59	84.23	81.58	74.08	83.36	83.94
50	58.80	46.15	82.75	70.58	88.46	85.54	92.51	89.58	85.24	77.85	87.30	85.72
55	60.41	54.13	85.99	79.62	95.80	88.90	97.26	94.14	88.93	84.11	92.61	92.80
60	56.15	60.65	93.86	87.74	97.19	93.02	**99.82**	**99.45**	87.09	90.80	95.99	95.35

Lornoxicam Biphasic Release TSGRT

Preformulation study of Lornoxicam Biphasic Release TSGRT

The bulk density and tapped density of the formulation ranged from 0.4878 – 0.6060 g/ml, 0.625 – 0.7262 g/ml respectively. The compressibility index and Hausner ratio ranged from 15.14 – 23.68 % and 1.1785 – 1.3103 respectively, signifying satisfactory flow property which was further confirmed by the angle of repose values ranging from 33.80°- 35.35° as shown in (**Table 6**) [9].

Characterization of Lornoxicam Biphasic Release TSGRT

The average weight of tablets ranged from 0.6462 to 0.6499 g for all the formulations which compiled with the monograph specification limit of ± 5%. As a measure of mechanical strength, these formulations exhibited satisfactory hardness of 4.2 to 4.8 kg/cm² and the same fact was further supported by friability of less than 1 %. The Drug content of all formulations ranged between 99.37 to 104.27 % and which was within the standard limits are showed in (**Table 7**) [11].

Table 6: Micrometric properties of Lornoxicam Biphasic Release TSGRT

Formulation Code	Bulk Density* g/cm³	Tapped density* g/cm³	Carr's Index (%)	Hausner Ratio	Angle of Repose (degree)
Buffer Layer	1.3157±0.013	1.3888±0.013	5.26±0.029	1.0555±0.015	31.70°
Immediate Layer	0.7142 ± 0.021	0.9523 ± 0.019	25.00±0.029	1.333±0.019	34.16°
FS_1	0.5263 ± 0.031	0.6896 ± 0.009	23.68±0.056	1.3103±0.032	34.85°
FS_2	0.5263 ± 0.014	0.6896 ± 0.006	23.68±0.061	1.3103±0.045	34.82°
FS_3	0.5555 ± 0.012	0.6896 ± 0.017	19.44±0.079	1.241±0.067	34.48°
FS_4	0.5882 ± 0.029	0.7142 ± 0.018	17.64±0.012	1.2142±0.078	33.80°
FS_5	0.6060 ± 0.026	0.7142 ± 0.024	15.14±0.032	1.1785±0.090	33.88°
FS_6	0.4878 ± 0.029	0.625 ± 0.026	21.95±0.052	1.2812±0.081	35.03°
FS_7	0.5882 ± 0.018	0.7262 ± 0.029	19.00±0.043	1.2346±0.089	33.82°
FS_8	0.5463 ± 0.019	0.6921 ± 0.030	21.06±0.056	1.2668±0.090	35.35°

***Mean ± SD (n=3)**

Table 7: Post compression parameters of Lornoxicam Biphasic Release TSGRT

Formulation code	Thickness (mm) [a]	Hardness (kg/cm²) [a]	Friability (%) [b]	Weight Uniformity (g) [b]	% Drug content [b]
FS_1	5± 0.0012	4.8±0.401	0.144 ± 0.024	0.6495±0.0080	103.18 ± 0.241
FS_2	5± 0.0022	4.4±0.489	0.115 ± 0.012	0.6488±0.0069	100.14 ± 0.311
FS_3	5± 0.0011	4.8±0.401	0.183 ± 0.018	0.6499±0.0069	99.37 ± 0.134
FS_4	5± 0.0027	4.6±0.489	0.208 ± 0.019	0.6479±0.0079	100.60 ± 0.121
FS_5	5± 0.0024	4.2±0.401	0.058 ± 0.028	0.6462±0.0035	104.27 ± 0.089
FS_6	5± 0.0015	4.4±0.489	0.106 ± 0.022	0.6491±0.0071	102.59 ± 0.157
FS_7	5±0.0021	4.4±0.400	0.132 ± 0 .009	0.6484±0.0079	99.81 ± 0.189
FS_8	5± 0.0014	4.4± 0.412	0.106 ± 0.013	0.6489±0.0082	100.87 ± 0.096

Mean ± SD ([a]n=5, [b]n=3)

In-vitro Dissolution Studies

The percentage cumulative drug release from all formulations of Lornoxicam Biphasic release TSGRT are shown in (**Table 8 and Figure 4**).

Though the formulation FS_1 (Xanthan gum: HPMC K4M, 4:1) released 99.28 % of Lornoxicam in 24 hours, it released 79.06 % in 12 hours which was not as per specifications for controlled release of drug. However the formulation FS_8 (Xanthan gum: Ethyl Cellulose, 4:1) release 99.47 % of Lornoxicam in 24 hours with 69.25 % of lornoxicam release in 12 hours which was within the specified limit to be released i.e. below 70 % in 12 hours [6]. Thus the formulation FS_8 was taken as optimized formulation.

TSGRT with Lornoxicam biphasic release and Lansoprazole immediate release

The optimized formulations F_1 and FS_8 were combined together to develop Trilayer Swelling Gastro Retentive Tablets with Lornoxicam biphasic release and Lansoprazole immediate release. The post compression parameters of the developed TSGRT were depicted in table 9 and are within the standard limits [11], i.e. the average weight was 0.6484 g (±5 %), Hardness was 5.2 kg/cm² (withstand mechanical stress), Friability was 0.35% (<1 %) and the drug content of Lornoxicam and Lansoprazole was 99.58 % and 98.18 % respectively (90 to 110 %). The formulated Trilayer tablets were shown in (**Figure 5**).

In-vitro Dissolution profile of formulated Trilayer swelling gastro retentive tablets is given in figure 6.

The Lansoprazole is released completely at the end of 50 minutes, whereas 25 % of Lornoxicam released within 50 minutes providing loading dose. 52.78 % of Lornoxicam was released at 8th hour (20 % < Q < 60 %). 69.63 % of Lornoxicam was released at 12th hour (<70%) and the release was extended for 24 hours [6].

The dissolution data of optimized formulation was fitted into several release kinetics and the regression coefficient values and n value are shown in the (**Table 10**). This shows that the release follows Zero order release kinetics and the 'n' value of 1.2431 indicates super case II non-fickian transport [13].

Table 8: Cumulative % drug release of Lornoxicam biphasic TSGRT

Time in hours	Cumulative % drug release							
	FS_1	FS_2	FS_3	FS_4	FS_5	FS_6	FS_7	FS_8
0.1666	6.82	6.21	12.52	4.00	6.33	9.52	6.04	5.70
0.3333	10.58	8.66	23.80	9.58	11.11	16.99	10.02	11.75
0.5	18.69	16.39	26.18	17.76	17.40	21.78	18.40	19.52
0.6664	21.35	22.81	26.59	22.53	22.66	21.65	23.14	23.72
0.833	22.51	24.90	25.83	27.10	27.27	25.71	24.79	24.10
1	25.46	28.30	34.81	31.33	31.12	26.36	25.21	26.78
2	29.88	29.99	35.00	36.66	44.07	40.33	28.48	30.19
3	32.78	39.25	39.43	43.08	53.00	44.69	33.58	34.21
4	36.76	42.91	34.29	47.74	48.02	53.44	38.38	36.24
5	42.52	47.24	37.07	53.53	52.84	59.01	42.77	39.35
6	48.84	51.20	49.65	60.27	58.62	71.06	46.01	42.34
7	55.58	53.74	54.03	67.31	60.88	76.23	48.56	47.01
8	59.78	57.07	56.58	69.32	64.82	79.75	54.50	51.06
9	67.15	69.16	58.12	76.92	79.40	86.02	60.43	54.64
10	71.76	77.08	72.45	76.28	86.77	87.58	63.08	60.11
11	76.20	79.64	91.53	85.32	100.15	91.63	68.73	64.39
12	**79.06**	89.08	95.67	89.87		104.11	75.29	**69.25**
16	82.14	93.11	110.53				83.67	74.91
18	85.35	95.34					89.86	77.72
20	91.12	97.89					94.72	80.74
22	95.36						100.06	90.80
24	**99.28**							**99.47**

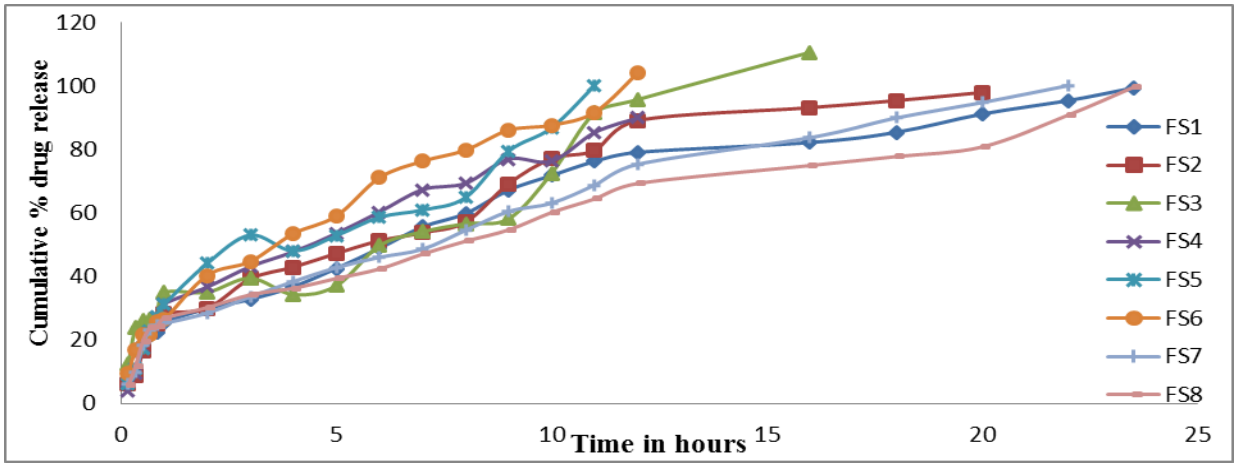

Figure 4: Cumulative % drug release of Lornoxicam Biphasic release tablets

Table 9: Post compression study of TSGRT

PARAMETERS		OBSERVATION
Uniformity of Weight (g) [b]		0.6484± 0.0034
Thickness (mm) [a]		5 ± 0.0023
Hardness (kg/cm²) [a]		5.2± 0.40
Friability (%) [b]		0.35 ± 0.29
Drug Content (%) [b]	**Lornoxicam**	99.58 ± 0.19
	Lansoprazole	98.18 ± 0.31

Mean ± SD ([a]n=5, [b]n=3)



Figure 5: Formulated Trilayer Gastro retentive tablets

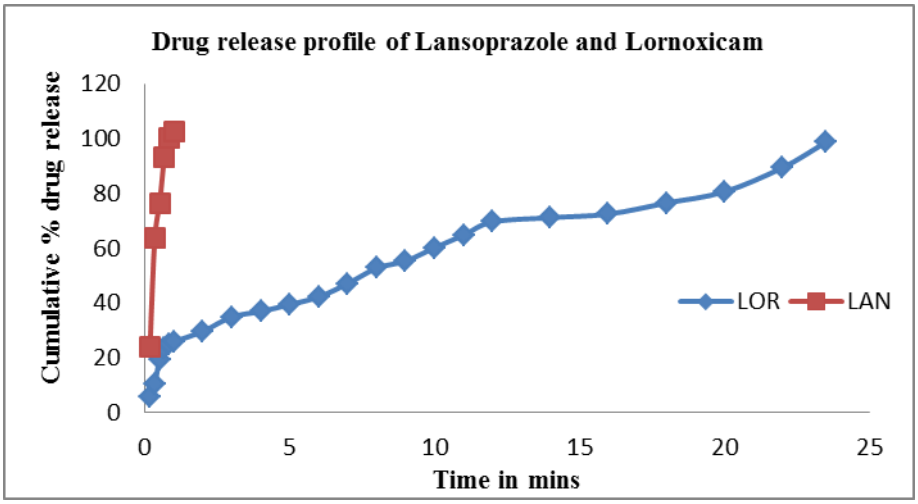

Figure 6: Dissolution data of developed TSGRT containing Lornoxicam and Lansoprazole

Table 10: Release kinetics of TSGRT

Release Kinetics type	Zero order	First order	Higuchi	Hixson	Korsmeyer Peppas	'n'
	0.9753	0.781	0.9375	0.9173	0.9475	1.2431

The Swelling study of TSGRT was given in (**Table 11**), showed that the swelling index of the tablet increases with increase in time upto 12 hours and at the end of 24th hour swelling index of tablet is reduced, this may be attributed to the fact that the erosion of biodegradable polymer Xanthan gum. This indicates that the drug will remain in gastric region till drug is released completely from the delivery system and promotes evacuation after its release.

Table 11: Swelling index of TSGRT

Time in Hours	% Swelling
0	0
1	161.33
2	212.66
3	323.94
4	410.00
6	554.00
8	692.19
10	745.66
12	826.23
24	629.66

CONCLUSION

The prepared tablets showed satisfactory results for various evaluation tests such as tablet dimension, hardness, friability, weight uniformity, drug content and *in-vitro* dissolution study. The swelling index of the tablet shown that the Psyllium husk (radial swelling polymer) in the formulation increased tablet dimension so that it can withstand migrating myoelectric cycle in gastric region, ethyl cellulose a hydrophobic polymer maintains the integrity of tablet and retards the drug release along with xanthan gum. The above facts showed that Trilayer tablets of lornoxicam and lansoprazole can offer better patient compliance and effective therapy in symptomatic treatment of Arthritis.

ACKNOWLEDGEMENTS

I sincerely acknowledge my thanks to Mr. S Balamurugan, Drug Inspector for arranging me Lornoxicam and Lansoprazole from Glenmark and Orchid healthcare ltd. respectively.

REFERENCES

1. Victoria Ruffing RN and Clifton O Bingham. Rheumatoid Arthritis. [online]. 2012 Nov 28; [5]. Available from: http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-symptoms/
2. Joo Hyun Lee and In Koo Chun. Effects of various vehicles and fatty acids on the skin permeation of lornoxicam. Journal of Pharmaceutical Investigation. 2012; 42: 235-241.
3. Frank L Lanza, Francis KL Chan and Eamonn MM Quigley. Prevention of NSAID – related ulcer complications. American Journal of Gastroenterology. 2009 feb 24; 104: 728-738.
4. Bruce T Vanderhoff and Rundsarah M Tahboub. Proton pump inhibitors: An update. American Family Physician. 2002 jul 15; 66(2): 273-281.
5. Sampath Kumar KP, Debjit Bowmik, Chiranjib, Magret Chandira and Tripathi K K. Innovations in sustained release drug delivery system and its market opportunities. Journal of Chemical and Pharmaceutical Research. 2010; 2(1): 349-360.
6. Sathiyaraj S, Devi R and Hari VB. Lornoxicam gastro retentive floating matrix tablets: Design and *in-vitro* evaluation. Journal of Advanced Pharmaceutical Technology and Research. 2011 jul-sep; 2(3): 156-162
7. Sonia Dhiman, Thakur Gurjeet Singh, Ashih Kumar Rehni, Surbi Sood and Sandeep Arora. Gastro retentive: A controlled release drug delivery system. Asian Journal of Pharmaceutical and Clinical Research. 2011; 4(1): 5-13
8. Mohamed Shafee M, Kandasamy R, Omar Abdulgani T, Shaikh Saleem Z and Kondaguli Anand V. Immediate release composition of acid labile drugs (WO2011083402). World Intellectual Property Organization, Patent Scope. 2011 jul 14; [7]. Available from https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011083402
9. United States Pharmacopoeia, 30th edition NF 25-242. The Official Compendia of Standards. 643, Pharmacopoeial forum 31(3):909
10. Kodalkar Swapnil J, Khutale Rohan A, Salunke Sachin S, Mali Sachin S and Nadaf Sameer J. Implementation of time release technology in formulation development and evaluation of sustained release tablet of Lornoxicam. Indian Journal of Pharmaceutical and Biological Research. 2014 mar 20; 2(1): 68-75
11. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Ghaziabad, India: The Indian Pharmacopoeia Commission. 2010; 1: 192-194.
12. Beckett A H and Stenlake J B. Practical Pharmaceutical Chemistry. CBS Publishers and Distributors, New Delhi. 4th edn. 2007: 284-6.
13. Suvakanda Dash, Padala Narasimha Murthy, Lilakanta Nath and Prasanta Chowdhary. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Poloniae Pharmaceutica.* Drug research.2010; 67(3): 217-23.