The Pharma Innovation Journal 2020; 9(9): 12-20

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2020; 9(9): 12-20

www.thepharmajournal.com
Received: 03-07-2020
Accepted: 06-08-2020

Balkrishna Gaikwad
College of Pharmacy, Dr. A. P. J. Abdul Kalam University, Village, Post, Indore Bypass Rd, Arandia, Jhalariya, Madhya Pradesh, India

Sourabh Jain
College of Pharmacy, Dr. A. P. J. Abdul Kalam University, Village, Post, Indore Bypass Rd, Arandia, Jhalariya, Madhya Pradesh, India

Karunakar Shukla
College of Pharmacy, Dr. A. P. J. Abdul Kalam University, Village, Post, Indore Bypass Rd, Arandia, Jhalariya, Madhya Pradesh, India

Corresponding Author:
Sourabh Jain
College of Pharmacy, Dr. A. P. J. Abdul Kalam University, Village, Post, Indore Bypass Rd, Arandia, Jhalariya, Madhya Pradesh, India

Design, development and *in vitro* evaluation of colon specific, pulsatile drug delivery system of lornoxicam

Balkrishna Gaikwad, Sourabh Jain and Karunakar Shukla

Abstract
The intent of the present investigation is to develop colon targeted press coated Lornoxicam pulsatile release tablets that retard the drug release in the upper gastro intestinal system but progressively release in the colon. Lornoxicam core tablets were prepared by direct compression method and were compression coated with LM Amidated pectin, polycarbophil and guar gum. The formulation is optimized based on the *in vitro* drug release study and further evaluated for stability studies. The optimized formulations (CP5 and CP12) showed maximum lag period followed by progressive release (98.89±0.98 % and 99.08±1.15 % respectively for 15h). It was concluded that prepared colonspecific pulsatile release tablet of Lornoxicam was found to be satisfactory in terms of release of the drug after a predetermined lag time. Lag time of formulation can be modified by varying the ratio of LM Amidated Pectin to Polycarbophil and LM Amidated Pectin to Guar gum in coating blend. Development of pulsatile release compression coated tablets using combination of time dependent and pH sensitive approaches was suitable to target the Lornoxicam to colon.

Keywords: Pulsatile drug delivery, lag period, pH dependent release, lornoxicam, colon targeted drug delivery

Introduction
Colon-specific drug delivery by oral route has gained increased importance from the last two decades, to treat local diseases associated with colon and for potential delivery of drugs used to treat colon associated ailments [1, 2]. Traditionally, colon targeting is achieved using prodrug approach, pH-sensitive drug delivery, time-dependent delivery systems and microbial degradation methods using tablets, capsules, multiparticulates, microspheres and liposomes [3]. Combination of two approaches has greater flexibility in the design of site specific delivery to colon than single method. Combining both methods can result in the optimum formulation which shows no release during the initial lag period but releases the drug completely and in a sustained fashion within the residence time of the tablet in gastrointestinal tract [4]. In order to achieve the chronopharmaceutical design for the time controlled pulsatile type of colon targeted preparations, formulation design to control the lag time is prior to the immediate release of drug. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time (a period of no drug release). Though most delivery systems are designed for constant drug release over a prolong period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile time release systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first pass effect, drugs administered for diseases that follow chronological behavior, drugs having specific absorption site in GIT, targeting to colon, where night time dosing is require [5]. Colon specific drug delivery can be achieved by the development of coated matrix tablets or coating the directly compressed tablets, either by film coating or compression coating. Among these types of tablets compression coated tablets offer coating methodology free of solvents which is safe and inexpensive that doesn't require special coating equipment and the coating formed through compression offers higher stability as compared to film coating. Compression coating is a simple method as compared to other methods like coating of tablets with different polymers and chemical conjugation of the drug to achieve colon delivery [6]. Lornoxicam, also known as chlortenoxicam [7], is a member of the oxicam group of non steroidal antiinflammatory drugs (NSAIDs) with extremely potent anti-inflammatory and analgesic activities [8]. Lornoxicam is commercially available in the form of conventional immediate-release tablets (4 and 8mg), rapid-release tablets (8 mg),

and parenteral formulations (4mg/ml) for intravenous and intramuscular use. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis [9]. 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. However, lornoxicam's usefulness is limited due to its short half-life that ranges from 3 to 5 h [10, 11]. Added to that, lornoxicam shows a distinct pH-dependent solubility characterized by very poor solubility in acidic conditions present in the stomach. Thus, it remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration. The colon targeted pulsatile drug delivery has been utilized to develop controlled release formulation. 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 [12, 13].

Material and Methods

Material

Lornoxicam was obtained as a gift sample from Glenmark generics Ltd, Mumbai. Guar gum, Polycarbophil and pectin were acquired as gift samples from Matrix Laboratories, Hyderabad, India. Polacrilin Potassium was purchased from SD fine Chemicals, Mumbai. All other chemicals used were of analytical grade.

Methods

Pulsatile tablet formulation [14-18]

Core tablets formulation

The inner core tablets were prepared using drug (Lornoxicam) with microcrystalline cellulose (MCC, Avicel PH-101), polacrillin potassium and magnesium stearate by direct compression method. Drug, MCC and polacrillin potassium were dry blended for 20 min, followed by addition of magnesium stearate. The mixtures were then further blended for 10 min. The resultant powder blend was compressed using Single Punch Tablet Compression Machine (Cadmach Machinary, Ahmedabad) with 8mm punch and die to obtain the core tablet. Flat punch was used to make tablets of 100mg. The composition of all formulation is given in Table 1.

Table 1: Composition of Core Tablets

S. No.	Ingredients (Mg)	C1	C2	C3	C4
1	Lornoxicam	12	12	12	12
2	Microcrystalline cellulose	85	83	81	79
3	Polacrillin potassium	2	4	6	8
4	Magnesium stearate	1	1	1	1
	Total	100mg	100mg	100mg	100mg

Formulation of press-coated tablets

Coating blends were made using different ratio of polymeric combination of Pectin with Polycarbophil and Pectin with Guar Gum. Blends were lubricated with 1% magnesium stearate and used for tablet coating by direct compression method. The optimized core tablets were press-coated with 400 mg of mixed blend as given in Table 2 & 3. Two hundred mg of coating material was weighed and transferred into a 12 mm die then the core tablet was placed manually at the center. The remaining 200 mg of the coating material was added into the die and compressed using single punch table machine (Cadmach, Ahmedabad, India).

Table 2: Composition of coating blends of pectin and polycarbophil in different formulations

S. No	Ingredients (mg)	Formulation Code						
		CP 1	CP 2	CP 3	CP 4	CP 5	CP 6	CP 7
1	Pectin	400	320	280	240	200	120	00
2	Polycarbophil	00	80	120	160	200	280	400
Total		400	400	400	400	400	400	400

Table 3: Composition of coating blends of pectin and guar gum in different formulations

S. No	Ingredients (mg)	Formulation Code						
		CP 8	CP 9	CP 10	CP 11	CP 12	CP 13	CP 14
1	Pectin	400	320	280	240	200	120	00
2	Guar Gum	00	80	120	160	200	280	400
Total		400	400	400	400	400	400	400

Evaluation of core lornoxicam tablet and press coated tablets

Spectrophotometric estimation of lornoxicam

Lornoxicam was estimated by UV visible spectroscopy. Spectrophotometric estimation of Lornoxicam was carried out in methanol, 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4.

Preparation of standard stock solution in 0.1 N HCl, phosphate buffer pH 6.8 and pH 7.4

Accurately weighed 100 mg of lornoxicam was placed in 100 ml volumetric flask and dissolved in 100 ml of 0.1 N HCl, phosphate buffer pH 6.8 and pH 7.4. From this solution, 10 ml solution was withdrawn and further diluted to 100 ml with 0.1 N HCl, phosphate buffer pH 6.8and pH 7.4 to yield the standard stock solution of lornoxicam (100 µg/ml).

Construction of calibration curve in 0.1 N HCl, phosphate buffer pH 6.8 and pH 7.4

From the stock solution, 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 ml were withdrawn and diluted to 100 ml with 0.1 N HCl to yield concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/ml respectively. For phosphate buffer pH 6.8 and phosphate buffer pH 7.4 same procedures was followed. Absorbance of each solution was measured at 364 nm using UV visible spectrophotometer (Model no. UV 2401 PC, Schimadzu Corporation, Singapore). Samples were analyzed in triplicate and the average values were used for plotting the graph of absorbance versus concentration (µg/ml). Regression analysis was done on each beer's plot using Microsoft excel.

Drug-excipient compatibility study

The compatibility of drug with polymeric excipients of press coated tablets was performed using Fourier transform infrared spectroscopy (FTIR).

Evaluation of flow property of powder blends

Powder blends used for preparation of Lornoxicam core tablets and compression coated tablets were evaluated for flow property by measuring bulk density, tapped density, Carr's index, hausner's ratio and angle of repose.

Post compression evaluation of lornoxicam core and press coated tablets

Weight variation

Twenty tablets from each batch were individually weighed using electronic digital and average weight was calculated. Individual weights of the tablets were compared with the average weight according to the official method in Indian Pharmacopoeia, 2007.

Hardness

Six tablets from each batch were selected and tested for tablet hardness using Monsanto hardness tester. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture that causes the tablet to break was recorded.

Thickness

The thickness of ten tablets from each batch was determined using vernier calipers as per Indian Pharmacopoeia, 2007.

Friability

The friability of the twenty tablets from each batch was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. A pre-weighed sample (20 tablets) was placed in the friabilator and is subjected to 100 revolutions. Tablets were dedusted and reweighed. The % friability (F) was calculated using following formula:

$$F = (W1\text{-}W2 / W1) \times 100$$

Where,

W1 is the initial weight of the sample of twenty tablets before the test

W2 is the weight of the tablet after the test

Drug content

For determination of drug content, ten tablets were crushed into powder and powder equivalent to 45 mg of Lornoxicam was weighed and dissolved in methanol then filtered through syringe filter (Axiva SFCA25X, 0.45µm). Solution was analyzed for Lornoxicam content by spectrophotometrically by UV spectrophotometer (Thermo Scientific Evolution 201) at wavelength of 364 nm using methanol as blank.

Disintegration Test

Six tablets were selected randomly from each batch for the disintegration test. Disintegration test was performed in purified water using Electro lab Disintegrationtester. Disintegration time (DT) was measured for all tablets and expressed as Mean ± SD (n=3).

Swelling studies

One tablet from each press coated formulation was randomly selected, weighed individually (W1) and placed separately in petridishes containing 20 ml of phosphate buffer pH 7.4. After 6 h, the tablets were carefully removed from petridishes and excess water was removed using filter paper. The swollen tablets were reweighed (W2) and swelling index of each tablet was calculated using the following equation and expressed in percentage:

$$\text{Swelling index} = (W2 - W1)/ W1 *100$$

***In-vitro* drug release study of lornoxicam press-coated tablets**

In-vitro drug release studies were carried out using USP Type II dissolution apparatus (Electrolab, TDT-08L) in a 900 ml of dissolution media at a temperature of 37±10°C at 100 rpm. In order to simulate the pH changes along the GI tract, multimedia dissolution studies were performed. Three dissolution media with pH 1.2, 6.8 and 7.4 were sequentially used. Initially dissolution study was performed using 0.1 N HCl (pH 1.2) as dissolution medium for 2 hrs (since the average gastric emptying time is 2 hrs), than dissolution medium was discarded and replaced with phosphate buffer pH 6.8 and dissolution study was continued for next 3 hrs (average small intestinal transit time is 3 hrs). After 3 hrs, the dissolution medium was removed and replaced with phosphate buffer pH 7.4 for subsequent hours. At regular time intervals, 10 ml of sample was withdrawn and same amount replaced by fresh medium. Samples were suitably diluted and filtered through syringe filter (Axiva SFCA25X, 0.45µm). Drug amount released was analyzed spectrophotometrically by UV spectrophotometer (Thermo Scientific Evolution 201) at wavelength of 364 nm. All studies were carried out in triplicates. The time for which the tablet does not show any release of the drug is known as its lag time. The lag time can be estimated through the dissolution profile of the tablet. The study was carried out in triplicates.

Scanning electron microscopy (SEM)

Tablet samples (CP5 and CP12) were removed from the dissolution apparatus at predetermined time intervals (8 hr& 7 hr) and dried to remove moisture then, sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross – under scanning electron microscope (SEM) (Model No. 6380 – A).

Stability study

Stability study of an optimized formulation (CP5 and CP12) was carried out by storing the Tablets (wrapping in aluminum foil) at 40±2^{0}c and 75±5% relative humidity for 3 months. At an interval of 1 month, the Tablets were visually examined for any physical changes and in-vitro release data. The results of physical parameter study and dissolution profile of formulation (CP5 and CP12) put under stability study.

Result and Discussion

From the scanning of lornoxicam in pH 1.2 buffer (0.1N HCl), phosphate buffer pH 6.8 and phosphate buffer pH 7.4 λ max were found to be 364.00, 376.00 and 376.80 nm respectively. Figure 1-3. Physical mixture of drug and polymers was characterized by FTIR spectral analysis for any physical as well as chemical alteration of drug characteristics. From result,(Figure 4-6) it was concluded that there was no interference in the functional group as the principal peaks of lornoxicam were found to be unaltered in the drug-polymer physical mixture. The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablets. The blends of different compositions for preparation of core tablets were evaluated for Precompression parameters. All the Precompression parameters were found in prescribed limit and indicated good free flowing properties of

blends (Table 4). The core tablets of different compositions were prepared by direct compression method and subjected to various evaluation tests, such as hardness, friability, weight variation and drug content. All the post-compression parameters of core tablet were found within prescribed limit. The results are shown in Table 5. The press coated tablets were prepared by coating the core tablets using different coating blends and subjected to various evaluation tests, such as hardness, friability, weight variation and drug content Table 6. All the post-compression parameters were found within prescribed limit. From Table 7 & 8 was observed that, the formulation CP7 (312±2.78 %) and CP14 (321±2.85%) exhibited the highest swelling index. Swelling studies of all formulations showed that minimum swelling in pH 1.2 buffer (0.1 N HCl) which increased in phosphate buffer pH 6.8 and showed maximum swelling in phosphate buffer pH 7.4. The percentage water uptake was increased as the concentration of polycarbophil and Guar gum concentration were from 0.0w/w to 100.00% w/w in the coating layer. From the Table 9 & 10, it was observed that all press coated tablet showed lag time. Incorporation of core tablet into press coated tablet produce a lag time prior to drug release. The results of *in vitro* release studies of different formulations revealed that all the formulations showed lag time between 4 to 8 hrs. LM Amidated Pectin alone as an outer coating polymer was not able to achieve desired lag time.In all formulations press coated with LM Amidated Pectin with Polycarbophil and LM Amidated Pectin with Guar gum increase in lag time was observed as compared with batches coated with LM Pectin alone.Formulations CP5 and CP6 showed fast and higher drug release 98.89±0.98 % and 94.23±0.78 % respectively after lag time as compared to other batches. Formulations CP5 which showed maximum lag time i.e. 8 hrs and drug release of 98.89±0.98 % was selected as an optimized batch, this might be due to optimum concentration of LM Amidated Pectin with Polycarbophil (50:50). Formulations CP12 and CP13 showed fast and higher drug release 99.08±1.15 % and 95.82±0.96% respectively after lag time as compared to other batches. Formulation CP12 which showed maximum lag time i.e. 7 hrs and drug release of 99.08±1.15% was selected as an optimized batch. As the concentrations of Polycarbophil& Guar gum in the coating blends were increased, the lag time of different formulations was increased. The results are shown in Table 11, 12. SEM study confirmed both diffusion and erosion mechanisms to be operative during drug release from optimized formulation CP5 and CP12 shown in figure 7& 8. SEM photomicrographs of the press coated tablets taken at different time intervals after the dissolution experiment showed that coating was intact and pores had formed throughout the coating layer. SEM photomicrographs of tablet surface at different time intervals also showed that erosion of the outer coating layer increased with time. SEM photomicrographs of the fresh tablet did not show any pores but diameter of pores were increased with the increase in dissolution time. These photomicrographs also revealed the formation of gelling structure indicating the possibility of swelling of coating layer of tablet. The optimized formulation CP5 and CP12were kept for stability study Table 13, 14, it was observed that formulation CP5 and CP12were stable for period of 3 months at 40±2^{0}C and 75±5%RH.

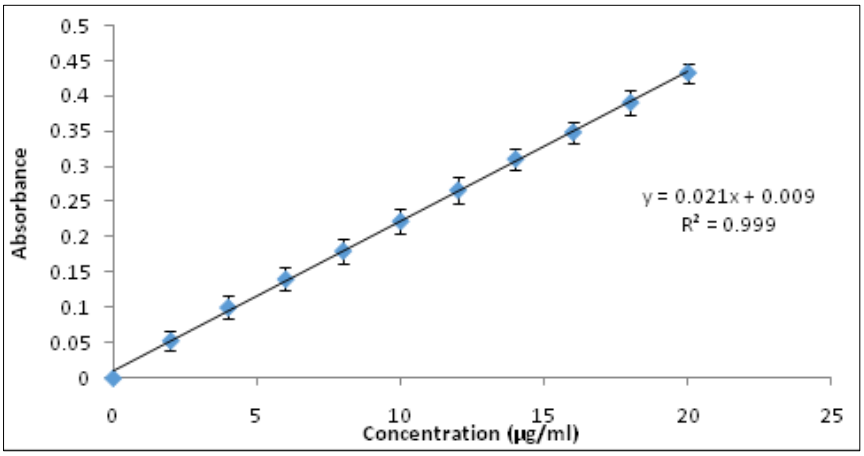


Fig 1: Standard calibration curve of lornoxicam in pH 1.2 Buffer (0.1 N HCl) at λmax 364.60 nm

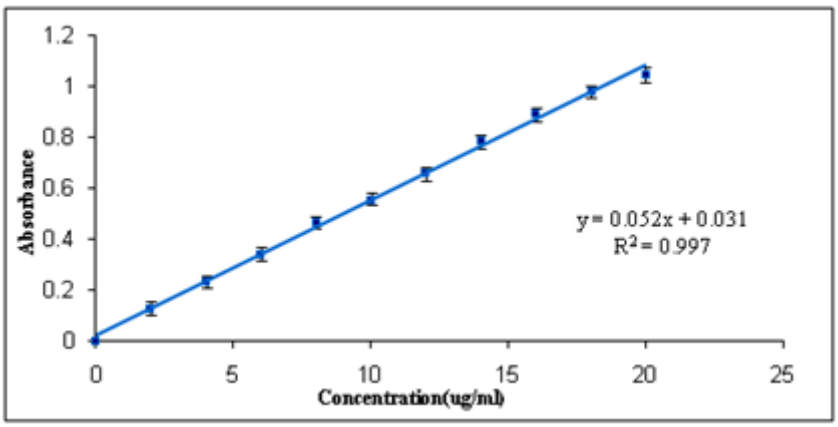


Fig 2: Standard calibration curve of lornoxicam in phosphate buffer pH 6.8 at 376.00 nm

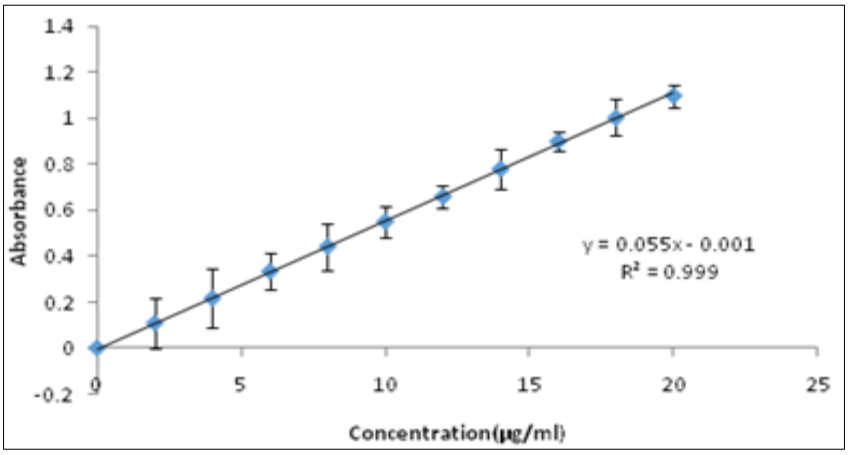


Fig 3: Standard calibration curve of lornoxicam in phosphate buffer pH 7.4 at 376.80 nm

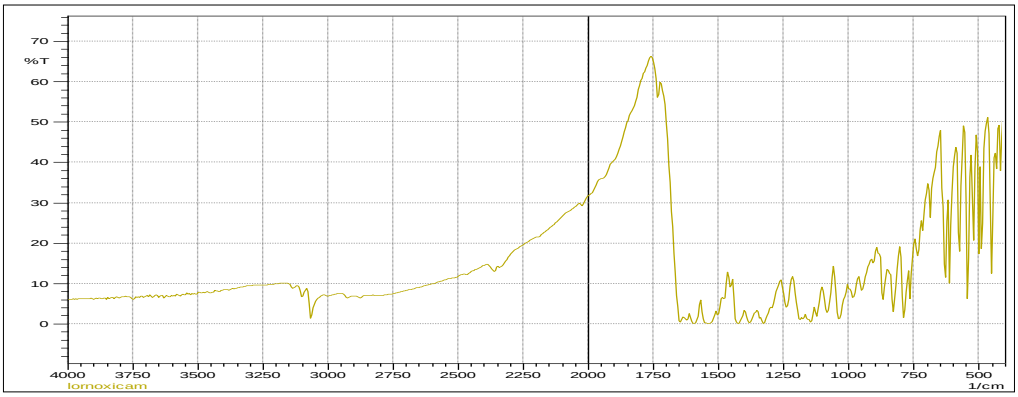


Fig 4: FTIR Spectra of Lornoxicam

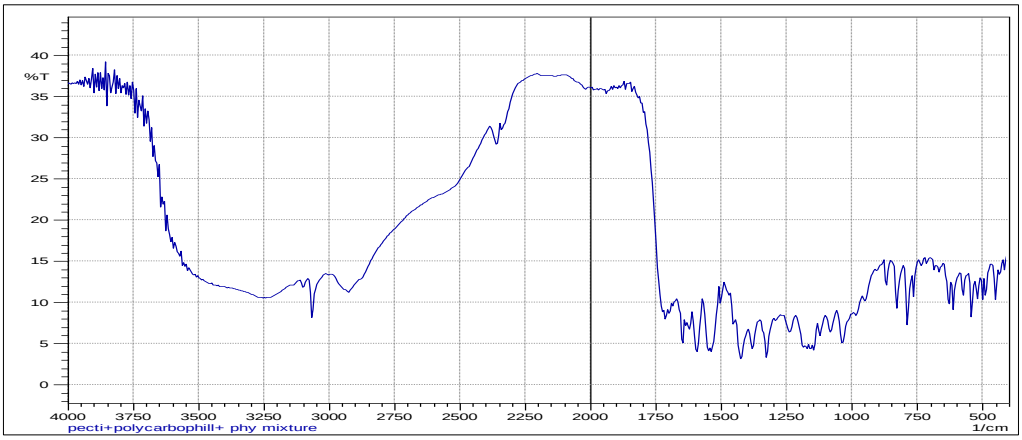


Fig 5: FTIR Spectra of Physical Mixture (Lornoxicam+Low Methoxy Amidiated Pectin+Polycarbophil +Polacrillin Potassium + MCC)

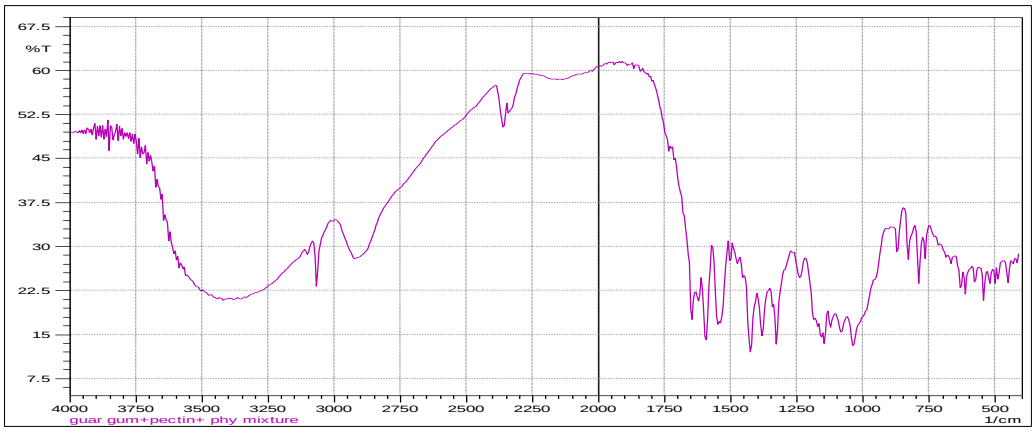


Fig 6: FTIR Spectra of Physical Mixture (Lornoxicam+Low Methoxy Amidiated Pectin + Guar Gum + Polacrillin Potassium + MCC)

Table 4: Precompression parameters of core tablet blend core and coating

Blend	Bulk Density (g/ml)*	Tapped Density (g/ml) *	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose (θ) *
Core tablet blend					
C1	0.58±0.02	0.71±0.01	18.53±1.17	1.22±0.05	$26^0$22'±1.01
C2	0.59±0.05	0.71±0.03	16.47±1.43	1.19±0.08	$27^0$24'±1.12
C3	0.62±0.07	0.71±0.07	16.29±1.22	1.19±0.04	$27^0$44'±1.33
C4	0.61±0.04	0.72±0.09	15.08±1.65	1.17±0.05	$28^0$89'±1.20
Coating blend in different formulations					
CP 1	0.443±0.03	0.520±0.03	14.80±1.82	1.17±0.003	24 ^{0}27'±1.23
CP 2	0.487±0.01	0.542±0.04	10.14±1.72	1.112±0.001	$24^0$33'±1.65
CP 3	0.486±0.05	0.542±0.06	10.33±1.32	1.115±0.03	$23^0$44'±1.46
CP 4	0.553±0.03	0.622±0.01	11.09±1.65	1.07±0.004	$22^0$39'±1.43
CP 5	0.487±0.03	0.542±0.05	10.14±1.30	1.112±0.006	$25^0$43'±0.65
CP 6	0.479±0.04	0.549±0.07	12.75±1.33	1.14±0.008	$22^0$23'±1.36
CP 7	0.486±0.05	0.542±0.02	10.33±1.22	1.15±0.001	$24^0$44'±0.55
CP 8	0.443±0.06	0.520±0.07	14.80±1.43	1.17±0.05	$24^0$27'±1.44
CP 9	0.476±0.08	0.533±0.08	10.69±1.53	1.119±0.07	27 ^{0}44'±1.82
CP 10	0.443±0.07	0.520±0.07	14.80±1.43	1.17±0.08	$26^0$39'±1.22
CP 11	0.401±0.03	0.501±0.05	21.52±0.98	1.274±0.007	$26^0$23'±0.04
CP 12	0.486±0.07	0.542±0.03	10.33±0.98	1.115±0.003	$23^0$67'±0.37
CP 13	0.479±0.06	0.549±0.01	12.75±1.50	1.14±0.09	$28^0$89'±0.54
CP 14	0.580±0.02	0.720±0.06	19.86±1.54	1.24±0.08	$29^0$47'±0.76

*Each value represent the mean ± standard deviation (n=3)

Table 5: Post compression evaluation of lornoxicam core tablets

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness Kg/cm^2	% Friability	Weight Variation(mg)	%Drug Content	Disintegration Time (Sec)
C1	1.73±0.02	7.96±0.03	3.26±0.02	0.685±0.09	98.3±7.55	96.23±0.91	121±0.33
C2	1.75±0.05	7.96±0.06	3.17±0.03	0.735±0.17	97.8±7.75	97.23±0.43	106±0.66
C3	1.72±0.08	8.04±0.05	3.24±0.08	0.632±0.06	99.5±6.2	96.88±0.77	89±0.66
C4	1.77±0.04	7.99±0.09	3.26±0.05	0.712±0.05	99.7±5.4	99.58±0.55	52±0.34

Table 6: Post-compression parameter for pulsatile tablet

Formulation code	Thickness* (mm)	Diameter* (mm)	Hardness* (kg/cm^2)	% Friability*	Weight Variation* (mg)	% Drug Content*
CP1	5.02 ± 0.02	11.99±0.002	6.2 ± 0.03	0.183 ± 0.06	502.3 ± 3.77	96.23±0.77
CP2	5.96 ± 0.05	11.96±0.001	6.2±0.01	0.223 ± 0.04	499.2 ± 2.96	94.60±0.33
CP3	5.16 ± 0.06	11.97±0.004	6.6±0.02	0.518 ± 0.02	501.8 ± 4.44	97.3±0.69
CP4	5.01 ± 0.02	11.97±0.005	6.4±0.06	0.113 ± 0.04	502.3 ± 4.88	95.04±0.89
CP5	6.01 ± 0.01	12.01±0.003	5.8±0.06	0.623 ± 0.02	502.4 ± 2.78	98.94±0.93
CP6	6.09 ± 0.03	12.0±0.002	6.2±0.03	0.331 ± 0.04	500.5 ± 4.78	98.13±0.94
CP7	5.02 ± 0.02	11.94±0.001	6.4±0.07	0.613 ± 0.05	499.9 ± 3.98	98.20±0.44
CP8	5.86±0.03	11.99±0.003	5.2±0.08	0.514 ± 0.05	502.3 ± 4.12	96.20±0.78
CP9	6.06 ±0.06	12.0±0.002	6.2±0.06	0.119 ± 0.02	501.7 ± 3.97	95.87±0.34
CP10	5.93±0.07	11.96±0.002	5.4±0.04	0.123 ± 0.03	505.2 ± 2.78	96.08±0.78
CP11	6.01 ± 0.02	12.01±0.004	6.6±0.03	0.399 ± 0.06	500.3 ± 3.87	96.03±0.56
CP12	5.95 ± 0.04	11.99±0.007	5.2±0.06	0.783 ± 0.01	501.2 ± 1.34	98.23±0.69
CP13	5.03±0.05	11.94±0.006	6.0±0.05	0.413 ± 0.03	499.0 ± 4.12	97.7±0.38
CP14	5.01 ± 0.04	12.01±0.001	6.6±0.002	0.683 ± 0.07	504.2 ± 2.67	94.23±0.58

Table 7: Percentage swelling indices of formulations CP1 to CP7

Time (Hrs)	% *Swelling Index						
	CP1	**CP2**	**CP3**	**CP4**	**CP5**	**CP6**	**CP7**
0	0	0	0	0	0	0	0
2	8.3±0.25	12.17±0.26	19.56±0.14	30.45±0.39	44.10±0.16	58.44±0.34	62.92±0.44
4	47.78±0.35	59.02±0.46	70.00±0.36	75.55±0.46	76.38±0.18	84.56±0.48	121.77±1.16
6	103.6±0.42	112.6±1.37	123.56±1.49	132.1±1.47	146.4±1.24	159.0±1.54	174.7±1.32
8	126.1±1.45	143.4±1.28	164.3±1.68	174.4±1.67	179.2±1.30	203.91±1.58	244.4±1.47
10	144.2±1.67	163.3±1.42	178±1.46	186.1±1.77	202.4±1.66	239.7±2.66	259.5±2.55
12	166.8±1.85	179.3±1.82	189.9±1.71	194.8±1.88	213.2±1.77	258.7±2.78	275.2±2.68
14	177.3±1.72	203.2±1.68	216.4±1.87	244.8±2.66	267.3±2.68	287.2±2.88	312.4±2.78

*Each value represent the mean ± standard deviation (n=3)

Table 8: Percentage swelling indices of formulations CP8 to CP14

Time (Hrs)	% *Swelling Index						
	CP8	**CP9**	**CP10**	**CP11**	**CP12**	**CP13**	**CP14**
0	0	0	0	0	0	0	0
2	8.3±0.15	19.85±0.38	29.03±0.38	33.4±0.36	49.86±0.23	63.20±0.46	92.58±0.45
4	47.78±0.24	58.02±0.47	72.00±0.28	76.83±0.43	83.06±0.32	95.25±0.44	106.02±1.46
6	103.6±1.34	115.3±1.34	129.3±2.43	143.2±1.33	149.28±1.46	154.3±1.36	174.7±1.33
8	126.1±1.44	139.2±1.43	148.2±1.57	158±1.64	174.1±1.45	189.3±1.54	244.4±1.56
10	144.2±1.47	159.3±1.56	177.2±1.48	193.6±1.72	209.4±1.67	231.5±1.63	241.13±1.65
12	166.8±1.66	179.3±1.63	189.1±2.67	224.4±1.84	259.04±1.74	264.3±1.64	276.14±2.73
14	177.3±2.69	213.7±2.73	229.4±2.84	247.2±2.92	274.3±2.95	294.12±2.94	321.06±2.85

*Each value represent the mean ± standard deviation (n=3)

Table 9: *In-Vitro* dissolution profiles of lornoxicam from formulations CP1- CP7

S. No.	Time (hrs)	% Cumulative Drug Release						
		CP1*	**CP2***	**CP3***	**CP4***	**CP5***	**CP6***	**CP7***
1	0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
2	1	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
3	2	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
4	3	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
5	4	4.23±0.32	4.48±0.36	4.12±0.27	4.32±0.34	0±0.00	0±0.00	4.02±0.47
6	5	52.4±0.45	6.34±0.45	5.77±0.43	6.43±0.55	4.12±0.43	4.23±0.42	5.33±0.49
7	6	78.71±0.56	70.01±0.56	67.33±0.49	7.14±0.46	5.45±0.53	5.11±0.52	6.76±0.58
8	7	92.51±0.47	75.05±0.76	75.39±0.78	70.55±0.69	6.54±0.67	6.28±0.68	7.14±0.74
9	8	99.8±1.89	82.87±0.49	83.87±0.95	76.53±0.79	7.22±0.69	7.32±0.53	34.87±0.62
10	9	-	91.11±0.88	88.58±0.87	80.58±0.67	72.91±0.78	39.91±0.78	49.43±0.58
11	10	-	97.11±0.98	96.58±0.79	87.81±0.93	77.25±0.89	65.58±0.85	59.20±0.28
12	11	-	-	-	97.25±1.22	82.23±0.99	74.83±0.68	65.23±0.49
13	12	-	-	-	-	87.49±0.87	86.39±0.98	70.55±0.79
14	13	-	-	-	-	93.64±1.80	90.78±0.89	76.44±0.41
15	14	-	-	-	-	98.89±0.98	94.23±0.78	80.37±1.11

Table 10: *In-vitro* dissolution profiles of lornoxicam from formulations CP8- CP14

S. No	Time (hrs)	% Cumulative Drug Release						
		CP8*	**CP9***	**CP10***	**CP11***	**CP12***	**CP13***	**CP14***
1	0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
2	1	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
3	2	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
4	3	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
5	4	4.23±0.32	3.88±0.36	4.55±0.39	4.67±0.24	4.13±0.23	4.56±0.32	4.55±0.35
6	5	52.4±0.45	57.11±0.45	5.56±0.49	5.98±0.32	5.33±0.33	5.24±0.44	5.22±0.44
7	6	78.71±0.56	70.54±0.54	69.44±0.59	71.5±0.45	6.45±0.42	6.95±0.65	6.77±0.44
8	7	92.5±0.47	74.64±0.54	77.92±0.38	77.3±0.43	7.12±0.54	36.44±0.77	7.87±0.34
9	8	99.8±0.86	85.04±0.79	81.66±0.48	83.77±0.56	72.33±0.67	55.23±0.89	34.23±0.55
10	9	-	90.44±0.87	88.18±0.55	90.77±0.78	76.82±0.45	65.67±0.78	51.20±0.58
11	10	-	99.33±1.11	94.23±0.76	95.00±0.66	79.23±0.78	71.74±0.59	63.03±0.64
12	11	-	-	97.16±0.89	98.75±0.98	84.76±0.89	78.13±0.87	69.09±0.79
13	12	-	-	-	-	90.83±0.98	85.55±0.86	75.66±0.83
14	13	-	-	-	-	95.58±0.85	90.89±0.67	80.74±1.13
15	14	-	-	-	-	99.08±1.15	95.82±0.96	86.83±0.91

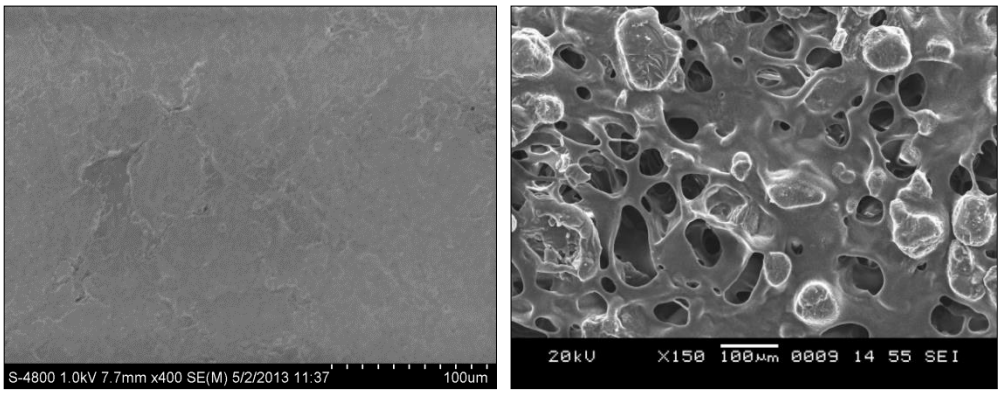
Table 11: Lag time of pulsatile formulation CP1 to CP7

S. No.	Formulation Code	Approximate Lag time
1	CP1	4 hrs.
2	CP2	5 hrs.
3	CP3	5 hrs.
4	CP4	6 hrs.
5	CP5	8 hrs.
6	CP6	8 hrs.
7	CP7	7 hrs.

Table 12: Lag time of pulsatile formulation CP8 to CP14

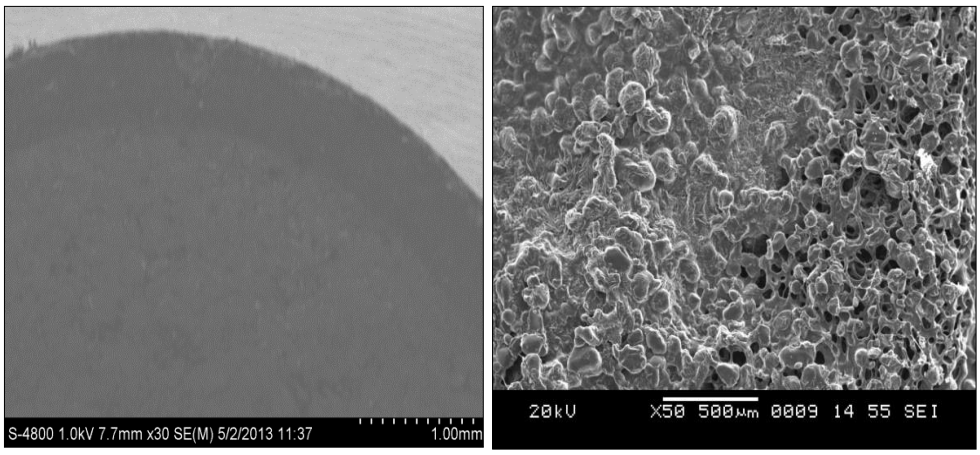
S. No.	Formulation Code	Approximate Lag time
1	CP8	4 hrs.
2	CP9	4 hrs.

3	CP10	5 hrs.
4	CP11	5 hrs.
5	CP12	7 hrs.
6	CP13	6 hrs.
7	CP14	7 hrs



A- 0 Hrs **B- 8Hrs**

Fig 7: SEM photomicrographs of optimized formulation CP5 showing surface morphology after A -0 hrs and B- 8 hrs of dissolution study



A- 0Hrs **B- 7 Hrs**

Fig 8: SEM photomicrographs of optimized formulation CP12 showing surface morphology after A -0 hrs and B- 7hrs of dissolution study

Table 13: Evaluation of formulation CP5kept under stability study

Parameters	0 Month	1 Month	2 Months	3 Months
Appearance	White	White	White	White
Thickness (mm) *	6.0±0.08	6.1±0.06	6.0±0.08	6.1±0.07
Hardness * (kg/cm^2)	5.8±0.05	5.6±0.06	5.8±0.02	5.8±0.03
% Friability*	0.134±0.01	0.140±0.06	0.140±0.03	0.150±0.05
Drug Content*	96.78±0.59	97.35±0.86	97.85±0.43	97.88±0.03

* Each value represents the mean ±standard deviation (n=3).

Table 14: Evaluation of formulation CP12 kept under stability study

Parameters	0 Month	1 Month	2 Months	3 Months
Appearance	White	White	White	White
Thickness (mm) *	6.0±0.05	6.0±0.04	6.4±0.06	6.2±0.05
Hardness * (kg/cm^2)	5.6±0.06	5.4±0.07	5.4±0.02	5.5±0.03
% Friability*	0.173±0.01	0.179±0.03	0.178±0.12	0.216±0.14
Drug Content*	95.67±0.61	96.23±0.63	96.12±0.69	97.86±0.86

* Each value represents the mean ±standard deviation (n=3)

Conclusion

The present study was aimed at the development of colon-specific release pulsatile tablets of Lornoxicam using press coating technique using different blends of LM Amidated Pectin with Polycarbophil and LM Amidated Pectin with Guar gum as a coating polymer. Formulations CP5 and CP12 showed desirable lag time of 8 hrs and 7 hrs followed by rapid drug release (98.89±0.98 %, 99.08±1.15%) respectively. This study revealed that the tablets were able to prevent release of Lornoxicam in simulated upper GI conditions and release at simulated colonic condition. It was concluded that prepared colon- specific pulsatile release tablet of Lornoxicam was found to be satisfactory in terms of release of the drug after a predetermined lag time Lag time of formulation can be

modified by varying the ratio of LM Amidated Pectin to Polycarbophil and LM Amidated Pectin to Guar gum in coating blend.

References

1. Vincent HL, Suman KM. Drug delivery-oral colon-specific. In: Swarbick J, Boylan CJ, ed. Encyclopedia of Pharmaceutical Technology New York: Marcel Dekker. 2002; 1:871-885.
2. Maroni A, Zema L, Del Curto MD, Foppoli A, Gazzaniga A. Oral colon delivery of insulin with the aid of functional adjuvants. Adv Drug Deliv Rev. 2012; 64:540-556.
3. Vemula SK, Veerareddy PR. Different approaches to design and evaluation of colon specific drug delivery systems. Int J Pharm Tech. 2009; 1:1-35.
4. Asghar LF, Chure CB, Chandran S. Colon specific delivery of indomethacin: effect of incorporating pH sensitive polymers in xanthan gum matrix bases. AAPS Pharm Sci Tech. 2009; 10:418-429.
5. Tekade BW, Sadaphal KP, Thakare VM, Gandhi BR. Formulation and evaluation of pulsatile drug delivery system for chronobiological disorder: asthma. Int J Drug Delivery. 2011; 3:348-356.
6. Hashem FM, Shaker DS, Nasr M, Saad IE, Ragaey R. Guar gum and hydroxy propyl methylcellulose compressed coated tablets for colonic drug delivery: *in vitro* and *in vivo* evaluation in healthy human volunteers. Drug Discov Ther. 2011; 5:90-95.
7. Merck & Co, Inc. The Merck index.13th ed.Whitehouse Station: Merck & Co. Inc, 2001.
8. Homdrum EM, Likar R, Nell G. Xefo Rapid: novel effective tool for pain treatment. Eur Surg. 2006; 38:342-52.
9. Kidd B, Frenzel W. A multicenter, randomized, double blind study comparing lornoxicam with diclofenac in osteoarthritis. J Rheumatol. 1996; 3:1605-11.
10. Skjoodt NM, Davies NM. Clinical pharmacokinetics of Lornoxicam. A short half-life oxicam. Clin. Pharmacokinet. 1998; 34(6):421-428.
11. Lin SZ, Wouessidjewe D, Poelman MC, Duchene D. *In Vivo* evaluation of indomethancin/cyclodextrin complexes. Gastrointestinal tolerance and dermal anti-inflammatory activity. Int. J Pharm. 1994; 106:63-7.
12. Lopes CM, José M. Lobo S, Pinto F, Costa PC. Compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen, AAPS Pharm SciTech. 2007; 8(3):76.
13. Maggi L, Machiste EO, Torre ML, Conte U. Formulation of biphasic release tablets containing slightly soluble drugs. European journal of pharmaceutics and biopharmaceutics. 1998; 48:37-42.
14. Shan-Yang L, Mei-Jane L, Kung-Hsu L. Hydrophilic excipients modulate the time lag of time-controlled disintegrating press-coated tablets. Am Pharm Sci Tech. 2004; 5(4):54.
15. Rane AB, Gattani SG, Kadam VD, Tekade AR. Formulation and evaluation of press coated tablets for pulsatile drug delivery using hydrophillic and hydrophobic polymers. Chem Pharm Bull. 2009; 57(11):1213-1217.
16. Janugade BU, Patil SS, Patil SV, Lade PD. Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system. Int J Chem Tech Res. 2009; 3:690-691.
17. Moon A, Kondawar M, Shah R. Formulation and evaluation of press-coated indomethacin tablets for pulsatile drug delivery system. J Pharm Res. 2011; 4(3):564-566.
18. Patil S, Pund S, Joshi A, Shishoo CJ, Shahiwal A. Chronomodulated press-coated pulsatile therapeutic system for acelofenac: optimization of factors influencing drug release and lag time. Chrono Physiology Ther. 2011; 1:1-10.