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Formulation and *In-Vitro* Evaluation of Pulsatile Release Tablet of Lornoxicam

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ABSTRACT

The aim of present investigation was to develop press coated tablet for pulsatile drug delivery of lornoxicam using hydrophilic and hydrophobic polymers. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. The press coated tablets containing lornoxicam in the inner core was formulated with an outer shell by different weight ratio of hydrophobic polymer (ethyl cellulose) and hydrophilic polymers (sodium alginate). The release profile of press coated tablet exhibited a lag time followed by burst release, in which outer shell ruptured into two halves. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. It was observed that lag time decreases with increasing concentration of sodium alginate. The optimized formulation (F5) comprised 10: 90%w/w concentration ratio of sodium alginate: Ethocel 10 cps with a 245 mg coating weight, and showed a desired lag time of 308 minutes, which mimics the fluctuating symptoms of rheumatoid arthritis, followed by rapid release of lornoxicam.

Keyword: Press-coated pulsatile tablet, lag time, ethyl cellulose, Sodium alginate, pulsatile drug delivery, Rheumatoid arthritis

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INTRODUCTION

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our body's function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production.[1] There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Coordination of biological rhythms and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.[2]

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the patho-physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. These systems are beneficial for the drugs having chronopharmacological behavior (where night time dosing is required), first pass effect and having specific site of absorption in gastro intestinal tract (GIT). From the viewpoint of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and hypercholesterolemia. The pathophysiology of arthritis and patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day.[3, 4]

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration. This novel system is not only rate controlled but is also time controlled. The dry-coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture.[5]

Lornoxicam, also known as chlortenoxicam, is a member of the oxicam group of NSAIDs with extremely potent anti-inflammatory and analgesic activities.[6] It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis.[7, 8] Like all other NSAIDs, lornoxicam mechanism of action is based on decreasing prostaglandin synthesis by inhibition of cyclooxygenase enzymes.[9] However, lornoxicam has a relatively superior gastrointestinal (GI) tolerability when compared with other NSAIDs which is advantageous in terms of fewer side effects.[10] Added to that, Lornoxicam shows a distinct pH-dependent solubility characterized by poor solubility in low pH conditions present in the stomach.[11]

The purpose of this study was to develop press coated tablets for pulsatile drug delivery of lornoxicam. The oral press coated tablet was developed to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. Press-coated tablet containing lornoxicam and other excipients in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer (ethyl cellulose) and hydrophilic polymers (sodium alginate). Ethyl cellulose (EC) is a well-known water-insoluble polymer that has been used as a rate-controlling membrane to regulate drug release.EC powder has been directly compressed to form compact EC in which plastic deformation is the predominant consolidation mechanism and Sodium alginate has an erosion property. These hydrophilic polymers were responsible for rupturing the outer coat.[12, 13]

MATERIALS AND METHODS

Materials

Lornoxicam was received as a gift sample from Micro Labs Ltd., Hosur, Tamil Nadu, India, Ethyl cellulose (Ethocel) 10 cps was a gift from Colorcon Asia Pvt. Ltd., Goa, India, Sodium alginate, Magnesium stearate, Aerosil were obtained from Finar chemicals pvt. ltd., Ahmedabad, India, Croscarmellose sodium, Micro crystalline cellulose, Lactose, were obtained from Orbicular pharmaceutical Tech. Pvt. Ltd., Hyderabad, India.

Drug excipients compatibility study

FT-IR spectra of drug and mixture of optimized formulation were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan, 8400s) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100. The disc was placed in the sample holder and scanned from 4000 to 400 cm^{-1}.

Experimental design

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in pulsatile release tablet. To study all possible combination of all factors at all levels (two factors, three levels) full factorial design was constructed. Two independent factors concentration ratio of Sodium alginate and Ethocel 10cps (X_1) and coating weight in mg (X_2) were set as three different levels. Whereas lag time (Y, minutes) was chosen as the dependent variables shown in Table 1.

Table 1: Formulation Design layout for 3^2 full factorial design

Batch Code	Coded factor level		Actual value	
	X_1	X_2	X_1 (%w/w ratio of Na alginate: Ethocel 10cps)	X_2 (coating weight in mg)
F1	-1	-1	5 : 95	210
F2	-1	0	5 : 95	245
F3	-1	1	5 : 95	280
F4	0	-1	10 : 90	210
F5	0	0	10 : 90	245
F6	0	1	10 : 90	280
F7	1	-1	15 : 85	210
F8	1	0	15 : 85	245
F9	1	1	15 : 85	280

A statistical model incorporating interactive and polynomial term was utilized to evaluate response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_{12}$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

Preparation of Lornoxicam press coated tablets

Preparation of Lornoxicam Core Tablet

The core tablets of lornoxicam were prepared by direct compression technique. As shown in Table 2 Lornoxicam, croscarmellose sodium, micro crystalline cellulose, lactose, magnesium stearate, Aerosil were mixed with each other according to the geometric dilution method. Rapid release core tablets were prepared by compressing all the ingredient shown in Table 2 using 6 mm flat faced punch and die cavity on a rotary tablet press (Rimek 10 station minipress, Ahmedabad, India).

Table 2: Formulation of core tablets

Ingredients	Quantity (mg)
Lornoxicam	8
Microcrystalline cellulose (Avicel PH-102)	14
Lactose	43.1
Croscarmellose sodium (5%)	3.5
Aerosil (1%)	0.7
Magnesium stearate (1%)	0.7
Total weight	70

Preparation of Compression-Coated Tablets

The core tablets were compression coated with different weight ratios (w/w) of Ethocel/sodium alginate mixtures. Half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed tablet using 6 mm flat faced punches placed in the centre on the above powder blend. The remaining equivalent powder was filled in the die, and the content was compressed using a flat faced punch, 10 mm in diameter, as summarized in Table 3.

Table 3: Formulation of factorial batches of Lornoxicam Tablet

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Lornoxicam core tablet	70	70	70	70	70	70	70	70	70
Compression Coating									
Ethocel 10 cps	199.5	232.75	266	189	220.5	252	178.5	208.2	238
Sodium alginate	10.5	12.25	14	21	24.5	28	31.5	36.5	42
Total coating wt.	210	245	280	210	245	280	210	245	280
Final weight	280	315	350	280	315	350	280	315	350

EVALUATION PARAMETER [14, 15]

Weight variation test

To study weight variation 20 tablets of each formulation were weight using a electronic balance and the test was performed according to the official method.

Hardness

For each formulation, the hardness of 3 tablets was determined using the validated Pfizer and Monsanto hardness tester.

Friability

Friability was performed by using Roche friabilator; normally pre-weighed 20 tablets were placed in the plastic chamber of friabilator and then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed.

$$\textbf{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness

The thickness of the tablets was determined by using vernier caliperse. Three tablets from each formulation were used and average values were calculated.

Content Uniformity of core tablet:

Ten tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 8 mg of lornoxicam, dissolved in 20 ml dimethyl formamide and the volume was adjusted to 100ml by addition pH 6.8 phosphate buffer in 100 ml volumetric flask. It was shaken for 15 minutes and filtered. 10 ml of the filtrate was diluted to 100 ml with phosphate buffer pH 6.8 in 100 ml volumetric flask. The absorbance of the resulting solution was measured at the maximum at about 376 nm. And found the amount of the lornoxicam using the calibration curve method.

Determination of tablet tensile strength:[16, 17, 18]

This is the stress needed to fracture a tablet by diametral compression. It is given by Fell and Newton as:

$$T = \frac{2P}{\pi Dt}$$

Where P is the fracture load that causes tensile failure of a tablet of diameter D, and thickness t. The fracture load (kg) of ten tablets was determined individually with a Monsanto hardness tester (Tab Machines, Mumbai, India), using the procedure of Brook and Marshal. The mean values of the fracture loads were used to calculate T values for the various tablets.

Rupture test[19]

The lag time of pulsatile release tablets is defined as the time when the outer ethyl cellulose coating starts to rupture due to swelling. It was determined visually using 900 ml of phosphate buffer pH 6.8, 37 ± 0.5◦C, and at 50 rpm in the USP paddle type (type II) dissolution apparatus.

In Vitro Dissolution Studies[20]

Dissolution studies were carried out using USP XXIII Apparatus II paddle type (Electrolab TDL-08L) at a rotation speed of 50 rpm and at 37 ± 0.5°C using 700 ml of 0.1N HCl (pH 1.2) for two hours, after which 200 ml of a 0.2M trisodium phosphate solution was added into the dissolution media and the pH was adjusted to 6.8. A 10 ml sample was withdrawn at 30 minutes time intervals and replaced by an equal volume of pre-warmed 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8 respectively. Samples withdrawn were filtered through whatmann filter paper (0.45 micron). The amount of lornoxicam released was analyzed at 374 and 376 nm for samples tested in 0.1N HCl and the phosphate buffer pH 6.8 respectively, using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). All dissolution experiments were done in triplicate.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies

Fourier Transformed Infrared Spectroscopy of lornoxicam, mixture of optimized formulation shown in Figure 1 & Figure 2. The characteristic peak at 3067 cm^{-1} corresponding to NH stretching. Intense absorption peak was found at 1646 cm^{-1} because of the CO stretch of carboxamide group other peaks were observed at 1596 cm^{-1} and at 1539 cm^{-1} and were assigned to bending vibrations of CC aromatic ring. The stretching vibrations of the SO_2N group appeared at 1147, 1160. Other prominent peaks appeared at 831 cm^{-1} corresponding to CCl stretching at 1041 cm^{-1} corresponding to CS stretch. In physical mixture the intensity of lornoxicam peak was reduced, due to presence of other excipients.[21]

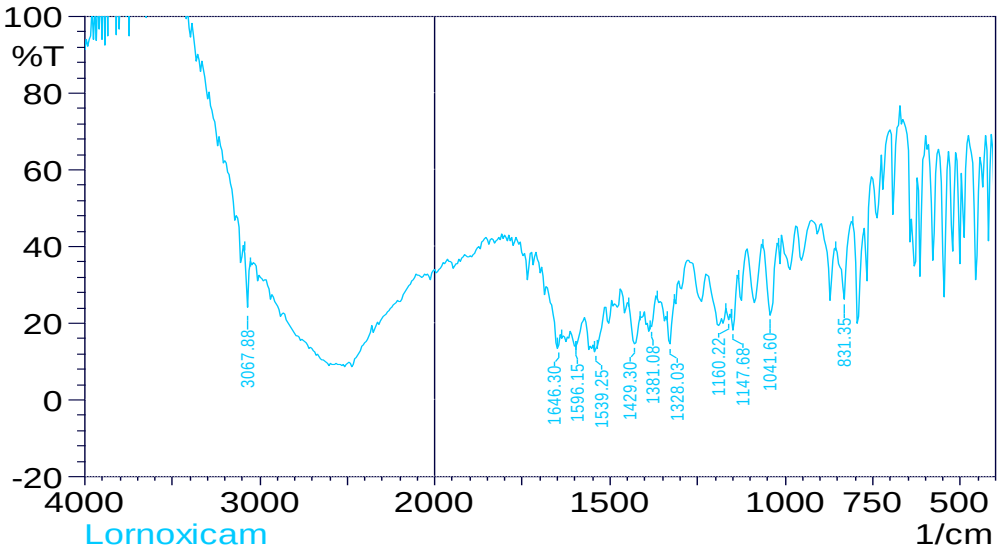


Figure 1: FT-IR spectra of pure Lornoxicam

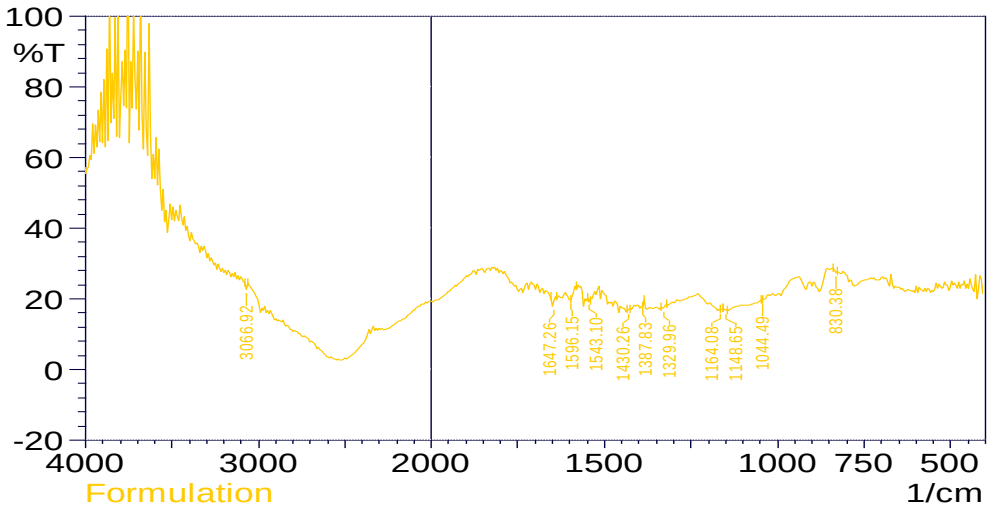


Figure 2: FT-IR spectra of optimized formulation

Characterization of tablets

The longitudinal and horizontal cross-sections of prepared compress coated pulsatile release tablet shown in Figure 3. Weight variation was found to be within IP limit. All the formulations showed uniform thickness. The thickness of the tablets was in the range of 3.22 to 4.15 mm. The hardness of the tablets were found to be in the range of 10.17-11.17 kg/cm^2. Tablet hardness is not the absolute indicator of the strength, another measure of tablets strength is friability and tensile strength. Conventional compressed tablets that loose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of all formulations was below 1% indicating that the friability is within the prescribed limits, while the tensile strength of batches F1 to F9 was found to be within the range 1.63 to 1.99 MPa, which is an indication of good mechanical resistance of the tablet. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet (Table 4). Drug content of core tablet was observed 98.93%w/w.

Figure 3: Photograph of longitudinal and horizontal cross-sections Press coated pulsatile tablet

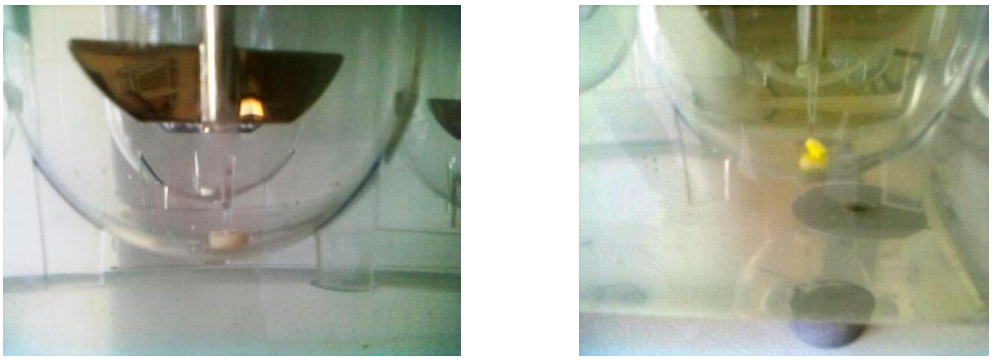
Table 4: Characteristics of prepared pulsatile release tablet of Lornoxicam

Formulation code	Thickness* (mm)	Friability (%)	Hardness* (kg/cm^2)	Tensile strength* (MPa)	Weight variation** (mg)	Lag time of Rupture* (Minutes)
Core tablet	2.06 ± 0.05	0.74	4 ± 0.1	2.06 ± 0.05	67.95 ± 3.50	-
F1	3.22 ± 0.02	0.16	10.17 ± 0.3	1.96 ± 0.04	281 ± 2.28	280 ± 3
F2	3.50 ± 0.02	0.13	10.33 ± 0.3	1.83 ± 0.05	316.2 ± 3.17	462± 3.51
F3	4.13 ± 0.02	0.19	10.83 ± 0.3	1.63 ± 0.05	349.9 ± 2.61	634 ± 3.61
F4	3.23 ± 0.01	0.12	9.83 ± 0.3	1.89 ± 0.06	279.3 ± 4.20	235 ± 5.59
F5	3.51 ± 0.01	0.16	10.50 ± 0.5	1.86 ± 0.09	313.3 ± 3.50	308 ± 4
F6	4.12 ± 0.03	0.11	11 ± 0.5	1.65 ± 0.09	348.9 ± 3.72	426 ± 7.81
F7	3.22 ± 0.02	0.13	10.33 ± 0.6	1.99 ± 0.10	279.8 ± 4.06	149± 4.51
F8	3.50 ± 0.04	0.19	10.67 ± 0.3	1.89 ± 0.07	313.9 ± 3.96	210 ± 4.58
F9	4.15 ± 0.01	0.16	11.17 ± 0.3	1.67 ± 0.05	348.4 ± 3.89	261 ±7.55

* Mean ± SD, Standard Deviation (n=3), ** Mean ± SD, Standard Deviation (n=20)

Rupture test

A prepared compress coated pulsatile release tablet of lornoxicam was release drug after rupturing outer coating due to erosion of sodium alginate from outer coat and breakdown of outer coating into two halves that shown in Figure 4.



(A) **(B)**

Figure 4: Rupture behavior of press coated pulsatile tablet of Lornoxicam at A) Initial t = 0 min and B) After t = 308 min.

***In Vitro* Dissolution Studies**

In vitro dissolution studies are valuable tools to judge quality and stability of dosage forms and are often used to predict in vivo performance. In vitro release studies were carried out for the formulations in both acidic and basic media to simulate in vivo conditions. The release studies were carried out at 0.1N HCl for 2 h, to mimic the acidic conditions prevailing in the stomach and for the remaining hours in basic medium, i.e., pH 6.8 (phosphate buffer), to mimic the environment in the small intestine. From the results of dissolution profile of factorial batches (Table 5, Figure 5) it was concluded that concentration ratio of sodium alginate: Ethocel and

coating weight had significant effect on lag time and after rupture of outer coat drug was release from PRTs. More than 80% of the drug was release in 1.5 hrs after rupture of coating from the optimized batches F1 to F9.

Table 5: Dissolution profiles of tablets for factorial design batches

Time (hours)	Cumulative percentage drug release (n=3)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.41	0.41	0.41	0.41	0.41	0.41	0.41	0.41	0.41
2	0.83	0.83	0.83	0.83	0.83	0.83	1.44	0.83	0.83
3	1.21	1.21	1.21	1.21	1.21	1.21	47.55	1.21	1.21
4	1.82	1.23	1.23	25.35	1.82	1.53	94.83	43.11	1.82
5	44.83	1.84	1.55	95.18	3.90	1.56	101.09	89.67	46.99
6	95.82	1.88	1.59	96.81	77.96	1.89	-	97.91	92.51
7	97.74	1.92	1.62	-	98.71	4.54	-	-	96.71
8	-	35.35	1.94	-	-	79.69	-	-	-
9	-	93.35	1.98	-	-	97.83	-	-	-
10	-	96.98	2.02	-	-	-	-	-	-
11	-	-	41.93	-	-	-	-	-	-
12	-	-	90.90	-	-	-	-	-	-
13	-	-	93.63	-	-	-	-	-	-

Standard deviation values of all batches were within the limit of ±5

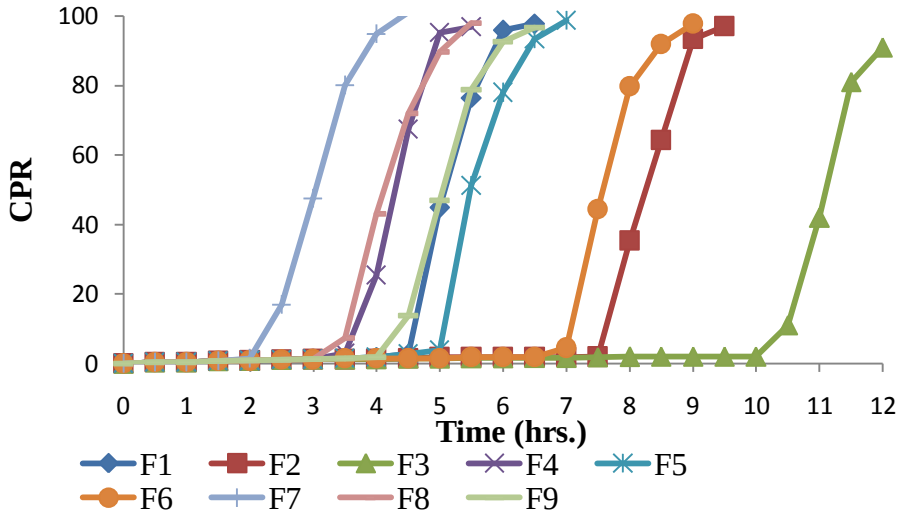


Figure 5: Dissolution profiles of tablets for factorial design batches

Comparison of dissolution profile of batch F4, F5 and F6 shows that with increasing the coating weight, the lag time of pulsatile release tablet increases. Coating weight was directly proportional to the lag time of rupture of PRTs because the larger amount of coating material produces tablets with higher thickness and longer path for buffer media to penetrate into the core. Comparison of dissolution profile of batch F2, F5 and F8 shows that with increasing the concentration of sodium alginate in outer coating decreases the lag time, because the hydrophilic

polymers used in this outer coating having ability to modulate the lag time. Sodium alginate increased in formulation leads to faster erosion which is responsible for breakdown of outer coating, so concentration of sodium alginate was inversely proportional to the lag time.

From the result of Dissolution of factorial batches, F5 release drug after lag time of 308 ± 4 minute, which is near to the said hypothesis of the study 300 minute. Thus, batch F5 was the optimized batch of the present study.

Statistical analysis

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). Table 6 shows the results of the Regression analysis, which was performed to identify insignificant factors. The high values of correlation coefficient for all variables indicate a good fit, i.e., good agreement between the dependent and independent variables.

Table 6: Regression output of 3^2 full factorial design

Full Model						
Full Model Equation	$Y = 320.22 - 126 X_1 + 109.5X_2 + 9.67X_{11} + 4.17X_{22} - 60.5X_{12}$					
R^2	0.9949					
Variable	Intercept	X_1	X_2	X_{11}	X_{22}	X_{12}
Coefficients	320.2222	-126	109.5	9.6667	4.1667	-60.5
P-value	0.000149	0.000401	0.000608	0.4928	0.7592	0.006253
Reduced Model						
Reduced Model Equation	$Y = 329.44 - 126 X_1 + 109.5X_2 - 60.5X_{12}$					
R^2	0.9937					
Variable	Intercept	X_1	X_2	X_{11}	X_{22}	X_{12}
Coefficients	329.4444	-126	109.5	-	-	- 60.5
p - value	1.6E-08	5.25E-06	1.05E-05	-	-	0.000495

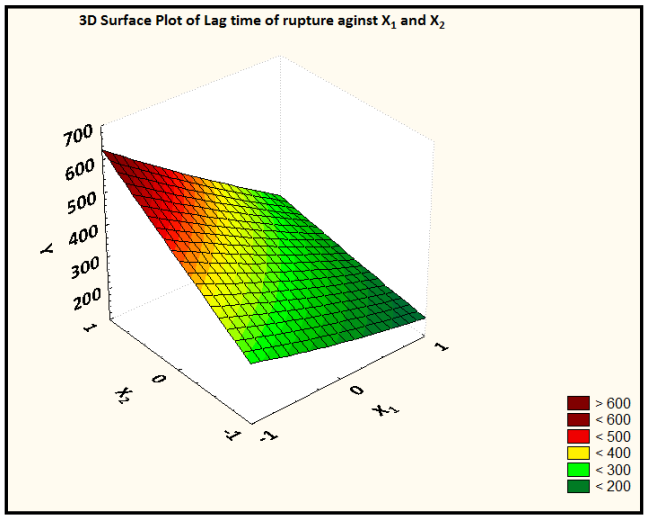


Figure 6: Response surface plot for lag time of rupture

The statistical analysis of the factorial batches was performed by multiple regression analysis and analysis of variance (ANOVA) using Microsoft Excel® 2007.

$$\mathbf{Y = 320.22 - 126\ X_1 + 109.5X_2 + 9.67X_{11} + 4.17X_{22} - 60.5X_{12}}$$ (Full Model Equation)

$$\mathbf{Y = 329.44 - 126\ X_1 + 109.5X_2 - 60.5X_{12}}$$ (Reduced Model Equation)

The full model for lag time of rupture was developed by using the coefficients. The significance level of coefficient b_{11} and b_{22} were found to be p = 0.4928 and 0.7592 respectively, hence it was omitted from the full model to generate the reduced model. The coefficients b_1, b_2 and b_{12} were found to be significant at $p < 0.05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{11} and b_{22} contribute significant information for the prediction of lag time of rupture or not. The results for testing the model in portions are shown in Table 7. The critical value of F for $\alpha = 0.05$ is equal to 9.55 (df = 2,3). Since the calculated value (F = 0.359) is less than critical value, it may be concluded that the interaction term b_{11} and b_{22} does not contribute significantly to the prediction of lag time of rupture and therefore can be omitted from the full model.

Table 7: Calculation for testing the model in portions

Lag time of rupture						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	182060.1	36412.02	118.2066	0.9949	**F_{cal}** = 0.359
RM	3	181838.5	60612.83	264.518	0.9937	
Error						**F_{tab}** = 9.55
FM	3	924.1111	308.037	-	-	
RM	5	1145.722	229.1444	-	-	**DF** = (2,3)

DF: degree of freedom, SS: sum of squares, MS: mean of squares, F: Fischer's ratio, R^2: regression coefficient, FM: full model, RM: reduced model

From the reduced model generated for lag time of rupture, it can be concluded that factor X_1 (concentration ratio of Sodium alginate: Ethocel 10 cps) has strong negative effect on response (lag time of rupture), while factor X_2 (coating weight) has strong positive effect on response (lag time of rupture). The interaction between X_1 and X_2 has negative effect on lag time of rupture. While combination of X_{11} and X_{22} should be avoided.

Surface response curve

To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Statistica 8.0 software. The response surface plots for factorial are depicted as Figure 6. The value of $P < 0.05$ was considered to be significant.

CONCLUSION

The present study demonstrates that lornoxicam from the formulated system could be delivered when needed most by design of the time-dependent modified press-coated tablet using a combination of hydrophilic polymer sodium alginate and hydrophobic polymer ethocel 10 cps. The lag time may be controlled by controlling press-coating weight as well as coating polymer ratio of Sodium alginate/Ethocel. The optimized formulation F5 gives a lag time of 5:08 h before rapid and transient release of the drug. Thus, if this formulation is administered at bedtime (10 pm), it may release the drug between 4–6 am, when the symptoms of rheumatoid arthritis are at its peak.

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