



# GASTRORETENTIVE CHRONOPHARMACEUTICAL FORMULATION OF LAFUTIDINE FOR EARLY MORNING ACID BREAKTHROUGH

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## ABSTRACT

The goal of the current study is to design a chronomodulated medicine delivery system for nocturnal acid situations. This strategy is based on a combination of floating and pulsatile principles. With this idea in mind, a floating-pulsatile drug delivery system of lafutidine was created to lengthen the time the dosage form, which has a lag phase followed by a burst release of the drug, stays in the stomach. Accordingly, floating pulsatile tablets were developed in three different steps viz. Preparation of drug-containing core tablets using a super disintegrant, pulsatile layer by compression coating using a mixture of hydrophilic erodible polymers like HPMC E5M and guar gum; and buoyant layer using gel-forming polymer like Carbopol 934P with sodium bicarbonate and citric acid. The effects of the independent variables—the weight ratio of HPMC E5M: Guar gum and the total weight of coating—on the dependent variables, the drug release lag time and cumulative percent drug release at 6 h, were studied using the response surface approach. Developed formulations were evaluated for buoyancy, dissolution, and stability studies. Results indicated the dependence of lag time on the ruptured nature of polymers used. Drug release lag time of optimized batch was found to be  $6.20 \pm 0.35$  h with  $98.45 \pm 2.24$  % of drug release at the end of 8 h. Accelerated stability studies suggested stability of dosage form for at least one month. In order to achieve the best treatment efficacy and increase patient compliance, a successful, stable, floating, pulsatile tablet was created. It can be administered after dinner at around 22:00 h.

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## Introduction

The benefit of increased patient therapeutic effectiveness and compliance is helping the chronomodulated drug delivery system acquire wider acceptability. In accordance with the pathophysiological requirements of the disease, the delivery system administers a pulsatile medication at a precise time [1-4]. The systems are made to provide programmable lag phases that come before a drug's rapid release by releasing it repeatedly or over a long period of time. The medicine is typically released in the lower half of the body after a delay of 5–6 hours with traditional pulsatile oral drug administration [5-8]. However, the viscous content of the region may produce a hindrance in the diffusion process of the drug and also enzymatic degradation of the drug may take place because of colon microflora present [9, 10]. This may result in bioavailability and in-vivo variability problems. On the contrary, the gastroretentive drug delivery system is designed to be retained in the upper region of GIT for a prolonged time and is not affected by gastric emptying rate, local environment, and/or variability in pH. The dosage form is also beneficial for drugs that are either absorbed from the stomach region or are delivered locally in the stomach. The development of floating-pulsatile drug delivery systems was influenced by these factors [11-16]. Normal gastric acid secretion exhibits a diurnal cycle with a sharp increase in stomach acidity when the gastric pH level falls significantly below 4 for at least 1 hour at midnight [17]. According to the study, approximately 70% of patients appear to be resistant to even high dosages of proton pump inhibitors (PPI), which are used to treat stomach acidity. As a result, PPI fails to effectively control nocturnal acid production [18]. This limitation can be overcome by making the drug available at the highest concentration during the peak h of acid secretion in the early morning h. The aforementioned goal is achieved through a pulsatile/delayed/chronomodulated drug delivery system, which facilitates drug release after a specified, predetermined lag period.

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An experimental design is an experimental set-up to concurrently estimate several factors at the given number of levels in a predefined number of experiments [19]. Response surface methodology (RSM) aids in the development and optimization of product parameters with the least amount of testing and time to produce an effective and economical ideal end product [20]. A three-level two-factor full factorial design consists of all possible combinations between the factors and their levels leading to 9 experiments, including one center point.

Lafutidine (LFN), ( $\pm$ )-2-(furfuryl sulfinyl)-N-(4-[4-piperidinomethyl]-2-pyridyl)oxy-(Z)-2-butenyl acetamide, is a histamine H<sub>2</sub>-receptor antagonist having biological half-life  $1.92 \pm 0.94$  h [21]. It contains a window that allows nutrients to be absorbed from the upper gastrointestinal tract (GIT). It travels from the systemic circulation to the gastric cells and quickly binds to histamine H<sub>2</sub>-receptors because it is more soluble in the gut pH [22]. Famotidine, ranitidine, and cimetidine all have receptor binding affinities that are 2-80 times lower than LFN [23]. LFN's floating pulsatile drug delivery system will effectively deliver the therapeutic concentration at the site of absorption by releasing the medication in a burst after a predetermined delay in the upper GIT.

The current study reveals the creation of a straightforward floating pulsatile LFN tablet that can be taken in the morning to prevent gastric acid breakthrough. To examine the impact of independent variables on dependent factors and to produce the best batch, a full factorial design with two components and three levels was used. Further regression analysis was carried out to statistically analyze the data.

## Materials and Methods

### Materials

LFN was obtained as a gift sample by Vapi Care, Vapi, India. Crospovidone was obtained from Sun Pharma, Silvassa, India. HPMC E5M and HPMC E15M were gifted by Colorcon, Goa, India. Carbopol 934 and lactose monohydrate were purchased from Thomas Baker, Mumbai, India. Sodium bicarbonate, citric acid, xanthan gum, and guar gum were obtained from Astron Chemicals, Ahmedabad, India. Methanol and other reagents used were of standard analytical grade. Double distilled water was used throughout the study.

### Methods

#### Formulation of Rapid Release Core Tablet (RRCT)

The core tablets containing LFN (10 mg per tablet), crospovidone (C1)/sodium starch glycolate (C2)/croscarmellose sodium (C3) (15 % w/w), lactose monohydrate (75 mg), magnesium stearate (5 mg) and talc (5 mg) were prepared by direct compression technique. Initially, the powder blends of the core tablet ingredients were mixed in the double cone blender for 10 min. The core tablets (diameter, 6 mm; flat; average tablet weight, 100 mg) were compressed using the multi-station tablet compression machine (Hardik Engineering, Ahmedabad, India).

#### Formulation of Floating Pulsatile Tablet (FPT)

RRCT was taken as core, respectively and the pulsatile tablet was prepared by a press coating method. Dry coating of optimized RRCT was done by using different grades of HPMC (E5M and E15M) and natural polymers at different concentrations (**Table 1**) (T1 to T7 batches). Magnesium stearate (5 mg) and talc (5 mg) were added to the coating layer along with polymers. Sodium bicarbonate (20 mg) and citric acid (10 mg) were added to the floating layer along with Carbopol 934. Dry coated tablets (diameter, 10 mm; flat; average tablet weight, 460 mg) were prepared by placing 50 % of pulsatile release layer in the die cavity of 10 mm, optimized RRCT was placed in the center of it and then other 50 % of retardant material was added to cover the core tablet. Finally, the buoyant layer was placed on it and compressed using the multistation tablet compression machine (Hardik Engineering, Ahmedabad, India) [24-26].

#### Drug-Excipient Compatibility Study

The compatibility study of the drugs and excipients was checked out using the FTIR spectrophotometer. The sample compartment was purged with nitrogen gas before runs, and filled with dry desiccant to absorb any moisture present. Samples were prepared by physically mixing the drug and different excipients separately in the ratio of 1:1 and were kept for a month at 40°C/75% relative humidity. Then the mixture was mixed thoroughly with dry KBr (IR grade) in the ratio of 1:5 (mixture and KBr) and triturated in a small size mortar pestle. Then pellet of the mixture was prepared by compressing the powder in a hydraulic press. Pure KBr powder was used as background, and for baseline correction. Samples were scanned in the region of 4000-450 cm<sup>-1</sup> using an FT-IR spectrophotometer.

#### Dissolution Studies of LFN Pulsatile Tablets

Dissolution of LFN pulsatile tablets was performed in a USP dissolution tester (Type II), paddle method (Electrolab Dissolution Tester, India) under stirring at 50 rpm. The dissolution media consisted of 900 ml of 0.1 N HCl at  $37 \pm 0.5^\circ\text{C}$ . Samples (5 ml) were withdrawn every 1 h, then filtered through Whatman filter paper (0.5  $\mu$ ) and analyzed at 286 nm using a UV-Visible spectrophotometer against 0.1 N HCl as blank. An equivalent amount of fresh media was added following the removal of each sample to maintain the sink condition.

#### *In-vitro Buoyancy Study of Floating Pulsatile Tablets*

The floating behavior of the compressed-coated tablets was visually determined in triplicate. The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 M HCl, maintained in a water bath at  $37 \pm 0.5$  °C. The time required for the compressed-coated tablet to rise to the surface and float was determined as floating lag time and the time up to which the tablet remained buoyant is determined as total floating time.

#### *Optimization by Using $3^2$ Full factorial Experimental Design*

A  $3^2$ -randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials was carried out at all nine possible combinations. Independent variables selected were: Weight ratio of HPMC E5M: Guar gum ( $X_1$ )(-1:50:50, 0:70:30 and +1:90:10) and Total weight of coating ( $X_2$ )(-1:225, 0:250 and +1:275). Dependent variables were  $Y_1$ : Drug release lag time (h) and  $Y_2$ : Cumulative drug release at 6 h (%). Statistical validation of the polynomial equations generated by Design Expert 7.1.6 was established based on the ANOVA provision in the software. A total of 9 runs with one center point were generated. The models are evaluated in terms of statistically significant coefficients and  $R^2$  values. Various feasibility and grid searches are conducted to find the composition of optimized formulations. Response surface graphs were generated from the software to study the influence of independent variables on dependent variables in a graphical manner. Checkpoint formulation was obtained from the overlay plot. The resultant experimental values of the responses are quantitatively compared with the predicted values to validate the equation. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where, Y is the dependent variable,  $b_0$  is the arithmetic mean response of the nine runs, and  $b_i$  ( $b_1$ ,  $b_2$ ,  $b_{12}$ ,  $b_{11}$ , and  $b_{22}$ ) is the estimated coefficient for the corresponding factor  $X_i$  ( $X_1$ ,  $X_2$ ,  $X_{12}$ ,  $X_1^2$  and  $X_2^2$ ), which represents the average results of changing one factor at a time from its low to high value. The interaction term ( $X_{12}$ ) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms ( $X_1^2$  and  $X_2^2$ ) are included to investigate nonlinearity.

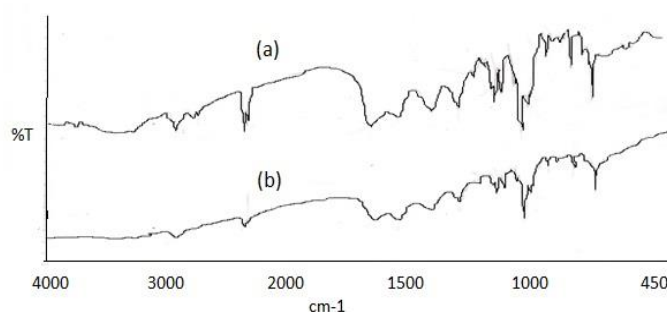
#### *Accelerated Stability Studies*

The accelerated stability study was carried out with the optimized formulation. The sample of tablets was wrapped in laminated aluminum foil and placed in the stability chamber at  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  relative humidity for one month. Sampling was done at predetermined time intervals of 0, 3, and 6 months. The tablets were evaluated for different physicochemical parameters.

### **Results and Discussion**

#### *Drug Excipient Compatibility Studies*

Drug-excipient compatibility study was done using the FT-IR spectroscopy method. FT-IR spectra (**Figure 1**) suggested minor changes such as broadening of the peak in N-H bands due to hydrogen bonding, decrease in intensity of N=C=O, and Conjugated -CONH band. This indicated that, when compared to spectra of the pure drug, no significant change was observed in major peaks of LFN in presence of excipients, which indicates the absence of any major interaction.



**Figure 1.** Compatibility Studies (a) LFN and (b) LFN with excipients

#### *Preliminary Trial Batches of Core Tablets*

Pre- and post-compression parameters were characterized for core tablets of LFN (C1 to C3 batches). The tabulated form includes results for the angle of repose, Carr's Index, tapped density, bulk density, hardness, and Hausner's ratio disintegration time (**Table 1**). The outcomes showed that the powder mixture is appropriate for the direct compression method because it has acceptable compressibility and passable flow qualities. This preliminary trial batch showed that the C1 batch that contained Crospovidone in the concentration of 15% w/w could disintegrate rapidly ( $18.48 \pm 1.23$  s) which fulfills the requirements for the burst release. So, batch C3 was used for the development of a floating pulsatile tablet.

#### *Preliminary Trial Batches of Pulsatile Tablets*

The time of lag is the most important parameter in pulsatile drug delivery. Lag times more than 5 h and less than 7 h are primary requirements or criteria for pulsatile drug delivery. As a result, it was discovered from this test batch of floating pulsatile tablets that when a single HPMC E5M or E15M was used for pulsatile coating, the medication released before 5 h, which was insufficient to meet the requirement. The medication released after 3, 4, and 4.6 hours when the concentration of HPMC E5M was combined with E15M, Xanthan gum, and Guar gum in the ratio of 90:10. On increasing the concentration of guar gum to 70%, lag time increased up to 9.33 h which was not given drug release when required. But when the concentration of HPMC E5M and Guar gum in the ratio of 50:50 were used it gave a lag time of around 6 h which fulfilled the criteria of pulsatile drug delivery. The amount of coating material has a significant effect on drug release lag time as shown in **Table 4**. When coating weight was increased, the lag time was increased in direct proportion. The buoyant layer was prepared using the composition described above in material and method. Both the amount of time the tablet spends floating on the water's surface before it emerges (floating lag time) and the amount of time it spends floating there continuously (duration of floating) were assessed. The results are shown in **Table 1** (T1 to T7 batches).

**Table 1.** Evaluation of preliminary batches

Batches	Angle of Repose (°)	Bulk Density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Carr's Index (%)	Hausner's ratio	Disintegration time (s)	Hardness (kg/cm <sup>2</sup> )
C1	26.11	0.51 ± 0.01	0.58 ± 0.04	13.79	1.16	18.48 ± 1.23	3.30 ± 0.18
C2	29.25	0.46 ± 0.04	0.55 ± 0.02	16.36	1.19	49.14 ± 1.08	3.60 ± 0.59
C3	30.68	0.40 ± 0.03	0.49 ± 0.04	18.36	1.22	96.15 ± 1.96	3.55 ± 0.52
Batches							
	T1	T2	T3	T4	T5	T6	T7
HPMC E5M (mg)	250	-	225	225	225	125	75
HPMC E15 M (mg)	-	250	25	-	-	-	-
Guar gum (mg)	-	-	-	-	25	125	175
Carbopol P934 (mg)	30	70	70	70	70	70	70
Parameters							
Lag time (h)	3.30 ± 0.26	4.60 ± 0.11	3.00 ± 0.10	4.00 ± 0.05	4.65 ± 0.05	6.70 ± 0.10	9.40 ± 0.26
Buoyancy lag time (s)	486 ± 3.60	126 ± 1.50	120 ± 0.50	106 ± 5.50	128 ± 1.30	121 ± 1.50	126 ± 1.20

#### Evaluation of Experimental Design Batches

The degrees of independent variables were chosen based on preliminary studies. Utilizing the program Design Expert 7.1.6, an experimental design with 32 complete factorial variables was utilized to examine the link between dependent and independent variables. The nine experimental runs performed in line with **Table 2** are shown in **Figure 2R** along with their respective dissolution profiles. The findings shown in **Table 5** showed responses for each of the nine factorial batches: response Y1 (Lag duration, h) and response Y2 (cumulative percent drug release in 6h, %). The data indicated that X<sub>2</sub> (Total weight of coating polymers) and X<sub>1</sub> (Weight ratio of HPMC E5M: Guar gum) influences the selected responses; Y<sub>1</sub> and Y<sub>2</sub>.

The buoyancy lag time of all 9 factorial batches was studied and the results indicated that all the tablets remained buoyant for up to 24 h. Design batches were investigated for the drug release lag time (**Table 2**). Results suggested that drug release lag time was found to be higher with the decrease in the weight ratio of the polymers and increase in the total coating weight. This could be attributed to an increase in the number of polymers used and to the high viscosity property of the gum-based polymer.

**Table 2.** Evaluation of experimental design batches

Factorial batches	X <sub>1</sub> Weight ratio of polymer	X <sub>2</sub> Total coating weight	Y <sub>1</sub> Drug release lag time, h	Y <sub>2</sub> Cumulative % drug release at 6h
F1	-1	-1	5.30 ± 0.57	25.21 ± 0.90
F2	0	-1	5.00 ± 0.00	28.11 ± 1.24
F3	1	-1	4.00 ± 0.00	75.23 ± 1.45
F4	-1	0	5.60 ± 0.57	20.34 ± 0.12
F5	0	0	5.00 ± 0.00	40.45 ± 1.56
F6	1	0	4.60 ± 0.57	69.12 ± 0.16
F7	-1	1	6.60 ± 0.58	4.50 ± 0.14
F8	0	1	6.30 ± 0.57	7.21 ± 0.17
F9	1	1	5.60 ± 0.58	45.43 ± 0.78

The analysis of variance's findings were displayed in **Table 3** (ANOVA). Because the applied quadratic model's p-value was less than 0.05, it was likely significant.

**Table 3.** Analysis of Variance results

Source	Sum of squares	Degrees of freedom	Mean square	F value	p-value
For $Y_1$ = Drug release lag time (h)					
Regression	5.14	5	1.029	39.81	0.006
Residual	0.08	3	0.026		
Total	5.22	8			
For $Y_2$ = Cumulative % drug release at 6 h					
Regression	4862.98	5	972.59	24.55	0.012
Residual	118.85	3	39.62		
Total	4981.84	8			

Multiple linear regression analysis was used to examine each parameter and create a mathematical relationship between dependent variables and independent factors in order to determine the ideal values that would provide the intended result. **Table 4** shows the fitted polynomial equation and corresponding p-values for the responses  $Y_1$  and  $Y_2$  to the modified factors. If the effects significantly differ from zero and the p-value is less than 0.05, a factor is thought to have an impact on the response. According to the data in **Table 4**, the important variables that affected the response  $Y_1$  were antagonistic and synergistic with the linear contributions of the major impacts of  $X_1$  and  $X_2$ , respectively, without creating any interaction. The synergistic and antagonistic contributions of  $X_1$  and  $X_2$ 's linear contributions, respectively, had a considerable impact on the reaction  $Y_2$ .

**Table 4.** Summary of results of multiple regression analysis for responses

Dependent variables	$Y_1$		$Y_2$	
	Drug release lag time		Cumulative % drug release at 6 h	
	Coefficients	p-value	Coefficients	p-value
$X_0$	5.17	<0.0001	33.50	0.00565
$X_1$	-0.55	0.0035	23.30	0.00283
$X_2$	0.70	0.0017	-11.89	0.01895
$X_1X_2$	0.075	0.4195	-2.29	0.52245
$X_{11}$	-0.15	0.2785	14.70	0.04552
$X_{22}$	0.40	0.03893	-12.37	0.06922

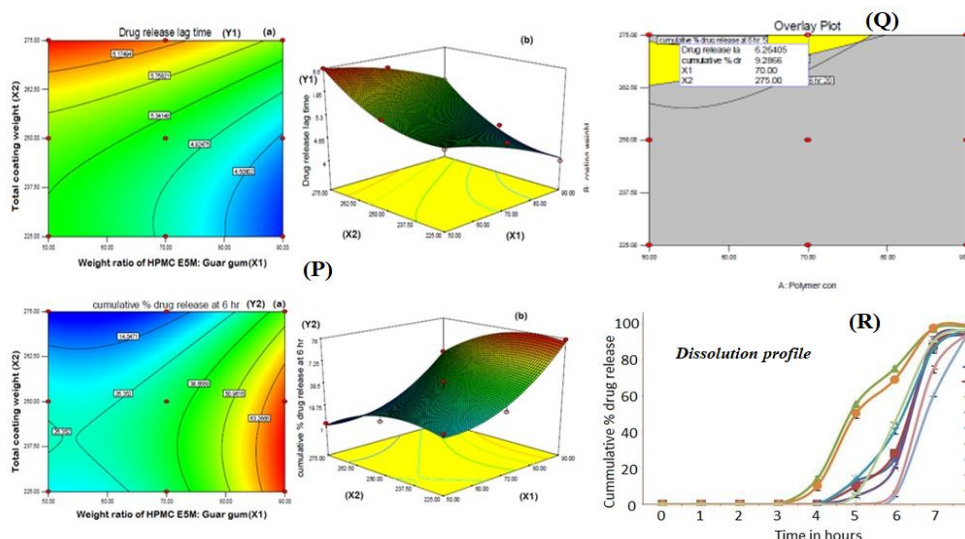
By building 3D surface plots and contour plots based on the full factorial design presented in **Figure 2P**, the link between the independent and dependent variables was further clarified.

Two-dimensional and three-dimensional plots describing the influence of  $X_1$  and  $X_2$  on  $Y_1$  are shown in **Figure 2P**. The increase in the lag time was due to the higher viscosity of the swellable guar gum. However, the effect of the weight ratio was not observed to be profound as compared to the total coating weight.

The opposite effect was observed on cumulative percent drug release at 6 h. This might be attributed to less amount of polymeric material present in the formulation which makes it incapable to remain intact for a long time.

In order to determine whether the constructed mathematical model is reliable, two extra random checkpoints covering the full experimental region were used in addition to the dissolution test of the formulation with the estimated ideal polymer ratio and coating amount [27].

An optimized batch was found and formulated from the overlay plot (**Figure 2Q**) and was further evaluated for various parameters. Experimental results ( $Y_1$ :  $6.20 \pm 0.35$  and  $Y_2$ :  $8.92 \pm 0.51$ ) for both the response variables were in accordance with the predicted values with low percentage relative error ( $Y_1$ : 0.96 and  $Y_2$ : 3.87). As desired, the prepared tablets achieved the lag time of 6 h and complete drug release from the core tablet within the next 2 h.



**Figure 2.** (P) Response surface (a: Contour plot and b: 3d surface plot), (Q) Overlay plot, and (R) Dissolution profile of design batches

In accelerated circumstances of  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  RH, the improved batch was studied for six-month stability experiments. The findings shown in **Table 5** revealed that physicochemical parameters like buoyant drug release lag time, lag time, percent drug release, and drug content are not significantly different from one another.

**Table 5.** Results of stability studies

Condition	Buoyancy lag Time (s)	Drug release lag time (h)	% Drug content	% Drug release at 8 h
Initial	$144.50 \pm 4.38$	$6.20 \pm 0.35$	$101.57 \pm 2.92$	$98.45 \pm 2.24$
After 3 months				
$40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH	$158.56 \pm 2.30$	$6.16 \pm 0.28$	$101.24 \pm 1.76$	$97.56 \pm 0.56$
After 6 months				
$40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH	$150.21 \pm 4.21$	$6.10 \pm 0.15$	$101.22 \pm 1.67$	$97.23 \pm 1.02$

## Conclusion

The results of the current investigation demonstrated the successful development of a chronomodulated LFN medication delivery system to relieve morning acid reflux. The formulation should be consumed approximately 22:00 hours after dinner. This will result in an appropriate treatment regimen and improved patient compliance. In order to formulate an ideal batch, the experimental design that was utilized to manipulate the formulation parameters gave the ideal levels of independent variables. The release profile of the improved formulation was quite similar to the predicted profile. Therefore, the proposed formulation should be taken into consideration as one of the prospective treatments for the reduction of early morning, severe stomach acid secretion.

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**Conflict of interest:** None

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**Ethics statement:** None

## References

- Hasan MDW, Komuravelly S, Patha C, Mohd AB, Ande P, Rao VUM. Formulation and evaluation of press-coated tablets of salbutamol sulphate for time-controlled release. *Asian J Pharm.* 2014;8(3):161-70.
- Jaiswal H, Ansari VA, Pandit JN, Ahsan F. Pulsatile drug delivery system: An overview with special emphasis on losartan and captopril. *Res J Pharm Technol.* 2019;12(7):3175-88.
- Gowda J, Shankar SJ, Munisamy M, Akshatha RS, Sagar VS. Development of pH dependent chronomodulated delivery systems of 5-Fluorouracil and oxaliplatin to treat colon cancer. *Int J App Pharm.* 2020;12(5):118-30.

4. Kumar PJ, Muzib YI, Misra G. Formulation and evaluation of pulsatile drug delivery of lovastatin. *Res J Pharm Technol.* 2018;11(7):2797-803.
5. Khalifa AZ, Ziad H, Mohammed H, Ihsan K, Alrawi L, Abdullah M, et al. Recent advances in remotely controlled pulsatile drug delivery systems. *J Adv Pharm Technol Res.* 2022;13(2):77-82.
6. Rane AB, Gattani SG, Kadam VD, Tekade AR. Formulation and evaluation of press-coated tablets for pulsatile drug delivery using hydrophilic and hydrophobic polymers. *Chem Pharm Bull.* 2009;57(11):1213-7.
7. Roy P, Shahiwala A. Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. *Eur J Pharm Sci.* 2009;37(3-4):363-9.
8. Marzouk MAE, Darwish MK, Yassin GE, El-Fattah MAA. Pulsatile Chronotherapeutic Drug Delivery for Controlling Early Morning Surge in Blood Pressure; Effect of Coating on Eplerenone In-vitro, In-vivo Release and Urinary Na/K Ratio. *Braz J Pharm Sci.* 2022;58. doi:10.1590/s2175-97902022e19306
9. Innominato PF, Karaboué A, Focan C, Chollet P, Giacchetti S, Bouchahda M, et al. Efficacy and safety of chronomodulated irinotecan, oxaliplatin, 5-fluorouracil and leucovorin combination as first- or second-line treatment against metastatic colorectal cancer: Results from the International EORTC 05011 Trial. *Int J Cancer.* 2020;148(10):2512-21.
10. Yang YY, Liu ZP, Yu DG, Wang K, Liu P, Chen X. Colon-specific pulsatile drug release provided by electrospun shellac nanocoating on hydrophilic amorphous composites. *Int J Nanomed.* 2018;13:2395-404.
11. Kshirsagar SJ, Patil SV, Bhalekar MR. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. *Int J Pharm Investig.* 2011;1(4):207-13.
12. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. *Int J Pharm.* 2004;277(1-2):141-53.
13. Jagdale SC, Bari NA, Kuchekar BS, Chabukswar AR. Optimization Studies on Compression Coated Floating-Pulsatile Drug Delivery of Bisoprolol. *BioMed Res Int.* 2013;2013. doi:10.1155/2013/801769
14. Karavas E, Georgarakis E, Bikiaris D. Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. *Eur J Pharm Biopharm.* 2006;64(1):115-26.
15. Mohamad A, Dashevsky A. Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacoat® ECD. *Int J Pharm.* 2006;318(1-2):124-31.
16. Gifty MJ, Behin S, Punitha ISR. Formulation and evaluation of floating pulsatile drug delivery system of ibuprofen and ranitidine combination. *Int J Pharm Sci Nanotechnol.* 2015;8(4):3009-17.
17. Fass R. Nocturnal acid breakthrough: a critical assessment. *Hosp Physician.* 2004;40:47-52.
18. Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. *Aliment Pharmacol Ther.* 2001;15(9):1351-6.
19. Dejaegher B, Heyden YV. Experimental designs and their recent advances in set-up, data interpretation, and analytical applications. *J Pharm Biomed Anal.* 2011;56(2):141-58.
20. Setia A, Goyal S, Shrivastva B, Goyal N. Design, optimization, preparation and evaluation of solid dispersions of albendazole using factorial design. *Der Pharmacia Sinica.* 2011;5:30-42.
21. Ikawa K, Shimatani T, Hayato S, Morikawa N, Tazuma S. Pharmacokinetic and pharmacodynamic properties of lafutidine after postprandial oral administration in healthy subjects: comparison with famotidine. *Biol Pharm Bull.* 2007;30(5):1003-6.
22. Patil S, Talele GS. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. *Drug Deliv.* 2015;22(3):312-9.
23. Bhupesh D, Raghuram C. An open-label randomized cross-over bioequivalence study of lafutidine 10 mg under fasting condition. *World J Gastrointest Pharmacol Ther.* 2010;1(5):112-8.
24. 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;1(3):690-1.
25. Ghimire M, McInnes FJ, Watson DG, Mullen AB, Stevens HNE. In-vitro/in-vivo correlation of pulsatile drug release from press-coated tablet formulations: a pharmacoscintigraphic study in the beagle dog. *Eur J Pharm Biopharm.* 2007;67(2):515-23.
26. Fukui E, Miyamura N, Yoneyama T, Kobayashi M. Drug release from and mechanical properties of press-coated tablets with hydroxy propyl methylcellulose acetate succinate and plasticizers in the outer shell. *Int J Pharm.* 2001;217(1-2):33-43.
27. Joshi A, Pund S, Nivsarkar M, Vasu KK, Shishoo CJ. Dissolution test for site-specific release isoniazid pellets in USP apparatus 3 (reciprocating cylinder): optimization using response surface methodology. *Eur J Pharm Biopharm.* 2008;69(2):769-75.