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Research Article

FLOATING PULSATILE DRUG DELIVERY OF RANITIDINE HYDROCHLORIDE FOR NOCTURNAL ACID BREAKTHROUGH: DESIGN, OPTIMIZATION, IN- VITRO AND IN- VIVO EVALUATION

RAJENDRA T. MOGAL, UPENDRA C. GALGATTE*, PRAVIN D. CHAUDHARI

Department of Pharmaceutics, P.E.S's Modern College of Pharmacy, Nigdi, Pune 411044, Maharashtra, India.
Email: ucgpharm@rediffmail.com

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ABSTRACT

Objective: In chronopharmacotherapy, drug administration is synchronized with circadian rhythms. The present study was based on objective whether drug delivery would provide a maximum drug release approximately in 6 h after taken orally at bedtime.

Methods: The strategy adopted for tablet formulation include preparation of core tablet by direct compression containing drug, ranitidine hydrochloride (RH), which was coated with ethyl cellulose (EC N10) and hydroxypropyl methylcellulose (HPMC E15) followed by coating of HPMC E15 and sodium bicarbonate for generation of effervescence which was further coated by eudragit RL 100 for effervescence entrapment to produce density <1. Central composite design (CCD) was applied by using design-expert 8.0.4 to optimize composition of EC N10 and HPMC E15 for pulsatile release.

Floating pulsatile tablets were evaluated for uniformity of weight, hardness, friability, dimensions, content uniformity, *in vitro* buoyancy, drug release, in vivo study and stability studies.

Results: Ratio of EC N10 and HPMC E15 (80:20 % w/w) was optimized experimentally which could provide drug release 97.56% in pulsatile manner with a lag time of 3 to 3.5 h. HPMC E15 and sodium bicarbonate (1:4 % w/w) was found satisfactory for generation of effervescence and to provide floating lag time of 5 min. Eudragit RL 100 (5% w/w) was found to be good at weight gain of 1% for entrapment of effervescence to provide floating behavior.

Conclusion: Present tablet formulation would be synchronized with the need of nocturnal symptoms of acid secretion at midnight (peak 2 to 4 am) thus can provide better compliance over conventional tablet formulation.

Keywords: Chronopharmacology, Circadian, Floating pulsatile, Nocturnal acid breakthrough.

INTRODUCTION

In present day with the advancement of the new technologies in the pharmaceutical field, pulsatile drug delivery systems are gaining a great interest because the drug is released completely at the site after predetermined lag time. With pulsatile drug delivery we can achieve time and site specific drug delivery that's why increasing patient compliance. Due to inherent hurdles in drug discovery nowadays, the pharmaceutical research is going towards the development of more efficacious drug delivery systems on already existing molecule [1]. Certain diseases like rheumatic disease, ulcer, bronchial asthma, myocardial infarction, angina pectoris, hypertension, diabetes, and hypercholesteromia shows circadian rhythm [2, 3, 4]. Conventional pulsatile drug delivery releases drug into large intestine after a lag time of 5-6 h [5]. Where the viscous contents of lower part of GI track cause hindrance to drug absorption and enzymatic degradation of some drugs makes it an unfavorable site for drug release [6]. Gastro-retentive dosage forms are unaffected by pH, gastric emptying therefore gastro- retention is preferred for drugs having absorption window in stomach, or get degraded by enzymes in intestine [7, 8, 9].

Nocturnal acid breakthrough (NAB) is defined as the state in which intragastric pH goes far below less than 4 during the overnight period for at least 60 continuous minutes and clinical consequences is more in patients with complicated gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal motility abnormalities [10]. Symptoms associated with NAB are heartburn, coughing or choking due to fluid in throat, wheezing, breathlessness and morning phlegm and is more critical in *H. pyroli*- negative patient on proton pump inhibitors (PPIs) [2, 11, 12, 13]. NAB follows circadian rhythm with intensity of peak is more between 2 a.m. to 4 a.m. in early morning [14]. Around 70% patient taking PPIs twice daily arrears to be resistant, so it results in failure of PPIs to control nocturnal acid secretion which is due to high nocturnal histamine concentration [2, 15]. Study had shown that addition of bedtime H_2-antagonist to an evening dose of PPIs controls night time acid secretion but long time efficacy of combination is still debatable due to possible development of tolerance on repeated administration [14, 16, 17].

These limitations can be overcome by chronotherapeutic approach in which drug releases after predetermined lag time and there we can achieve synchrony between plasma concentration of drug and peak symptoms associated with NAB. Ranitidine hydrochloride (RH), a H_2 receptor blockers used for control gastric acidity until PPIs were introduced and replace H_2 blockers for controlling acidity. Failure of PPIs in controlling night time gastric acid secretion opens new era for existing H_2 antagonist drugs. Colonic metabolism of ranitidine is partly responsible for poor bioavailability from colon [18, 19, 20, 21]. In present work, response surface methodology is used in order to study the effects of independent variables on dependent variables and from this mathematical polynomial equations were constructed which shown effect of each factor on responses.

MATERIAL AND METHODS

Materials

Ranitidine hydrochloride was the generous gift from Zim Laboratories, Nagpur, India. Ethyl cellulose (Aqualon EC N10, Signet Chemical Corporation, Mumbai, India), hydroxypropyl methyl cellulose (Methocel E15, Loba Chemie Pvt. Ltd., Mumbai, India), eudragit RL100 (Evonik Degussa, Pvt. Ltd., Mumbai, India), microcrystalline cellulose RQ102 (RanQ Pharma, Thane, India), croscarmellose sodium, aerosil 200, dibutyl phthalate (Research Lab Fine Chem, Mumbai, India), magnesium stearate, sodium bicarbonate (Hexon Laboratories Pvt. Ltd, Pune, India), polyethylene Glycol 6000, talc (Loba Chemie Pvt. Ltd., Mumbai, India). All chemical reagents used were of analytical grade.

Preparation of burst release core tablet

The core tablet contained ranitidine hydrochloride equivalent to 75 mg of ranitidine and other additives microcrystalline cellulose (RQ 102, 50.15 % w/w), croscarmellose sodium (5% w/w), magnesium

stearate (0.5 % w/w), aerosil 200 (2.5% w/w). Initially, the core tablet excipients were blended in a dry form double cone blender according to ascending bulk density (Kalweka, Karnavati Eng. Ltd., India) for 15 min. Final powder blend was evaluated for flow properties like hausner ratio, carr's index, angle of repose etc. The core biconvex tablets of diameter 8 mm; hardness 4 to 5 kg/cm^2; average weights of 200 mg were prepared by using 8 station compression machine (CIP, Ahmedabad, India).

Coating of core tablet for pulsatile release

The coating solution 5 % w/w, combination of ethyl cellulose N10 (rupturable polymer) and hydroxypropyl methyl cellulose E15 (erodible polymer) was prepared in 90:10% w/w isopropyl alcohol: distilled water. The combinations of these polymers were based on weight ratio as shown in table 1. The solution plasticized with dibutyl phthalate 20% w/w and talc 5% w/w added as glidant. These percentages were based on dry polymer weight. The dispersion was stirred by using magnetic stirrer throughout the coating process. The prepared dispersion sprayed on previously dried core tablet for 20 min in conventional pan (Pharma R and D coater, Ideal Cures Pvt. Ltd., Mumbai, India) until the desired percentage weight gain achieved. The coating parameters set during coating are listed in table 2. After coating, the tablets were dried in coating pan for 30 min at 50 ^{0}C and then in hot air oven for 1 h at 45 ^{0}C to remove residual solvent.

Table 1: Experimental runs using CCD

Formulation	% EC (w/w)	% coating
F1	70	5
F2	90	15
F3	70	5
F4	90	15
F5	65.86	10
F6	94.14	10
F7	80	2.93
F8	80	17.07
F9-F13	80	10

Table 2: Process parameters sets during coating of tablets

Process parameter	Condition set		
	Pulsatile Coating	Effervescent layer	Gas entrapment
Inlet temperature (^{0}C)	58-62	72-77	46-50
Pan speed (rpm)	25	25	25
Pump speed (rpm)	1	1	1
Nozzle diameter (mm)	1	1	1

Experimental design for pulsatile coating

Optimization of inner coating layer for pulsatile release was carried out by using Central Composite Design (CCD). With help of this it was suitable to check the quadratic response surfaces and construction of second order polynomial equation by using Design-Expert software (8.0.4.1, Stat-Ease). Selection of independent variables (percentage of ethyl cellulose in composition and percentage coating level) and dependent variables (lag time in min and drug release in 6 hours) was based on preliminary experiments. Table 3 summarizes the independent variables along with their levels. Response surface analysis and evaluation was carried out in order to check whether current study was fitted in model. From 3D response surface, the effects of independent variables on dependent variables were observed. The polynomial equation also shows effect of interaction of each factor on dependent variables. Finally the optimized batch with optimum polymer concentration and coating level was prepared and evaluated.

Table 3: Experimental design; Coded and actual value

Name of independent variable	- α	- 1	0	+ 1	+ α
Coded value	- 1.414	- 1	0	+ 1	+ 1.414
% w/w EC in ratio	65.86	70	80	90	94.14
% coating level	2.93	5	10	15	17.07

Effervescent layer coating

Effervescent coating solution (10% w/w) consists of 1:4% w/w ratio of hydroxypropyl methyl cellulose E15 and sodium bicarbonate was prepared in distilled water. The solution plasticized with 10% w/w polyethylene glycol 6000 and 5% w/w talc as glidant based on dry polymer weight. The coating solution was sprayed on the previously coated tablets in coating pan. The coating parameters were set as mentioned in table 2. The coating was continued until desired weight (12% w/w) determined experimentally was achieved. The coated tablets further dried 30 min in pan and then 1 h in hot air oven to remove residual solvent.

Gas entrapment coating

Solution of Eudragit RL100 (5% w/w) was prepared in 60:40 % v/v of isopropyl alcohol and acetone and sonicated for 15 min to dissolve polymer. The solution was plasticized with 20% w/w dibutyl phthalate and talc 5% w/w as glidant based on polymer weight. The coating parameters were set as mentioned in table 2. After desired weight gain the tablets further dried 30 min in pan and 1 h in hot air oven to remove residual solvent.

***In vitro* evaluation of tablets**

Uniformity of weight

Twenty tablets were randomly selected and average weight was calculated. Then individual tablets were compared with the average.

Hardness[22]

The hardness of the tablets were determined by using Monsanto type hardness tester and expressed in kg/cm^2.

Thickness and diameter [23,24]

The thickness and diameter of tablets were measured by using digital vernier caliper and expressed in mm.

Friability[25]

Twenty tablets were randomly selected and weighed. Then it was placed in friability test apparatus (Electrolab India Pvt. Ltd., EF-2, Mumbai, India). After 100 revolutions at 25 rpm for 4 min, tablets were removed, dedusted, and again weighed. The percentage weight loss was calculated.

Content uniformity

Twenty tablets were selected randomly and amount of drug present in each tablet was determined. The tablets were crushed in a mortar. Powder equivalent to 75 mg of drug was transferred into 5 ml of 0.1 N hydrochloric acid (HCl) in 100 ml volumetric flask. After thorough mixing, the solution filtered through 0.45 µ Whatmann filter paper. Lastly after appropriate dilution, sample analyzed for drug content by UV spectrophotometer at 313 nm.

Buoyancy study[26,27]

Six tablets were randomly selected and placed in a 100 ml beaker containing 0.1 N HCl of pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Drug release

In order to study the release pattern from the coated pulsatile tablet drug release profile, *in vitro* dissolution studies were carried out using USP dissolution type I (basket) type; (Electrolab India Pvt. Ltd., Mumbai, India) in 900 ml 0.1 N HCl (pH 1.2) at 50 rpm and temperature at 37 ± 0.5 ^{0}C. A 5 ml sample was withdrawn after every 30 min and filtered through 0.45 µ Whatmann filter paper. The same volume was replaced with fresh dissolution medium. The sample analyzed at 313 nm using a UV/Visible spectrophotometer (Jasco V-530, double beam spectrophotometer, Japan). The drug release was estimated by using PCP disso 208 software with a help of correlation coefficient, constant and slope from calibration curve (n=6).

Stability study[28]

The optimized formulation was kept in the humidity chamber (Oswal Scientific, India) at 40 ± 2 ^{0} C/75 ± 5 relative humidity for 3 months. Samples were withdrawn after every 2 weeks and tablets were examined for organoleptic properties, hardness, thickness, drug content, *in vitro* buoyancy, *in vitro* drug release etc.

***In vivo* evaluation[29]**

In vivo study was carried out by administering a formulation to healthy rabbit and monitoring it by X- ray imaging technique. The protocol was approved (MCP/IAEC/11/2011) by the Institutional Animal Ethics Committee as per CPCSEA guidelines. Study was carried out on female New Zealand white strain rabbit weighing approximately 2 to 2.5 kg. For X- ray imaging visibility, ranitidine hydrochloride was replaced with 17.5 % X-ray grade barium sulfate (this amount was determined by experimentally to allow X- ray visibility but not sinking of tablet) and diameter of tablet was 6 mm (for ease of administration in rabbit). Before carried out experiment, the rabbit was kept on overnight fasting. Then tablet prepared was administered orally using a flexible tube and finally 4 to 5 ml water was administered using syringe to push inside. The position of tablet was monitored using X- ray imaging at 2 and 5 h. X-ray photographs were taken at Ayurved Rugnalaya Akurdi Pradhikaran, Pune, India.

RESULT AND DISCUSSION

Preparation of core tablet for burst release

As per literature, most of the floating unit dosage forms were formulated as either swellable gel matrix which leads to sustained drug release or effervescent systems without coating. In this study, the polymer composition was selected in order to provide burst release following rupture of outer coat. Therefore, crosscarmellose sodium (5%) was added as superdisintegrant for immediate release. Microcrystalline cellulose (RQ 102) was used as binder and partially as disintegrant to show synergistic effect with crosscarmellose sodium to achieve immediate release. Table 4 summarizes the evaluation of powder blend while table 5 summarizes the evaluation of core and coated tablets. From above observations, the final powder blend had good to fair flow properties. The evaluation of tablets was carried out as per I.P 2007. The tablets comply with weight variation, friability, drug contents test.

Table 4: Evaluation of powder blends for flow properties

Name of parameter	Value	Inference
Bulk density g/mL	0.435	_
Tapped density g/mL	0.526	_
Compressibility index %	17.4	Fair flow properties
Hausner ratio	1.21	Good flow properties
Angle of repose	22.3	Good flow properties

Table 5: Evaluation of tablets

Name of parameter	Core tablet [a]	Coated tablet [a]
Average weight (mg)	205.64 ± 3.92	238.93± 5.37
Thickness (mm)	4.11 ± 0.05	4.72 ± 0.16
Diameter (mm)	8.00 ± 0.01	8.62 ± 0.12
Hardness (kg/cm^2)	4-5	4-5
Friability (%)	0.287 ± 0.07	0.01 ± 0.00
Drug content (%)	98.81 ± 2.49	98.37 ± 3.12

[a]Mean of 6 ± S.D.

Central Composite Design (CCD) for pulsatile release

The coating composition and coating level were found responsible mainly for time-lagged coating for pulsatile release. In order to find out the optimum composition of coating and coating level to give predetermined lag time, optimization was carried out by using CCD. The central point of design is a point where occurrence or probability of optimum coating composition and coating level is more. The dissolution profiles of all experimental runs are given in fig 1. Responses that are lag time (Y_1) and drug release at the end of 6 h (Y_2) were plotted according to CCD experimental design as shown in table 6.

Table 6: Dissolution studies as per CCD full factorial experimental design.

Run	Lag time (min) [a]	% drug release in 6 h[a]
F1	85 ± 3.57	98.89 ± 0.33
F2	254 ± 11.79	75.26 ± 4.85
F3	141 ± 8.68	98.35 ± 1.12
F4	305 ± 14.35	32.91 ± 5.22
F5	113 ± 6.51	98.76 ± 1.37
F6	287 ± 13.67	50.20 ± 3.56
F7	164 ± 6.45	98.71 ± 0.84
F8	225 ± 7.43	80.12 ± 3.35
F9-13	196 ± 5.78	98.63 ± 1.14

[a] Mean of 6 ± S.D. (n=6)

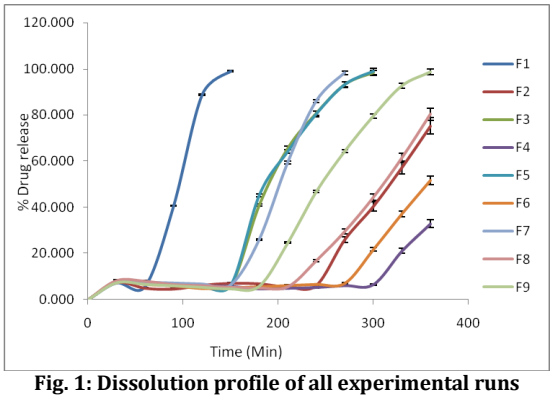


Fig. 1: Dissolution profile of all experimental runs

Effervescent layer coating

The effervescent layer composition was determined experimentally at 1:4 w/w of HPMC E15 and sodium bicarbonate and concentration kept constant at 10% w/w. The percentage coating level 12% w/w was determined experimentally. Above 12% coating the floating lag time was found to be increased. This is attributed to increase in weight of tablet. A 12% w/w effervescent coating was supposed to be better as tablets could float within 5 min.

Gas entrapment coating

Ethyl cellulose was not flexible enough and upon carbon dioxide (CO_2) generation gets ruptured. Therefore, polymethacrylates such as eudragit RL100, a highly water permeable and higher flexible polymer, was used due to its hydrophilic group, twice as many quaternary ammonium groups in the structure than Eudragit RS100. Tablets coated with alone Eudragit RL100 were floated within 5-6 min and with increase in coating level floating lag time was found to be increased. Lower coating that is 1% w/w was selected as less floating lag time was desired. However, higher coating level had shown more sustained type of release instead of pulsatile.

Multiple regression and mathematical model building

The central composite design was selected for optimization because central composite design require 5 levels of each factor -α, -1, 0, 1, and +α. One of the commendable attributes of the central composite design is that its structure lends itself to sequential experimentation. A statistical model incorporating interactive and polynomial terms were used to evaluate the responses.

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

One way ANOVA (analysis of variance) was used for statistical analysis of targeted response at 5% significant level and the significance of model, factors were determined using Design- Expert. In above equation, b_0 is the intercept representing the arithmetic averages of all 9 runs and b_1, b_2, b_{12}, b_{11} and b_{22} are the coefficients computed from the observed experimental values of responses Y_1 and Y_2; and X_1 and X_2 stand for main response of independent variables. The terms X_1X_2, X_{11} and X_{22} represent interaction and quadratic terms of independent variables respectively. In table 7 factor effects involved in CCD model and associated *p*-values for the responses Y_1 and Y_2 are given. The model F- value of 65.25 for Y_1 implies the model is significant and there is only 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1 and X_2 are significant model terms. The Model F-value of 43.75 for Y_2 implies the model was significant. In this case X_1, X_2, X_1X_2, X_{11} and X_{22} were significant model terms.

After eliminating insignificant terms the final equation of the responses are given below

$$Y_1 = 196 + 72.38X_1 + 24.16X_2 \text{ ---------- } (2)$$

$$Y_2 = 98.01 - 9.47X_1 - 8.54X_2 - 10.43X_1X_2 - 12.88X_1^2 - 5.85X_2^2 \text{ ---------- } (3)$$

Positive sign in front of the factors indicates synergistic effect and negative sign indicates antagonistic effect of the factors on responses Y_1 and Y_2.

Table 7 : Effect of each factor and its *p*-value.

Factor	Y_1		Y_2	
	Factor effect	***p*-value**	**Factor effect**	***p*-value**
X_1	+72.38	<0.0001	- 19.47	<0.0001
X_2	+24.16	0.0007	- 8.54	0.0018
X_1X_2	-1.25	0.8403	- 10.43	0.0039
X_1^2	+1.75	0.7109	- 12.88	0.0002
X_2^2	-1.00	0.8317	- 5.85	0.0167
R^2	0.9790		0.9690	

Response surface analysis

Fig. 2 shows 3D response surface for lag time. From this graph a linear synergistic relationship between the two independent factors on a dependent variable lag time Y_2 was observed. There was no interaction between the factors for response Y_2. This was due to decrease permeation with increase in hydrophobic nature of coating due to increase ethyl cellulose concentration and coating thickness. However percentage of ethyl cellulose in coating composition was affecting the response Y_2 more significantly than coating thickness.

Fig. 3 shows a curvilinear relationship for response drug release at 6 h (Y_2). There was potential interaction between factors for response Y_2. This was due to increase in ethyl cellulose concentration in coating composition and coating thickness, which decrease drug diffusion. The decrease in effect was due to less pore forms for drug diffusion with increase in hydrophobic nature of ethyl cellulose and coating thickness further retard drug release.

After mathematical modeling and 3D response surface analysis plotting the numerical optimization technique used for selection of composition of independent variable for optimized formulation. The targeted response of 195 min (constraints between 180-210 min) of Y_1 and 95% drug release at 6 h (constraints between 92-98% drug releases) of Y_2 were set and final formulation selected based on desirability approach. The composition of optimized formulation with the experiment and predicted value was as: 79.48 % w/w of ethyl cellulose in coating composition and 10.57% w/w coating level with desirability 1.000 shown in table 8.

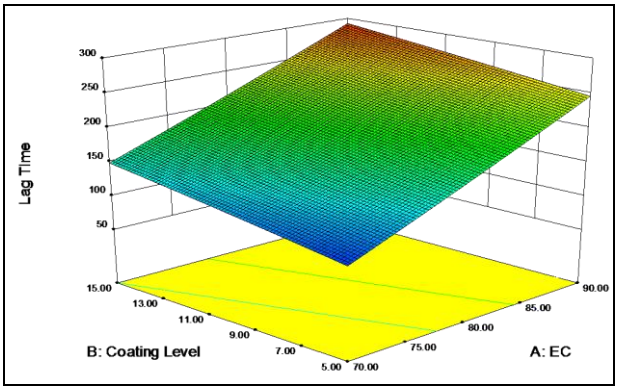


Fig. 2: Response surface for lag time (min)

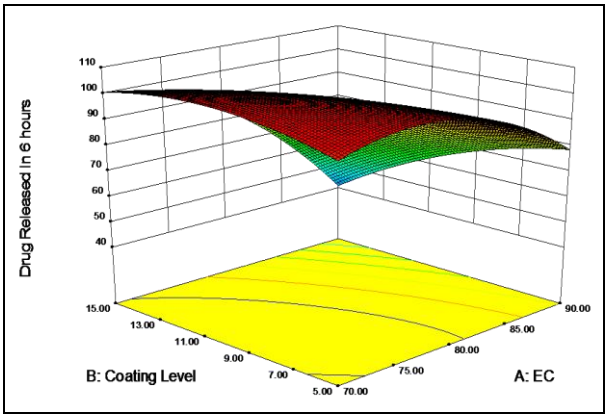


Fig. 3: Response surface for drug release in 6 h

Table 8: Composition of optimized formulation

Response	Experimental value [a]	Predicted value	% error
Lag time (min)	190 ± 4.67	195	-2.56
% Drug released at 6 h	97.56 ± 3.11	95.1	+ 2.52

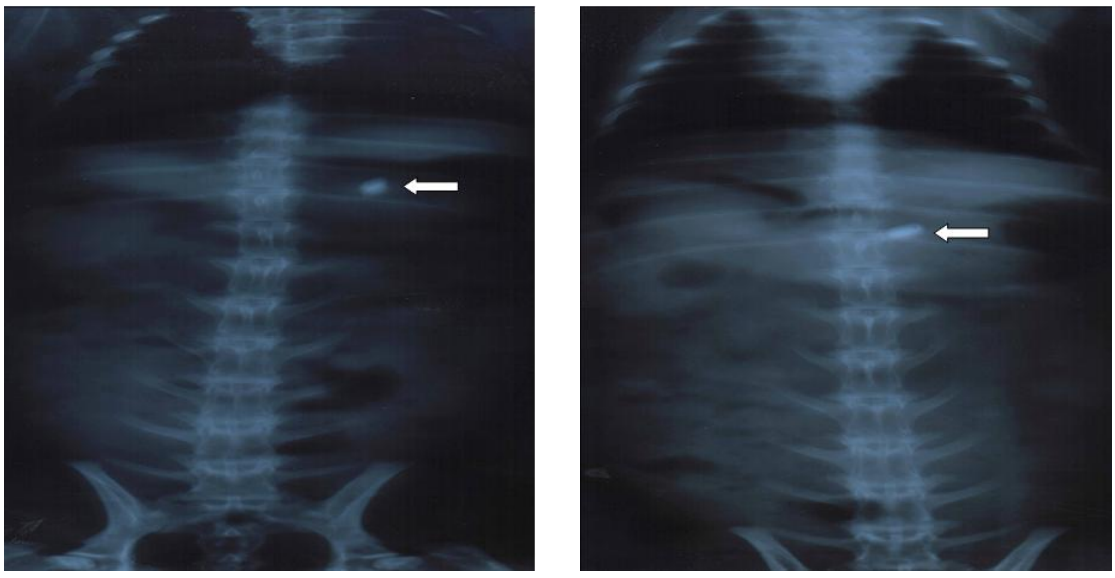
[a] Mean of 6 ± S.D. (n=6)

In vivo study

An *in vivo* study was carried out with aim that whether the prepared coated tablet system can float into stomach and remain floated in stomach for sufficient time of period to get desired effect. The tablet images taken at the end of 2 h and 5 h as shown in fig. 4. It was observed that tablet remained float for more than 5 h which means tablet unit get swell due to effervescent layer which forms CO_2 and these unit have density less than unity. The tablet floats and after rupture of time- lagged coating, the drug releases into stomach for more than 5 hours.

Stability study

The result in table 9 has shown no significant difference between the initial and respective value during study and at the end of 3 months.



A **B**

Fig. 4: X- ray imaging of floating tablet, A) After 2 h, B) After 5 h

Table 9: Stability study

Parameter	Initial	1 Month	2 Month	3 Month
Color	White	White	White	White
Thickness	4.73 ± 0.03	4.71 ± 0.02	4.72 ± 0.03	4.72 ± 0.03
Hardness Kg/cm^2	4-5	4-5	4-5	4-5
FLT (min)	5.37 ± o.43	5.29 ± 0.31	5.41 ± 0.37	5.35 ± 0.38
TFT (h)	> 8	> 8	> 8	> 8
Lag time (min)	191 ± 2.57	185 ± 3.21	194 ± 5. 73	189 ± 4.54
% drug release	97.41 ± 2.81	96.87 ± 3.27	97.59 ± 2.34	97.13 ± 2.67

CONCLUSION

The present study demonstrates that with the help of floating pulsatile chronopharmaceutical drug delivery system, ranitidine hydrochloride could be successfully delivered for control of night time gastric acid secretion and therefore relief from acidity. Regarding the optimization, it was shown that optimization by using central composite design is appropriate. Central composite design can successfully used in the development of time-lagged coating formulation which is based on combination of ethyl cellulose (rupturable) and hydroxyl propyl ethyl cellulose (erodible) in percent (w/w) ratio of polymers and percent (w/w) coating level for achieving desired responses, lag time and drug release profile, after preprogrammed off period. From response surface methodology, it is easy to understand the change of responses with independent variable and for locating the desired area of interest. *In vivo* study has shown that the prepared tablet was floating for sufficient time in stomach in order to release drug at the site of absorption. From stability study it was observed that the optimized formulation remains stable for the period to which study was carried out.

This work can be extended for time controlled and site specific drug delivery of drugs having high solubility, poor bioavailability from intestine, having absorption window into upper part of gastro-intestinal tract, or degraded into intestine. The tablet prepared with simple techniques and therefore can be considered as one of the promising formulation technique for preparing floating pulsatile drug delivery and therefore effective in chronotherapeutics management of nocturnal acid breakthrough by new techniques for existing drug ranitidine hydrochloride.

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