Research Article

Formulation and Evaluation of Floating Tablets of Verapamil Hydrochloride by using Gastroretentive Technology

S. R. Dawange,* S. S. Khadabadi, S. S. Saboo
Dept of Pharmaceutics, Government College of Pharmacy, Opp Govt polytechnic, Osmanpura, Aurangabad, Maharashtra, India.
***Corresponding author's E-mail:** sunitadawange111@gmail.com

Accepted on: 03-08-2015; **Finalized on:** 31-08-2015.

ABSTRACT

The Verapamil hydrochloride anti-hypertensive agent is primarily dissolved and absorbed from the upper part of the GI tract. Therefore aimed to develop a prolonged release gastro retentive (GT) formulation of Verapamil hydrochloride. Drug was evaluated by UV and DSC. A variety of polymers and effervescent properties were utilized to optimize the desired disposition profile. Tablets were prepared by the direct compression technique and evaluated for physical properties, swelling, floating, and drug release. The purpose of this research was to formulate and evaluation of a floating tablet of Verapamil hydrochloride by using Gastro retentive technology using 3^2 factorial design. Floating tablets were prepared by incorporating HPMC K15M, sodium alginate, sodium bicarbonate and citric acid. A 3^2 Factorial design was applied systemically; the amount of HPMC K15M (X1) and sodium alginate (X2) were selected as independent variables. The time required for 100% drug release and floating lag time (FLT) were selected as dependent variables. It was found that HPMC K4M, sodium alginate and their interaction had significant influence on the % drug release and floating lag time of the delivery system.

Keywords: Verapamil hydrochloride, HPMCK 15M, sodium alginate, sodium bicarbonate, citric acid, gastro retentive technology.

INTRODUCTION

Oral drug is most popular and convenient route for various drugs Oral route generally consider as a ideal drug delivery system that will posses two main properties:

- It should be in single dose for prolonging action.
- It should deliver the active drug directly to the target site.

These considerations have led to the development of a control or sustain delivery system. Sustained delivery describes drug delivery system with delayed and/or prolonged release of drug.[1] Sustained release products are designed to bring the blood level of a drug immediately to therapeutic concentrations of an initial dose portion and then sustain this level for a certain predetermined time with maintenance portion.[4] Oral controlled drug primarily aimed at more predictable and increased bioavailability of drugs an oral controlled release drug delivery system is not just to sustain the drug release but also prolonging the presence of the dosage from within the gastrointestinal tract (GIT) until all drugs is completely released at the desired period of time.[3]

The objective of present work was to develop gastro retentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. Example of substance whose bioavailability is strongly dependent on the local physiology in the GI tract and which preferably is absorbed in the higher sections of the intestine is Verapamil. Verapamil is readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail; however, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine. There is a need for systems that reside in the stomach over a relatively long time and release the active compound there in a sustained manner. This necessitated the design and evaluation of floating tablet of gastroretentive drug delivery system for Verapamil hydrochloride using suitable polymers.

MATERIALS AND METHODS

Materials

Verapamil HCL was received as a gift sample from Nicholas Pharma Limited, Mumbai, India. HPMC K15M and sodium alginate were received as gift samples from Colorcon Pvt Ltd, Goa, India. Citric acid, sodium bicarbonate, hydrochloric acid, magnesium stearate and microcrystalline cellulose were purchased from Dipa chemicals, Aurangabad.

Methods

Floating matrix tablets containing Verapamil HCL were prepared by direct compression technique using varying concentration of different grade of polymer such as HPMCK15M (14%, 16% and 18%) and sodium alginate (9%, 11% and 13%) with sodium bicarbonate and citric acid. All the ingredients except magnesium stearate were blended in polythene bags. After sufficient mixing of drug as well as other component, magnesium stearate was added and further mixed for additional 2 to 3 minutes as shown in table 1. The tablets were compressed by single punch machine. The weight of the tablet was kept constant for all formulations.

Table 1: Factorial batches set

Batch	Drug	HPMC k15	Sodium Alginate	Sodium Bicarbonate	Citric Acid	Mg. Stearate	MCC 102	Total wt
F1	120	70	40	30	10	5	175	450
F2	120	70	50	30	10	5	165	450
F3	120	70	60	30	10	5	155	450
F4	120	75	40	30	10	5	170	450
F5	120	75	50	30	10	5	160	450
F6	120	75	60	30	10	5	150	450
F7	120	80	40	30	10	5	165	450
F8	120	80	50	30	10	5	155	450
F9	120	80	60	30	10	5	145	450

(All quantities in table mg)

Evaluation of Factorial Batches

Uniformity of Thickness and Diameter

The uniformity of the diameter and thickness was measured using Vernier caliper. The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average.[24]

Hardness

Monsanto hardness tester was used to check the hardness of the tablet. The tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load was increased, and at collapse the applied pressure from the spring was measured in kg/cm^2.[24]

Density

Density of the tablet was calculated from their volumes and masses (n=3). The volumes V of the cylindrical tablets were calculated from their heights h and radii r (both determined with a Vernier caliper) using the mathematical equation for the cylinder $V = \pi \times r2 \times h$. The tablets equal to 1g/cm^3 density or less were chosen for further studies.[24]

Weight Variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, and the test was performed according to the official method. Since the average weight of tablet is more than 250mg, the test requirements are met if none of the individual tablet weights are less than 95% or more than 105% of the average weight.[24]

Friability

Tablets were subjected to tumbling in Roche friability tester. Six tablets were weighed and tumbled at the rate of 25 rpm for 4 min.

The tablets were weighed and percent friability was calculated by the following formula:

$$\%Friability = \frac{Wo - W}{Wo} \times 100$$

Where,

Where,

F=friability

$W0$=initial weight of six tablets

W=final weight of six tablets[24]

Drug Content

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing 0.1 g of Verapamil Hydrochloride, shake with 150 ml of 0.1 M hydrochloric acid for 10 minutes, add sufficient 0.1 M hydrochloric acid to produce 200.0 ml and filter. Dilute 10.0 ml of the filtrate to 100.0 ml with water and measure the absorbance of the resulting solution at the maximum at about 277.80 nm. Calculate the content of $C_{27}H_{38}N_2O_4$, HCL taking 118 as the specific absorbance at 277.80 nm.[24]

In Vitro Buoyancy Study (floating lag time study)

All formulations were subjected to buoyancy test. Buoyancy test was done using USP type II apparatus at 50 rpm maintained at 37±0.5°C. Tablets were placed in 900 ml jar containing 0.1N HCL as dissolution medium. The FLT (Floating lag time) and FT (Floating time) was noted.[6]

Dissolution Studies

The release rate of Verapamil HCL from floating matrix tablet (n=3) was determined using Dissolution medium 0.1 N Hydrochloric acid and USP dissolution test apparatus. The specifications are (Volume of dissolution medium-900ml, Speed of paddle- 50 RPM, Temperature-37±0.5°C, Sample size - Tablet equivalent to 450 mg, Sampling interval- 1,2,3,4,5,6,7,8,9,10,11,12hrs). The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no.41 and the volume made up to 5 ml with 0.1N HCL. The samples were analyzed at 277.80 nm.[22]

Swelling Study

The previously weighed tablets were placed in dissolution vessels containing 0.1 N HCL at 37±0.5°C. At selected time interval (2, 4, 6, 8, 10 and 12hr respectively) tablets were withdrawn after a selected time interval. The swelling index was calculated by the following equation, and was shown in table 4.

$$Swelling\ Index = \frac{Wt - Wo}{Wo}$$

Where,

Wo= Initial weight of tablet.

Wt= Weight of tablet at time t.[8]

Factorial design for formulation

A factorial design is used to evaluate two or more factors simultaneously. A study in which there are 2 factors with 3 levels is called a 3^2 factorial design. For the present work 3^2 factorial designs was selected.[25] The two independent variables selected were HPMC K15M (X_1) and sodium alginate (X_2), and the nine formulations formulated as per the experimental design.

Mathematical modeling of kinetic release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release by using a DD Solver software, and the model with the higher correlation coefficient was considered to be the best model. The n value is used to interpret the release table 7. A 3^2 full factorial design was selected and the two factors were evaluated at three levels. HPMC K15M, sodium alginate combination were selected as independent variables and Q_{12} (% drug released at 12 hr) and floating lag time were the dependent variables.[25]

RESULTS AND DISCUSSION

Evaluation of Factorial Batches

Table 2: Evaluation of factorial batches

Code	Thickness (mm)	Hardness (kg/cm^2)	Tablet Density (gm/cm^3)	Weight Variation (Average Weight (mg)±SD)	Friability (%)	Drug Content (%)
F1	3.7±0.05	7.3±1.23	1.18±0.01	448±2.03	0.31±0.04	101.98±1.13
F2	3.68±0.01	7.0±0.59	1.14±0.01	446.6±1.42	0.21±0.03	96.55±2.18
F3	3.77±0.01	7.3±0.48	1.19±0.01	447.3±1.45	0.27±0.05	99.55±1.04
F4	3.79±0.06	7.1±1.14	1.18±0.03	449±0.23	0.18±0.06	99.1±1.54
F5	3.84±0.05	7.2±1.65	1.16±1.18	451±0.58	0.22±0.03	98.25±0.99
F6	3.77±0.04	7.3±0.42	1.17±0.01	451.2±1.52	0.18±0.06	98.36±1.27
F7	3.88±0.03	6.8±0.35	1.15±0.01	450.6±1.65	0.40±0.12	98.36±2.3
F8	3.89±0.02	6.5±1.65	1.13±0.01	448.4±2.13	0.33±0.02	99.32±0.45
F9	3.78±0.02	7.8±1.12	1.14±0.01	447±1.23	0.13±0.05	99.16±2.27

(All readings were taken in triplicate, n ± S.D.)

Floating lag time evaluation of Factorial batches

Floating lag time of factorial batches was found between the ranges of 45 sec to 480 sec as shown in figure 1.

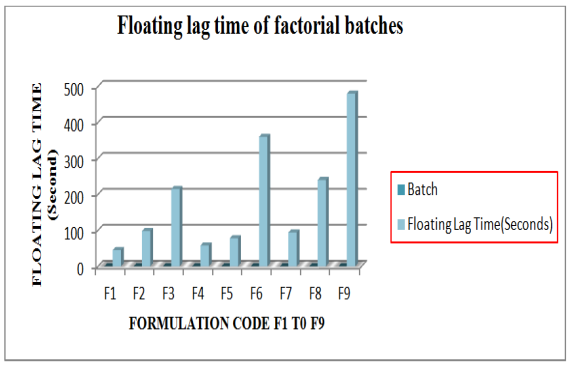

Figure 1: Floating lag time evaluation of factorial batches

Dissolution Studies for factorial batches

Dissolution study was performed in 0.1 N HCL for 12 h and the obtained result are summarised in table 3 while Figure 2 graphically represents the data.

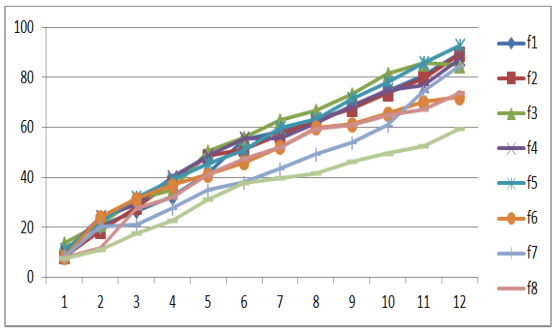

Figure 2: Cumulative % drug release of F1 to F9 Batches

The in vitro release of all the factorial design batches was studied table and Figure 2. Indicated that all the formulations follow a linear pattern of Verapamil release at least in their initial phase, which indicates the appropriate choice of the selected range of formulation variables. Percentage drug release at 12 hr (Q12) of the formulations F1, F2 and F3 containing ratio 14% of the

HPMC K4M and 9%, 11% and 13% of sodium alginate polymer showed significant similarity between F1 and F2 batches and sudden decrease in F3 and F4 batch indicating the rate retarding effect of polymer. The Q12 i.e. drug release after 12 hrs for other formulations were not selected because their %drug release was not found within limits. So that F5 batch was selected as optimized formulation.

Swelling index studies

The swelling studies revealed that the swelling index is increased with an increase in the polymer concentration. The swelling behavior of the polymer HPMC K15M at different concentration also affects the drug release profile. Higher swelling leads to imbibitions of more liquid medium, thus leading to polymer chain relaxation with volume expansion and subsequently affecting drug release profile.

The higher penetration rate of gastric fluid into the tablet leads to faster CO_2 gas generation and thereby reducing the floating lag time (FLT).

Mathematical modeling of Kinetic release

In present study the dissolution data were analyzed by DD Solver software to study the kinetics of drug release mechanism. The results showed that most of the factorial design batches followed Korsemeyer Peppas model.

The R^2 value of Korsemeyer Peppas model was found close to one as shown in table 5. In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated.

The n value is used to interpret the release mechanism as shown in table 5. The n values were found to be non-Fickian diffusion or anomalous transport.

Analysis of data by Design Expert software

The floating lag time and Q_{12} for the nine batches (F1-F9) showed a wide variation (i.e., 45-490 seconds, and 59.31-92.85%, respectively). The data clearly indicate that the floating lag time and Q_{12} values are strongly dependent on the selected independent variables.

The fitted regression equations relating the responses floating lag time and Q_{12} are shown in the following equations, respectively.

Response surface methodology was used for optimization of factorial batches and shown in figure 3.

Final equations in Terms of Actual Factors

FLT=+10813.66667-218.80000*A-136.70000*B+1.08000*A*B+1.20000A^2+0.70000B^2

Final equations in Terms of Actual Factors

Q12 = -1147.611131+26.63668*A+12.55676*B-0.10298*A*B-0.15365*A2-0.55862*B2

Response surface plot

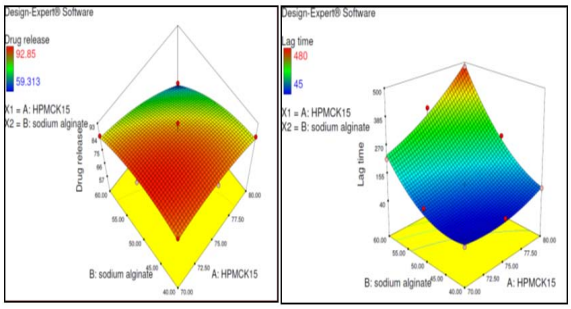

Figure 3: Response Surface Plot for FLT and Response surface plot for drug release

Optimization

Optimization was performed using design expert 7.0.0 software. So finally, from all above evaluation parameters, Batch F5 was optimized as best sustained release floating tablet for floating drug delivery system of Verapamil HCL.

SUMMARY AND CONCLUSION

The conclusions concluded from the experimental work are summarized below:

Analytical method based on UV-Visible spectrophotometer was developed for Verapamil HCL in pH 1.2 i.e. 0.1 N HCL at λ_{max} 277.80 nm.

- The polymer selected for the sustaining the release i.e. HPMC K15M and Sodium alginate are compatible with the drug.
- Floating tablet of Verapamil HCL were successfully prepared using HPMC K15M and Sodium alginate and other excipients.
- Direct compression method was used for preparation of Floating tablet of Verapamil HCL.
- The 3^2 factorial designs successfully applied for the optimization of the batches. The selected independent variable exhibits significant effect on dependent variables like drug release, Floating Lag time.
- The formulation F5 showed desired responses with respect to drug release (92.85%), Floating Lag Time (78sec).
- The study reveals optimized formulation F5 followed Korsmeyer Peppas model and mechanism of drug release was found to be Non-Fickian.
- Graphical presentation of the data using response surface plot helps to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis.
- Thus, an attempt to design an effective formulation technology was feasible.

Table 3: Cumulative % drug release of F1 to F9 batches

batch	Time interval in hr											
	1	2	3	4	5	6	7	8	9	10	11	12
F1	8.02±0.007	20.64±0.009	26.54±0.007	32.26±0.118	41.57±0.370	55.24±0.016	58.37±0.022	63.08±0.020	67.94±0.046	74.34±0.328	80.67±0.101	89.76±0.162
F2	8.35±0.118	18.69±0.153	28.09±0.014	37.97±0.008	48.51±0.022	51.37±0.131	57.03±0.067	63.00±0.133	67.51±0.395	73.74±0.046	79.62±0.021	89.42±0.067
F3	13.84±0.006	21.66±0.012	31.1±0.157	35.11±0.441	50.53±0.262	56.08±0.018	62.77±0.182	66.81±0.012	73.22±0.042	81.51±0.108	83.75±0.021	85.12±0.065
F4	10.04±0.035	24.12±0.013	29.16±0.045	40.11±0.014	48.51±0.056	54.86±0.015	56.33±0.100	61.74±0.019	68.9±0.016	74.79±0.058	76.67±0.099	87.45±0.152
F5	11.04±0.042	22.42±0.108	32.07±0.071	38.92±0.024	45.46±0.193	50.74±0.164	59.77±0.009	63.16±0.054	71.28±0.067	78.14±0.022	85.76±0.112	92.85±0.014
F6	8.35±0.171	24.12±0.025	31.39±0.041	36.9±0.088	41.32±0.011	46.08±0.017	52.25±0.014	59.97±0.0072	61.43±0.086	65.68±0.022	70.23±0.063	72.13±0.030
F7	8.51±0.238	20.44±0.036	21.02±0.002	27.61±0.036	35.14±0.035	38.26±0.012	43.53±0.131	49.21±0.009	53.98±0.005	61.13±0.013	74.66±0.023	84.55±0.046
F8	7.87±0.013	11.98±0.001	27.79±0.030	32.14±0.011	41.05±0.044	47.34±0.129	52.05±0.025	59.28±0.002	61.08±0.015	64.9±0.013	67.05±0.037	73.65±0.022
F9	7.43±0.030	11.05±0.054	17.74±0.006	22.64±0.155	31.28±0.086	37.66±0.013	39.84±0.033	41.59±0.089	46.36±0.181	49.59±0.074	52.33±0.032	59.31±0.144

(All readings were taken in triplicate, n ± S.D.)

Table 4: Swelling index of factorial batches

Time (Hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	0.880±0.009	0.881±0.040	0.944±0.010	0.872±0.015	0.901±0.013	0.925±0.005	0.897±0.040	0.912±0.007	0.969±0.016
4	1.105±0.004	1.108±0.008	1.164±0.002	1.102±0.580	1.133±0.064	1.175±0.322	1.116±0.027	1.161±0.005	1.205±0.008
6	1.189±0.002	1.228±0.023	1.345±0.034	1.212±0.011	1.257±0.067	1.361±0.008	1.255±0.353	1.334±0.011	1.483±0.057
8	1.287±0.140	1.311±0.020	1.468±0.016	1.301±0.005	1.316±0.036	1.542±0.022	1.315±0.376	1.463±0.028	1.569±0.008
10	1.688±0.020	1.741±0.008	1.812±0.037	1.732±0.017	1.755±0.015	1.864±0.101	1.745±0.110	1.809±0.012	1.872±0.025
12	1.817±0.007	1.867±0.025	1.987±0.034	1.862±0.017	1.974±0.039	2.056±0.372	1.879±0.050	1.984±0.030	2.230±0.080

(All readings were taken in triplicate, n ± S.D.)

Table 5: Application of model to drug release

BATCH	R^2 Value					n	K
	Zero	First	Higuchi	Korsemeyer Peppas	Hixon Crowell		
F1	0.9743	0.9579	0.8749	**0.9907**	0.9416	0.844	10.868
F2	0.9598	0.9608	0.8942	**0.9907**	0.9578	0.797	12.034
F3	0.9333	0.9516	0.9109	**0.9872**	0.9795	0.749	14.105
F4	0.9163	0.9684	0.9213	**0.9858**	0.9739	0.722	14.163
F5	0.9676	0.9477	0.8988	**0.9968**	0.9715	0.802	12.433
F6	0.8672	0.9684	0.9452	**0.9867**	0.9728	0.664	14.296
F7	0.9603	0.9131	0.8122	**0.9706**	0.9377	0.973	6.949
F8	0.9321	0.9464	0.8944	**0.9773**	0.9672	0.765	11.274
F9	0.9569	0.9488	0.8856	**0.9852**	0.9466	0.805	7.930

REFERENCES

1 Sharma N, Agarwal D, Gupta MK, Khinchi MP, A comprehensive review on floating drug delivery system, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2(2), 2011, 428-440.

2 Kim KH, Brahma NS, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release, 63, 2000, 235–259.

3 Tadros MI, Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers, European Journal of Pharmaceutics and Biopharmaceutics, 74, 2010, 332–339.

4 Nayak RK, Manjunath B, Narayanswami VB, Senthil A, Thakkar HK, Kumar DM, Mahalaxmi R, Design and evaluation of sustained release floating tablets of loratadine, Asian Journal of Biochemical and Pharmaceutical Research, 1, 2011, 105-126.

5 Gnanaprakash K, Chandhrashekhar KB, Chetty CM, Floating tablets of famotidine with natural polymer: an approach for gastric treatment, Journal of Pharmaceutical Sciences and Research, 2(10), 2010, 657-662.

6 Srikanth MV, Rao NS, Songa AS, Battu JR, Statistical design and evaluation of a propranolol HCl gastric floating tablet, Acta Pharmaceutica Sinica, 2(1), 2012, 60–69.

7 Nasa P, Mahant S, Floating systems: a novel approach towards gastroretentive drug delivery systems, International Journal of Pharmacy and Pharmaceutical Sciences, 2, 2010, 2-7.

8 Chavanpatil MD, Jain P, Chaudhary S, Shear R, Vavia PR, Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, International Journal of Pharmaceutics, 316, 2006, 86–92.

9 ICH Guidelines, Validation of Analytical Procedures: Text and Methodology, Q2 (R1), 2005.

10 Chowdhury R, Verma P, Floating drug delivery system – a new era in novel drug delivery, International Journal of Pharmaceutical research and Bioscience, 1(5), 2012, 91-107.

11 Jain NK, Controlled and novel drug delivery, 1st ed., BS publisher and distributers, New Delhi, 1997, 52-75.

12 Inez JM, Tomas QB, Leopoldo VR, Sustained delivery of captopril from floating matrix tablets, International Journal of Pharmaceutics, 362, 2008, 37–43.

13 Kumar DA, Mishra J, Recent advances in gastro retentive drug delivery system: a review, Mintage Journal of Pharamaceutical and Medical Science, 2, 2013, 25-27.

14 Bagherwal A, Patidar DK, Sharma P, Studies on formulation and evaluation of floating tablets of ciprofloxacin HCl, International Journal of Comprehensive Pharmacy, 5(2), 2010, 1-4.

15 Swarbrick J, Boylan JC, Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 1992, 1185-1186.

16 Panigrahy R, Formulation and *in-vitro* evaluation of combined floating Mucoadhesive tablet of metoprolol succinate, International Journal of Pharmacy and Pharmaceutical Science, 3, 2011, 221-226.

17 Liandong H, Yang X, Liu W, Jia Y, Shang C, Hongxin X, Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: *in vitro* and *in vivo* evaluation in healthy volunteers, European Journal of Pharmaceutical Sciences, 42, 2011, 99–105.

18 Dave BS, Avani F, Patel MM, Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation, AAPS pharm scitech, 5(2), 2004, 2-6.

19 Bolton S, Desai P, Cresskill S, Floating sustained release therapeutic compositions, U.S. patent number:4814179, mar.21, 2004.

20 The Indian Pharmacopoeia, The Indian Pharmacopoeia Commission, II, Ghaziabad, 2007, 185-354.

21 Tripathi, KD, Essentials of medical pharmacology, 7th ed, Jaypee brothers medical publisher, New Delhi, 2013, 535-540.

22 United State Pharmacopoeia NF, The official compendia of standard, The United State Pharmacopoeia Convention, 12601, Twinbrook parkway rockwille, I, 2009, 263-271.

23 Raymond C, Paul JS, Owen SC, Handbook of Pharmaceutical Excipients, 5th ed, Pharmaceutical press and the american pharmacists association, 2006, 346, 665, 185, 656, 430.

24 Lachman L, Liberman H, Kanig J, The theory and practice of industrial pharmacy,3rd ed, varghese publishing house, 1987, 296-301.

25 Dean A, Voss D, Design and analysis of experiments, 1st ed, Springer International Publication, New York, 1999, 18, 48, 244, 465, 523-528, 554.

Source of Support: Nil, **Conflict of Interest:** None.