ORIGINAL ARTICLE

Design and Optimization of Modified Tamarind Gum-based Floating-bioadhesive Tablets of Verapamil Hydrochloride

Kailas K. Mali[1], Shashikant C. Dhawale[2]

[1]Department of Pharmaceutics, YSPM's Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara, Maharashtra, India, [2]Department of Pharmacology, School of Pharmacy, SRTM University, Nanded, Maharashtra, India

Abstract

Aim: The present investigation deals with the formulation of floating-bioadhesive matrix tablets of verapamil hydrochloride (VH). The main objective of this work was to overcome the limitations of the conventional floating matrix tablets. **Materials and Methods:** Hydroxypropyl methylcellulose (HPMC) K15M was used as a matrix-forming agent whereas carboxymethyl tamarind gum (CMTG) was used to promote bioadhesion. Systematic optimization was performed using a central composite design with two independent variables and six dependent variables. Tablets were prepared by using the wet granulation method. The effect of polymer ratio (HPMC:CMTG) and sodium bicarbonate (SB) concentration on the total floating time (TFT), floating lag time (FLT), bioadhesion, swelling, and drug release (DR) was studied and optimized. **Results and Discussion:** Floating-bioadhesive matrix tablets of VH showed good physicochemical properties. The FLT was within the range of 2.87-14.41 min and TFT was more than 12 h. The tablets showed 17-30% of burst release in the 1st h and controlled release over a period of 12-h. DR and swelling were significantly ($P < 0.05$) affected by polymer ratio and concentration of SB in formulation. The polynomial mathematical models, generated for various response variables using multiple regression analysis, were found to be statistically significant ($P < 0.05$). Optimized batch showed FLT of 6.14 min, bioadhesion of 17.23 g, swelling of 74.83% at 5 h, and DR of 75.48% at 10 h, with anomalous release mechanism. The observed values were near to the predicted values obtained by the experimental design. **Conclusion:** The floating-bioadhesive tablets of VH prepared using HPMC and CMTG exhibited a potential to retain and control the release of drug in stomach for more than 12 h and may be used as an alternative to the conventional floating tablets of VH.

Key words: Bioadhesion, carboxymethyl tamarind gum, central composite design, floating drug delivery, hydroxypropyl methylcellulose, verapamil hydrochloride

INTRODUCTION

Verapamil hydrochloride (VH) is a calcium channel blocker used in the treatment of cardiovascular disorders such as hypertension, angina pectoris, and arrhythmia. Due to its short biological half-life (2-8 h), it requires frequent administration (40-180 mg, TD). Although it shows good absorption (90%) in the digestive tract following oral administration, only 10-20% of it reaches the systemic circulation in an unchanged form.[1] This occurs due to the narrow absorption window of the drug.

To improve the bioavailability of VH and reduce the frequency of administration, various researchers have prepared gastroretentive floating or bioadhesive systems which may slowly release the VH in stomach and promote its absorption in the upper gastrointestinal tract (GIT).[2-5] However, a major limitation of the floating systems is the requirement of adequate amount of fluid in the stomach to support their buoyancy. As the stomach empties, the floatability of the system may get hampered due to the depletion of fluids.[6] On the other hand, bioadhesive systems face the problem of mucus turnover. The secretion of mucus from the mucosal

Address for correspondence:
Kailas K. Mali, YSPM's Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara - 415 011, Maharashtra, India. Phone: +91-9552527353.
E-mail: malikailas@gmail.com

Received: 07-07-2016
Revised: 02-08-2016
Accepted: 31-08-2016

lining of the stomach may detach the bioadhesive dosage form from the wall of the stomach, further leading to its passage into the lower GIT. This problem can be resolved by making the floating system that adheres to the wall of the stomach when the fluid level depletes. The use of synthetic polymers such as carbopol, polymethacrylic acid, polyacrylic acid[7,8] and natural polymers such as xanthan gum and guar gum[9] as bioadhesive agents in the floating matrix tablets is reported in literatures.

Natural polymers primarily remain attractive as hydrophilic matrix for drug delivery system because of their easy availability, cost-effectiveness, biodegradability, biocompatibility, and acceptance by regulatory authorities.[2,10] Tamarind seed gum (TG) is a natural polymer well known for its applicability in food industry. It consists of non-ionic, neutral, branched polysaccharide chain having cellulose-like backbone.[11] TG can be chemically modified using various groups such as acetyl, carboxymethyl, and hydroxyalkyl to overcome its drawbacks such as unpleasant odor, dull color, and fast degradability. Carboxymethyl group disrupts the organization of TG structure by exposing the polysaccharide network of hydration resulting in higher viscosity and lower biodegradability and thus enhances its shelf life.[11-13] Recently, carboxymethylated TG (CMTG) has attracted the formulation scientists for its application in drug delivery systems.[14-18] However, no study has been reported till date, where hydroxypropyl methylcellulose (HPMC) and CMTG have been used together for achieving gastroretention by combining the floating and bioadhesion approach.

Pharmaceutical scientists often confront the challenge of finding an appropriate combination of independent process variables (factors) that will produce an optimum product.[19,20] Response surface methodology is used for optimization of drug delivery systems which involve the use of various types of experimental designs, generation of polynomial relationships, and mapping of the response over the experimental domain to select the optimum formulation.[21-23] Among various experimental designs, the central composite design has been commonly used for designing and optimizing different pharmaceutical formulations and processes.[24,25] This technique is more flexible, effective, and provides a large extent of information on experimental variable effects. In addition, it requires a minimum number of experimental runs and time.

In this study, we have prepared floating-bioadhesive tablet of VH using HPMC as a matrix-forming agent and CMTG as a bioadhesive agent. Sodium bicarbonate (SB) was added as a gas-forming agent. Central composite design was used to obtain an optimized batch. The study aimed at obtaining an efficient gastroretentive dosage form using this novel polymer combination.

MATERIALS AND METHODS

Materials

VH was obtained as a gift sample from Zydus Cadila, Ahmedabad. Polymers and other excipients used were of pharmaceutical grade and were procured from Loba Chemie, Mumbai, India.

Methods

Extraction of tamarind gum

20 g of defatted tamarind seed powder was added to 200 ml of cold distilled water to prepare slurry. The slurry was poured into 800 ml of boiling distilled water containing citric acid (0.2%). The solution was boiled for 20 min with stirring in a water bath. The resulting thin clear solution was kept overnight (24 h) so that most of the proteins and fibers settle out, following which the solution was centrifuged at 5000 rpm for 20 min. The supernatant liquid was separated and poured into the excess of absolute alcohol with continuous stirring (1:1). The precipitate was washed with 200 ml of absolute ethanol, diethyl ether, and petroleum ether and/or acetone and dried at 50-60°C for 10 h. The dried polymer was powdered, sieved, and stored in a desiccator until further use.[26]

Preparation of CMTG

Carboxymethylation of TG was carried out using the method reported by Goyal *et al*., 2007.[11] TG (0.05 mol) was dispersed in 80 ml alkaline aqueous methanol (0.158 mol sodium hydroxide). To this dispersion, monochloroacetic acid (0.09 mol) was added in solid form with continuous stirring for 15 min. The flask was immersed in a thermostatic water bath, and temperature was maintained at 70°C for 60 min. The contents of the flask were shaken occasionally during the course of the study. The reaction product was filtered, dissolved in water, and neutralized with dilute acetic acid. The reaction product was precipitated in ethanol and washed twice with aqueous methanol (80%, v/v) followed by pure methanol. The product was initially dried at room temperature and then in a vacuum oven at 40°C for 4 h to obtain CMTG. The degree of substitution of CMTG was determined by titrimetric method.[27]

Experimental design

A central composite design was employed containing two factors evaluated at three levels, and the experimental trials were performed at all 13 possible combinations. The studied factors (independent variables) were ratio of polymer (HPMCK15M: CMTG) (X_1) and concentration of SB (X_2), while total floating time (TFT) (Y_1), floating lag time (FLT) (Y_2), bioadhesion (Y_3), swelling index at 5 h (Y_4), and drug release (DR) at 1 h (Y_5) and 10 h (Y_6) were used as dependent

variables (responses). The process variables (factors) and levels with experimental values are reported in Table 1.

Design-Expert software (Stat-Ease Inc., USA) was used for the generation and evaluation of experimental design. The polynomial mathematical model generated by central composite design is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \quad (1)$$

Where, Y is the response; b_0 is the intercept, and b_1, b_2, b_3, b_4, and b_5 are regression coefficients. X_1 and X_2 are individual effects; X_1^2 and X_2^2 are quadratic effects and X_1X_2 is the interaction effect. One-way analysis of variance (ANOVA) was applied to estimate the significance of the model ($P < 0.05$).

Preparation of floating bioadhesive tablets of VH

Floating tablets of VH were prepared by wet granulation method [Table 1]. All the ingredients including drug, polymers, diluents, and gas-generating agent were weighed accurately and blended for 30 min. Polyvinylpyrrolidone K30 in isopropyl alcohol was added to form cohesive mass. The cohesive mass was screened through sieve #12 to get the granules. The granules were dried and dry screened through sieve #16. The granules were lubricated and compressed at predetermined hardness (5-6 kg/cm^2) on a rotary tableting machine (Remek Minipress, Karnavati, Mumbai, India) using 10 mm flat punches.

Excipient compatibility and physical characterization

The prepared physical mixtures of drug and polymers were evaluated for compatibility between drug and excipients using attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) (MIRacle 10, IRAffinity-1, Shimadzu, Japan).

Floating tablets of VH were evaluated for the physicochemical parameters such as compressibility index, thickness, diameter, hardness, friability, drug content, and weight variation.

Table 1: Design summary

Normalized levels	Independent variables (factors)	
	HPMC:CMTG (X_1)	SB (mg) (X_2)
−1.414	1.17	2.93
−1	2	5
0	4	10
1	6	15
1.414	6.83	17.07

HPMC: Hydroxypropyl methylcellulose K15M,
CMTG: Carboxymethylated tamarind gum, SB: Sodium bicarbonate

Floating characteristics

The time required for the tablets to reach the surface of the dissolution medium (FLT) and the period for which the tablets constantly float on the surface of the dissolution medium (TFT) were determined by using USPXXII paddle apparatus (TDT - 06LP, Electrolab, Mumbai). The dissolution medium consisted of 900 ml of 0.1 N HCl maintained at 37 ± 0.5°C throughout the study. The matrix integrity of the prepared formulations was supervised during the study.[28]

In vitro DR and release kinetics

In vitro dissolution tests were conducted in 900 ml 0.1 N HCl at 37 ± 0.5°C using USPXXII tablet dissolution apparatus (TDT - 06LP, Electrolab, Mumbai) for 12 h. The speed of rotation was maintained at 50 rpm. At predetermined time intervals, 5 ml sample was withdrawn and diluted. The samples were analyzed for DR by measuring the absorbance at 278 nm using spectrophotometric method (UV-1800, Shimadzu, Japan).[2]

To predict and correlate the release behavior of VH floating tablets, the release data were fitted into suitable mathematical models such as zero order, first order, Higuchi, and Korsmeyer–Peppas model. Percent dissolution efficiency (DE) and mean dissolution time (MDT) were calculated for all formulations.[29]

Ex-vivo bioadhesion studies

The working of a double-beam physical balance formed the basis of the bioadhesion test apparatus. The right pan of the physical balance was removed and replaced with a steel cylinder hanged with a lightweight thread. The height of this total setup was adjusted to accommodate a glass container below it, leaving a head space of about 0.5 cm in between. A steel block was fabricated with an upward protrusion on one of its faces. This was kept inside the glass container, which was then placed below the right hand setup of the balance. The two sides were then balanced.

The sheep mucus membrane was excised and washed (equilibrated at 37 ± 1°C for 30 min in phosphate buffer saline medium before the bioadhesion evaluation study) and tied tightly with the mucosal side upward, using a thread over the protrusion in the steel block. The block was then lowered into the glass container, which was then filled with isotonic phosphate buffer maintained at 37 ± 1°C. The level of buffer was adjusted along the surface of mucosal membrane so as to keep it moist and kept below the right hand setup of the balance. The tablet was then stuck to the cylinder, using cyanoacrylate glue, and the balance beam was raised. A constant weight of 10 g was then placed over the steel block for the total contact period of 5 min. Bioadhesive strength was then assessed by adding weights

on the left pan till the tablet separated from the mucosal surface, in terms of the weight (in g) required to detach tablet from the membrane.[30]

Swelling study

Initially, the dry weight of tablets was taken, and tablets were placed in the basket attached to the shaft of dissolution apparatus (Type I). The baskets were then immersed into 0.1 N HCl (900 ml) at 37 ± 0.5°C. At predetermined time intervals, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water, and weighed on the analytical balance (BL-220H, Shimadzu, Japan) to get the wet weight of the tablet. Swelling was calculated by using the following formula.[30]

$$\text{Swelling (\%)} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}} \times 100 \quad (2)$$

Statistical analysis of the data and optimization

Polynomial models including linear, interaction, and quadratic terms were generated for all the response variables using Design-Expert software. The best-fitting model was selected based on the comparisons of several statistical parameters provided by Design-Expert software. In addition, ANOVA was used to identify the significant effect of factors on response regression coefficients. The *F*-test and *P* value were also calculated with the software. The relationship between the dependent and independent variables was further determined by using three-dimensional (3D) response surface plots. These plots are useful to study the effects of various factors on the response at one time and predict the responses of dependent variables at the intermediate levels of independent variables. Subsequently, a numerical optimization technique by the desirability approach and numerical optimization technique were used to generate the new formulations with the desired responses.

RESULTS AND DISCUSSION

Extraction of TG and preparation of CMTG

The addition of trisodium phosphate in the boiling aqueous solution of citric acid helps to separate the proteins from the TG due to precipitation. The TG present in the supernatant solution is separated by alcohol precipitation.[31] The dispersion of TG in sodium hydroxide solution leads to the formation of TG-alkoxide. When this solution is heated in the presence of methyl cation affinity (MCA), a SN^2 reaction takes place in between TG-alkoxide and MCA, resulting in the carboxymethylation of TG.[11] The carboxymethylation of TG was confirmed from the infrared spectroscopy. The degree of substitution was calculated using titrimetric method and was found to be 0.18.

Compatibility and physicochemical characterization

The spectrum of VH showed characteristic peaks at 3041, 2960.7/cm (superimposed C-H stretching vibration in methyl and methylene groups), 2578.8/cm (aldehydic C-H stretching vibration), 1597, 1516, 1462/cm (C = C in aromatic ring); 1255.7, 1147.6/cm (C-O stretching in aromatic and aliphatic), and 1026.13/cm (C-N aliphatic stretching vibration). HPMC showed characteristic O-H vibrational stretching peak at 3421.7/cm, symmetric stretching mode of methyl and hydroxypropyl at 2912.51/cm, stretching vibration of C-O for six-membered cyclic rings at 1645.3/cm, and the symmetric vibration of methoxy group at 1373.3/cm and asymmetric at 1454/cm. CMTG showed broadband at 3361.9/cm due to OH stretching and a prominent peak at 1413.8/cm corresponding to the C=O stretch of COO^-. The characteristic peaks of VH were observed in the spectra of physical mixtures with negligible shifts possibly due to peaks of CMTG and HPMC lying in the same region. The noticeable shifts or disappearance of peaks was not observed which showed lack of drug-polymer or polymer-polymer interactions [Figure 1].

The data of evaluation parameters such as thickness, hardness, friability, weight variation, and drug content of floating-bioadhesive tablets of VH are shown in Table 2. The physicochemical properties of floating tablets showed satisfactory results for all the studied parameters.

Experimental design

Central composite design was used to study the effect of dependent variables. Experimental trials were performed at all 13 possible combinations, and the observed responses on independent variable are shown in Table 3.

All responses were fitted into the quadratic response surface model to study the effect of independent variables. The polynomial equations for responses were derived which comprised the coefficients for intercept, main effects, and interaction effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The influence of polymer ratio and concentration of SB on each response was further elucidated by 3D response surface plots.

The results of ANOVA and statistical parameters, as shown in Tables 4 and 5, indicated that the model was significant for all the studied responses. Further, adequate precision which measures signal-to-noise ratio was observed to be inadequate (>4), indicating that the models can be used to navigate the design space.

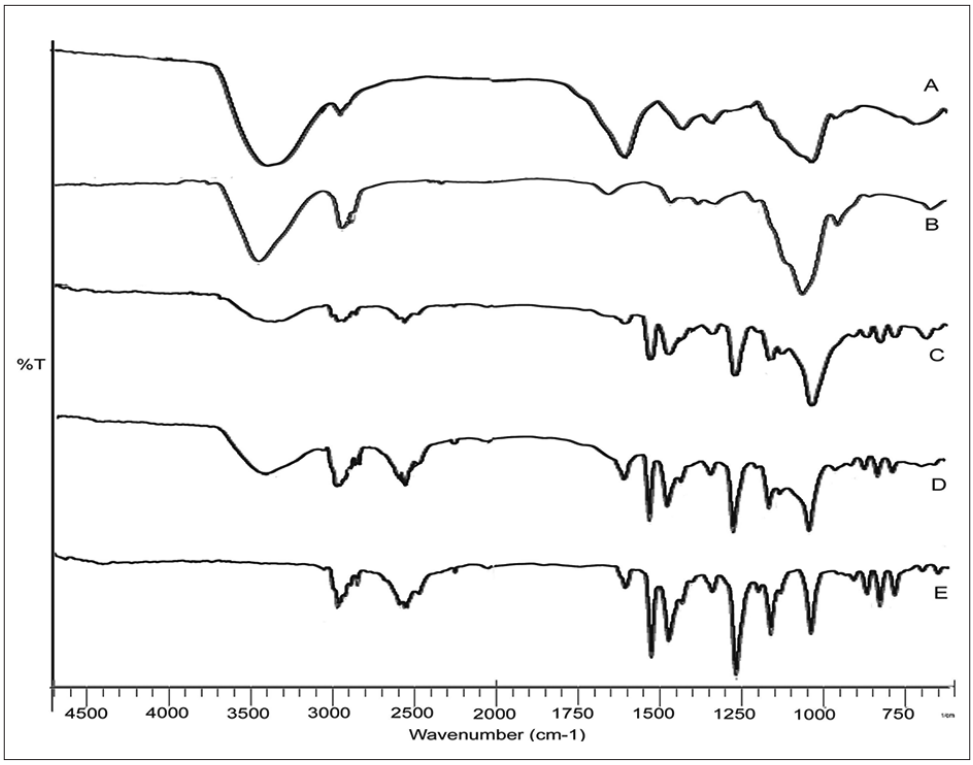

Figure 1: Overlay attenuated total reflectance-Fourier transform infrared spectroscopy spectra of verapamil and physical mixtures. (A) Carboxymethyl tamarind gum (CMTG), (B) hydroxypropyl methylcellulose (HPMC), (C) physical mixture of verapamil hydrochloride (VH) and CMTG, (D) physical mixture of VH, CMTG, and HPMC; (E) VH

The polynomial equations for TFT, FLT, bioadhesive strength, percent swelling, and DR at 1 and 10 h are as follows:

$$Y_1(\text{TFT}) = 21.51 + 3.25X_1 + 1.06X_2 - 0.025X_1X_2 - 0.52X_1^2 - 2.2X_2^2 \quad (3)$$

$$Y_2(\text{FLT}) = 4.67 - 0.35X_1 - 3.83X_2 - 0.27X_1X_2 - 0.22X_1^2 + 2.01X_2^2 \quad (4)$$

$$Y_3(\text{Bioadhesive strength}) = 18.58 - 2.30X_1 + 0.45X_2 \quad (5)$$

$$Y_4(\text{Percent swelling}) = 76.36 - 3.58X_1 - 2.11X_2 - 5.06X_1^2 - 3.48X_2^2 - 7.19X_1X_2 \quad (6)$$

$$Y_5(\text{Drug release at 1 h}) = 18.89 + 0.67X_1 + 2.53X_2 + 4.06X_1X_2 + 2.59X_1^2 + 1.9X_2^2 \quad (7)$$

$$Y_6(\text{Drug release at 10 h}) = 83.05 - 5.98X_1 + 9.44X_2 + 1.25X_1^2 - 0.50X_2^2 - 0.45X_1X_2 \quad (8)$$

Effect of formulation variables on TFT and FLT

Equation (3) indicates that TFT was highly influenced by the polymer ratio. An increase in the polymer ratio was found to increase the TFT [Figure 2a]. This may be due to the increase in the amount of HPMC which may increase the gel strength of the swollen matrix and enhance the entrapment of the generated CO_2 bubbles.[28] Formulations containing low polymer ratio and SB concentration exhibited less TFT.

From Equation (4), it was found that the concentration of SB showed a prominent effect on the FLT. The FLT was found to be decreased with increase in the SB concentration [Figure 2b]. This can be explained on the basis of the interaction between HCl present in the dissolution medium and SB. The HCl reacts with SB within the tablet resulting in the formation of CO_2 which gets entrapped within the polymeric matrix. This results in the buoyancy of the tablet. An increase in the concentration of SB may increase the formation of CO_2 and thus reduce the time required for the tablet to float. The results of FLT were in good agreement with earlier reports which state that FLT is more dependent on the concentration of SB than the polymer ratio.[32]

Effect of formulation variables on bioadhesive strength

Equation (5) shows the negative and prominent effect of polymer ratio on bioadhesion. In addition, the 3D response surface plot [Figure 2c] showed the significant changes in bioadhesion caused by variation in the polymer ratio. At low polymer ratio, the bioadhesion was found to be increased

Table 2: Physicochemical characterization of floating tablets of verapamil HCl

Formulation code	Thickness (mm; *n*=10)	Hardness (kg/cm²; *n*=3)	Friability (%)	Weight variation (*n*=20)	Drug content (%)	Swelling index (%; *n*=3; 12 h)
R1	3.08±0.04	5.75±0.27	0.33	297.6±2.03	96.04	57.83±1.76
R2	3.1±0.02	5.75±0.41	0.13	295.9±2.35	97.7	50.97±1.44
R3	3.09±0.03	5.75±0.27	0.15	296.1±2.02	99.4	43.89±1.68
R4	3.09±0.02	5.66±0.25	0.27	295.3±2.31	99.1	29.54±1.51
R5	3.1±0.02	5.58±0.2	0.33	294.3±2.60	97.7	26.11±1.99
R6	3.1±0.04	5.66±0.25	0.46	295.62.38	100.25	43.45±1.58
R7	3.09±0.02	5.83±0.25	0.33	298.7±1.60	104.3	47.641.53
R8	3.06±0.04	5.91±0.2	0.47	294.9±2.36	97.9	50.33±1.69
R9	3.08±0.05	5.75±0.27	0.27	294.6±1.82	98.55	21.37±1.54
R10	3.09±0.01	5.83±0.25	0.4	294.8±1.70	96.85	31.29±1.17
R11	3.07±0.04	5.91±0.2	0.13	295.05±1.53	99.6	64.98±1.11
R12	3.12±0.01	5.83±0.25	0.47	295.1±1.58	97.4	45.33±1.52
R13	3.09±0.05	5.75±0.27	0.28	297.8±1.30	96.85	43.9±1.07

All values are mean±SD. SD: Standard deviation

Table 3: Formulations with the levels of independent variables and observed responses

Run	Independent variables		Observed responses					
	X_1	X_2	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
R1	6.00	5.00	23.26	7.29	15.83	72.71	17.2	68.36
R2	4.00	2.93	12.63	14.41	18.13	72.00	19.91	69.76
R3	4.00	10.00	21.4	4.16	18.66	76.07	20.23	80.44
R4	4.00	17.07	17.96	3.57	18.76	66.03	28.82	98.60
R5	1.17	10.00	13.5	5.02	22.13	70.90	25.91	97.40
R6	4.00	10.00	21.3	4.47	18.36	75.75	20.37	81.23
R7	4.00	10.00	21.16	4.76	18.63	77.04	17.7	82.01
R8	2.00	5.00	17.5	8.91	20.86	71.08	22.41	77.60
R9	6.00	15.00	23.66	2.87	18.46	50.96	29.14	84.84
R10	6.83	10.00	23.76	4.02	14.43	60.78	25.56	77.94
R11	2.00	15.00	18	5.59	20.91	78.11	18.1	95.88
R12	4.00	10.00	21.9	5.07	19.16	75.96	18.46	82.40
R13	4.00	10.00	21.76	4.91	18.06	76.99	17.68	89.06

X_1 - Ratio of HPMC to CTG (w/w); X_2 – SB (mg); Y_1 - TFT (h); Y_2 – FLT (min), Y_3 - Bioadhesion (g); Y_4 - Swelling at 5 h (%); Y_5 - Cumulative drug release at 1 h (%); Y_6 - Cumulative DR at 10 h (%). SB: Sodium bicarbonate, HPMC: Hydroxypropyl methylcellulose, CTG: Carboxymethyl tamarind gum, FLT: Floating lag time, TFT: Total floating time, DR: Drug release

which can be due to high concentration of CMTG. CMTG shows bioadhesive nature due to the presence of carboxylic groups which can form hydrogen bonds with oligosaccharide chains of mucin.[17,33] The observed results for bioadhesion were in contrast to results obtained by Rajab *et al*., describing the non-adhesive nature of CMTG.[34]

Effect of formulation variables on percent swelling at 5 h

Equation (6) reveals the negative effect of polymer ratio, concentration of SB, and their interaction on the percent swelling. The same can be observed in Figure 2d. The results of swelling study are shown in Figure 3. Swelling of matrices was found to be increased gradually upto 5-6 h and thereafter, it was reduced due to erosion.

The formulations containing low polymer ratio and high amount of SB (R9 and R11) exhibited high values of percent swelling. It was found that the concentration of CMTG altered the swelling in the presence of SB and HPMC. It is already reported that CMTG shows increase in the gelation and swelling as the pH of its aqueous solution approaches the neutral value.[16] When the dissolution medium penetrates

Table 4: Summary of ANOVA for responses

Source	Sum of squares	d.f.	Mean square	*F* value	*P* value *P*>*F*
TFT (h) (quadratic model)					
Model	127.34	5	25.47	5.31	0.0247
X_1	84.50	1	84.50	17.63	0.0040
X_2^2	33.54	1	33.54	7.00	0.0332
Lack of fit	33.16	3	11.05	112.8	0.0003
FLT (min) (cubic model)					
Model	109.04	7	15.58	63.74	0.0001
X_2	58.75	1	58.75	240.41	0.0001
X_2^2	28.12	1	28.12	115.06	0.0001
$X_1^2 X_2$	7.20	1	7.20	29.47	0.0029
Lack of fit	0.70	1	0.70	5.30	0.0828
Bioadhesion (g) (linear model)					
Model	43.80	2	21.90	42.89	<0.0001
X_1	42.19	1	42.19	87.67	<0.0001
Lack of fit	4.44	6	0.74	4.46	0.0847
% Swelling at 5 h (cubic model)					
Model	727.61	7	103.94	191.37	<0.0001
X_1	51.21	1	51.21	94.28	0.0002
X_2	17.82	1	17.82	32.81	0.0023
X_1^2	178.40	1	178.40	53.50	0.0002
X_2^2	84.08	1	84.08	25.21	0.0015
X_1X_2	207.07	1	207.07	62.09	0.0001
Lack of fit	1.24	1	1.24	3.36	0.1400
Percent DR at 1 h (quadatic model)					
Model	184	5	36.95	6.91	0.0123
X_2	51.16	1	51.16	9.57	0.0175
X_1X_2	66.02	1	66.02	12.35	0.0098
X_1^2	46.63	1	46.63	8.72	0.0213
X_2^2	25.22	1	25.22	4.72	0.0664
Lack of fit	30.37	3	10.12	5.74	0.0622
Percent DR at 10 h (quadratic)					
Model	1013.74	5	202.75	14.96	0.0013
X_1	285.61	1	285.61	21.07	0.0025
X_2	713.40	1	713.40	52.64	0.0002
Lack of fit	47.30	3	15.77	1.33	0.3832

TFT: Total floating time, FLT: Floating lag time, DR: Drug release

the tablet matrix, the SB reacts with the HCl and neutralizes it and thus may increase the pH of the medium within the tablet. This may favor the gelation as well as swelling of CMTG. Therefore, at low polymer ratio, an increase in the concentration of SB increased the swellability of the tablets. Exactly opposite results were obtained for the tablets with

Table 5: Statistical parameters

Parameters	TFT (h)	FLT (min)	Bioadhesion (g)	% Swelling at 5 h	% DR at 1 h	% DR at 10 h
SD	2.19	0.49	0.71	0.74	2.31	3.68
Mean	19.84	5.77	18.65	71.11	21.65	68.51
CV %	11.04	8.56	3.83	1.04	10.68	4.41
PRESS	236.45	45.38	10.56	81.69	226.96	410.70
R-Squared	0.7914	0.9889	0.8956	0.9963	0.8316	0.9144
Adeq Precision	7.128	28.236	18.92	46.96	8.393	12.38

TFT: Total floating time, FLT: Floating lag time, DR: Drug release, SD: Standard deviation

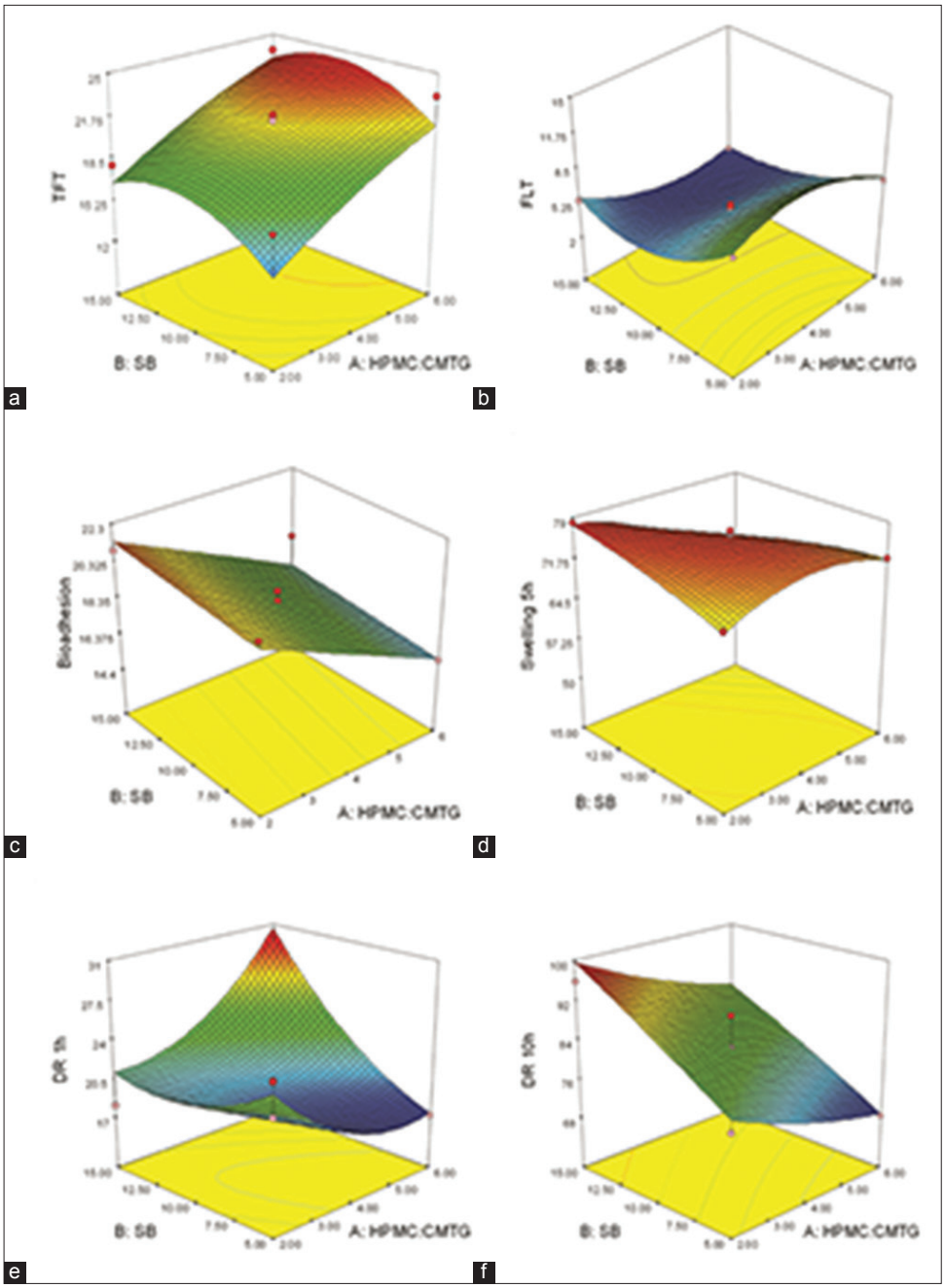

Figure 2: Influence of polymer ratio and SB on total floating time (a), floating lag time (b), bioadhesion (c), percent swelling at 5 h (d), percent drug release at 1 h (e), and percent drug release at 10 h (f)

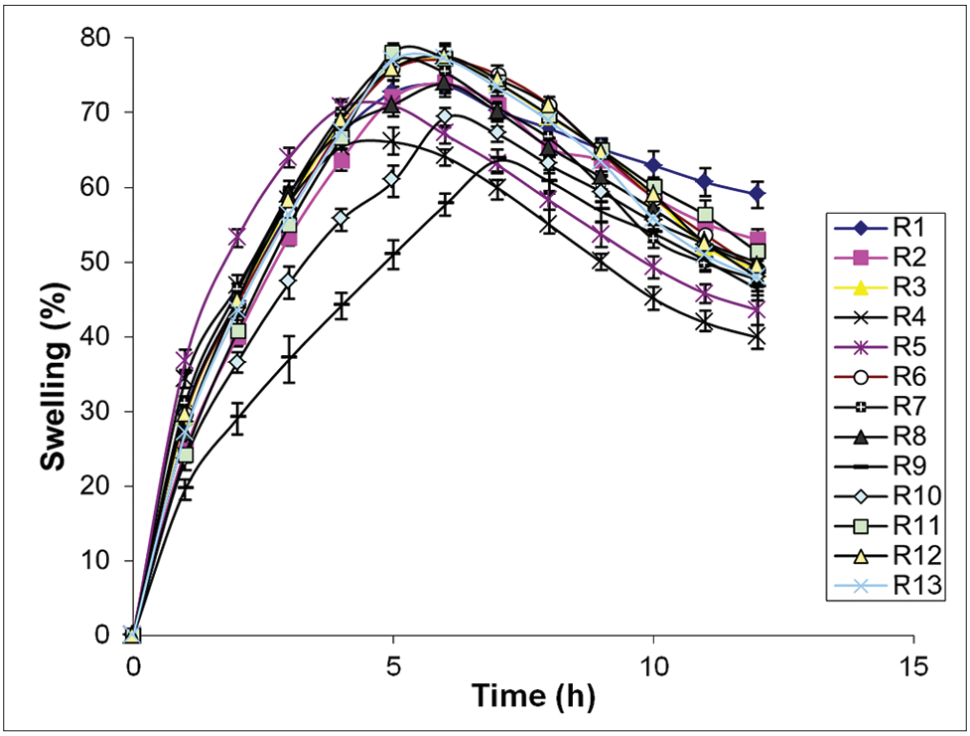

Figure 3: Swelling behavior of run R1 to R13

high polymer ratio where increase in the concentration of SB led to reduced swellability. This may be due to the decrease in the amount of CMTG and increase in the erosion of the tablet matrix, which is discussed under "Effect of formulation variables on DR." Besides, at low SB concentration, increase in the polymer ratio increased the swelling of the tablets followed by a slight decrease at the end. The reason for this slight decrease was unknown. However, at high SB concentration, the percent swelling was found to be decreased with increase in polymer ratio, which is mainly attributed to the matrix erosion. To properly understand the swelling behavior of HPMC and CMTG, further studies are required in the absence of SB.

Effect of formulation variables on DR

The DR profile of all the formulations is shown in Figure 4. Equation (7) suggests a marked effect of the interaction in between the SB and HPMC:CMTG polymer ratio on the DR at 1 h. This may be due to increase in pH within the tablet matrix due to the presence of SB, which ultimately affects the gelling behavior of CMTG as explained previously. It was observed that at low polymer ratio, increase in the amount of SB led to decrease in the DR at 1 h [Figure 2e]. This may be attributed to an increase in the gelation and swelling of the CMTG associated with increase in the pH, further causing an increase in the diffusion pathlength of VH, thus retarding its release. However, at low SB concentration, as the polymer ratio increased, the DR is retarded. This may be ascribed to the increase in the amount of HPMC which has good gel strength. On the other hand, increase in the concentration of SB increased the DR in the tablets with a high polymer ratio. The reduction in the gel strength of HPMC, increase in the porosity of the tablets, and erosion related to the increase in the concentration of gas-forming agent may be the reasons behind this increase in the DR.

The DR at 10 h was found to be influenced by polymer ratio and SB concentration (Equation 8). As the time progresses, the SB completely reacts with HCl, following which the pH of the tablet matrix may reduce. Under such circumstances, gelation of CMTG may reduce and DR from the tablet may increase. Therefore, at 10 h, even at low polymer ratio, increase in the amount of SB led to an increase in the DR [Figure 2f]. The retardation of DR with increase in the polymer ratio may be due to increase in the amount of HPMC as explained above.

The curve fitting results of the *in vitro* DR data are shown in Table 6. The formulations (R4, R5) having lower values of MDT and higher values of DE exhibited faster, complete, and Fickian release of drug whereas all the remaining formulations showed controlled release over a period of 12 h with non-Fickian diffusion. This indicates that DR from the floating-bioadhesive tablets of VH is governed by diffusion coupled with erosion.

Optimization

A numerical optimization technique using the desirability approach was used to develop floating tablet of VH

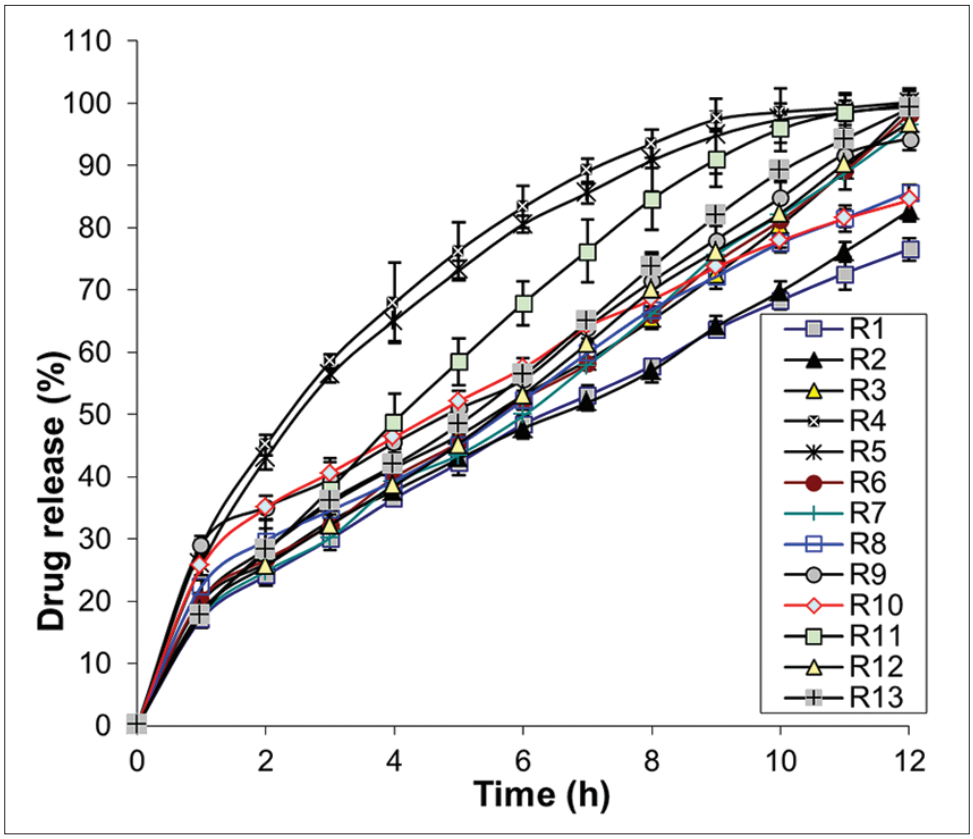

Figure 4: *In vitro* release profile for run R1 to R13

Table 6: *In vitro* release data of floating tablet of VH

Formulation code	% DR 12 h	DE (%)	MDT (h)	Correlation coefficient (R^2)				Release exponent (*n*)
				Zero order	First order	Higuchi	Korsmeyer-Peppas	
R1	76.56±1.80	46.04	4.78	0.995	0.952	0.996	0.998	0.66
R2	82.78±1.73	47.31	4.85	0.996	0.980	0.974	0.984	0.63
R3	97.34±2.06	53.44	5.54	0.991	0.988	0.960	0.977	0.68
R4	100.2±1.73	73.99	3.13	0.891	0.829	0.952	0.963	0.45
R5	99.9±2.54	71.75	3.38	0.918	0.851	0.970	0.975	0.47
R6	98.32±1.32	52.92	5.54	0.997	0.981	0.971	0.985	0.74
R7	96.2±1.55	51.96	5.51	0.997	0.976	0.975	0.986	0.78
R8	85.73±1.15	52.04	4.71	0.994	0.970	0.984	0.981	0.63
R9	94.37±1.76	57.77	4.65	0.995	0.987	0.973	0.969	0.59
R10	84.41±2.53	55.42	4.12	0.992	0.962	0.995	0.993	0.51
R11	99.4±1.64	62.95	4.40	0.961	0.888	0.989	0.988	0.73
R12	96.9±4.44	53.52	5.37	0.999	0.970	0.983	0.991	0.76
R13	99.17±1.58	56.83	5.12	0.996	0.969	0.984	0.989	0.73

DR: Cumulative drug release, DE: Dissolution efficiency, MDT: Mean dissolution time

formulation with the desired responses. The optimization was done to locate the optimal polymer ratio and concentration of SB under the constraints of minimizing the FLT, increase the bioadhesion, and attain sufficient swelling and DR. The numerical optimization tool provided us with different sets of optimal solutions.

The optimized formulation was prepared with the polymer ratio of 5 and SB concentration of 7.5 mg. The batch was evaluated for FLT, bioadhesion, swelling, and DR. The formulation showed the FLT of 6.14 min (predicted - 6.27 min), bioadhesion of 17.23 g (predicted - 17.05 g), percent swelling at 5 h of 74.83% (predicted - 75.00%), and DR

at 1 and 10 h of 17.54% (predicted - 18.19%) and 75.48% (predicted - 75.80%), respectively. The observed values of dependent variables were found to be near to the predicted values, indicating the reliability of developed mathematical models.

CONCLUSION

In this work, we successfully designed a floating-bioadhesive tablet based on the combination of HPMC and CMTG for achieving the gastroretention of VH by employing central composite design. The compatibility of the polymer combination with VH was confirmed from the ATR-FTIR study. The FLT of the formulations was found to be decreased significantly with increasing concentration of SB whereas a marked increase in the TFT was observed on increasing the polymer ratio. A decrease in the polymer ratio increased the bioadhesion. The change in pH associated with the SB concentration was found to affect the swelling and DR of the formulations. The DR was found to be retarded at high polymer ratio and low SB concentration.

The results obtained for the optimized formulation were in a proper correlation with the predicted values. The optimized formulation showed reduced FLT and promising bioadhesion. It also minimized the burst effect and controlled the DR. Thus, we conclude that the floating-bioadhesive tablet containing optimized combination of HPMC and CMTG can be a better alternative to the other gastroretentive systems prepared using the synthetic polymers to achieve bioadhesion. However, further *in vivo* studies are required to validate the *in vitro* results of the HPMC-CMTG-based floating bioadhesive tablet of VH.

ACKNOWLEDGMENTS

The authors are thankful to Zydus Cadila, Ahmedabad, for providing gift sample of VH. The authors are also thankful to Prof. Dasharath Sagare, Founder President, YSPM's Yashoda Technical Campus, Satara, for providing laboratory facilities.

REFERENCES

1. Sweetman SC. Martindale, The Complete Drug Reference. 36th ed. London: The Pharmaceutical Press; 2009. p. 1421-5.
2. Patel A, Modasiya M, Shah D, Patel V. Development and *in vivo* floating behavior of verapamil HCl intragastric floating tablets. AAPS PharmSciTech 2009;10:310-5.
3. Gangadharappa HV, Rahamath-Ulla M, Pramod-Kumar TM, Shakeel F. Floating drug delivery system of verapamil hydrochloride using karaya gum and HPMC. Clin Res Regul Aff 2010;27:13-20.
4. Shahi SR, Shinde S, Zadbuke N, Padalkar A, Shahi S. Formulation development and evaluation of floating matrix tablet of verapamil HCl. Asian J Pharm 2013;7:27-35.
5. Elkheshen S, Yassin AE, Alkhaled F. Per-oral extended-release bioadhesive tablet formulation of verapamil HCl. Boll Chim Farm 2003;142:226-31.
6. Siddam H, Kotla NG, Maddiboyina B, Singh S, Sunnapu O, Kumar A, *et al.* Formulation and evaluation of atenolol floating bioadhesive system using optimized polymer blends. Int J Pharm Investig 2016;6:116-22.
7. Varshosaz J, Tavakoli N, Roozbahani F. Formulation and *in vitro* characterization of ciprofloxacin floating and bioadhesive extended-release tablets. Drug Deliv 2006;13:277-85.
8. Sharma S, Nanda A, Singh L. Formulation and optimization of gastric bioadhesive tablets of diltiazem hydrochloride using central composite design. Trop J Pharm Res 2013;12:861-7.
9. Malakar J, Nayak A. Floating bioadhesive matrix tablets of ondansetron HCl: Optimization of hydrophilic polymer-blends. Asian J Pharm 2013;7:174-83.
10. Hua S, Ma H, Li X, Yang H, Wang A. pH-sensitive sodium alginate/poly(vinyl alcohol) hydrogel beads prepared by combined Ca2+ crosslinking and freeze-thawing cycles for controlled release of diclofenac sodium. Int J Biol Macromol 2010;46:517-23.
11. Goyal P, Kumar V, Sharma P. Carboxymethylation of tamarind kernel powder. Carbohydr Polym 2007;69:251-5.
12. Rao PS, Beri RM. Acetylation of tamarind seed jellose. Proc Indian Acad Sci A 1955;42:199-203.
13. Prabhanjan H. Studies on modified tamarind kernel powder Part I: Preparation and physicochemical properties of sodium salt of carboxymethyl derivatives. Starke 1989;11:409-14.
14. Shaw GS, Uvanesh K, Gautham SN, Kumar GV. Development and characterization of gelatin-tamarind gum/carboxymethyl tamarind gum based phase-separated hydrogels: A comparative study. Des Monomers Polym 2015;18:434-50.
15. Kaur G, Jain S, Tiwary AK. Chitosan-carboxymethyl tamarind kernel powder interpolymer complexation: Investigations for colon drug delivery. Sci Pharm 2010;78:57-78.
16. Pal S, Sen G, Mishra S, Dey RK, Jha U. Carboxymethyl tamarind: Synthesis, characterization and its application as novel drug-delivery agent. J Appl Polym Sci 2008;110:392-400.
17. Kaur H, Ahuja M, Kumar S, Dilbaghi N. Carboxymethyl tamarind kernel polysaccharide nanoparticles for ophthalmic drug delivery. Int J Biol Macromol 2012;50:833-9.
18. Madgulkar AR, Bhalekar MR, Padalkar RR, Shaikh MY. Optimization of carboxymethyl-xyloglucan-based tramadol matrix tablets using simplex centroid mixture design. J Pharm (Cairo) 2013;2013:396468.

19. Ghosh A, Bose A, Mandal U, Gowa K, Pal T. Application of response surface methodology in the formulation of sustained release matrix tablets of metformin hydrochloride. Asian J Chem 2008;20:5541-56.
20. Dayal P, Pillay V, Babu RJ, Singh M. Box-Behnken experimental design in the development of a nasal drug delivery system of model drug hydroxyurea: Characterization of viscosity, *in vitro* drug release, droplet size, and dynamic surface tension. AAPS PharmSciTech 2005;6:E573-85.
21. Singh SK, Reddy IK, Khan MA. Optimization and characterization of controlled release pellets coated with an experimental latex. II. Cationic drug. Int J Pharm 1996;141:179-95.
22. Boza A, De la Cruz Y, Jordán G, Jáuregui-Haza U, Alemán A, Caraballo I. Statistical optimization of a sustained-release matrix tablet of lobenzarit disodium. Drug Dev Ind Pharm 2000;26:1303-7.
23. Singh B, Chakkal SK, Ahuja N. Formulation and optimization of controlled release mucoadhesive tablets of atenolol using response surface methodology. AAPS PharmSciTech 2006;7:E3.
24. Gil EC, Colarte AI, Bataille B, Pedraz JL, Rodríguez F, Heinämäki J. Development and optimization of a novel sustained-release dextran tablet formulation for propranolol hydrochloride. Int J Pharm 2006;317:32-9.
25. Srikanth MV, Rao NS, Sunil SA, Ram BJ, Kolapalli VR. Statistical design and evaluation of a propranolol HCl gastric floating tablet. Acta Pharm Sin B 2012;2:60-9.
26. Sumathi S, Ray AR. Release behaviour of drugs from tamarind seed polysaccharide tablets. J Pharm Pharm Sci 2002;5:12-8.
27. Ponnikornkit B, Ngamsalak C, Huanbutta K, Sittikijyothin W. Swelling behaviour of carboxymethylated tamarind gum. Adv Mater Res 2015;1060:137-40.
28. Havaldar VD, Kulkarni AS, Dias RJ, Aloorkar NH, Mali KK. Floating matrix tablets of atenolol: Formulation and *in vitro* evaluation. Asian J Pharm 2009;3:286.
29. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.
30. Dias RJ, Sakhare SS, Mali KK. Design and development of mucoadhesive acyclovir tablet. Iran J Pharm Res 2009;8:231-9.
31. Rao P, Srivastava H. Tamarind. In: Whistler RL, editor. Industrial Gums. 2nd ed. New York: Academic Press; 1973. p. 369-411.
32. Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: Design and optimization using combination of polymers. Acta Pharm 2008;58:221-9.
33. Khutoryanskiy VV. Advances in mucoadhesion and mucoadhesive polymers. Macromol Biosci 2011;11:748-64.
34. Rajab M, Tounsi A, Jouma M, Neubert RH, Dittgen M. Influence of tamarind seed gum derivatives on the *in vitro* performance of gastro-retentive tablets based on hydroxypropylmethylcellulose. Pharmazie 2012;67:956-7.

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