ORIGINAL ARTICLE

Optimization of Valsartan Floating Tablets by 3^2 Factorial Design

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Abstract

Aim: The present study aimed at the development of valsartan floating tablets (VFTs) using *Ocimum basilicum* mucilage (OBM) and hydroxypropyl methylcellulose (HPMC) K100M by applying response surface methodology-based 3^2 factorial design. **Materials and Methods:** OBM (A) and HPMC K100M (B) were selected as independent factors, and swelling index (Y_1) and time taken for 90% drug release (Y_2) were as responses. Experimentally designed 9 runs assessed for Y_1 and Y_2, and analysis of variance (ANOVA) was applied ($P < 0.05$) to define significant terms. Multicriterion decision approach anticipated optimized formulation VFT was developed and evaluated for physicochemical parameters such as weight variation, hardness, friability, thickness, and drug content. *In vitro* drug release and buoyancy studies, *in vivo* buoyancy studies, and Fourier transform infrared (FTIR) studies were carried out along with the validation of experimental design. **Results and Discussion:** Synergistic effect between polymers was observed in experimental runs, and ANOVA indicated a significant effect of A and B on Y_1 and Y_2. Physicochemical parameters as well as floating lag time and total floating time of VFT were within the limits. FTIR studies unveiled drug and polymer compatibility. *In vitro* drug release studies demonstrated a good fit in zero-order and super Case-II transport drug release mechanism. Experimental values of VFT exhibited good agreement with predicted values generated by the software. *In vivo* buoyancy study in rabbit confirmed floatability of the VFT for 12 h. **Conclusion:** The present investigation concluded that statistically optimized VFT with OBM and HPMC K100M as rate retarding polymers exploiting as a promising formulation for gastric delivery of valsartan for longer periods.

Key words: Factorial design, floating tablets, *invivo* buoyancy studies, optimization,valsartan

INTRODUCTION

Orally administered controlled drug delivery systems have been getting widespread importance day-by-day in view of their ease of administration and other added advantages. Such controlled delivery for longer periods in the upper part of the gastrointestinal tract (GIT) is a prerequisite for drugs have the gut as primary absorption site, especially for narrow absorption window drugs. This controlled delivery at gastric region is facilitated by many approaches.[1] Gastroretentive floating drug delivery system (GRFDDS) is one of the approaches, which has been proven its efficiency to such an extent that deliver drug exactly at the upper part of GIT, where the drug has it's site of absorption. This is evidenced by extensive research work that has been conducting since 1990's to till date.[2-4]

In addition to this, recently, many researchers have been developing GRFDDS by optimization technique which utilizes optimum concentrations of combination of polymers to get product with desirable qualities.[5-10] This optimization technique provides the study of factors in all possible combinations with minimum experimentation and time[11] based on the design expert software, response surface methodology (RSM) graphs. This has been cited as a main reason for exploiting this technique as a promising tool to deliver drug at the site of absorption.

In this study, hydroxypropyl methylcellulose (HPMC) K100M was used as a polymer due to its suitability in the

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tailoring of GRFDDS, which has been evidenced by many research works.[12-15] A new polymer *Ocimum basilicum* mucilage (OBM) was also included, which was obtained from seeds of *O. basilicum* Linn., family Lamiaceae. Currently, natural polymers gained widespread importance in view of their advantages. Hence, OBM was selected as a polymer, in this study, to explore it as sustaining polymer. It is inexpensive, abundantly available, biodegradable, biocompatible, forms viscous solution, and also extensively investigated for various properties such as binding,[16] emulsification,[17] disintegrant,[18] drug release retardant property,[19,20] and additionally proven its potentiality in food industry.[21] However, till now, combined effect of it with HPMC K100M has not yet been studied in the development of GRFDDS. Synergistic action produced by the combination of two polymers at specific concentrations served as a main basis for this study. Blends of ingredients as a result of their specific characteristic of each ingredient and synergistic effects find usefulness in cost reduction and development of GRFDDS with desirable qualities.[22]

Valsartan is chemically N-(1-oxopentanyl)-N-((2'-(1H-tetrazol-5-yl) (1-1'-biphenyl)-4-yl)methyl)-L-valine. It is angiotensin II receptor antagonist class of drug and is a FDA approved one for the treatment of hypertension, myocardial infarction, and congestive heart failure. It is a weak acidic drug that has absorption window in the acidic environment of the stomach.[23] It's dose is 40-320 mg/day as individual tablets/capsules or in combination with diuretics, and it's action lasts only for 4-6 h.[24] It has oral bioavailability of 23%. Hence, to overcome this, aforementioned a formulation with controlled delivery at the upper part of the GIT is highly recommended. As per our literature, there is no evidence to improve its bioavailability by formulating GRFDDS of valsartan with optimized concentrations of HPMC K100M and OBM using 3^2 factorial design.

MATERIALS AND METHODS

Materials

Valsartan was obtained as a gift sample from Dr. Reddy's Labs, Hyderabad, India. *O. basilicum* seeds were purchased from Local Market Rajampet, Andhra Pradesh, India. HPMC K100M was obtained from Vijaya Chemicals Pvt., Ltd, Pune, India. Microcrystalline cellulose was obtained from Thermo Fisher Scientific Pvt., Ltd., Mumbai, India. Lactose was obtained from Genuine Chemicals Co., Mumbai, India. Magnesium stearate and sodium bicarbonate were procured from Universal Laboratories Pvt., Ltd., Mumbai, India. All other chemicals used were of pharmaceutical or analytical grade.

Extraction of *O. basilicum* seed mucilage

Mucilage extraction from *O. basilicum* seeds was carried out by a modified method of Razavi *et al*.,[25] where 100 g of cleaned *Ocimum* seeds were allowed to soak in distilled water: Seed ratio of 10:1 (at 35°C for 12 h) and blended at 1500 rpm for 15 min to scrap the gum layer of the seed surface. Blended mass squeezed with many folds of muslin cloth to separate the mucilage. Mucilage subjected for precipitation with acetone (volume of acetone is equal to volume of filtrate), and precipitated mucilage was separated, dried, milled, sieved through sieve no.80, packed, and kept in a dry condition until further use.

Formulation of valsartan floating tablets (VFT)

VFTs of different factorial batches were fabricated by direct compression method using OBM and HPMC K100M as drug release retarding polymers, lactose as diluent, sodium bicarbonate as gas generating agent, microcrystalline cellulose, and magnesium stearate were as directly compressible polymer and lubricants, respectively (composition of each ingredient outlined in Table 1). All the ingredients including drug passed through sieve no. 40. Polymers, lactose, and microcrystalline cellulose mixed for 10 min, to this required quantity of valsartan were added and mixed. Accurately weighed quantity of sodium bicarbonate also mixed with the drug blend. The whole mixture was collected in a plastic bag and mixed for 3 min. To this, magnesium stearate was added for lubrication and mixed for 2 min. The mixture (equivalent to 400 mg) was compressed into tablets with 10 mm flat punches (Cadmach, Ahmadabad, India) to get gastroretentive floating tablet (GRFT) of valsartan. Compression force was adjusted to control the hardness of 4-5 kg/cm^2.

Experimental design

A 3-level two-factorial (3^2) design chosen for the present experimentation using a software DESIGN EXPERT® version 8.0.7.1. Independent variables selected were the concentration of OBM (A) and HPMC K100M (B) with low (−1), medium (0), and high settings (+1) as coded factorial levels.[26,27] Swelling index (SI) (Y_1) and time taken for 90% drug release ($t_{90\%}$-Y_2) were selected as dependent variables for investigation as shown in Table 2. A total

Table 1: Composition of floating tablets of valsartan

Ingredients	Quantity per tablet (mg)
Valsartan	80
OBM	0-120
HPMC K100M	0-120
Microcrystalline cellulose	16
Sodium bicarbonate	48
Lactose	12-240
Magnesium stearate	4

OBM: *Ocimum basilicum* mucilage, HPMC: Hydroxypropyl methylcellulose

Table 2: 3^2 factorial design of VFTs

Factors employed	Levels used			Responses observed (dependent variables)
	–1 (low)	0 (mid)	+1 (high)	
A - Amount of OBM	0	20	40	Y_1 - SI Y_2 - Time for 90% drug release ($t_{90\%}$)
B - Amount of HPMC K100M	0	20	40	

OBM: *Ocimum basilicum* mucilage, HPMC: Hydroxypropyl methylcellulose, VFT: Valsartan floating tablets, SI: Swelling index

of 9 experimental runs were conducted to optimize and analyze the interaction of each level on the parameters of formulations. Multiple factorial regression analysis (quadratic model) was carried out to measure the effect of two variables on responses (Y_i).

$$Y_i = b_0 + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2 \quad (1)$$

Where Y_i - Dependent variable (response); b_0 - Intercept; b_1, b_2, b_3, b_4, b_5 - Regression coefficients; A, B - Individual effects; AB - Interaction effects; A^2 and B^2 - Quadratic effects.

The significance of two factors and their interactions were estimated with analysis of variance (ANOVA) ($P < 0.05$) as well as by *F* statistics and *t*-values.[28]

Fourier-transform infrared (FTIR) studies

FTIR studies were conducted to know the interaction of valsartan with excipients. In this study, pure valsartan, pure OBM, and optimized VFT were grounded thoroughly with IR grade KBr, then compressed in a hydraulic press at a pressure of 10,000 psig, to get a disc. Each disc was scanned over a range of 400-4500 cm^{-1} using FTIR instrument (FTIR-1600, Shimadzu, Japan). The characteristic peaks were observed and recorded.

Evaluation of experimentally designed formulations

SI

The swelling behavior of 9 runs studied in triplicate for their dimensional changes, weight gain, or water uptake ability as described by Mohammed *et al*.[29] SI measurement was carried out by placing a weighed tablet (W_0) in 200 ml of 0.1 N HCl in a beaker, which was maintained at 37 ± 0.5°C. At selected intervals, the tablet was withdrawn, and excess surface water was removed with filter paper and reweighed (W_t). Percentage swelling of the tablet was expressed as SI calculated from the following equation.[30]

$$SI = \frac{W_t - W_0}{W_t} * 100 \quad (2)$$

Where W_t is the weight of the swollen tablet and W_0 is the initial weight of the tablet.

In vitro drug release studies

The release of valsartan was studied using USP Type II dissolution test apparatus (ELECTROLAB- TDT-08L) using 900 ml 0.1 N HCl as dissolution medium maintained at 37 ± 0.5°C with rotation speed of 50 RPM. Aliquots of 5 ml were collected at predetermined time intervals and were replenished with an equivalent volume of fresh medium. The samples were filtered through a 0.45 um filter and diluted to a suitable concentration with 0.1 N HCl. They were analyzed using ultraviolet (UV)-visible double-beam spectrophotometer at 250 nm (Elico SL 164, India). The results were expressed as mean ± standard deviation ($n = 3$).

Statistical analysis and validation of design

Multiple regression analysis was applied to ascertain polynomial models (linear, interaction, and quadratic terms) for all the response variables. Design expert software analyzed data (of all GFT formulations) were used to generate the contour plots and the response surface plots. In addition, ANOVA was also used to identify significant effects of factors on response regression coefficients.

The *F* test and *P* values were also calculated using the software. Three-dimensional (3D)-response surface graphs depicted main effects and interaction effects, and on the other hand, two-dimensional contour plots depicted values of responses.[31] Subsequently, numerical optimization technique (using the desirability approach) and graphical optimization technique (using overlay plots) were used to generate new formulation with the desired responses. Comparison of responses (experimental values) with predicted values was carried out quantitatively to validate the selected experimental design. Relative error was calculated as per equation (3).

$$\text{Relative error}(\%) = \frac{(\text{Predicted value} - \text{Experimental value})}{\text{Predicted value}} * 100\% \quad (3)$$

Preparation of checkpoint batch

A new formulation (optimized formulation, VFT) was generated using the desirability approach (numerical optimization technique) and overlay plots (graphical optimization technique) with optimized concentrations of

A and B to get desired constraints such as maximizing the time taken for 90% drug release ($t_{90\%}$) and SI. This VFT was evaluated for Y_1 and Y_2 responses as well as parameters such as weight variation, hardness, thickness, friability, drug content, SI, *in vitro* buoyancy and drug release, kinetics of drug release, and *in vivo* buoyancy.

In vitro evaluations of the optimized formulation (VFT)

Physicochemical characteristics of tablets

All these post compression parameters were carried out as per USP.[32]

Weight variation test

It was performed by weighing 20 tablets individually and by measuring average weight of twenty tablets (n = 3) using an electronic balance (Shimadzu ELB300), then individual weight was compared with an average weight.

Hardness test

Hardness was determined individually (n = 3) using a Monsanto hardness (LABGO1174, Mumbai, India).

Friability test

The friability of floating tablets was measured (n = 3) using a friability pharma tester (PTF20E, Germany) by operating at 25 rpm for 4 min. The tablets were removed, dedusted, and accurately weighed, and the percent weight loss was calculated.

Tablet thickness

A Vernier calipers (For-bro Engineers, Mumbai, India) were utilized to measure thickness of tablets (n = 3).

Drug content

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to 80 mg of valsartan was transferred into a 100 ml volumetric flask containing 0.1 N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm) and 1 ml of the above solution was diluted to 100 ml with 0.1 N HCl, and the drug content of the resulting solution was determined by a UV spectrophotometer at 250 nm.

In vitro buoyancy studies

The *in vitro* floating behavior of VFT was determined in terms of floating lag time and total floating time. The time required for the tablet to rise to the surface of the dissolution medium and the duration for which the tablet continuously floated on the dissolution medium was noted as floating lag time and total floating time, respectively. The test was performed using a 250 ml beaker containing 200 ml of 0.1 N HCl solution at 37 ± 0.5°C.[33]

Analysis of drug release kinetics

This is an important parameter to correlate *in vitro* and *in vivo* drug responses. It is necessary to analyze and predict *in vitro* drug release behavior from optimized VFT formulation as well as to describe the mechanism of drug release from polymeric matrices.[34] Hence, various mathematical models such as zero-order, first-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas models were applied to *in vitro* data.

In vivo floating studies

In vivo buoyancy studies were carried out in healthy rabbits, after getting approval from the Institutional Animal Ethics Committee, Sri Padmavati Mahila Visva Vidyalayam, Tirupati, Andhra Pradesh, India (1677/PO/Re/S/2012/CPCSEA/11). The study was employed using 2.5 kg healthy rabbit which was housed 3 days and fasted for 12 h but provided excess water, before the study. VFT prepared with $BaSo_4$ as X-ray opaque material (to enable visibility) in place of drug was made to swallow using stomach sonde needle. Before tablet administration, first X-ray photograph of rabbit abdomen was made to ensure the absence of radiopaque material in the stomach. Further, gastric X- ray photographs were taken at preidentified time intervals of 2, 6, and 12 h.[35]

RESULTS AND DISCUSSION

Evaluation of experimentally designed formulations

SI (Y_1)

As per 3^2 factorial design, a total of 9 trial batches [Table 3] were anticipated by DESIGN EXPERT® version 8.0.7.1 software for two independent variables A and B at three levels of −1, 0, and +1. In addition to this, polynomial equations were described, to know the influence of independent variables on selected optimized responses Y_1 and Y_2.

The proposed polynomial equation for response Y_1 is as follows:

$$(Y_1) = +196.93 + 33.33*A + 80.50*B - 32.50*A*B - 11.76*A^2 - 20.26*B^2 \quad (4)$$

Table 3 revealed that, when independent variable A (OBM) alone used in formulation F1, it showed SI of 95, and on the other hand, formulation F7 prepared with independent variable B alone showed 165. This confirmed the high SI value of HPMC K100M than OBM. Formulation F6 which has high concentrations of OBM and HPMC K100M has

Table 3: Experimental plan of 3^2 factorial design with observed responses

Formulation	Factor 1 % OBM (A)	Factor 2 % HPMC K 100M (B)	SI (Y_1)	$t_{90\%}$ (Y_2)
F1	20.00 (0)†	0.00 (−1)*	95	6.5
F2	0.00 (−1)*	0.00 (−1)*	15	0.33
F3	40.00 (+1)‡	0.00 (−1)*	155	6.5
F4	0.00 (−1)*	40.00 (+1)‡	235	9.5
F5	40.00 (+1)‡	20.00 (0)†	215	11.5
F6	40.00 (+1)‡	40.00 (+1)‡	245	13
F7	0.00 (−1)*	20.00 (0)	165	8
F8	20.00 (0)†	40.00 (+1)‡	268	12
F9	20.00 (0)†	20.00 (0)†	195	10

*Low setting, †medium setting, ‡high settings of polymers. OBM: *Ocimum basilicum* mucilage, HPMC: Hydroxypropyl methylcellulose, SI: Swelling index

exhibited highest SI of 245, which indicated the synergistic effect of both polymers. Such type of synergistic effect between two polymers was also reported for Karaya and Ghatti gums by Moin *et al*.[36] This high SI value was ascribed by the high viscosity of the formulation which might be ascertained by the blend of polymers at high concentrations. This discussion concluded that, as polymer concentration increased, SI was also increased. It is also supported by polynomial equation (4) where positive sign represents the direct relationship of independent variable with response. Hence, A and B variables in this equation carried a positive sign as a proof of its direct relationship with response Y_1.

Time taken for 90% drug release - $t_{90\%}$ (Y_2)

Designed 9 batches were also analyzed for response Y_2, and values were presented in Table 3. The results of Table 3 revealed that formulation F1 (OBM only used as polymer) exhibited 6.5 h of $t_{90\%}$, and on the other hand, formulation F7 (HPMC K100M only used as polymer) showed 8 h. This confirmed the highest drug release retarding property of HPMC K100M than OBM. Similar type of less efficiency in drug release of OBM was proposed by Majid *et al*. in their study.[37] Formulation F6 which has high concentrations of OBM and HPMC K100M showed more time for 90% of drug release, which indicated the synergistic effect of both polymers which is comparable with that of results of SI. This discussion is also supported by polynomial equation (5) where A and B variables in this equation carried positive sign as a proof of its direct relationship with response Y_2.

$$(Y_2) = +10.37 + 1.86*A + 3.36*B - 1.17*A*B - 1.54*A^2 - 1.54*B^2 \quad (5)$$

Statistical analysis and optimization

ANOVA results [Table 4] inferred that all models were significant ($P < 0.05$) for investigated responses Y_1 and Y_2. From Table 3, SI as response implies that model *F*-value of 161.65 reveals that it is significant. There is only a 0.01% chance that a "model *F*-value" this large could occur due to noise. Values of "$P > F$" < 0.0500 indicate model terms are significant. In this case, A, B, AB, A^2, and B^2 are significant model terms. Values >0.1000 indicate that the model terms are not significant. 3D-response surface graph and corresponding contour plot [Figure 1] concerning SI (Y_1) depicts the increment of SI with increase of both Factors A (%OBM) and B (%HPMC K100M). Response surface graph indicating that HPMC K100M has predominant influence on swelling than OBM, and this might be due to the development of high viscosity by the HPMC K100M (high molecular weight substance) than OBM.

From the ANOVA results [Table 4] of model, relating $t_{90\%}$ as response portraits that the model $F = 32.36$ implies that the model is significant. There is only a 0.01% chance that a "model F value" could occur due to noise. Values of "$P > F$" < 0.0500 indicated that model terms were significant. In this case, A, B, AB, A^2, and B^2 are significant model terms. In the same way, 3D-response surface graph and corresponding contour plot [Figure 2] concerning time taken for 90% of drug release (Y_2) explained similar increment of Y_2 with increase of both Factors A and B. This increase in Y_2 with increase in polymer concentrations might be due to slower water uptake into the core of the tablet. Similar reports were anticipated between guar gum and xanthan gum by Bhaskar *et al*.[38] This is also supported by the polynomial equation (5), where the mathematical sign it carried was positive for both Factors A and B. Response surface plot also inferred that response Y_2 is more dependent on Factor B than Factor A.

FTIR studies

FTIR spectrum of valsartan [Figure 3a] exhibited characteristic peaks at 3286 cm^{-1} (N-H functional group), 3059 cm^{-1} (saturated C-H group stretching), 2962 cm^{-1} (unsaturated C-H group stretching), 1728 cm^{-1} (carboxyl carbonyl), and 1600 cm^{-1} (amide carbonyl group). The peak at 1469 cm^{-1} indicated the presence of C=C aromatic group.

Table 4: Summary of ANOVA for quadratic models

Source	Sum of squares	df	Mean square	*F* value	*P* *P>F*
For SI					
Model	52132.19	5	10426.44	161.65	< 0.0001
A - OBM	6666.67	1	6666.67	103.36	< 0.0001
B - HPMC K 100 M	38881.50	1	38881.50	602.81	< 0.0001
AB	4225.00	1	4225.00	65.50	< 0.0001
A^2	381.88	1	381.88	5.92	0.0452
B^2	1133.52	1	1133.52	17.57	0.0041
Time taken for 90% drug release ($t_{90\%}$)					
Model	115.15	5	23.03	32.36	0.0001
A - OBM	20.79	1	20.79	29.22	0.0010
B - HPMC K100 M	67.80	1	67.80	95.27	< 0.0001
AB	5.45	1	5.45	7.66	0.0278
A^2	6.53	1	6.53	9.18	0.0191
B^2	6.53	1	6.53	9.18	0.0191

OBM: *Ocimum basilicum* mucilage, HPMC: Hydroxypropyl methylcellulose, SI: Swelling index

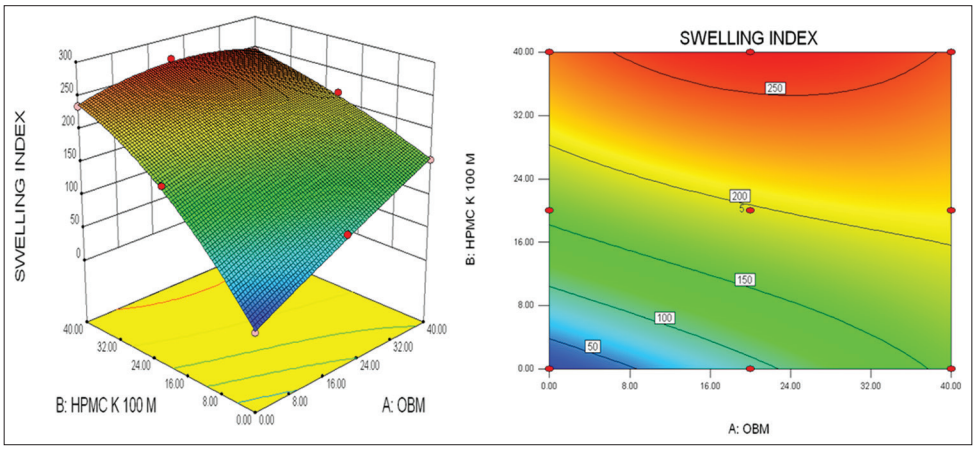

Figure 1: Response surface plot and contour plots of swelling index

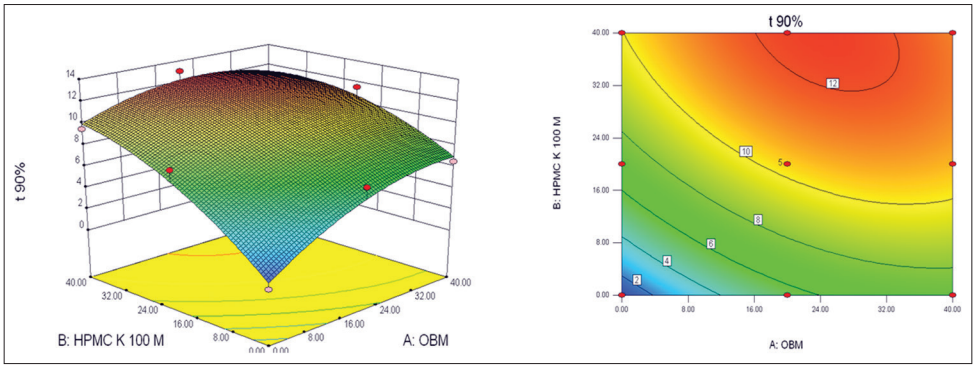

Figure 2: Response surface plot and contour plots of $t_{90\%}$

In the FTIR of OBM [Figure 3b], peak at 2958 cm^{-1} owing to C-H stretching of alkyl group and at 3429 cm^{-1} due to OH stretching of alcohol and also observed the characteristic peaks at 1060 cm-1 & 952 cm^{-1} for N-H primary amide and C-H aromatic bond respectively. The appearance of principal peaks in the optimized VFT formulation [Figure 3c] indicated the absence of incompatibility between drug and polymers.

Evaluation of the optimized formulation (VFT)

VFT (optimized formulation) generated from values of desirability approach and overlay plot of Figure 4 comprised of 23.68% of OBM and 40% of HPMC K100M was prepared and evaluated for Y_1 and Y_2 responses, which were in good correlation with the predicted values as shown in Table 5 with desirability of 0.962. Further, VFT was evaluated for parameters such as weight variation, thickness, drug content, friability, SI, *in vitro* buoyancy, *in vitro* drug release, kinetics of drug release, and *in vivo* buoyancy, and its results are exhibited in Table 5.

Physicochemical characteristics of tablets

The results weight variation, thickness, drug content uniformity, and friability tests were found to be within the limits according to the standards setup in the USP, and the results were exhibited in Table 5.

In vitro buoyancy and *in vitro* drug release studies

Floating lag time and total floating time of VFT formulation were found to be 64.6±3.78 s and >24 h, respectively [Figure 5], and were ascribed by the presence of sufficient concentration of floating agent (sodium bicarbonate) and viscosity of HPMC K100M. In general porosity of the formulation and bulk density less than one are demonstrated to be prerequisites for floating dosage forms.[10] Both characteristics might be assisted by HPMC K100M. *In vitro* drug release studies also performed on VFT until time taken to release 90% of the drug and values were reported in Table 5. Each experiment was conducted in triplicate.

Analysis of drug release kinetics by mathematical model

Various mathematical models applied to *in vitro* data and their results are presented in Table 5. Based on these results, it was concluded that zero-order kinetics considered predominant release mechanism as it possessed the highest R^2 value. Korsmeyer-Peppas has shown n value of 1.033, which described super Case-II transport mechanism of drug release from VFT, and it confirmed the role of water diffusion and polymer rearrangement during drug release.

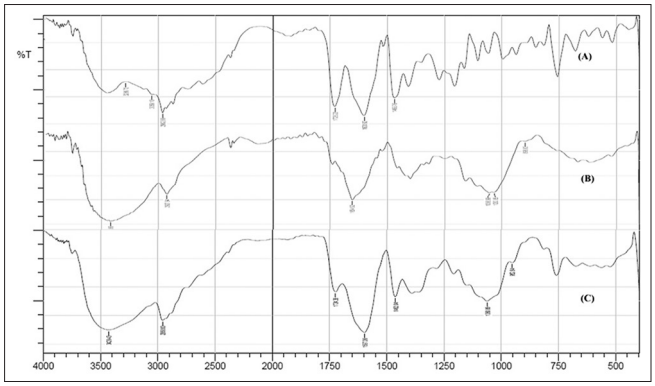

Figure 3: Fourier-transform infrared spectrum of (A) Valsartan, (B) *Ocimum basilicum* mucilage, and (C) valsartan floating tablet

Table 5: Results of different parameters of VFT

Parameter	Values
SI (%)	260.8±0.45
$t_{90\%}$ (h)	12.3±0.34
Floating lag time (s)	64.6±3.78
Total floating time (h)	>24
Weight variation (%)	298.3±2.08
Hardness (kg/cm^2)	4.7±0.707
Friability (% loss)	0.17±0.04
Thickness (mm)	3.38±0.091
Drug content (%)	98.29±0.93
Drug release kinetics	
Zero order (R^2)	0.983
Higuchi (R^2)	0.922
Hixson Crowell (R^2)	0.965
Korsmeyer-Peppas (R^2)	0.975
Korsmeyer-Peppas (n)	1.033

All values are expressed as mean±SD, n=3, SD: Standard deviation, SI: Swelling index, VFT: Valsartan floating tablets

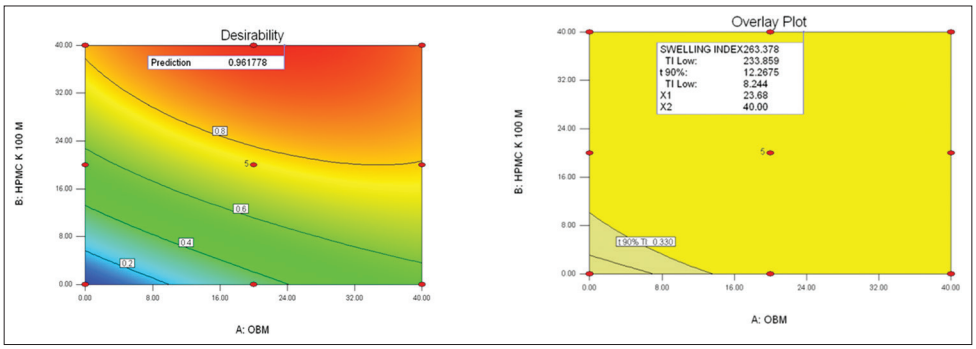

Figure 4: Desirability approach and overlay plot

Table 6: Comparison between predicted and experimental values for VFT

Parameter	Predicted values	Experimental values
SI (Y_1)	263.39	260.8±0.45
$t_{90\%}$ h (Y_2)	12.26	12.3±0.34

All values are expressed as mean±SD, *n*=3. SD: Standard deviation, SI: Swelling index, VFT: Valsartan floating tablets

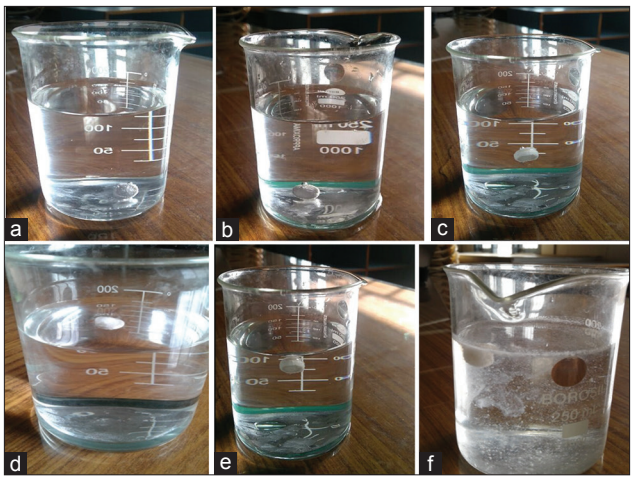

Figure 5: Photographs taken during *in vitro* buoyancy study of valsartan floating tablet in 200 ml 0.1 N HCl at different time intervals. (a) After 5 s, (b) after 10 s, (c) after 30 s, (d) after 20 min, (e) after 1 h, and (f) after 24 h

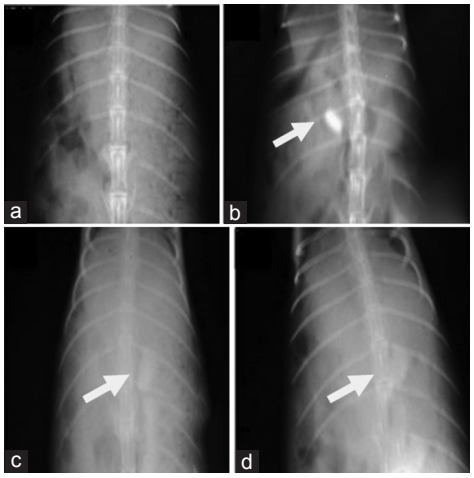

Figure 6: X-ray photographs showing floating ability of valsartan floating tablet formulation at different time intervals, (a) 0 h, (b) 2 h, (c) 6 h, and (d) 12 h (arrow mark indicating the location of the tablet)

Validation of the optimized formulation

SI studies and *in vitro* drug release studies were carried out on VFT to verify the theoretical prediction. Experimental values of Y_1 (260.8 ± 0.45) and Y_2 (12.3 ± 0.34) were in close agreement with the model predicted values of Y_1 (263.39) and Y_2 (12.26) [Table 6]. Relative error (%) between predicted and experimental values was calculated for each response, and the values were found to be within 5%. Hence, good agreement of experimental values with predicted values confirmed the predictability and validity of the model.

In vivo buoyancy studies

X-ray photographs of VFT in rabbit exhibited continuous floating of formulation for more than 12 h. Figure 6a depicts the absence of VFT before administration, and based on Figure 6b-d, these studies confirmed that VFT remains float in the stomach after administration and continued for nearly 12 h without any disturbance.

CONCLUSION

Valsartan GRFT for oral drug delivery was developed through direct compression method optimized by RSM based on 3^2 factorial design to optimize the concentration of OBM and HPMC K100M. Among experimentally designed 9 formulations, formulations containing high concentrations of A and B exhibited highest values of SI and $t_{90\%}$ due to synergistic effect of both polymers. Multidecision approach proposed optimized formulation (VFT) and possessed desirable values of SI and $t_{90\%}$ and was found to be in close agreement with predicted values indicated the reliability and validity of the model. VFT also exhibited a low value of floating lag time and total floating time of >24 h. It's *in vitro* drug release followed zero-order release and super Case-II transport mechanism. *In vivo* buoyancy study also confirmed the floating of VFT in rabbit stomach for longer periods. It is promising for further conduction of *in vivo* pharmacokinetics studies. Thus, this study concluded that blend of two polymers exploiting as retardant polymers for development of GRFT of valsartan.

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