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Design, optimization and *in vitro* characterization of valsartan loaded floating tablets

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Abstract

The present work was aim to design and optimize floating drug delivery systems of Valsartan using HPMC K15M, HPMC K100M, Guar gum as polymer and sodium bicarbonate as a gas generating agent. The tablets were prepared by direct compression method. Response surface methodology (RSM) was adapted using Box Behnken Design (BBD) using amount of HPMC K15M (X1), HPMC K100M (X2) and Guar gum (X3) were selected as independent variables, buoyancy time (Y1) and t50 (Y2) selected as dependent variables. All the designed 15 trial batches of formulations were evaluated for precompression, postcompression, drug content uniformity, swelling index, *in vitro* buoyancy, floating period and *in vitro* drug release profile. The response data were analyzed by using Design Expert software trial V13 to study the influence of independent variables on dependent variables. Point prediction method was adapted to generate optimized formulation with predicted response values within the design space. Validity of the developed polynomial equation was verified by experimenting the optimized formula. The closeness of predicted and observed values for buoyancy time (Y1) and t50 (Y2) indicates validity of derived equations for the dependent variables. These studies indicated that the proper balance between HPMC K15M (X1), HPMC K100M (X2) and Guar gum (X3) can produce a desired buoyancy and predicted dissolution profile. The optimized formulations followed Korsemeyer peppas kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix.

Keywords: Buoyancy time; Floating tablets; BBD; ANOVA; Numerical optimization

1. Introduction

The oral route is the most versatile, convenient route of drug delivery for systemic action[1] and controlled release drug delivery by oral route is widely used because of its easy administration, patient suitability and formulation changeability[2]. Various approaches are being made to reduce the dosing frequency with effective therapeutic plasma concentrations for a prolonged period of time in a controlled and reproducible manner[3]. Gastro retentive drug delivery systems (GRDDS) is one novel approach used to prolong the residence time in upper gastro intestinal tract (GIT) for achieving local or systemic effects. Prolonged gastric retention may improve dissolution and bioavailability for drugs that are less soluble and stable in gastric environment[4,5]. Valsartan (VAL) is an angiotensin receptor blocker widely prescribed for hypertension and is absorbed from the upper part of gastrointestinal tract[6,7]. The oral bioavailability of VAL was reported to be 23% and largely present in unionized form in acidic pH. The recommended adult oral dosage of VAL is 80 mg for the effective treatment of hypertension[8,9]. The short biological half-life of drug (6 hr) also favors development of sustained release formulations[10-12]. Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is desired. The present study was aimed to design, optimize and characterize Valsartan floating tablets (VAL-FLT) using Design of Experiments. A 2^3 full factorial design such as Box Behnken Design (BBD) selecting amount of HPMC K15M (X1), HPMC K100M (X2), Guar gum (X3) as independent variables and Buoyancy time (Y1), t50 (Y2) as response variables. The optimized formulation was further validated within the design space.

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2. Materials and methods

2.1. Materials

Valsartan (VAL) was obtained as gift sample from Caplin Point Laboratories, Chenni, Tamilnadu, India. HPMC K15M, HPMC K100M, Guar gum (GU), Ethyl cellulose (EC), Sodium bicarbonate ($NaHCO_3$) and Dicalcium phosphate (DCP) were procured from S.D. Fine Chemicals, Mumbai, India. All other ingredients used throughout the study were of analytical grade and were used as received.

2.2. Methods

2.2.1. Experimental design

The DoE approach was applied for optimization by response surface design viz., BBD using Design Expert® Trial Version 13. The BBD is an effective method of indicating the relative significance of a number of variables and their interactions. 2^3 factorial design was used at 3 center points with 12 non center points. The 15 trials were generated and are subjected for evaluation. BBD and the regression analysis was used to optimize the influence of independent variables viz., amount of HPMC K15M (X1), HPMC K100M and Guar gum (X3) on the dependent variables viz., Buoyancy time (Y1), and t50 (Y2). The design and possible formula trials were shown in tables 1, 2 and second order polynomial equation was generated as,

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + \ldots + b_nX_n$$

Where,
Y_1 - Response;
Y_2 - Intercept;
b_1 to b_n - Regression coefficients;
X_1, X_2, X_3 - Independent variable

Table 1 Variables and levels as per BBD

Variables	**Levels used**	
Independent variables	Low (-)	High (+)
X_1 HPMC K15M (mg)	55	75
X_2 HPMC K100M (mg)	30	50
X_3 Guar gum (mg)	20	35
Response variables		
Y_1 - Buoyancy time (min); Y_2 - t50 (hr)		

2.2.2. Preparation VAL-FLT

The VAL, HPMC K15M, HPMC K100M, GU, EC, $NaHCO_3$ and DCP were mixed as per table 2 in a polybag for 10 min and study the precompression parameter. The powder was subjected for direct compression using 8 mm punch rotary tablet compression machine. The formulated tablets (batch size 40 tablets) were evaluated for postcompression parameters.

Table 2 Design trial formulae of VAL-FLT as per BBD

Design Trial	**VAL**	**HPMC K15M mg**	**HPMC K100M mg**	**GU mg**	**EC mg**	**$NaHCO_3$ mg**	**DCP mg**	**Total wt mg**
1	40	65	40	27.5	25	30	22.5	250
2	40	65	30	20	25	30	40	250
3	40	55	40	20	25	30	40	250
4	40	55	40	35	25	30	25	250

5	40	75	30	27.5	25	30	22.5	250
6	40	55	50	27.5	25	30	22.5	250
7	40	65	40	27.5	25	30	22.5	250
8	40	65	40	27.5	25	30	22.5	250
9	40	75	40	35	25	30	5	250
10	40	75	40	20	25	30	20	250
11	40	75	50	27.5	25	30	2.5	250
12	40	65	30	35	25	30	25	250
13	40	55	30	27.5	25	30	42.5	250
14	40	65	50	35	25	30	5	250
15	40	65	50	20	25	30	20	250

2.3. Evaluation

2.3.1. In vitro buoyancy

Buoyancy time (BT) and floating period (FP) were considered as *in vitro* buoyancy. The design trial tablets were placed in a 100 ml beaker containing 0.1 N HCl, which was maintained at 37 °C. The time required for the tablet to rise to the surface of the medium was determined as the buoyancy lag time. The total floating time was considered as the time duration for which the dosage form remained floating on the surface of medium[13,14].

2.3.2. Swelling index (%)

The tablets were weighed individually and placed separately in petri dish containing 5 ml of 0.1 N HCl and incubated at 37 °C ± 10 °C. At regular 2 hr time intervals until 12 hr, the tablets were removed from petri dish, and the excess surface liquid was removed carefully using the tissue paper. After draining free water by blotting with tissue paper, these were weighed for weight gain on the analytical balance[15,16]. The following formula was used for calculating swelling index

Swelling Index (SI) = (weight of tablet at time-weight of tablet before immersion)/ (weight of tablet before immersion) × 100

2.3.3. In vitro dissolution studies

The *in vitro* dissolution of all design trial batches were carried out in 0.1 N HCl as dissolution medium using USP Type II Apparatus at 50 rpm and maintaining the temperature at 37 ± 0.5 °C. The dissolution was carried out for 12 hr. The *in vitro* dissolution data were fitted various mathematical model like zero order, first order, Higuchi matrix, Korsemeyer peppas and Hixson-Crowell for analyzing mechanism of drug release[17-20].

2.4. Stability study

The short term stability studies were carried out following ICH guidelines. The OP-VAL-FLT was filled into the container and sealed packed. The studies were performed at 40 ± 2 °C and 75 ± 5% relative humidity (RH) in the desiccators with saturated salt solution for up to 3 months[21].

3. Results and Discussion

3.1. Preformulation studies

The model drugs VAL was subjected for preformulation studies viz., solubility, melting point and partition coefficient. The solubility of VAL complies with standard values. The melting point was 118^{o}C against standard i.e., 116^{o}C to 119^{o}C; partition coefficient (log P) value was 0.029 against standard value 0.033 and the obtained results were ratifying with the standard values. All other parameters were found to be within specified limits as per IP/USP and was found to be satisfactory to design floating tablets.

3.2. FTIR studies

FTIR spectra of VAL (figure 1) shows 1605.99 cm^{-1} absorption band assigned to NH-C=O group at that is characteristic of the amide, C=O group at 1731.94 cm^{-1} that is characteristic of the carbonate group. The other absorption bands shows at 1165.02, 1101.99 and 1062.47 cm^{-1} assigned to asymmetric stretching of C-O in carbonate group and symmetric stretching of C-O in amide group. The absorption bands assigned to asymmetric stretching of N-H in amine group was shown at 758.41 cm^{-1}. Furthermore, the broad absorption band at 3448.02 cm^{-1} assigned to stretching of O-H, absorption band at 2973.74 cm^{-1} assigned to stretching of N-H. The FTIR data was in accordance to the literature data indicate the VAL was and can be used for the further study.

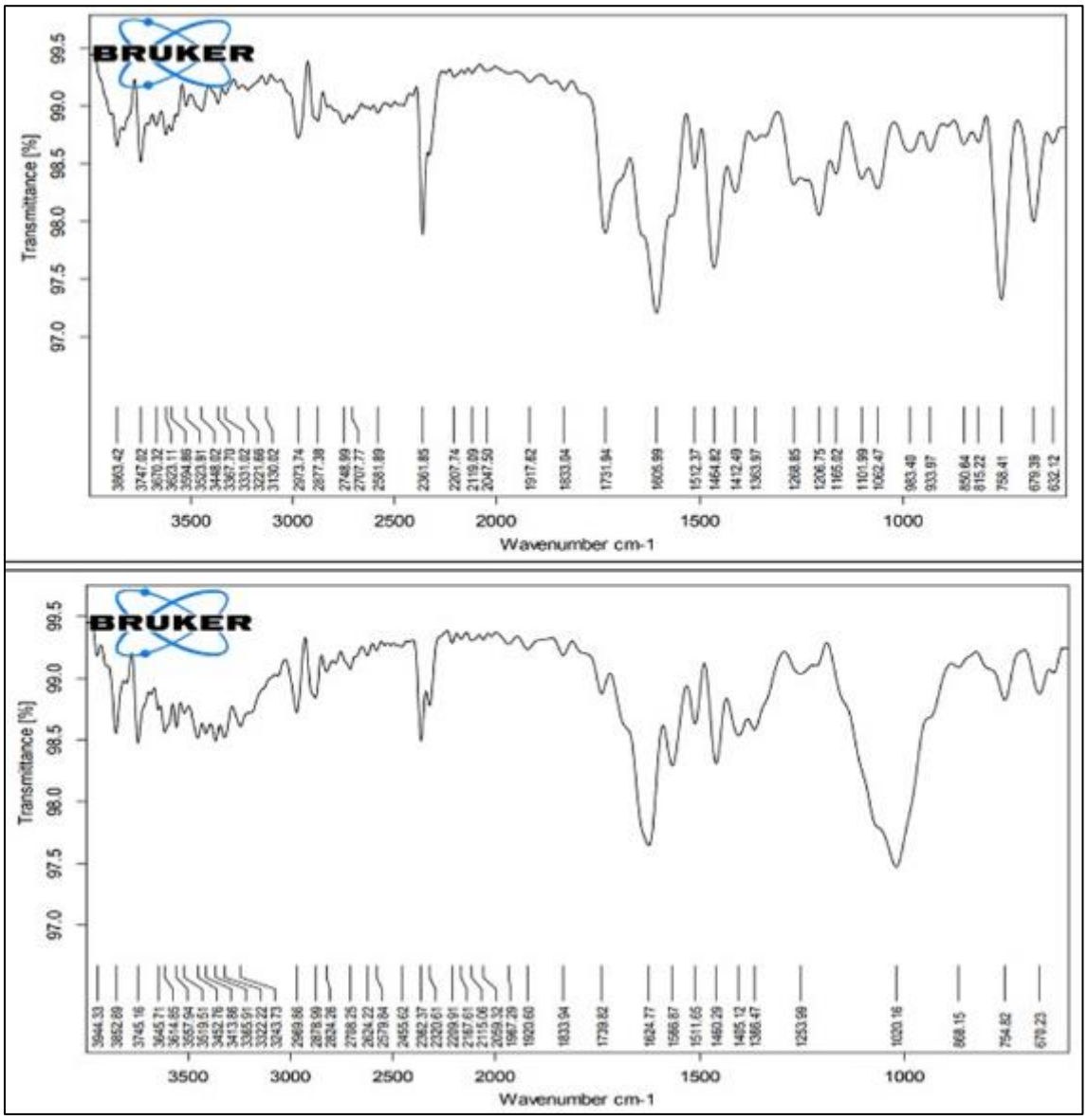

Figure 1 FTIR spectra of VAL and OP-VAL-FLT

3.3. Precompression and Postcompression studies: The precompression values were found to in the range of 0.685±0.047 gm/cm^3 to 0.722±0.080 gm/cm^3 bulk density; angle of repose 19.91±1.058 θ to 22.69±1.023 θ; Carr's index 3.21±0.252 to 7.31±0.499 and Hausner's ratios 1.12±0.305 to 1.23±0.618 for T1 to T15 tablet formulations. The material density depends on particle shape and size. All the formulations show the data within the specified standard limits. Carr's index (CI) is usually indicative of the material's flowability and packing degree and was found to be optimum. CI of < 15% suggests sufficient granule movement and balanced packing, the Hausner's ratio is usually associated with powder compressibility, and values < 1.25 suggest better compressibility. The angle repose was found to have strong flow properties and seem to be ideal for compression. The drug content in VAL was found to be in the range of 98.13 ± 0.167 to 99.25 ± 0.396 for T1 to T15 trial tablets, low SD (< 2%) indicated the drug is uniformly

distributed within the tablets. The diameter was found in the range of 7.9±0.132 to 8.0±0.099 mm; thickness 2.6±0.057 to 2.7±0.059 mm; average weight 248.6±1.206 to 251.6±0.805 mg; hardness 4.0±0.208 to 5.2±0.152 kg/cm^2; friability 0.193±0.0021 to 0.290±0.0018% for T1 to T15 trial tablets. The average weight and deviation in tablets passes the test for weight variation according to the IP specifications. The hardness results suggest that the formulated tablets have good strength, the weight loss % of tablet for friability study were less than 2% indicating tablets showing enough mechanical strength.

3.3. Analysis of BBD

The relationships between independent variables viz., amount of HPMC K15M (X1), amount of HPMC K100M (X2) and amount of GU (X3) at two levels (-1, +1), with dependent responses, such as Buoyancy time (Y1) and t50 (Y2) were assessed by the BBD. The response data of trial batches were experimentally generated and same were shown in table 3 and figure 2.

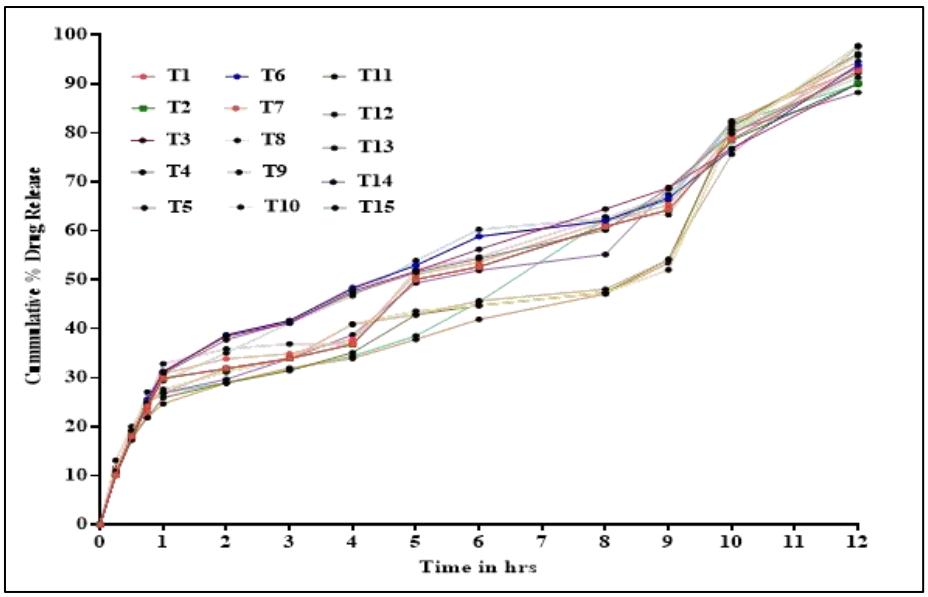

Figure 2 *In vitro* dissolution profile of Design trial VAL-FLT

The experiment response data was substituted in Design Expert Software and possible statistical data were generated. The variables were analyzed and relative models were found as the optimum for all of the dependent responses. According to BBD these observations ensure the selection of optimum independent variables in this investigation. The significance of the model was estimated by ANOVA, where, at p-value < 0.05, the model is considered significant. The p-value < 0.05 clarifies that, the models generated were statistically significant to describe the interrelationship among the independent factors and the dependent responses. The interpretation of the interrelationship between factors and response were done through generating diagnostic and response plots and same shown wherever applicable.

Table 3 Design trials with response as per BBD

Design Trials	X1 (A)	X2 (B)	X3 (C)	Y1	Y2
	HPMC K15 M mg	HPMC K100M mg	GU mg	Buoyancy time min	t50 hr
1	65	40	27.5	2.9	4.23
2	65	30	20	3.1	4.43
3	55	40	20	3.6	3.8
4	55	40	35	3.6	4.12
5	75	30	27.5	2.12	5.4
6	55	50	27.5	3.5	4.21

7	65	40	27.5	3.1	4.8
8	65	40	27.5	2.9	4.8
9	75	40	35	2.12	5.6
10	75	40	20	2.22	5.5
11	75	50	27.5	2.12	5.42
12	65	30	35	3.12	4.6
13	55	30	27.5	3.7	4.02
14	65	50	35	2.89	5.71
15	65	50	20	2.89	4.56

3.3.1. Effect of factors on Response Y_1 – Buoyancy time

ANOVA suggested Linear model (table 4) and F-value of 156.34 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Lack of Fit F-value of 0.62 implies the Lack of Fit is not significant relative to the pure error. There is a 75.02% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good so we want the model to fit. The regression of the linear model suggest 0.9771 (97.71 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.9581 is in reasonable agreement with the Adjusted R^2 of 0.9708; i.e. the difference is less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here the ratio of 32.715 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 3.27 which is less than 10 denotes good reproducibility of the model. The smaller Press (0.1837) suggest high degree of correlation as shown in figure 3a.

The polynomial equation was generated for actual factors. The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. The negative signs in the linear equation suggest significant model terms HPMCK15M and HPMCK100M has indirect or opposite influence on the particle size with positive intercept.

Buoyancy time Y1= +8.01075 - 0.072750*HPMCK15M - 0.008000*HPMCK100M -0.001333*GUAR GUM

The relationship between factors vs response were shown in response surface plots viz., Contour, 3D surface and interaction between factors vs response was shown in figure 3b, 3c. The interaction plot (figure 3d) clearly suggest no interaction between the factors and stated response and was further justified in ANOVA data where HPMCK15M and HPMCK100M are the only two significant model terms. The HPMC K15M helps tablets to float by forming a gel that traps carbon dioxide gas produced when $NaHCO_3$ reacts with HCl. This decreases the tablet's density, making it buoyant and prolong drug release. As the concentration of HPMC K15M increases decrease the buoyancy time and sustained the drug release at the same time at high concentrations HPMC K15M increases the floating lag time. In floating tablets, HPMC K15M can be used with other swellable polymer HPMC K100M in combination with guar gum to create a controlled release floating gastroretentive tablet.

3.3.2. Effect of factors on Response Y_2 – t50

ANOVA suggested Linear model (table 4) and F-value of 21.08 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, C are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Lack of Fit F-value of 0.63 implies the Lack of Fit is not significant relative to the pure error. There is a 74.10% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good so we want the model to fit. The regression of the linear model suggest 0.8519 (85.19 %) good positive correlation between the factors and stated response. The Predicted R^2 of 0.7308 is in reasonable agreement with the Adjusted R^2 of 0.8115; i.e. the difference is less than 0.2. The adequate precision measures the signal to noise ratio and ratio greater than 4 is desirable, here ratio of 13.194 indicates an adequate signal. This model can be used to navigate the design space. The % CV describes the dispersion degree of data points around the mean values, a small CV value % 5.81 which is less than 10 denotes good reproducibility of the model. The smaller Press (1.52) suggest high degree of correlation as shown in

figure 4a. The polynomial equation was generated for actual factors. The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. The negative signs in the linear equation suggest significant model terms HPMCK15M and HPMCK100M has direct or opposite influence on the particle size with negative intercept.

t50 Y2 = -1.46396 + 0.072125*HPMCK15 M + 0.018125*HPMCK100M + 0.029000* GUAR GUM

The relationship between factors vs response were shown in response surface plots viz., Contour, 3D surface and interaction between factors vs response was shown in figure 4b, 4c. The interaction plot (figure 4d) clearly suggest no interaction between the factors and stated response and was further justified in ANOVA data where HPMCK15M and HPMCK100M are the only two significant model terms. The HPMC K15M in combination with HPMC K100M controlled the drug release by forming gels which has direct impact on t50 response. In floating tablets, HPMC K15M can be used with other swellable polymer in combination with GU to create a controlled release floating gastroretentive tablet.

Table 4 ANOVA data of response as per BBD

Y1-Response Buoyancy time					
Linear Model	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**
Significant	4.29	3	1.43	156.34	< 0.0001
A-HPMC K15 M	4.23	1	4.23	463.32	< 0.0001
B-HPMC K100M	0.0512	1	0.0512	5.60	0.0373
C-GUAR GUM	0.0008	1	0.0008	0.0875	0.7728
Residual	0.1005	11	0.0091		
Lack of Fit Not significant	0.0739	9	0.0082	0.6155	0.7502
Pure Error	0.0267	2	0.0133		
Cor Total	4.39	14			
Y2- Response t50					
Linear Model	Sum of Squares	df	Mean Square	F-value	p-value
Significant	4.80	3	1.60	21.08	< 0.0001
A-HPMC K15 M	4.16	1	4.16	54.81	< 0.0001
B-HPMC K100M	0.2628	1	0.2628	3.46	0.0898
C-GUAR GUM	0.3784	1	0.3784	4.98	0.0473
Residual	0.8353	11	0.0759		
Lack of Fit Not Significant	0.6187	9	0.0687	0.6347	0.7410
Pure Error	0.2166	2	0.1083		
Cor Total	5.64	14			

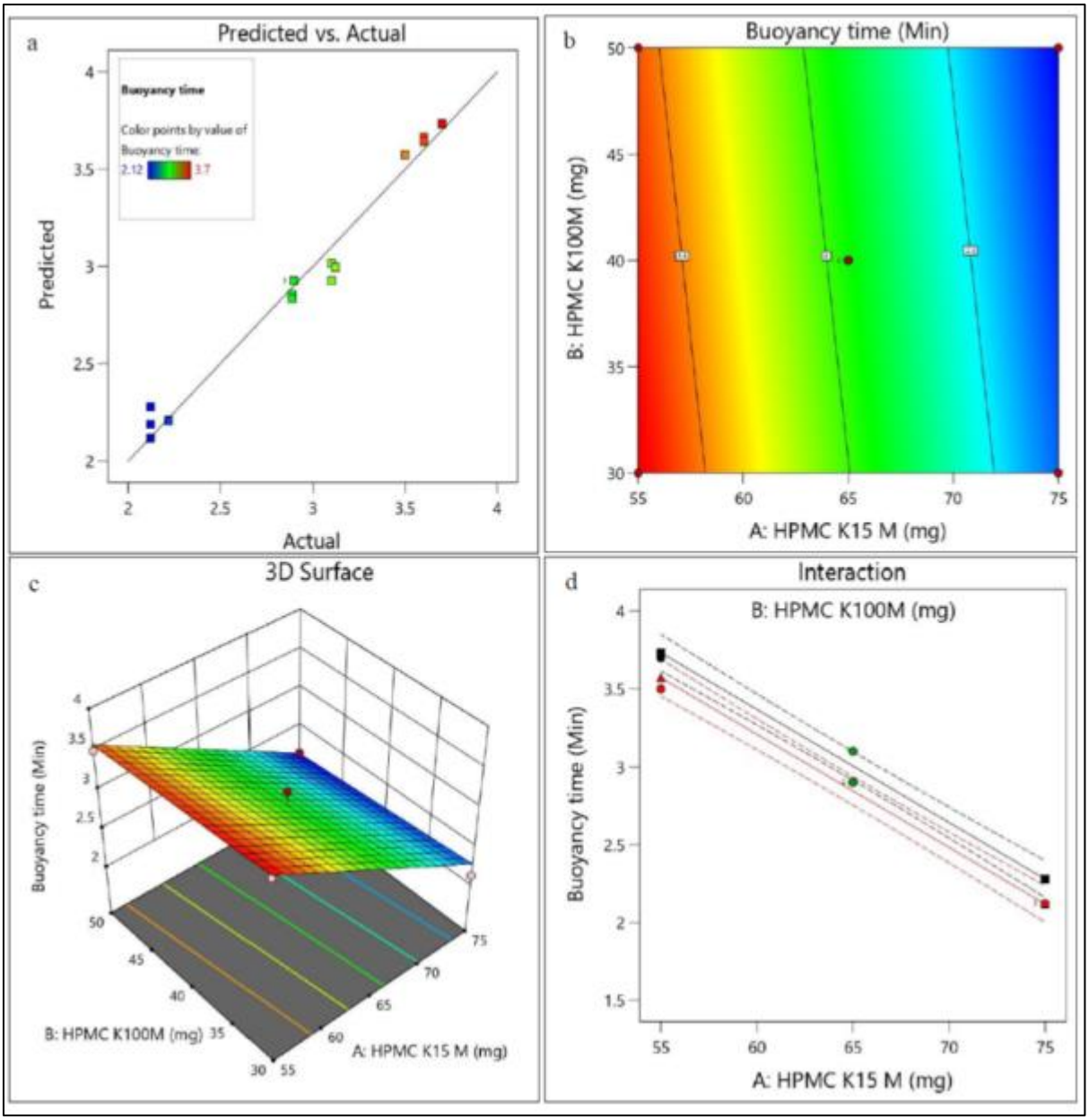

Figure 3 Diagnostic and model response surface plots representing influence of factors on Buoyancy time Y1 a) Predicted vs Actual plot b) Contour plot c) 3D plot d) Interaction plot

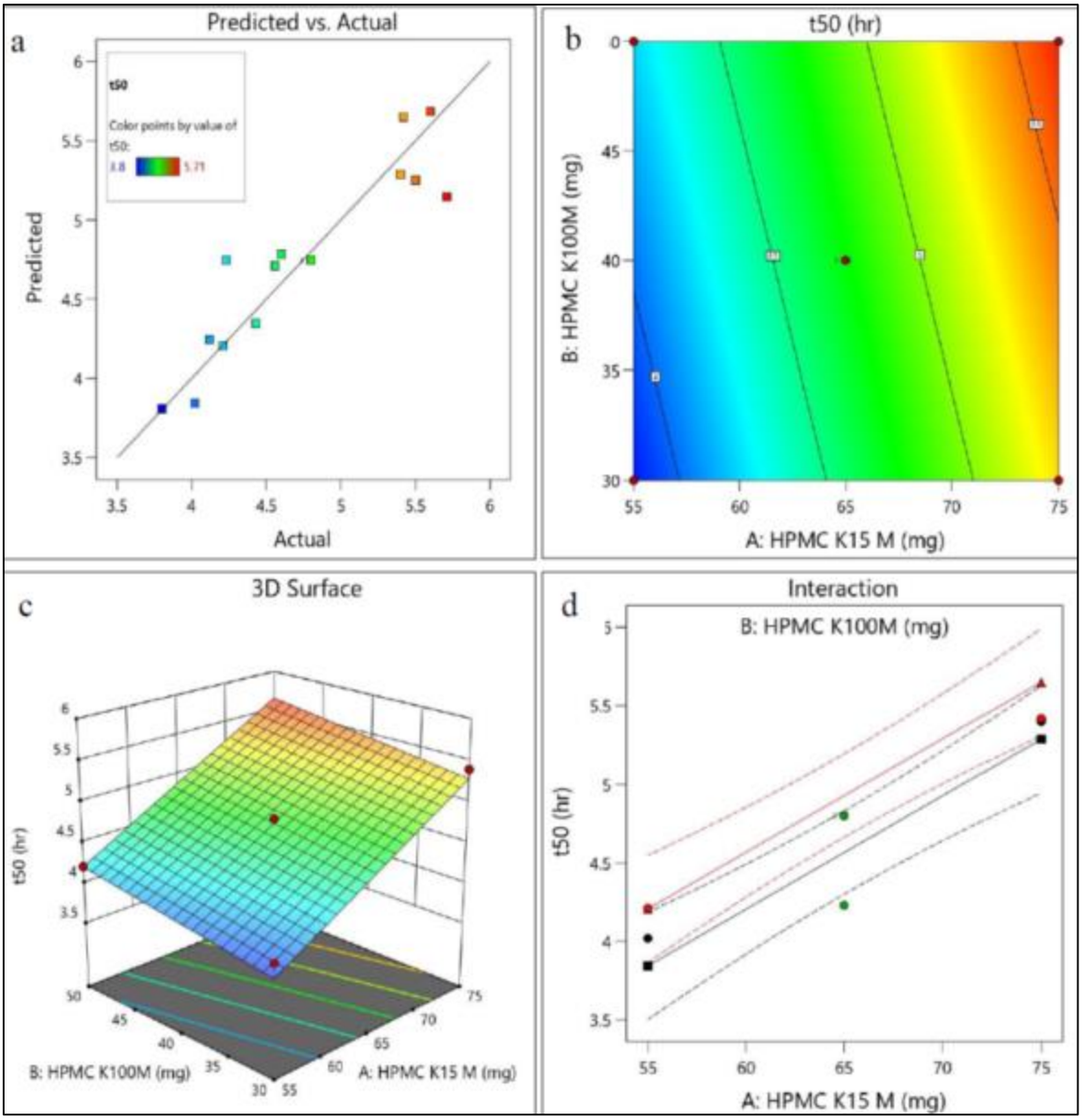

Figure 4 Diagnostic and model response surface plots representing influence of factors on Y2 t50 a) Predicted vs Actual plot b) Contour plot c) 3D plot d) Interaction plot

3.4. Numerical optimization

A numerical optimization technique using the desirability approach was employed to develop an optimized formulation with the desired responses. Fix the constraints for factors viz., in range the X_1 (HPMC K15 M) and maximize X_2 (HPMC K100M), in range for X_3 (GUAR GUM); for response, set in target Buoyancy time Y_1 (2.5 min), and t50 Y2 (5.15 hr). Optimize the constraints by using Deign Expert software to generate the possible solution with high degree of desirability as shown figure 5 and generate the possible overlay plot (figure 6) to explain the details of the optimized batch. The point prediction method confirms the concentrations of X_1, X_2 and X_3 and formula for optimized VAL loaded floating tablets (OP-VAL-FLT) was given in table 5.

Table 5 Experimental formula for OP-VAL-FLT as per BBD

VAL	HPMC K15M	HPMC K100M	Guar gum	EC	$NaHCO_3$	DCP	Total wt
40	69.8265	50	23.1545	25	30	50	250

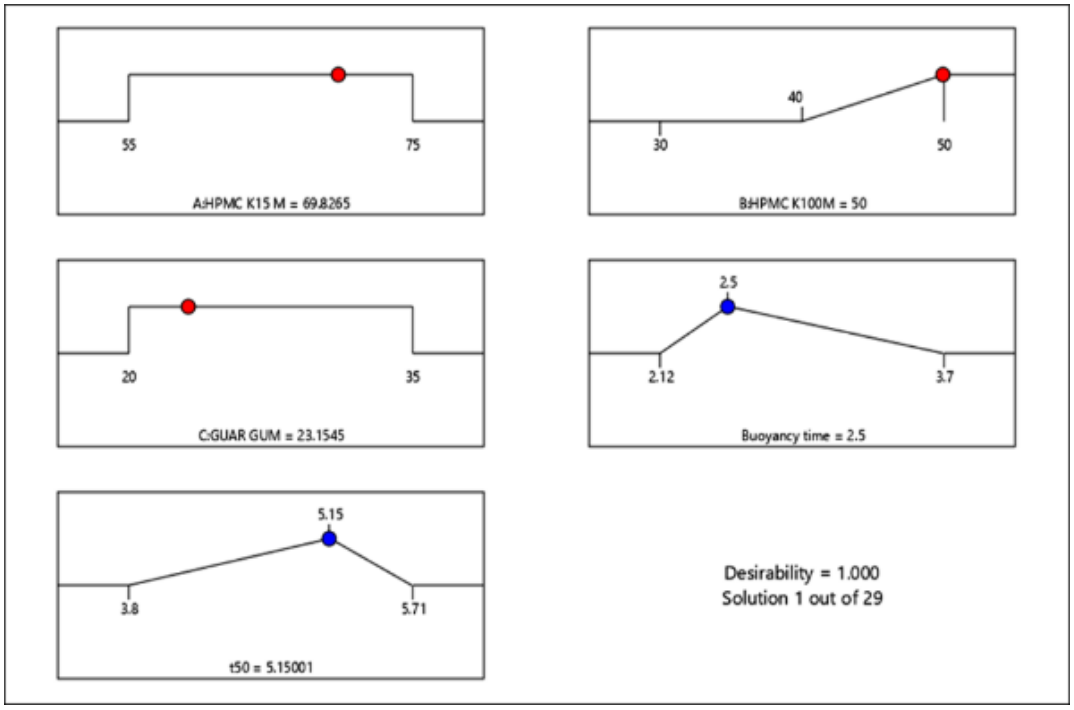

Figure 5 Possible solutions (1 out of 29) based on fixing constraints for factors and target values for response

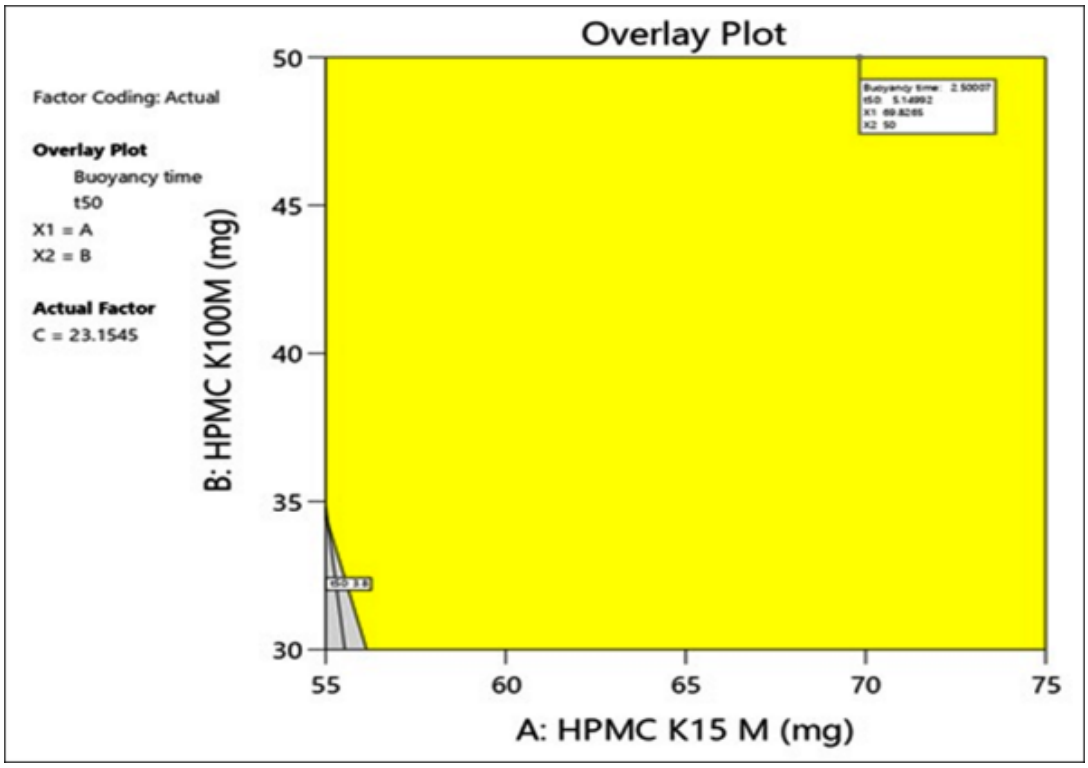

Figure 6 Overlay plot based on fixing constraints for factors and target values for response

3.5. Validation

The optimized formula of OP-VAL-FLT generated as per BBD was formulated experimentally by direct compression method. The formulated was evaluated for interaction studies, precompression parameters, postcompression parameters, drug content, *in vitro* buoyancy, swelling index, floating period, *in vitro* drug release studies. All the

characteristic bands of VAL FTIR were present in OP-VAL-FLT. FTIR indicate no interaction between the drug and added excipients as shown in figure 1. The precompression data such as bulk density (0.622±0.015 gm/cm^3), Carr's index (4.12±0.132), Hausner's ratios (1.08±0.568) and angle of repose 23.12±1.002 θ suggest the OP-VAL-FLT has desired packability, compressibility and flowability properties. The drug content in OP-VAL-FLT was 99.23 ± 0.148 with low SD (< 2%) indicated the drug is uniformly distributed within the tablets. The postcompression data of OP-VAL-FLT was found to be diameter 7.9±0.132 mm; thickness 2.7±0.059 mm; average weight 251.5±1.341 mg; hardness 4.8±0.152 kg/cm^2; friability 0.188±0.0112 % suggest the results are according to IP specifications. The *in vitro* buoyancy (figure 7) time was found to be 2.63 min, t50 5.25 hr, floating period was > 12 hr and swelling index was 158.45 %. The experimental results validate and ratified with predicted data, it clearly indicates the DoE studies can be used to study the influence of two factor on two responses. Validation of the predicted values of responses was performed by comparing with the experimental data, which indicated high degree closeness between the predicted and experimental values of the responses and confirmed excellent prognostic ability of the employed mathematical model. The less than 5 % relative error considered to be good agreement within the design space, here the 3.096 % for Buoyancy time and 1.9047 for t50 was within the agreement of design space suggest the adapted BBD model can be conveniently used for optimization.

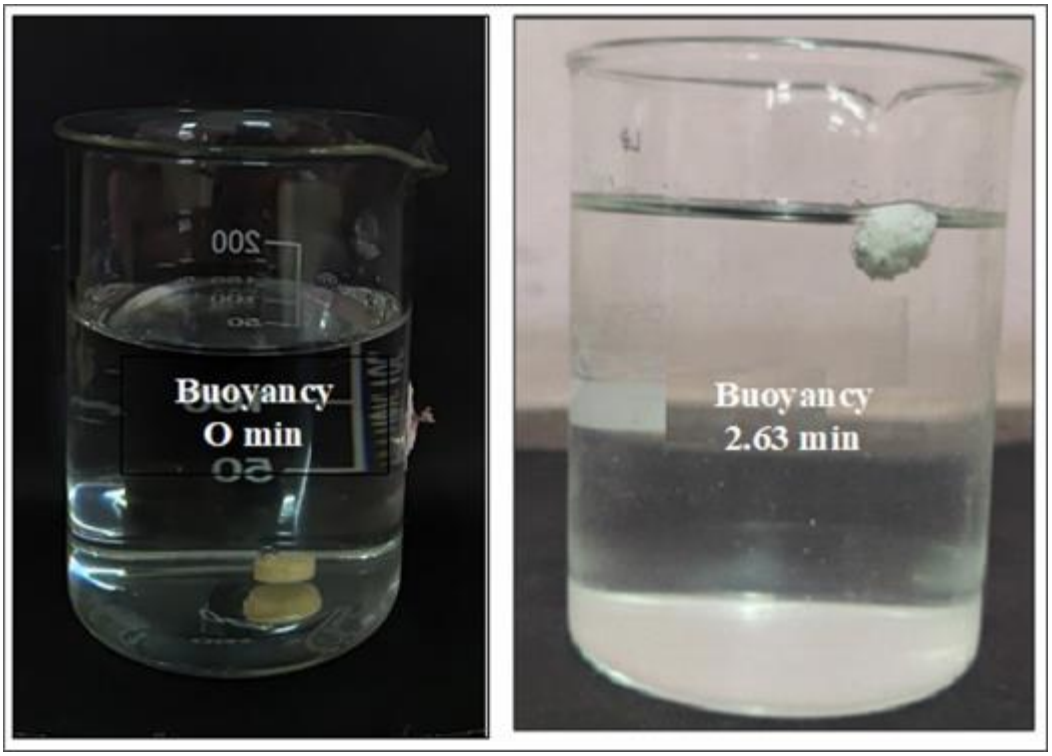

Figure 7 *In vitro* buoyancy of OP-VAL-FLT

Table 6 Comparative experimental response with predicted response of OP-VAL-FLT

Response	Predicted	Experimental	% Relative Error
Buoyancy time - Y_1	2.551	2.63	3.096
t_{50} -Y_2	5.15	5.25	1.9047

The *in vitro* drug release was studied for OP-VAL-FLT and given in figure 8. The cumulative percent drug release of OP-VAL-FLT was found to be, 10.62±1.84 after 2 hr, drug release at buoyancy period and complete exhaust of entrapped CO_3. After 6 hr the drug release was steady and found to be 38.74 ± 1.41 due swelling properties of HPMCK15M. The drug release was steady and controlled for 12 hr and was found to be, 93.14±1.07 may be due formation of swollen gel comprising combination of HPMC K15M, HPMCK100M and GU. The *in vitro* drug release data was further fitted into various kinetic equations to find out the order and mechanism of drug release and best fit model. The correlation

coefficient showed that the best fit model was matrix and the release exponent, n was found to be less than 0.5 (0.4848) indicated the drug release followed fickian and release mechanism was indicative of swelling followed by diffusion controlled.

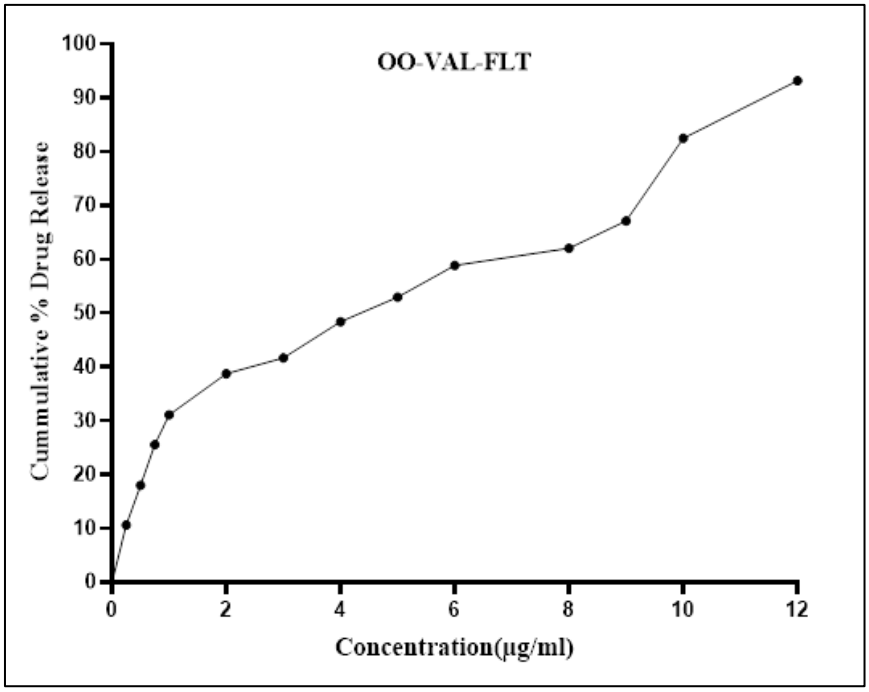

Figure 8 *In vitro* dissolution profile of OP-VAL-FLT

4. Conclusion

Response surface BBD can be successfully applied to formulate and optimize Valsartan loaded floating tablets and were conveniently prepared by direct compression method. The statistical tests in design experiment conclude that some linear and interaction terms of independent variables influence on the response. The numerical optimization was successfully used to generate optimized formula can be validated within the design space. The OP-VAL-FLT exhibited good buoyancy time and desired controlled release and floating period was greater than 12 hr.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There are no conflicts of interest.

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