STATISTICAL INTERPRETATION AND OPTIMIZATION OF VALSARTAN FLOATING TABLETS USING BOX-BEHNKEN DESIGN

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ABSTRACT

Objective: The main purpose of this study was to formulate and statistically evaluate 300 mg floating tablets of valsartan.

Methods: Floating tablets of valsartan was prepared in 16 station rotary punching machine by considering 300 mg of valsartan as drug, 40-60 mg of hydroxypropyl methylcellulose (HPMC) K100M and 20-40 mg of poly (styrene-divinylbenzene) as polymers and 20 mg of sodium bicarbonate as gas generating agents. Since upper stomach has maximum therapeutic window for valsartan absorption, hence Gastroretentive Floating Tablets (GRFTs) was prepared by implementing Box-Bentham Design. The pre and post compression parameters were optimized using Statistica 10 software. From the in vitro buoyancy and drug release studies and interpretation of statistical outcomes viz. Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Root Mean Squared Error (RMSE), Dissolution Efficiency (DE), Mean Dissolution Time (MDT), desirability study, it was concluded that batch VF5 formulation was found to be the most optimized formulation.

Results: The floating time of VF5 was found to be 132±0.33 sec, in vitro buoyancy time was 18 h, Akaike Information Criterion (AIC) was 54.97, Bayesian Information Criterion (BIC) was 5.13. percentage dissolution efficacy was 56.39%, mean dissolution time was 5.19hr. Further, six-month stability study was performed as per ICH Q1A guideline. After performing two-way ANOVA within stability study response variables, it was confirmed that the interaction was most significant.

Conclusion: Valsartan floating drug delivery system was successfully developed by considering HPMC K100M and poly (styrene-divinylbenzene) as polymers. Among all the nine batches, VF5 was found to be the best-optimized batch.

Keywords: Valsartan, Floating drug delivery system, Box-Bentham design, Akaike Information Criterion (AIC), Mean dissolution time

INTRODUCTION

Valsartan is basically an angiotensin II receptor antagonist. It has partial affinity for type I angiotensin receptor. Valsartan helps to reduce the blood pressure by blocking the action of angiotensin, which tends to dilate blood vessels. It has versatile use in the treatment of Congestive Heart Failure (CHF), Post-Myocardial Infarction (MI). Eventually, valsartan blocks the binding of angiotensin II to the AT1 receptor in adrenal gland and vascular smooth muscle [1]. Valsartan also restrict aldosterone secreting effects of angiotensin II, which ultimately leads to vasconstriction [2]. The Biopharmaceutics Classification System (BCS) class II drug valsartan, is a white to partially fine powder with a molecular weight of 435.5 Daltons. Valsartan is slightly soluble in water but has good solubility in methanol and ethanol. The dose of valsartan is 40 mg, 80 mg and 320 mg. The LogP value of valsartan is 5.8 with 7.5hr of plasma half-life during oral administration [3]. Valsartan has higher therapeutic window at upper stomach. To target the upper stomach, Gastro Retentive Drug Delivery System (GRDDS) is one of the best approaches for valsartan drug delivery [4]. Hence, valsartan floating drug delivery system was planned, considering hydroxypropyl methylcellulose (HPMC) K100M and poly (styrene-divinylbenzene) as polymer. Valsartan has only 3% oral bioavailability, which means improvement of its bioavailability by sustaining its duration of drug release could be a novel approach [5]. In floating drug delivery system, the formulation retains in upper stomach for prolong period of time as this system has lower density then the Gastrointestinal Tract (GIT) fluid [6]. But most importantly, statistical interpretation of evaluation variables and optimization using Box-Bentham design could make this research more reliable[5]. Therefore, the basic interest of this research was to establish a proper statistical model and based on that optimizing best formulation.

MATERIALS AND METHODS

The drug valsartan was purchased from Pro Lab Marketing Pvt. Ltd. New Delhi, HPMC K100M was purchased from Kalpana Polymers Private Limited. Mumbai-India, poly (styrene-divinylbenzene) was purchased from Rishichem Distributors Private Limited, Mumbai-India. Lactose, sodium citrate, dicalcium phosphate, magnesium stearate, t alc was gifted from Balaji Chemicals Vapi, Gujarat, India. All the other chemicals are reagents were used of pharmaceutical and analytical grades. For better results double distilled water was used throughout the experiment.

Drug excipient compatibility studies using FTIR and DSC

The pure drug valsartan was mixed with various polymers like HPMC K100M and poly (styrene-divinylbenzene). Further, IR mixture of all the components was prepared by considering potassium bromide (KBr); as an alkali halide which helps to form a sheet that is transparent in the infrared region during pellet formation [7]. The pellet was formed by applying 10 tons of pressure in hydraulic press. The prepared pellets were scanned at 400 to 4000 cm-1 wavenumber range in Fourier-Transform Infrared Spectroscopy (FTIR) Model ALPHAT, Libidinal Analytical Instrument. Same way possibilities of drug excipient compatibility were identified by Differential Scanning Calorimetry (DSC). The changes of melting endotherms or variations of corresponding enthalpy of reactions helps to identify possible drug excipient interactions. In this experiment, DSC thermographs of pure valsartan drug, a mixture of drug with HPMC K100M and poly (styrene-divinylbenzene) were recorded. Using aluminium cells, the samples were separately sealed and analysed using DSC-60 instrument (Shimadzu Corporation, Tokyo, Japan). During this experiment temperature range were set up to 50-200 °C. The experiment was carried out in a nitrogen atmosphere at a heating rate of 5 °C/minute.

Implementation of box-bentham design

When the variables and results of experiment having non-linear relationship, then Box-Bentham design could be the best alternative. With this design, nonlinear quadratic effect and interaction between two variables can be studied [8]. In this experiment, the joint influence of
independent variables concentration of HPMC K100M [X₁] and poly (styrene-divinylbenzene) [X₂] on the dependent variables, i.e. % Cumulative Drug Release (CDR) at 4th hour (Y₁) and % CDR at 8th hour (Y₂). In this design two factors were investigated each at three levels. The possible experimental trials were considered up to nine batches (table 1-2). The further polynomial equation was established. The full model polynomial equation was established for this design.

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon \]

Where, \( \beta_0 \) is intercepted. The \( \beta_1 \) and \( \beta_2 \) are coefficient of \( X_1 \) and \( X_2 \); \( \beta_{12} \) is the coefficient of interaction between \( X_1 \) \& \( X_2 \). The response variables mean \( Y_1 \) and \( Y_2 \) are subjected to multiple linear regression analysis. A further amount of formulation variables was optimized [9].

**Preparation of valsartan floating matrix tablet**

At first, the required quantities of drug, polymer, and excipients were accurately weighed and passed through sieve number 80 for proper size separation [10]. Further, along with valsartan, principal polymer HPMC K100M and low-density copolymer poly (styrene-divinylbenzene) were mixed geometrically. The effervescent agent i.e. Sodium bicarbonate, was added further in the tapped for 500 times and tapped volume was been measured (V₁).

Randomly twenty tablets were selected during process of compression handling or during storage. Friability test was performed by HMK Tablet 1601 friabilator. Where, rotation speed was maintained around 5±1 revolution/minute, timings at 9:59:59 min. During drum rotation, ten pre-weighted tablets were subjected to fall within six inches of rotary drum surface. After rotation cycle, tablets were dusted and once again weight was measured.

**Tapped density (TD)**

The powder mixture containing valsartan, which was in the 100 ml graduated cylinder was further compact using 50 ml capacities digital tapped density apparatus (DBK Instruments Jogeshwari, Mumbai), which could provide flexible drops of 14±2 mm at a marginal rate of 300 drops per minute. Initially, the cylinder was tapped for 500 times and tapped volume was been measured (V₁). Further, more 750 times tapping were recorded. The tapped volume was considered as V₂. As per procedure if the difference between V₁ and V₂ is lesser then %, then the final volume (V₂) can be considered for final tapped volume. The calculated tapped density (g/cm³) was measured by following formula:

\[ \text{Tapped density} = \frac{\text{Weight of the granules}}{\text{Final tapped volume}} \]

**Evaluation parameters for valsartan floating tablet**

**Precompression parameters**

**Bulk density (BD)**

Accurately 10 gm of excipients containing valsartan mixtures were taken and passed through sieve number #10 and transferred into 100 ml polypropylene-based graduated cylinder (Karter Scientific 19H2). Without any further compaction, settle the powder within and read the total volume it occupied. Then calculate the apparent bulk density (g/cm³) using following formula:

\[ \text{Bulk density} = \frac{\text{Total weight of granules}}{\text{Bulk volume}} \]

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\[ \text{Tapped density} = \frac{\text{Weight of the granules}}{\text{Final tapped volume}} \]

**Hausner ratio**

This is basically a fractional number which helps to predict flowability of powders or granules. If the Hausner ratio of any granules or powders is more than 1.25, which indicates poor flowability. Hausner Ratio can be represented by the following equation:

\[ \text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \]

**Carr’s index**

The particular compressibility and cohesivity of granules can be measured by Carr’s index or Carr’s compressibility index. This is also an important parameter to measure the particle size of granules. If Carr’s Index of any granules is between 5-15%, indicates that the granules have excellent flowability.

\[ \text{Carr’s Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \]

**Angle of repose**

Using the funnel method, the angle of repose of powder was determined. The funnel was filled with accurately weighted granules. The height of the funnel was adjusted such a way that, the funnel tip can touch apex of the powder blend. The final bland of granules were allowed to flow through the funnel tip into the surface of graph paper. The diameter of powder cone was measured and angle repose was calculated using following formula:

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

**Total porosity**

At first total volume of granules occupied in 100 ml cylinder was measured, then tapped volume was noted down after 100 tapping. The volume of the void was calculated as the difference between total volume of granules and tapped volume. The percentage porosity was calculated using the following formula:

\[ \text{Porosity} = \left( \frac{\text{Total Volume of the Solid}}{\text{Total Volume}} \right) \times 100\% \]

**Drug content**

An accurately weight of 100 mg of valsartan powder blend. This blend was further extracted with 0.1 N HCl and the solution was filter through 0.45µm membrane. The absorbance was measured at 50 nm after suitable dilution using Shimadzu UV-1601PC UV-Visible, Scanning Spectrophotometer.
In vitro buoyancy study
The time at which tablet rises to the surface of dissolution medium is considered as floating time and the duration on which tablet floated on the dissolution medium was noted as floating lag time respectively. The test was performed at 37±0.5 °C in 50 ml beaker containing 00 ml of 0.1N HCL solution [11].

In vitro drug release study
Drug release study was attained by TDT-06P (Electrolab) USP type II dissolution testing apparatus. In this in vitro drug release study, 900 ml of 0.1N HCL were used as a dissolution media. The paddle RPM was set to 50 and the temperature was maintained around 37±0.5 °C. During dissolution study at various time intervals, 5 ml of dissolution media was withdrawn and filtered using 0.45µm membrane filter. Simultaneously fresh 5 ml of 0.1N HCL was added in dissolution media to maintain 900 ml of system volume. The samples were withdrawing for each one-hour interval and up to 8th hour samples were withdrawn. Freshly withdrawn samples were further diluted with 0.1N HCL and absorbance was taken at 50 nm using Shimadzu UV-1601PC UV-Visible, scanning spectrophotometer [12]. The amount of drug release was calculated using standard curve equation.

Statistical analysis
The statistical analysis of the variables is very essential to established good correlation between dependent and independent variables. The Box-Bentham design was established using Design Expert 11 (STATE- EASE) and Minitab® 18 softwares. In this experiment, two factors that is % CDR at 24th hour and % CDR at 8th hour have been evaluated, considering each at three levels (-1, 0, +1). Total nine batches of possible combinations were generated by Design of Expert software. Further, two-way analysis of variance was established. With this statistical model various graphical representations were also established to analysis each factor with different level of responses. The various graphical representations like, FDS graphs, Residual vs Predicted, Residual vs Actual, Counterplot of % CDR at 24th and 8th hour respectively, 3D surface plot of % CDR at 24th and 8th hour respectively, desirability, overlay plot, pareto chart of the standard effects, individual value analysis, probability plot, overlay plots were helps to analysis statistical models completely.

Checkpoint batch and optimization of formulations
The checkpoint batch was mandatory to find correlation between the polynomial equations and counterplot while predicting the responses. Optimization of the variables was measured using significant coefficients and R value.

Kinetic studies
Drug release studies can be well defined by selecting suitable kinetic models like zero order kinetics, first-order kinetics, hixson model, hixson crowell cube root model, korsmeyer peppas equation [13]. Nevertheless, Akaife Information Criterion (AC) [14], Bayesian Information Criterion (BC) or Schwarz Criterion (SC), K1, Root Mean Squared Error (RMSEC), Dissolution Efficiency (DE), Mean Dissolution Time (MDT) estimation using KnitDS 3 rev 0.10 software, helps to estimate the best fit model and best formulation within nine formulations [15].

Stability study
Accelerated stability studies was performed as per ICH guideline at 40 °C±5 °C/75% RH±5% RH for 6 months. Accelerated stability study on optimized formulations helps us to find the effect of ingredients on physical and chemical stability of active pharmaceutical ingredient of the dosage form. Tablet was stored in an aluminium foil and formulation was exposed in elevated temperature and humidity conditions as specified earlier. Samples were withdrawn in every mounts and various evaluation tests were performed [12].

RESULTS AND DISCUSSION
IR and DSC results for valsartan and excipient compatibility
It was observed that there was no chemical interaction between Valsartan and the polymers used. The functional group present in drug give peaks to specify the presence of 5-cyclic ring with oxygen atom, diamine and alkenes, and other peaks for nitro groups. On the basis of DSC analysis, the valsartan melting point was found to be 102.12 °C; however the melting isotherm shifted to 198.56 °C while combination with drug and polymers.

Pre compression parameters and evaluations
Each batch was planned for 50 tablets, hence 15g blend was prepared. Bulk density was measured using VeeGo digital bulk density apparatus (Model number: VTPAT/MATIC-II). Bland was placed in 100 ml of polypropylene-based graduated cylinder (Karter Scientific 191H2) and bulk density was measured. Further using 100 tapping of cylinder, tapped density was recorded. The various pre-compression parameters were evaluated and were found to be within the prescribed limits. Using Statistica10® software, the pre-compression parameters were recorded and variable importance graph was plotted. It was observed that total percentage porosity (power value: 0.9896230) has maximum influence on floating tablet manufacturing and angle of repose (power value: 0.5358686) has less importance on tablet preparation. All these results indicate, all the batches blend have well to passable flow and micropolitics (table 3-4). In post-compression parameters at first, weight variations of tablets from the different batches was calculated and reported (table 5). Almost all the formulation passed the weight variation test and the percentage weight variation was in the pharmacopeia limits of±5% of the weight. The VF3 formulation possessed maximum average weight of 302.21 mg with a weight variation of±0.514%, and the VF2 batch has less average weight of 98.23 mg with a weight variation of±0.809%. Similarly, the average drug content of VF6 batch tablets was considered to be the highest i.e. 99.13%, where else VF1 shows less drug content of 92.24%. Further the hardness of all the batch samples was measured using tablet hardness tester (Monsanto Type); model number: VMT-1. The average hardness of VF3 batch was found to be maximum i.e. 6.4±0.27 kg/cm² and VF5 batch recorded lowest average hardness i.e. 4.8±0.51 kg/cm². The average thickness of all the tablets was recorded using vernier calliper, VF6 batch recorded 5.1±0.15 mm thickness; which was considered to be minimum among all the batches, where else VF7 recorded maximum thickness, which was recorded around 5.8±1.82 mm. As far as the percentage friability was concerned, friability was recorded using HMK Tablet 1601 friabilator, considering 10 tablets of one batch at a time in friabilator. All the batches were recorded within the limit of friability range, however VF5 recorded maximum friability of 0.61±0.22%, where else VF1 shows lest friability of 0.41±0.28% among all the batches. The floating time was a prerequisite variable for this formulation design. Floating time of VF1 was recorded 116±0.37sec which is least among of all the batches, where else VF3 shows maximum floating time of around 136±0.02sec. The formulation BF4, VF6 and VF9 shows maximum buoyancy where else VF1 shows minimum buoyancy with all the batches. Using Statistica10® software the post-compression parameters were recorded and variable importance graph was plotted. It was observed that average thickness (power value: 0.923526) has maximum influence on floating tablet manufacturing and (power value: 0.5358686) has less importance on tablet preparation. All these results indicate, all the batches blend has well to passable flow and micropolitics properties (table 6).

In-vito drug release study
All the nine batches (VF1-VF9) of valsartan floating tablets were developed considering HPMCK100M (40-60 mg) and poly (styrene-divinylbenzene); 0-40 mg as polymers. All the batches were subjected to in vitro drug release study using 0.1N HCL for 12 h. The cumulative drug release profile was mentioned (fig. 1). The result shows that, VF5 formulation has controlled and better drug release profile (99.38±0.145 at 12th hours of dissolution) with 50 mg HPMCK100M and 30 mg poly (styrene-divinylbenzene) polymer concentration. There for it can be considered as optimum batch, however, proper statistical analysis and kinetic analysis was warranted to come in a conclusion.

Statistical analysis
Box-Bentham design was implemented to identified best possible factors. Preliminary investigation revealed that factor concentration of

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poly (styrene-divinylbenzene) [20-40 mg]-X1 and HPMCK100M (40-60 mg)-X2 is highly influenced in the *in vitro* drug dissolution profile.

**Effect of polymers concentration on %CDR at 2^nd^ h**

Using Design Expert® 11 software in *in vitro* percentage cumulative drug release study was statistically interpreted at 2^nd^ hour. Based on ANOVA analysis, quadratic model was selected. In quadratic model, F value was 1201.78, which implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. Statistically, F value helps to indicate a group of variables are jointly significant or not. The F value of test is larger than F statistics, hence rejection of null hypothesis is palatable and accepting the alternative hypothesis was acceptable. Nevertheless, P-values less than 0.0500 indicate model terms were significant. In this case X1, X2, X1^2, X2^2 are significant model terms. Values greater than 0.1000 indicate the model terms were not significant. The Predicted Quadratic R^2 of 0.9944 is in reasonable agreement with the Adjusted R^2 of 0.9987; i.e. the difference is less than 0.2. The Predicted R^2 of 0.9944 is in reasonable agreement with the Adjusted R^2 of 0.9987; i.e. the difference is less than 0.2. Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. In this experiment adequate precision was 102.606, indicates an adequate signal. This model can be used to navigate the design space.

The polynomial equation for % CDR at 2^nd^ Hour (Y1) = +28.39 -6.32X1 -4.40X2 +3.04X1X2 +0.1100X1^2 +0.6450X2^2

The higher value of correlation coefficient for % CDR at 2^nd^ hour signifies a good fit model. The coefficient of X1 and X2 was significantly lower and negative, indicating decrease in polymer concentration [X1= HPMCK100M (40-60 mg), X2= poly (styrene-divinylbenzene)] (20-40 mg) could increase the percentage cumulative drug release at 2^nd^ hour. Where else, a combination of X1 and individual squares of X1 and X2 has agonistic effect with drug release, means drug release could get decrease with increase concentration of X1 and X2. But the coefficient values of X1, X2, and X1X2 were smaller, means has less influence on % CDR at 2^nd^ Hour. (table 7 and 8).

From the counterplot, it was confirmed that HPMC K100M; 50 mg and poly (styrene-divinylbenzene); 30 mg concentration provides good drug release profile (Coded value: 0, 0). That means VFS formulation batch have proper dissolution profile. On the other hand, from 3D surface plot, it was assumed that decrease concentration of polymers could increase the percentage cumulative drug release in parallel manner. From the residual vs run model it was confirmed that except one, all the formulation retained between the limits of externally standard units. From predicted vs actual curve, it was confirmed that the statistical model maintained good linearity and design predicted %CDR at 2^nd^ hour was almost coinciding with actual %CDR at 2^nd^ hour (fig. 3).

**Effect of polymers concentration on %CDR at 8^th^ hour**

Using Design Expert® 11 software in *in vitro* percentage cumulative drug release study was statistically interpreted at 8^th^ hour. Based on ANOVA analysis, quadratic model was selected. The F-value was 3.86X1 +0.458X2-3.86X2 +0.2400X1X2 +0.4150X1^2 +0.2100X2^2

The moderate-higher value of correlation coefficient for % CDR at 8^th^ hour signifies a good fit model. The coefficient of X1 and X2 was significantly lower and negative, indicating decrease in polymer concentration [X1= HPMCK100M (40-60 mg), X2= divinylbenzene] (20-40 mg) could increase the percentage cumulative drug release at 8^th^ hour. Where else, combination of X1X2 has shown negative sign lower coefficient value (0.2400), indicating increase in drug release profile. The numerical squares of X1 and X2 have agonistic effect with drug release, means drug release could get decrease with increase concentration of X1 and X2. But the coefficient values of X1, X2, and X1X2 were smaller, means has less influence on % CDR at 8^th^ Hour. From the counterplot, it was confirmed that HPMC K100M; 50 mg and poly (styrene-divinylbenzene); 30 mg concentration provides good drug release profile (Coded value: 0, 0), that means VFS formulation batch have proper dissolution profile after 8^th^ hour of dissolution. On the other hand, from 3D surface plot, it was assumed that decrease concentration of polymers could increase percentage cumulative drug release in parallel manner. From the residual vs run model it was confirmed that except one, all the formulation retained between the limits of externally standard units. From predicted vs actual curve, it was confirmed that the statistical model maintained good linearity and design predicted %CDR at 8^th^ hour was almost coinciding with actual %CDR at 8^th^ hour (fig. 3).

**Probability plot**

With probability plot one can easily predict whether response variables follow a normal distribution or not. The response variables should coincide with the theoretical distribution and form approximately a straight line. Probability plot also helps to provide highest correlation coefficient. In this experiment, %CDR at 2^nd^ and 8^th^ hour’s shows highest good correlations means drug releases with significance manner and maintain zero-order kinetics (fig. 4).

**Desirability function**

Desirability is a design function which ranged from zero to one. Among multiple function, numerically a point which is closer to one is more desirable. The overall desirability was found to be 0.927. From the 3D and counter desirability plot, it was confirmed that maximum desirability obtained at HPMC K100M (50 mg) and Poly (styrene-divinylbenzene) (30 mg) concentration (Coded value: 0, 0) (fig. 5).

**Checkpoint analysis and optimization of batch**

From the optimization parameters and desirability study, it was anticipating that VFS batches formulations could be the optimized one. To understand properly three checkpoint batches (VF10, VF11, and VF12) was prepared. The 2^nd^ and 8^th^ hours of %CDR was compared with predicted values of the overlay plot. In overlay plot, yellow colour space indicates maximum possibility to produce desired formulation within this lining. The relative standard error must not exist 9%. This is very crucial part of Response Surface Methodology (RSM); effect of studying the multiple variables on dependent variables or response variables, the optimum response was determined. It was observed that response variables of checkpoint batches were cognitive with VFS formulations (table 11), hence VFS batch can be considered as optimized batch. However, drug kinetic study is needed to select best formulation with good controlled release property.

**Kinetic studies**

The kinetic study of drug dissolution profiles of all the formulations was prerequisite to find best-optimized formulation. However, from the Design Expert output, VFS was selected as the best batch. But, without kinetic study one cannot predict the actual reality of drug release pattern. In this study, the drug release profile with time was fitted with various models. The criteria for selecting best fitting model were, the regression coefficient (R^2), which must be near to one. Similarly, AIC, BIC, K1, RMSE, Dissolution Efficiency (DE) must be in least number in best selected model as compare to other models. As far as Mean Dissolution Time (MDT) was concerned, which indicates 50% of drug release from the formulation, it helps to characterize the retarding rate of polymers and drug-releasing ability. A higher MDT value indicates a higher drug retarding ability of polymers. The formulation VFS has shown highest MTD value (5.19) as compared to other formulations, indicating 50 mg of HPMC K100M and 30 mg of...
poly (styrene-divinylbenzene) has good drug retarding ability, where else VF2 with 50 mg HPMC K100M and 0 mg poly (styrene-divinylbenzene) shows least MDT value of 3.431, indicating poor polymeric retention of drug with higher drug release. The Percentage Dissolution Efficacy (DE) was also found to be moderately high (56.39%). Similarly, Bayesian Information Criterion (BIC) or Schwarz Criterion and Akaike information criterion (AIC) also helps to find best model among finest set of models; the model with the lowest BIC and AIC values was preferred as best model. AIC helps to find best quality and goodness of fit model. Within all formulations once again, VF5 has lowest AIC (54.97) and BIC (55.13) value. On the contrary, VF5 follow zero-order kinetics as R² value (0.9396) was maximum as compared to First order, peppas, hixon crowell, higuchi model of VF5 formulation. Hence statistically it can be postulating that VF5 could be the best formulation with good diffusion-controlled released system (fig. 6 and table 12).

Stability study

The accelerated stability study of VF5; an optimized formulation was carried out as per ICH Q1A guideline at 40 °C±2°C/75% RH±5% RH for 6 mo using EZT-570S touch screen stability controller. Various physical parameters like hardness, friability, floating time, percentage drug content, %CDR at 12th hour was measured. After 6-month stability study VF5 formulations shows no significant changes in instability. However, floating time and % cumulative drug release was significantly increasing during stability study, it may be due to the slight deformation of API during stability study (table 13) To know more about actual interaction or changes during 6 mo of stability study, two-way ANOVA was implicated. It shows interaction account for 0.12% of total variables. The F value was 16.30, the degree of freedom number was 4. The P-value was<0.0001. As per two-way ANOVA the interaction was considered extremely significant and interaction was statistically significant.

Fig. 1: % CDR profile of valsartan floating tablets (VF1-VF9 batches) at 95.00% CI of differences and at mean±SD (n=3); **** indicates high statistically significance (p<0.005)

Fig. 2: Design expert output [A-counter, B-3D surface plot, C-residual vs run plot D-actual vs predicted plot] of effect of polymers concentration on % CDR at 24h
Fig. 3: Design expert output [A-counter, B-3D surface plot, C-residual vs run Plot D-actual vs predicted plot] of effect of polymers concentration on % CDR at 8th h

Fig. 4: Comparative probability plot of % CDR at 2nd and 8th h

Table 1: Selection of variables levels for independent variables

| (Independent variables) | Levels     | Coded value | Concentration of HPMC K100M in mg (X₁) | Concentration of poly (Styrene-divinylbenzene) in mg (X₂) |
|--------------------------|------------|-------------|---------------------------------------|-----------------------------------------------------------|
|                          | Low        | -1          | 40                                    | 20                                                         |
|                          | Intermediate | 0           | 50                                    | 30                                                         |
|                          | High       | +1          | 60                                    | 40                                                         |
Fig. 5: Desirability function [A-bar chart, B-ramps chart, C-3D surface plot chart, D-counter plot]

Fig. 6: [A]. Comparative mean dissolution study for VF1 to VF9 formulation at 95.00%, CI of differences, and at mean±SD (n=3) [B]. A comparative profile of AIC and BIC values are represented as mean±SD (n=3) on various valsartan floating formulations AIC and BIC at 95.00% CI of differences, ** indicates high statistically significance (p<0.005)

### Table 2: Composition of factorial design batch

| Ingredients (mg)          | VF1 | VF2 | VF3 | VF4 | VF5 | VF6 | VF7 | VF8 | VF9 |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Valsartan                 | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 |
| HPMC K100 M               | 40  | 50  | 60  | 40  | 50  | 60  | 40  | 50  | 60  |
| Poly (styrene-divinylbenzene) | 20  | 20  | 20  | 30  | 30  | 30  | 40  | 40  | 40  |
| DCP                       | 55  | 45  | 35  | 45  | 35  | 45  | 35  | 25  | 15  |
| Sodium bi carbonate       | 20  | 20  | 20  | 20  | 20  | 20  | 20  | 20  | 20  |
| Magnesium stearate        | 3   | 3   | 3   | 3   | 3   | 3   | 3   | 3   | 3   |
| Talc                      | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   |
Table 3: Pre compression parameters for all the factorial batches

| Batch number | Angle of repose (°) | Bulk density (g/ml) | Tapped density (g/ml) | Carr's compressibility index (%) | Hausner ratio (%) | Total porosity (%) | Drug content (%) |
|--------------|---------------------|---------------------|-----------------------|----------------------------------|------------------|-------------------|------------------|
| VF1          | 32.38±0.012         | 0.234±0.128         | 0.263±0.129           | 11.02±0.013                     | 1.12±0.014       | 11.02±0.031       | 92.12±0.056      |
| VF2          | 33.28±0.023         | 0.220±0.023         | 0.254±0.023           | 13.38±0.121                     | 1.15±0.123       | 13.38±0.023       | 93.17±0.034      |
| VF3          | 35.18±0.123         | 0.230±0.213         | 0.267±0.271           | 13.85±0.052                     | 1.16±0.014       | 13.85±0.128       | 94.18±0.112      |
| VF4          | 34.29±0.283         | 0.241±0.128         | 0.277±0.361           | 12.99±0.013                     | 1.14±0.022       | 12.99±0.313       | 97.19±0.312      |
| VF5          | 37.29±0.281         | 0.217±0.278         | 0.250±0.273           | 13.20±0.028                     | 1.15±0.015       | 13.20±0.122       | 93.22±0.023      |
| VF6          | 31.28±0.023         | 0.234±0.023         | 0.263±0.172           | 12.35±0.312                     | 1.12±0.014       | 11.02±0.028       | 96.29±0.003      |
| VF7          | 29.38±0.381         | 0.245±0.112         | 0.267±0.281           | 8.23±0.024                      | 1.08±0.341       | 8.23±0.112        | 98.18±0.912      |
| VF8          | 33.56±0.824         | 0.223±0.238         | 0.288±0.271           | 19.09±0.012                     | 1.29±0.023       | 22.5±0.091        | 94.18±0.923      |
| VF9          | 38.39±0.213         | 0.234±0.123         | 0.254±0.234           | 7.96±0.023                      | 1.08±0.044       | 7.87±0.012        | 95.29±0.021      |

All results were shown in mean±SD (n=3)

Table 4: List of variable importance for precompression parameters

| Pre compression variables | Variable number | Power | Importance |
|---------------------------|-----------------|-------|------------|
| Total porosity (%)        | 2               | 0.9623 | 1          |
| Hausner ratio             | 6               | 0.91326 | 2         |
| Carr's compressibility index (%) | 5            | 0.96503 | 3         |
| Tapped density (g/ml)     | 4               | 0.91676 | 4         |
| Bulk density (g/ml)       | 3               | 0.90547 | 5         |
| Drug content (%)          | 8               | 0.754903 | 6         |
| Angle of repose (°)       | 2               | 0.535868 | 7         |

Table 5: Post compression parameters for all the formulations

| Batch number | Average weight (mg) | Weight variation test (%) | Drug content (%) | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Floating Time (sec) | In vitro buoyancy study (h) |
|--------------|---------------------|---------------------------|------------------|-------------------|----------------|------------------|------------------------|-----------------------------|
| VF1          | 300.51              | ±0.050 (Pass)             | 92.3±0.45        | 5.6±0.02          | 5.4±0.18       | 0.412±0.28      | 116±0.37               | 14                         |
| VF2          | 298.23              | ±0.809 (Pass)             | 96.2±0.36        | 5.2±0.06          | 5.2±0.27       | 0.429±0.16      | 123±0.14               | 15                         |
| VF3          | 302.21              | ±0.514 (Pass)             | 97.38±0.11       | 5.7±0.13          | 5.6±0.37       | 0.491±0.08      | 136±0.02               | 18                         |
| VF4          | 301.20              | ±0.178 (Pass)             | 96.68±0.08       | 5.2±0.22          | 5.5±0.33       | 0.512±0.17      | 127±0.22               | >24                        |
| VF5          | 302.17              | ±0.005 (Pass)             | 98.11±0.38       | 4.8±0.51          | 5.7±0.38       | 0.613±0.22      | 132±0.33               | 18                         |
| VF6          | 300.47              | ±0.064 (Pass)             | 99.13±1.45       | 5.2±0.02          | 5.1±0.15       | 0.531±0.38      | 123±0.16               | >24                        |
| VF7          | 301.63              | ±0.321 (Pass)             | 96.19±0.41       | 5.9±0.22          | 5.8±1.82       | 0.556±0.08      | 117±0.05               | 17                         |
| VF8          | 300.28              | ±0.127 (Pass)             | 98.29±0.62       | 6.4±0.27          | 5.4±0.22       | 0.536±0.28      | 125±0.18               | 16                         |
| VF9          | 299.27              | ±0.463 (Pass)             | 96.31±0.42       | 5.7±0.28          | 5.3±0.02       | 0.572±0.31      | 130±0.37               | >24                        |

All results were shown in mean±SD (n=3)

Table 6: variables importance for post compression parameters

| Post compression variables | Variable number | Power | Importance |
|----------------------------|-----------------|-------|------------|
| Thickness (mm)             | 4               | 0.923526 | 1          |
| Average weight (mg)        | 1               | 0.832101 | 2          |
| Drug content (%)           | 3               | 0.776889 | 3          |
| Friability (%)             | 2               | 0.693686 | 4          |
| Floating time (sec)        | 5               | 0.620322 | 5          |
| Hardness (kg/cm²)          | 6               | 0.172067 | 6          |

Table 7: Level of significance of R2 value

| Std. Dev. | R² | Adjusted R² | Predicted R² | Adeq Precision |
|-----------|----|-------------|--------------|----------------|
| 0.2560    | 0.995 | 0.9987     | 0.9944       | 102.6078        |

Table 8: ANOVA for quadratic model on %CDR at 2nd h

| Source          | Sum of squares | df | Mean square | F-value | p-value |
|-----------------|----------------|----|-------------|---------|---------|
| Model           | 393.65         | 5  | 78.73       | 1201.78 | <0.0001 |
| X1*HMC K100 M   | 239.40         | 1  | 239.40      | 3654.37 | <0.0001 |
| X2*poly styrene divinylbenzene | 116.42         | 1  | 116.42      | 1777.17 | <0.0001 |
| X2*X3           | 36.97          | 1  | 36.97       | 564.28  | 0.0002  |
| X2*X4           | 0.0242         | 1  | 0.0242      | 0.3694  | 0.5863  |
| X2*X5           | 0.8321         | 1  | 0.8321      | 12.70   | 0.0377  |
| Residual        | 0.1965         | 3  | 0.0655      |         |         |
| Core Total      | 393.65         | 8  |             |         |         |
Table 9: Fit statistics for % CDR at 8th h

| Source of variation | Std. Dev. | R² | P-value | Significance |
|---------------------|-----------|----|---------|--------------|
| Mean                | 0.3608    |    |         |              |
| C. V. %             | 0.4271    |    |         |              |

Table 10: ANOVA for quadratic model at 2nd h of % CDR

| Source of variation | Sum of square | Df | Mean square | F-value | P-value | Significant? |
|---------------------|---------------|----|-------------|---------|---------|--------------|
| Model               | 216.17        | 5  | 43.23       | 332.16  | 0.0003  | significant  |
| A-HPMC K100 M       | 125.95        | 1  | 125.95      | 967.69  | <0.0001 |              |
| B-poly (styrene-divinylbenzene) | 89.55        | 1  | 89.55       | 688.04  | 0.0001  |              |
| AB                  | 0.2304        | 1  | 0.2304      | 1.77    | 0.2755  |              |
| A²                  | 0.3444        | 1  | 0.3444      | 2.65    | 0.0203  |              |
| B²                  | 0.0882        | 1  | 0.0882      | 0.6777  | 0.4707  |              |
| Residual            | 0.3905        | 3  | 0.1302      |         |         |              |
| Cor/Total           | 216.56        | 8  |             |         |         |              |

Table 11: Checkpoint batch and standard error:

| Checkpoint Batch | % CDR at 2nd h | % CDR at 8th h | % CDR at 2nd h | % CDR at 8th h | % CDR at 2nd h | % CDR at 8th h |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| VF10            | 29.67          | 87.48          | 28.39          | 84.05          | 4.31           | 3.92           |
| VF11            | 30.29          | 85.28          | 28.39          | 84.05          | 6.27           | 1.44           |
| VF12            | 29.36          | 86.67          | 28.39          | 84.05          | 3.30           | 3.02           |

Table 12: Comparative kinetic model for VF1 to VF9 batches

| Statistical analytical criteria | VF1 | VF2 | VF3 | VF4 | VF5 | VF6 | VF7 | VF8 | VF9 |
|---------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Zero                            | 0.8726 | 0.918 | 0.911 | 0.9162 | 0.9396 | 0.8949 | 0.878 | 0.8594 | 0.8899 |
| First                           | 0.9841 | 0.7801 | 0.8465 | 0.8809 | 0.7307 | 0.8994 | 0.9657 | 0.9529 | 0.9604 |
| Peppas                          | 0.8099 | 0.8253 | 0.8308 | 0.8256 | 0.8683 | 0.82 | 0.8357 | 0.8452 | 0.8427 |
| Hixon Crowell                   | 0.8573 | 0.8904 | 0.8531 | 0.8857 | 0.9198 | 0.8675 | 0.8767 | 0.8732 | 0.8765 |
| Higuchi                         | 0.9586 | 0.9523 | 0.961 | 0.961 | 0.9328 | 0.9669 | 0.9598 | 0.9502 | 0.9532 |
| AIC (Akaike Information Criterion) | 61.555 | 57.27 | 85.324 | 84.905 | 54.97 | 85.803 | 86.35 | 86.37 | 141.62 |
| BIC (Bayesian Information Criterion or Schwarz Criterion) | 61.714 | 57.44 | 85.848 | 85.064 | 55.13 | 85.961 | 85.51 | 86.53 | 141.78 |
| K1                              | 0.34 | 0.332 | 0 | 0.28 | 0.324 | 0 | 0 | 0 | 0.313 |
| RMSE (Root Mean Squared Error)  | 12.9037 | 98.73 | 56.99 | 55.527 | 8.55 | 58.731 | 60.802 | 60.877 | 192.235 |
| Percentage Dissolution Efficiency (DE) (%) | 70.1512 | 70.15 | 64.19 | 62.23 | 56.39 | 67.104 | 69 | 68.705 | 66.58 |
| Mean Dissolution Time (MDT)(hr) | 3.439 | 3.431 | 4.3056 | 4.377 | 5.19 | 3.947 | 3.71 | 3.75 | 3.861 |

Table 13: Accelerated stability study of VF5 formulation batch as per ICH Q1A guideline

| Duration | Hardness (Kg/cm²) | Friability (%) | Floating time (Sec) | %Drug content | % CDR at 12th hours |
|----------|-------------------|----------------|---------------------|--------------|-------------------|
| Initial  | 4.6±0.45          | 0.16±0.22      | 152±0.33            | 96.11±0.38   | 99.38±0.51        |
| 1st month| 4.4±1.51          | 0.60±0.51      | 133±0.45            | 98.10±0.11   | 100.23±0.67       |
| 2nd month| 4.1±0.23          | 0.58±0.47      | 134±0.13            | 97.76±0.30   | 101.34±1.51       |
| 3rd month| 3.8±0.32          | 0.56±0.31      | 137±0.18            | 97.51±0.34   | 102.45±1.34       |
| 4th month| 3.7±0.41          | 0.55±0.29      | 139±0.43            | 97.21±0.58   | 104.24±1.05       |
| 5th month| 3.6±0.46          | 0.54±0.27      | 141±0.11            | 96.13±0.18   | 104.34±1.22       |
| 6th month| 3.5±0.27          | 0.53±0.11      | 144±0.34            | 95.11±0.22   | 105.35±2.14       |

Table 14: Two-way ANOVA results for stability study for VF5 formulation batch as per ICH Q1A guideline

| Source of variation | % of total variation | P-value | P-value summary | Significant? |
|---------------------|----------------------|---------|-----------------|--------------|
| Interaction         | 0.1167               | <0.0001 | ****            | Yes          |
| Row factor          | 0.0294               | <0.0001 | ****            | Yes          |
| Column factor       | 0.0979               | <0.0001 | ****            | Yes          |
| ANOVA table         | SS                   | DF      | MS              | F (DFn, DFd)  | P-value |
| Interaction         | 885.8                | 24      | 36.91           | F (24, 210) = 16.3 | P<0.0001 |
| Row factor          | 223.7                | 6       | 37.29           | F (6, 210) = 16.47 | P<0.0001 |
| Column Factor       | 757.655              | 4       | 189.144         | F (4, 210) = 0.3649 | P<0.0001 |
| Residual            | 475.5                | 210     | 2.264           |              |         |

**** indicates a higher level of significance

All results were shown in mean±SD (n=3)

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DISCUSSION

The main intention of this research was to evaluate valsartan floating tablets using various statistical approaches. To prepare 160 mg valsartan to contain floating tablets, 40-60 mg of HPMC K100 M and 20-40 mg of poly (syrrene-divinylbenzene) were used as principal polymers as shown in table 2. From the precompression parameters of all the nine factorial batches shown in table 3, it was confirmed that all the formulation blend has fair to good angle of repose (29.38±0.381 to 38.39±0.213°), excellent bulk density (0.217±0.278 to 0.245±0.112 g/ml), excellent tapped density (0.250±0.273 to 0.288±0.271 g/ml), good percentage carr’s compressibility index (7.967±0.203 to 19.09±0.012 %), moderate hausner ratio (1.08±0.044 to 1.16±0.014), good percentage porosity (7.874±0.912 to 22.56c±0.091 %) and adequate drug content (92.12±0.056 to 98.18±0.912 %). From the variable importance study performed in Statistica 12 software on post compression parameters mentioned in table 4, it was confirmed that, among the pre-compression parameters, total porosity (%) has highest variable importance, hence total porosity (%) could influence valsartan floating tablet efficacy. In a similar pattern, from post-compression parameters, all the batches reported to have very good tablet average weight (298.23 to 302.21 mg), limited percentage weight variation, excellent percentage drug content (92.34±0.45 to 99.13±1.45 %), adequate hardness (4.8±0.51 to 56.39%) and higher Mean Dissolution Time (MDT) (5.19hr) as shown in table 12 on all the nine batches, it was proposed that VF5 formulations, it was also revealed that the VF5 formulation; encompassing 50 mg of HPMC K100 M and 30 mg poly (syrrene-divinylbenzene) shows no significant changes in physical and characteristic properties after six months accelerated conditions (40 °C±2 °C/75% RH±5% RH). Thus, from the above conclusion, it was summarized that valsartan floating tablets were successfully prepared but in vivo bouncy study and in vivo pharmacokinetics in an animal model is warrant to established proper in vitro and in vivo correlation.

RESEARCH INVOLVING HUMAN AND/OR ANIMAL RIGHTS

The author did not perform any study with human or animal subjects.

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AUTHOR CONTRIBUTION

All the work have been carried out by me

CONFLICT OF INTERESTS

Author did not receive any conflict of interest. The author is solely responsible for the conduct of experiments and writing of this article.

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