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Original Article

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 QIA 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

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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 tenses to dilate blood vessels. It has versatile use in the treatment of Congestive Heart Failure (CHF), Post-Myocardial Infraction (MI). Eventually, valsartan blocks the binding of angiotensin II to the ATI receptor in adrenal gland and vascular smooth muscle [1]. Valsartan also restrict aldosterone secreting effects of angiotensin II, which ultimately leads to vasoconstriction [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, talc was gifted from Balaji Chemicals Vapi, Gujarat, India. All the other chemicals are reagents used were of pharmaceutical and analytical grads. 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, Libindia 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 aluminum 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 quadric effect and interaction between two variables can be studied [8]. In this experiment, the joint influence of

independent variables concentration of HPMC K100M [X_1] and poly (styrene-divinylbenzene) [X_2] on the dependent variables, i.e. % Cumulative Drug Release (CDR) at 4th hour(Y_1) and % CDR at 8th hour (Y_2). 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.

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1^2+\beta_{22}X_2^2+E,$$

Where, β_0 is intercepted, which is constant. The β_1 and β_2 are coefficient of X_1 and X_2, β_{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, glidant i. e talc and magnesium stearate were added further in the polymeric drug mixture. These powder mixtures were than bladed using 1L Laboratory Blender (Thomas Scientific) and sieved using #40 mesh. This blend was compressed using 12 mm diameter flat punch. For punching purposes, 16 stations rotary punching machine (Pacific tool private limited) was utilized. For this operation, type B tooling tablet punch was functionalized with 133.6 mm punch length and 19 mm punch diameter. The die diameter was 30.15 mm and die height was 2.22 mm. The operational tablets were in plane face with 16±1.25 mm tablet size. The hardness of the operational twenty tablets was found on an average between 4-7 kg/cm^2.

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/cm^3) using following formula:

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

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 East, 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 (V_1). Further, more 750 times tapping were recorded. The tapped volume was considered as V_2. As per procedure if the difference between V_1 and V_2 is lesser then %, then the final volume (V_2) can be considered for final tapped volume. The calculative tapped density (g/cm^3) was measured by following formula:

$$\text{Tapped density}=\frac{\text{Weight of the granuls}}{\text{Final tapped volume}}$$

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.

$$\text{Carr's Index}=\frac{\text{Tapped density}-\text{Bulk dennsity}}{\text{Tapped density}}\times100$$

Angle of repose

Using the funnel method, the angle of repose of powder was determined. The funnel was filed 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.

$$\theta = \tan^{-1} h/r$$

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:

Porosity = (Total Volume-Volume of the Solid)/Total Volume) x 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 0.45µ membrane. The absorbance was measured at 50 nm after suitable dilution using Shimadzu UV-1601PC UV-Visible, Scanning Spectrophotometer.

Post compression parameters

Weight variation

Randomly twenty tablets were selected during process of manufacturing and average weight was measured. The individual tablet weight was measured and compared with average weight of tablets. The weight variation of tablet was estimated and percentage deviation was reported. Weight variation of all the batches of formulations was determined and recorded.

$$\text{Percentage deviation}=\frac{\text{Individual weight}-\text{Average weight}}{\text{Individual weight}}$$

Hardness

The hardness of the tablet was determined by Vin Syst Manual Tablet Hardness Tester (Monsanto Type); Model Number: VMT–1. Randomly three tablets from each batch were selected and the average hardness with standard deviation was recorded.

Friability

Friability test for uncoated tablets is prerequisite to know the tendency of tablets to chip, crumble or break during shipping, 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 rotatory drum surface. After rotation cycle, tablets were dusted and once again weight was measured.

$$\text{Friability}=\frac{\text{Ten tablets weight before frability}-\text{Ten tablets weight after friability}}{\text{Ten tablets weight before friability}}\times100$$

Drug content

At first, ten tablets were taken and the average weight was measured. Further, tablets were triturated to get fine powder. A certain quantity of powder equivalent to 80 mg of valsartan was taken and admixed with 100 ml of 0.1N HCL. The solution was further filtered using cellulose acetate membrane filter (0.30 µm). Further, 1 ml of this solution was diluted with 100 ml of 0.1N HCL and using Shimadzu UV-2600 spectrophotometer at 50 nm absorbance was taken to measure drug content.

***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 °C±0.5 °C. During dissolution study at various time intervals, 5 ml of dissolution media was withdrawn and filtered using 0.45µ 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 2^{nd} hour and % CDR at 8^{th} hour have been evaluated, considering each at three levels (-1, 0,+1). Total nine batches of possible combinations were generated by Design of Expert 11 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 2^{nd} and 8^{th} hour respectively, 3D surface plot of % CDR at 2^{nd} 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^2 value.

Kinetic studies

Drug release studies can be well defined by selecting suitable kinetic models like zero order kinetics, first-order kinetics, higuchi model, hixson crowell cube root model, korsmeyer peppas equation [13]. Nevertheless, Akaike Information Criterion (AIC) [14], Bayesian Information Criterion (BIC) or Schwarz Criterion (SC), K1, Root Mean Squared Error (RMSC), Dissolution Efficiency (DE), Mean Dissolution Time (MDT) estimation using KinetDS 3 rev 010 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± °C/75% RH±5% RH for 6 mo. 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 aluminum foil and formulation was exposed in elevated temperature and humid conductions 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 alkene, 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 shafted to 198.56 °C while combination with drug and polymers.

Pre compression parameters and evaluations

Each batch was planned for 50 tablets, hence 15g bland was prepared. Bulk density was measured using Veego digital bulk density apparatus (Model number: VTAP/MATIC-II). Bland was placed in 100 ml of polypropylene-based graduated cylinder (Karter Scientific 19H2) 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: 0.996230) has maximum influence on floating tablet manufacturing and angle of repose (power value: 0.535868) has less importance on tablet preparation. All these results indicate, all the batches blend has 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 as the percentage weight variation was within 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 VF8 batch was found to be maximum i.e. 6.4±0.27 kg/cm^2 and VF5 batch recorded lowest average hardness i.e. 4.8±0.51 kg/cm^2. 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 0.613±0.22%, where else VF1 shows lest friability of 0.412±0.28% among all the batches. The floating time was a prerequisite variable for this formulation design. Floating time of VF1 was recorded 116±0.37see which is lest among of all the batches, where else VF3 shows maximum floating time of around 136±0.02see. The formulation BF4, VF6 and VF9 shows maximum buoyancy where else VF1 shows minimum buoyancy within 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: 0.535868) 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 12^{th} 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

poly (styrene-divinylbenzene) (20-40 mg)-X_2 and HPMCK100M (40-60 mg)-X_1 is highly influenced the *in vitro* drug dissolution profile.

Effect of polymers concentration on %CDR at 2nd h

Using Design Expert® 11 software *in vitro* percentage cumulative drug release study was statistically interpreted at 2nd hour. Based on ANOVA analysis, quadric model was selected. In quadric model, F-value was 1201.78, which implies the model was 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 palpable and accepting the alternative hypothesis was acceptable. Nevertheless, P-values less than 0.0500 indicate model terms were significant. In this case X_1 X_2, X_1X_2, X_2^2 are significant model terms. Values greater than 0.1000 indicate the model terms were not significant. The Predicted Quadric 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 102.608, indicates an adequate signal. This model can be used to navigate the design space.

The polynomial equation for % CDR at 2nd Hour (Y_1) =+28.39-6.32X_1-4.40X_2 3.04X_1X_2+0.1100X_1^2+0.6450X_2^2

The higher value of correlation coefficient for % CDR at 2nd hour signifies a good fit model. The coefficient of X_1 and X_2 was significantly lower and negative, indicating decrease in polymer concentration [X_1= HPMCK100M (40-60 mg), X2=poly (styrene-divinylbenzene) (20-40 mg)] could increase the percentage cumulative drug release at 2nd hour. Where else, a combination of X_1X_2 and individual squares of X^2_1 and X^2_2 has agonistic effect with drug release, means drug release could get decrease with increase concentration of X_1 and X_2. But the coefficient values of $X_{21,}$ X^2_2 and X_1X_2 was smaller, means has less influence on % CDR at 2nd 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 VF5 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 2nd hour is almost coincide with actual %CDR at 2nd (fig. 2).

Effect of polymers concentration on %CDR at 8th hour

Using Design Expert® 11 software *in vitro* percentage cumulative drug release study was statistically interpreted at 8th hour. Based on ANOVA analysis, quadric model was selected. In the quadric model, F-value was 332.16, which implies the model was significant. There was only a 0.03% 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 palpable and accepting the alternative hypothesis was accepted. Nevertheless, P-values less than 0.0500 indicate model terms were significant. In this case X_1 X_2, X_1X_2, X_2^2 are significant model terms. Values greater than 0.1000 indicate the model terms were not significant.

The Predicted R^2 of 0.9859 is in reasonable agreement with the Adjusted R^2 of 0.9952; i.e. the difference is less than 0.2. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. In this experiment ratio was 57.338 indicates an adequate signal (table 9and10). This model can be used to navigate the design space.

Polynomial equation for % CDR at 8th Hour (Y_2) =+84.05-4.58X_1-3.86X_2 0.2400X_1X_2+0.4150X_1^2+0.2100X_2^2

The moderate-higher value of correlation coefficient for % CDR at 8th hour signifies a good fit model. The coefficient of X_1 and X_2 was significantly lower and negative, indicating decrease in polymer concentration [X_1= HPMCK100M (40-60 mg), X_2= divinylbenzene) (20-40 mg)] could increase the percentage cumulative drug release at 8th hour. Where else, combination of X_1X_2 has shown negative sign with low coefficient value (0.2400), indicating increase in drug release profile. The individual squares of X^2_1 and X^2_2 have agonistic effect with drug release, means drug release could get decrease with increase concentration of X_1 and X_2. But the coefficient values of $X^2_{1,}$ X^2_2 and X_1X_2 were smaller, means has less influence on % CDR at 8th 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 VF5 formulation batch have proper dissolution profile after 8th 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 8th hour was almost coinciding with actual %CDR at 8th 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 2nd and 8th 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 VF5 batches formulations could be the optimized one. To understand properly three checkpoint batches (VF10, VF11, and VF12) was prepared. The 2nd and 8th hours of %CDR was compared with predicted values of the overly 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); as after studying the effect of independent variables on dependent variables or response variables, the optimum response was determined. It was observed that response variables of checkpoint batches were cognitive with VF5 formulations (table 11), hence VF5 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, VF5 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 lest 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, can 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 VF5 has shown highest MTD value (5.19) as compare 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 lest 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 R^2 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.

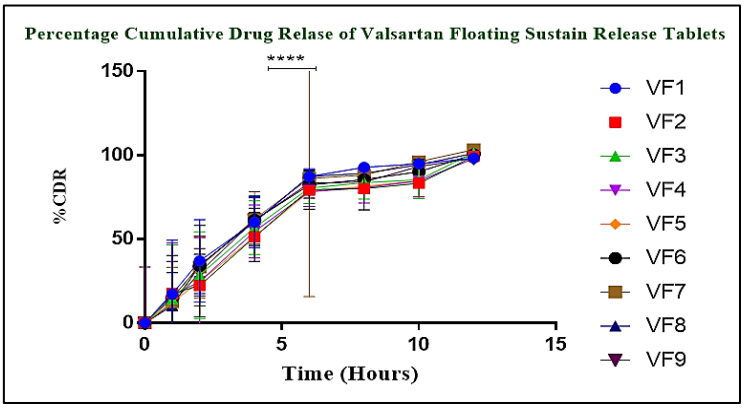

Fig. 1: % CDR profile of valsartan floating tablets (VF1-VF9 batches) at 95.00% CI of differences and at mean±SD (n=3); ** indicates high statistically significance (p<0.005)**

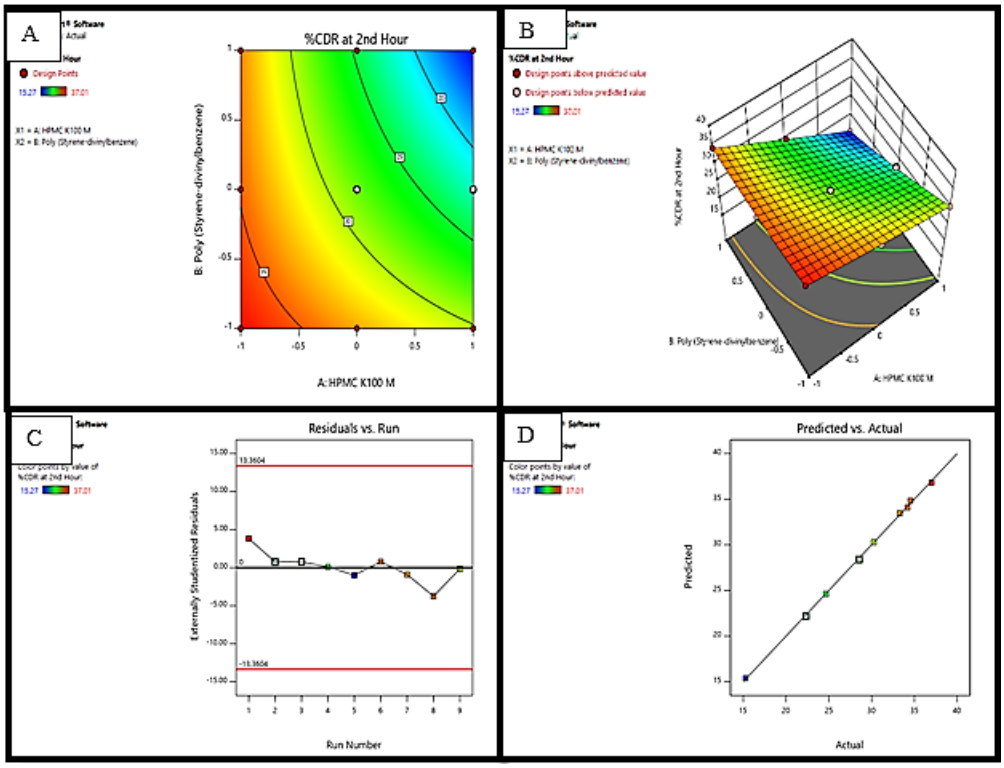

Fig. 2: Design expert output [A-counter, B-3D surface plot, C-residual vs run plot D-actual vs predicted plot] of effect of polymers concentration on % CDR at 2nd h

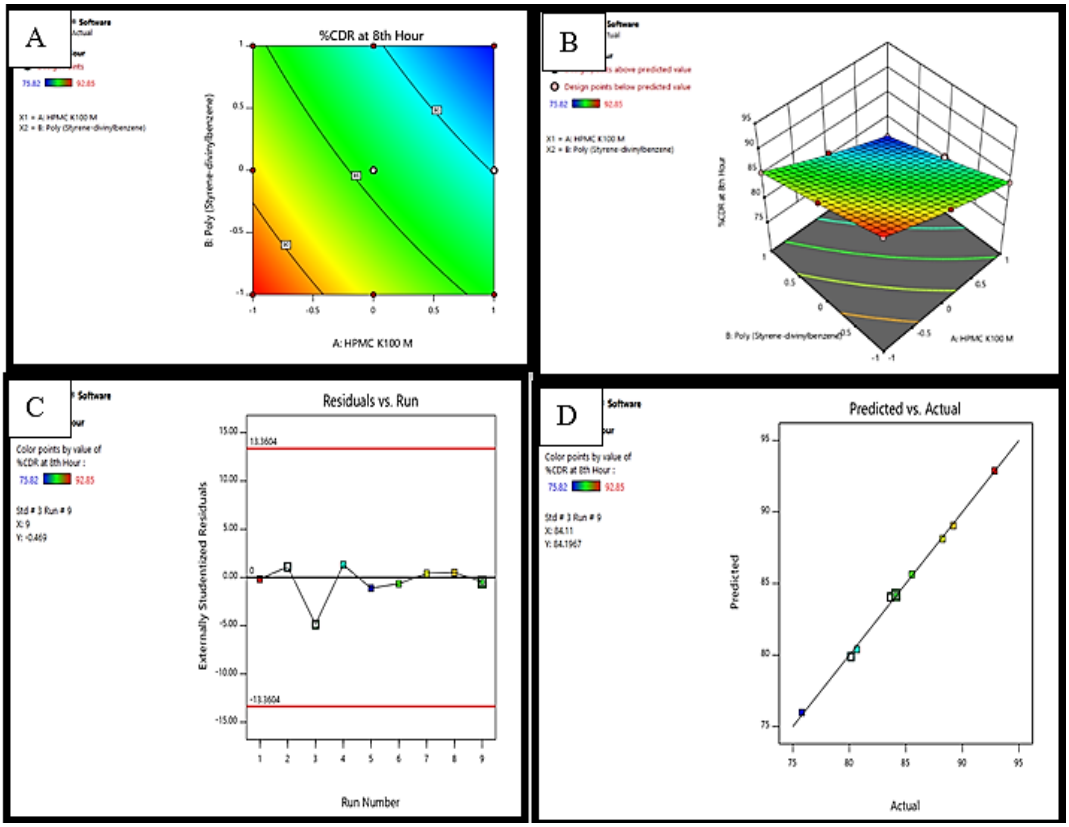

Fig. 3: Design expert output [A-counter, B-3D surface plot, C-residual vs run Plot D-actual vs predicted plot] of effect of polymers concentration on % CDR at 8th h

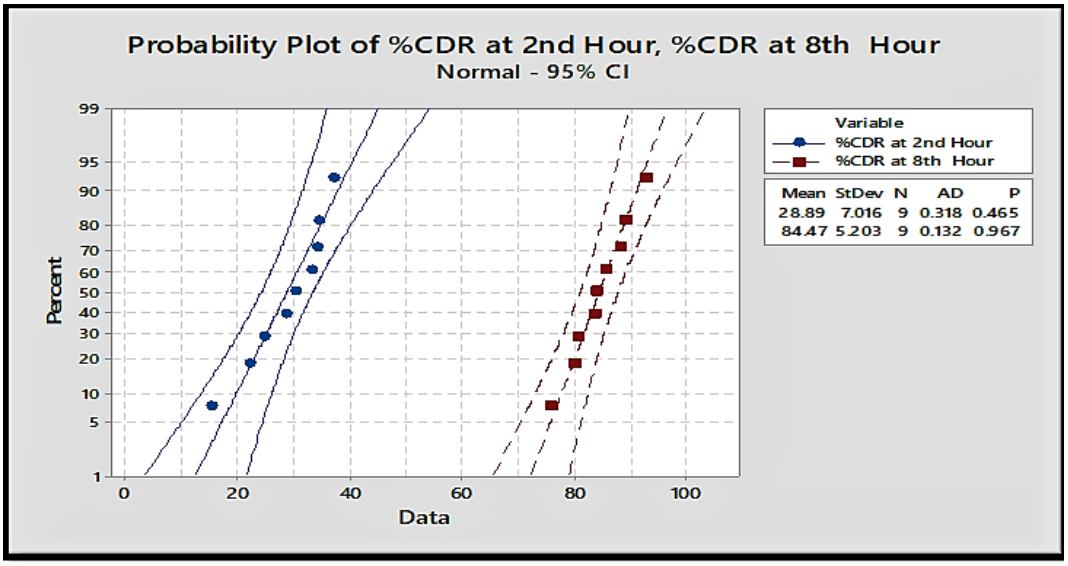

Fig. 4: Comparative probability plot of % CDR at 2nd and 8th h

Table 1: Selection of variables levels for independent variables

(Independent variables)			
Levels	**Coded value**	**Concentration of HPMC K100M in mg (X_1)**	**Concentration of poly (Styrene-divinylbenzene) in mg (X_2)**
Low	-1	40	20
Intermediate	0	50	30
High	+1	60	40

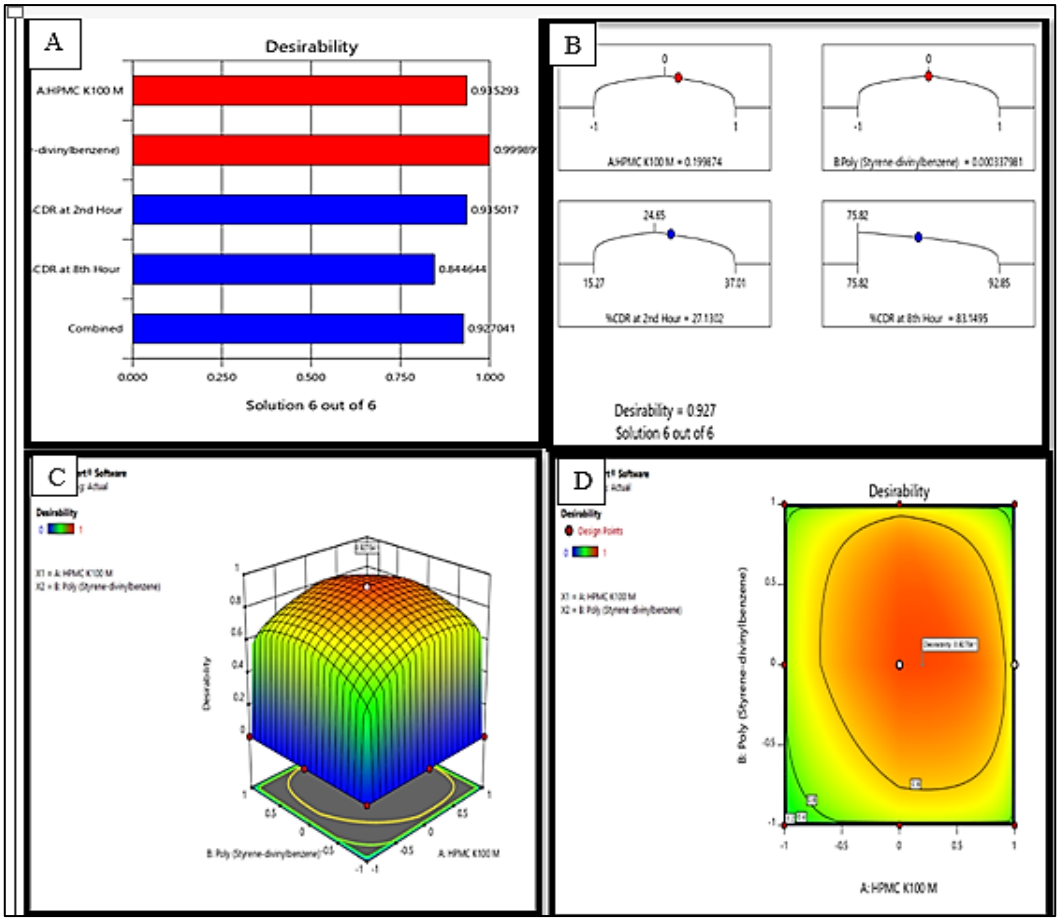

Fig. 5: Desirability function [A-bar chart, B-ramps chart, C-3D surface plot chart, D-counter plot]

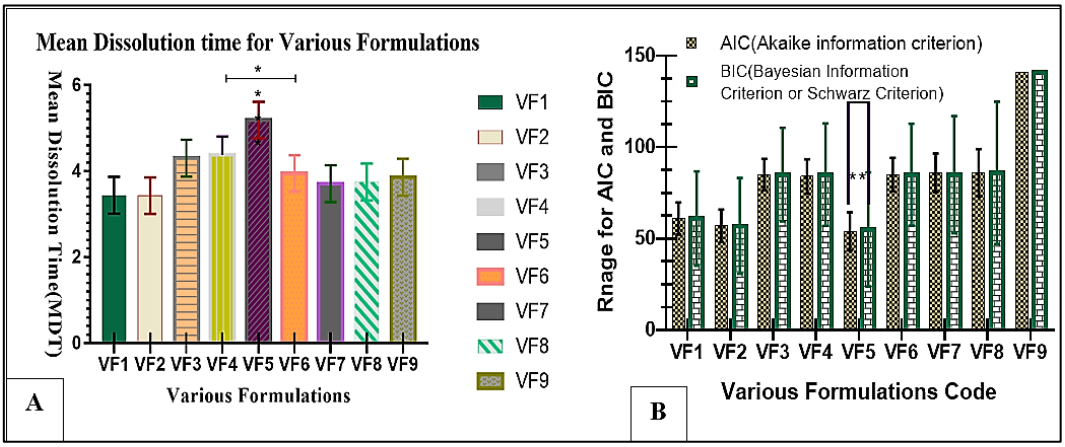

Fig. 6: [A]. Comparative mean dissolution study for VF1 to VF9 formulation at 95.00%, CI of differences, and at mean±SD (n=3) [B]. A comparative profile of AIC and BIC values are represented as mean±SD (n=3) on various valsartan floating formulations AIC and BIC at 95.00% CI of differences, ** indicates 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	25	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	32.87±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±0.025	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	8.239±0.024	1.08±0.341	8.239±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	22.56±0.091	94.18±0.923
VF9	38.39±0.213	0.234±0.123	0.254±0.234	7.967±0.023	1.08±0.044	7.874±0.912	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 (%)	7	0.996230	1
Hausner ratio	6	0.991326	2
Carr's compressibility index (%)	5	0.965853	3
Tapped density(g/ml)	4	0.916766	4
Bulk density (g/ml)	3	0.905470	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)	92.34±0.45	5.6±0.02	5.4±0.18	0.412±0.28	116±0.37	14
VF2	298.23	±0.809(Pass)	96.23±0.36	5.2±0.06	5.2±0.27	0.429±1.61	123±0.14	15
VF3	302.21	±0.514(Pass)	97.38±0.11	5.7±0.13	5.6±0.37	0.491±0.82	136±0.02	18
VF4	301.20	±0.178(Pass)	96.68±0.87	5.2±0.22	5.5±0.33	0.512±1.27	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 (see)	5	0.620322	5
Hardness (kg/cm²)	6	0.172067	6

Table 7: Level of significance of R2 value

Std. Dev.	0.2560	**R^2**	0.9995
Mean	28.89	Adjusted R^2	0.9987
C. V. %	0.8858	Predicted R^2	0.9944
		Adeq Precision	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	significant
X_1-HPMC K100 M	239.40	1	239.40	3654.37	<0.0001	
X_2-poly (styrene divinylbenzene)	116.42	1	116.42	1777.17	<0.0001	
X_1X_2	36.97	1	36.97	564.28	0.0002	
X_1^2	0.0242	1	0.0242	0.3694	0.5863	
X_2^2	0.8321	1	0.8321	12.70	0.0377	
Residual	0.1965	3	0.0655			
Core Total	393.85	8				

Table 9: Fit statistics for % CDR at 8th h

Std. Dev.	0.3608	R^2	0.9982
Mean	84.47	Adjusted R^2	0.9952
C. V. %	0.4271	Predicted R^2	0.9859
		Adeq Precision	57.3382

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

Source	Sum of square	Df	Mean square	F-value	P-value	
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	
A^2	0.3444	1	0.3444	2.65	0.2023	
B^2	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:

	Actual		Predicted		Standard error	
Checkpoint Batch	%CDR at 2nd Hour	%CDR at 8th Hour	%CDR at 2nd Hour	%CDR at 8th Hour	for %CDR at 2nd Hour	For % CDR at 8th Hour
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	0.85948	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	0.8831	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	5.74E+01	85.483	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	1923.25
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 (See)	%Drug content	%CDR at 12th hours
Initial	4.8±0.43	0.613±0.22	132±0.33	98.11±0.38	99.38±0.51
1st month	4.4±1.51	0.602±0.51	133±0.45	98.10±0.11	100.23±0.67
2nd month	4.1±0.23	0.588±0.71	134±0.13	97.76±0.30	101.34±1.51
3rd month	3.8±0.32	0.561±0.29	137±0.18	97.51±0.34	102.45±1.34
4th month	3.7±0.41	0.551±0.31	139±0.43	97.21±0.58	104.24±1.05
5th month	3.6±0.46	0.543±0.72	141±0.11	96.13±0.18	104.34±1.22
6th month	3.5±0.27	0.531±0.11	144±0.34	95.11±0.22	105.35±2.14

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

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	0.02947	<0.0001	****	Yes	
Column factor	99.79	<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	757655	4	189414	F (4, 210) = 83649	P<0.0001
Residual	475.5	210	2.264		

**** indicates a higher level of significance

DISCUSSION

The main intention of this research was to evaluate valsartan floating tablets using various statistical approach. To prepare 160 mg valsartan to contain floating tablets, 40-60 mg of HPMC K100 M and 20-40 mg of poly (styrene-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 bland 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±0.023 to 19.09±0.012 %), moderate hausner ratio (1.08±0.044 to1.16±0.014), good percentage porosity (7.874±0.912 to 22.56±0.091 %) and adequate percentage drug content (92.12±0.056 to 98.18±0.912 %). From the variable importance studies 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 6.4±0.27 kg/cm^2), moderate thickness (5.1±0.15 to 5.8±1.82 mm), limited percentage friability (0.412±0.28 to 0.613±0.22 %) and effective floating time (116±0.37 to 136±0.02 see). From the statistical variable importance study performed in Statistica 12 software (table 6) on post-compression parameters, it was confirmed that tablet thickness has higher influence on floating tablets of valsartan. From the comparative kinetic model studies shown in table 12 on all the nine batches, it was proposed that VF5 happened to be the optimized formulation because it follows best zero-order kinetics (R2=0.9396), minimum AIC value (54.97) and minimum BIC (55.13) value as compared with the rest of the formulations. Nevertheless, VF5 reported to have marginal RMSE value (8.55) and least Percentage Dissolution Efficacy (PDE) (56.39%) and higher Mean Dissolution Time (MDT) (5.19hr) as compared to other formulations. Further, by performing desirability study it was confirmed that VF5 was found to be the best-optimized batch. The optimized VF5 formulation was observed in accelerated stability condition as per ICH Q1A guideline; and found to have very stable after six-month stability studies.

CONCLUSION

Valsartan floating drug delivery system was developed by considering HPMC K100M and poly (styrene-divinylbenzene) as principal polymers. Total nine formulations were prepared (VF1-VF9) and optimized by Response Surface Mythology (RSM) based Box-Bentham design. The main intention of this research was to evaluate valsartan floating tablets using various statistical approach. After all the evaluation studies VF5 formulations was emerges as an optimized formulation. From the six-month stability study results of VF5 formulations, it was also reviled that the VF5 formulation; encompassing 50 mg of HPMC K100M and 30 mg poly (styrene-divinylbenzene) shows no significant changes in physical and chemical characteristics 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.

REFERENCES

1. Iborra Egea O, Galvez Monton C, Roura S, Perea Gil I, Prat Vidal C, Soler Botija C, *et al.* Mechanisms of action of sacubitril/valsartan on cardiac remodeling: a systems biology approach. NPJ Syst Biol Appl 2017;3:12.
2. Ansara AJ, Kolanczyk DM, Koehler JM. Neprilysin inhibition with sacubitril/valsartan in the treatment of heart failure: mortality bang for your buck. J Clin Pharm Ther 2016;41:119-27.
3. Verdecchia P, Angeli F. Assessment of the optimal daily dose of valsartan in patients with hypertension, heart failure, or both. Clin Thera 2004;26:460-72.
4. Kshirsagar SJ, Patil SV, Bhalekar MR. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. Int J Pharm Invest 2011;1:207-13.
5. Sokar M, Hanafy A, Elkamel A, El-Gamal S. Design of chronomodulated drug delivery system of valsartan: *in vitro* characterization. Indian J Pharm Sci 2015;77:470-7.
6. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their *in vivo* success: a recent update. Asian J Pharm Sci 2016;11:575-84.
7. Marini A, Berbenni V, Moioli S, Bruni G, Cofrancesco P, Margheritis C, *et al.* Drug-excipient compatibility studies by Physico-chemical techniques: the case of Indomethacin. J Therm Anal Calorim 2003;73:529-45.
8. Vemula S, Venisetty RK, Veerareddy P. Valsartan floating bioadhesive compression-coated mini-tablets: formulation and pharmacokinetics; 2017.
9. Ahmed MS, Afaf AR, Amal SmAE-e, Yasmin IMM. Formulation and optimization of itraconazole proteasomes using box behnken design. Int J Appl Pharm 2018;10:41.
10. Anas TA, Ali Khidher A. Formulation and *in vitro* evaluation of amlodipine gastro retentive floating tablets using a combination of hydrophilic and hydrophobic polymers. Int J Appl Pharm 2018;10:126-34.
11. Gharti KP, Thapa P, Budhathoki U, Bhargava A. Formulation and in vitro evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. J Young Pharm JYP 2012;4:201-8.
12. Senjoti FG, Mahmood S, Jaffri JM, Mandal UK. Design and *in vitro* evaluation of sustained-release floating tablets of metformin HCl based on effervescence and swelling. Iranian J Pharm Res 2016;15:53-70.
13. Malana MA, Zohra R. The release behavior and kinetic evaluation of tramadol HCl from chemically cross-linked ter polymeric hydrogels. DARU J Pharm Sci 2013;21:10.
14. Brewer MJ, Butler A, Cooksley SL. The relative performance of AIC, AICC and BIC in the presence of unobserved heterogeneity. Methods Ecol Evolution 2016;7:679-92.
15. Bose A, Wong TW, Singh N. Formulation development and optimization of sustained release matrix tablet of Itopride HCl by response surface methodology and its evaluation of release kinetics. Saudi Pharm J 2013;21:201-13.