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FORMULATION DEVELOPMENT OF VALSARTAN FLOATING TABLETS EMPLOYING A NEW MODIFIED STARCH – OPTIMIZATION BY 2^3 FACTORIAL DESIGN

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Abstract:

The objective of the present study is optimization of valsartan floating tablet formulation by 2^3 factorial design. Floating tablets of valsartan (80 mg) were formulated employing Cross linked starch-urea, a new modified starch (50 %) as matrix forming polymer, sodium bicarbonate as gas generating agent and beeswax and starch acetate as floating enhancers. Valsartan is an orally active anti-hypertensive drug, majorly absorbed from stomach and upper small intestine. Formulation of sustained release floating tablets of valsartan is needed because of its poor oral bioavailability and short biological half-life. Valsartan floating tablets were formulated as per 2^3 factorial design and were evaluated.

The individual effects of sodium bicarbonate (Factor A) and starch acetate (Factor C) and their combined effect (AC) on the floating lag time were significant ($P < 0.05$).Whereas the individual effect of bees wax (Factor B) and all other combined effects of the three factors involved were not significant in influencing floating lag time of the tablets. Formulations F_a, F_{ab}, F_{ac} and F_{abc} exhibited excellent floating over more than 12 h with a floating lag time in the range 12-40 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time. Valsartan release from the floating tablets prepared except formulation F_a was slow and spread over 12 h and dependent on the composition of the tablets. Drug release from formulation F_a was very rapid. Valsartan release from the floating tablets was by non-fickian diffusion mechanism in all the cases except F_a. In the case of formulation F_a that gave rapid release of drug fickian diffusion was the drug release mechanism.

Optimization of valsartan floating tablet formulation was done taking floating lag time as the parameter for optimization. The polynomial equation describing the relationship between the response, Y and the variables, X_1, X_2 and X_3 based on the observed data was found to be $\mathbf{Y = 8.996 - 8.596\ (X1) + 2.396\ (X2) - 2.431\ (X1\ X2) + 0.561\ (X3) - 0.521\ (X1\ X3) + 0.396\ (X2\ X3) - 0.271\ (X1\ X2\ X3)}$*.Based on the polynomial equation developed, the optimized valsartan floating tablet formulation with a floating lag time of 20 seconds could be formulated employing sodium bicarbonate (160mg/tablet), beeswax (28mg/tablet) and starch acetate (10mg/tablet). The optimized formulation (F_{opt}) exhibited a floating time of 12-14 h with a lag time of 21 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed.*

Key words: *Cross Linked starch Urea, Floating tablets, Valsartan, Optimization, Factorial design, Sustained release.*

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INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms [1]. However the oral route of administration suffers with certain limitations such as short residence time of the dosage form in the g.i. tract, unpredictable gastric emptying, degradation of the drug due to highly reactive nature of g.i. contents and existence of an absorption window in the gastric and upper small intestine for several drugs. Gastric emptying is a complex process and makes *in vivo* performance of the drug delivery system uncertain. Formulation of floating drug delivery systems is a useful approach to avoid this variability with increased gastric retention time of the drug delivery system. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time .While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach .This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration [2], [3]. Several approaches are currently used to retain the dosage in the stomach. These include bioadhesive systems, swelling and expanding systems ,floating systems and other delayed gastric emptying devices[4,5].

The principle of floating tablets offers a simple and practical approach to achieve increased residence time in the stomach and upper g.i. tract to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer, a gas generating agent and a floating enhancer such as beeswax. Several polymers such as various viscosity grades of HPMC, Carbopol 934P, Eudragit RL, calcium alginate, Chitosan, Xanthan gum, guargum, etc., have been used in the design of floating tablets of various API. Sodium bicarbonate is the preferred gas generating agent in the formulation of floating tablets.

In the present study sustained release floating tablets of valsartan were formulated employing Cross linked starch-urea, a new modified starch (50 %) as matrix forming polymer, sodium bicarbonate as gas generating agent and beeswax and starch acetate as floating enhancers. Valsartan is an angiotensin receptor blocker widely prescribed for hypertension. It is absorbed from stomach and upper small intestine[6,7] . The oral bioavailability of valsartan was 23 %. It has a short biological half life of 3-6 hrs[8]. Hence sustained release floating tablet formulation is needed for valsartan to enhance its oral bioavailability and to prolong its therapeutic effect, to reduce dosage frequency and to increase patient compliance.

Floating tablets of valsartan were designed in the present study to enhance its bioavailability and to achieve sustained release over 12 h for b.i.d. administration. Sustained release of valsartan over 12h is aimed in addition to good floating characteristics. Formulation of valsartan floating tablets was optimized by 2^3 factorial design. Optimization[9] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. The objective of the present study is optimization of valsartan floating tablet formulation by 2^3 factorial design.

MATERIALS AND METHODS:

Materials

Valsartan was a gift sample from M/s Micro Labs Ltd, Pondicherry. Cross linked starch-urea was prepared in the laboratory. Starch acetate (50 cps), sodium bicarbonate, Lactose and beeswax were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Preparation of Cross linked Starch - Urea Polymer [10]

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to

boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85ºC for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Formulation of Floating Tablets

Matrix tablets each containing 80 mg of valsartan were formulated employing Cross linked starch- urea (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and starch acetate and beeswax as floating enhancers. Valsartan floating tablets were formulated as per 2^3 factorial design. The three factors involved in the 2^3 factorial design are sodium bicarbonate (Factor A), beeswax (Factor B) and starch acetate (Factor C). The two levels of sodium bicarbonate (Factor A) are 10 % and 20 %, the two levels of beeswax (Factor B) are 2 % and 5 % and the two levels of starch acetate (Factor C) are 5% and 10%. Eight valsartan floating tablet formulations were prepared employing selected combinations of the levels of the three factors as per 2^3 factorial design. The floating tablets were prepared by melting- wet granulation method as per the formula given in Table 1.

Table 1: Formulae of Valsartan Floating Tablets Prepared as Per 2^3 Factorial Design and Optimized Formulation

Ingredient (mg/tab)	**F (1)**	**F (a)**	**F (b)**	**F (ab)**	**F (c)**	**F (ac)**	**F (bc)**	**F (abc)**	**F (opt)**
Valsartan	80	80	80	80	80	80	80	80	80
Sodium bicarbonate	80	160	80	160	80	160	80	160	160
Bees wax	16	16	40	40	16	16	40	40	28
Starch acetate	40	40	40	40	80	80	80	80	10
Cross linked Starch Urea	400	400	400	400	400	400	400	400	400
Lactose	164	84	140	60	124	44	100	20	102
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight (mg)	800	800	800	800	800	800	800	800	800

The required quantities of valsartan, Cross linked starch-urea, starch acetate, lactose and sodium bicarbonate were thoroughly mixed in a dry mortar by following geometric dilution technique. Beeswax was melted in a dry beaker and the blend of the above mentioned ingredients was added to the molten beeswax and mixed thoroughly. The blend was transferred to a dry mortar and granulated with hydro-alcoholic (1:1) solution. The dried granules formed were passed through mesh No. 16 to break the aggregates. The lubricants talc and magnesium stearate were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were then compressed into 800mg tablets on a 8-station tablet punching machine (Karnavathi Rimek Minipress II) to a hardness of 4-5 Kg/cm^2.

Evaluation of Tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a Paramount tablet disintegration test machine using water, 0.1N HCl and phosphate buffer of pH 7.4 as the test fluids.

Estimation of Valsartan

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 250 nm in 0.1N HCl was used for the estimation of valsartan. The method obeyed Beer-Lambert's law in the concentration range of 0-10 µg / mL. When a standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.75% and 1.45% respectively. No interference from the excipients used was observed.

Floating Lag Time and Floating Time

In Vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 ml glass beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration in which the tablet remains floating was determined as floating time.

Drug Release Study

Drug release from the floating tablets prepared was studied using 8-station dissolution rate test apparatus (Labindia, DS 8000) employing a paddle stirrer at 50 rpm and at a temperature of 37 ± 1^0C. Hydrochloric acid, 0.1 N (900 mL) was used as dissolution fluid. A 5mL aliquot of dissolution medium was withdrawn through a filter (0.45µm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 250 nm. All drug release experiments were conducted in triplicate (n=3).

Data Analysis

Drug release data were analysed as per Zero order, first order, Higuichi[11] and Korsemeyer - Peppas[12] equation models to assess drug release kinetics and mechanism from the floating tablets prepared.

RESULTS AND DISCUSSION:

The principle of floating tablets offers a simple and practical approach to achieve increased residence time in the stomach and upper G.I. tract to enhance the bioavailability and to obtain controlled release. Floating tablets of valsartan were designed based on gas generating principle. The objective of the present study is formulation development and optimization of valsartan floating tablets based on gas generating principle.

Matrix tablets each containing 80 mg of valsartan were formulated employing Cross linked starch- urea (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and starch acetate and beeswax as floating enhancers. Valsartan floating tablets were formulated as per 2^3 factorial design. The three factors involved in the 2^3 factorial study are sodium bicarbonate (Factor A), beeswax (Factor B) and starch acetate (Factor C). The two levels of sodium bicarbonate (Factor A) are 10 % and 20 %, the two levels of beeswax (Factor B) are 2 % and 5 % and the two levels of starch acetate (Factor C) are 5% and 10%. Eight valsartan floating tablet formulations were prepared employing selected combinations of the levels of the three factors as per 2^3 factorial design. The floating tablets were prepared by melting- wet granulation method as per the formula given in Table 1. All the floating tablets prepared were evaluated for drug content, hardness, friability, disintegration time, floating lag time, floating time and drug release characteristics.

The physical parameters of the floating tablets prepared are given in Table 2.

Table 2: Physical Parameters of Valsartan Floating Tablets Prepared as per 2^3 Factorial Design and Optimized Formulation

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (mg/tablet)	Floating lag time (min- sec)	Floating Time (h)
F_1	4.5	0.65	79.60	12-30	>12
F_a	5.5	0.45	80.05	0-40	>12
F_b	5.0	0.58	80.25	20-40	>12
F_{ab}	4.5	0.30	80.15	0-12	>12
F_c	5.5	0.45	79.20	13-20	>12
F_{ac}	5.5	0.48	79.45	0-30	>12
F_{bc}	5.0	0.72	79.80	24-10	>12
F_{abc}	4.5	0.45	80.20	0-32	>12
F_{opt}	5.5	0.60	80.15	0-21	>12

Hardness of the tablets was in the range 4.5-5.5 Kg/cm^2.Weight loss in the friability test was in the range of 0.35 % – 0.72 % in all the cases. All the tablets prepared contained valsartan within 100±2% of the labelled claim. All the floating tablets prepared were found to be non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such the prepared floating tablets were of good quality with regard to drug content, hardness, friability and were suitable for controlled release.

In the *in vitro* buoyancy study, the floating lag time of various tablets was in the range 12 seconds to 24.17 minutes. Floating time of all the tablets prepared was more than 12 hours. The floating lag time values were subjected to ANOVA to find out the significance of the individual and combined effects of the three factors, sodium bicarbonate, beeswax and starch acetate on the floating characteristics of the tablets prepared. The results of ANOVA indicated that the individual effects of sodium bicarbonate (Factor A) and starch acetate (Factor C) and their combined effect (AC) on the floating lag time are significant ($P < 0.05$).Whereas the individual effect of bees wax (Factor B) and all other combined effects of the three factors involved are not significant in influencing floating lag time of the tablets.

The order of increasing floating lag time observed with various floating tablets prepared was $F_{ab} < F_{ac} < F_{abc} < F_a < F_1 < F_c < F_b < F_{bc}$. Formulations F_a, F_{ab}, F_{ac} and F_{abc} exhibited excellent floating over 12-14 h with a floating lag time in the range 12-40 seconds. Sodium bicarbonate at 20 % strength gave less floating lag time than at 10 % strength. Formulations F_a, F_{ab}, F_{ac} and F_{abc} are considered as the best floating tablets formulated based on the floating characteristics.

Valsartan release from the floating tablets formulated was studied in 0.1 N hydrochloric acid. Drug release parameters of the tablets prepared are summarized in Table 4. Valsartan release from the floating tablets prepared was slow and spread over 12 - 14 h and depended on the composition of the tablets. The release data were analyzed as per zero order, first order, Higuchi and Korsemeyer- Peppas kinetic models. The correlation coefficient (r) values in the analysis of release data as per different kinetic models are given in Table 3. The drug release plots are shown in Figs 1 – 2.

Drug release from all the floating tablets prepared was diffusion controlled as indicated by the linear Higuchi plots. When the release data were analyzed as per Korsemeyer- Peppas equation, the release exponent 'n' was found to be in the range 0.51 - 0.63 in all the cases except formulation F_a indicating 'non-Fickian diffusion' as the release mechanism from these floating tablets. In the case of formulation Fa, that gave rapid release of drug, the release exponent 'n' was found to be 0.10 indicating fickian diffusion as the drug release mechanism.

Table 3: Correlation Coefficient (r) values in the analysis of Release data of Floating Tablets of Valsartan as per various Kinetic models

Formulation	Zero Order	First Order	Higuchi	Korsemeyer - Peppas
F_1	0.9272	0.9726	0.9978	0.9955
F_a	0.492	0.9808	0.9878	0.9818
F_b	0.9582	0.9612	0.9936	0.9928
F_{ab}	0.9497	0.9673	0.9978	0.9978
F_c	0.9328	0.9837	0.9928	0.9879
F_{ac}	0.9793	0.9758	0.9810	0.9898
F_{bc}	0.9558	0.9873	0.9923	0.9905
F_{abc}	0.9570	0.9487	0.9869	0.9792
F_{opt}	0.9609	0.9407	0.9932	0.9964

Table: 4 Release Parameters of Valsartan Floating Tablets Prepared as per 2^3 Factorial Design and Optimized Formulation

Formulation	T_{50} (h)	Release Rate		Release Exponent (n)
		K_0 (mg/h)	$K_1(h^{-1})$	
F_1	3.1	8.32	0.2513	0.51
F_a	0.36	18.22	1.9455	0.10
F_b	4.6	6.79	0.1554	0.55
F_{ab}	3.9	7.32	0.1920	0.52
F_c	3.8	7.71	0.1812	0.57
F_{ac}	6.4	6.56	0.1283	0.63
F_{bc}	4.6	7.24	0.1505	0.61
F_{abc}	5.7	6.31	0.1392	0.53
F_{opt}	4.5	6.88	0.1810	0.58

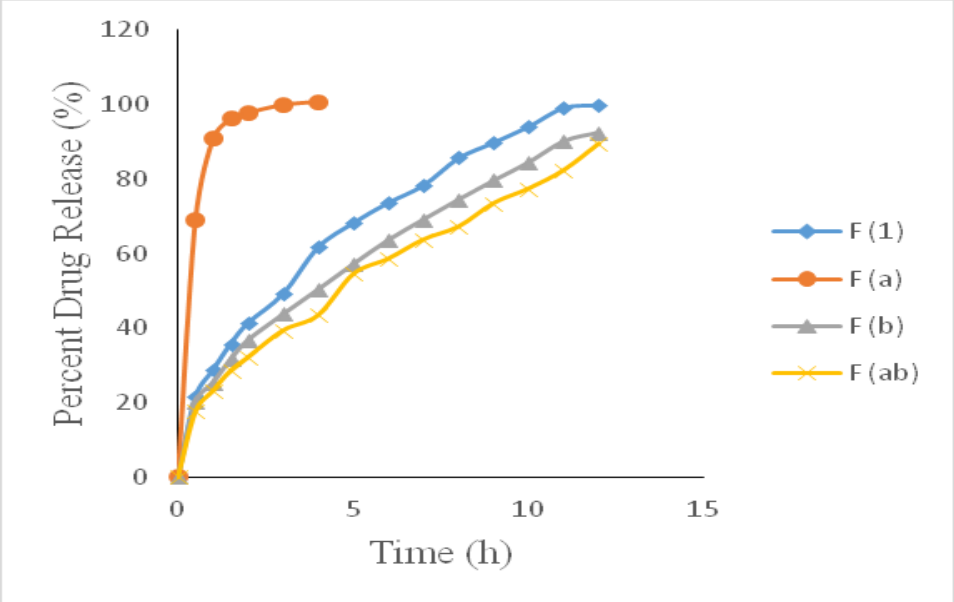

Fig. 1: Drug Release Profiles of Valsartan Floating Tablets Prepared (F_1, F_a, F_b, F_{ab})

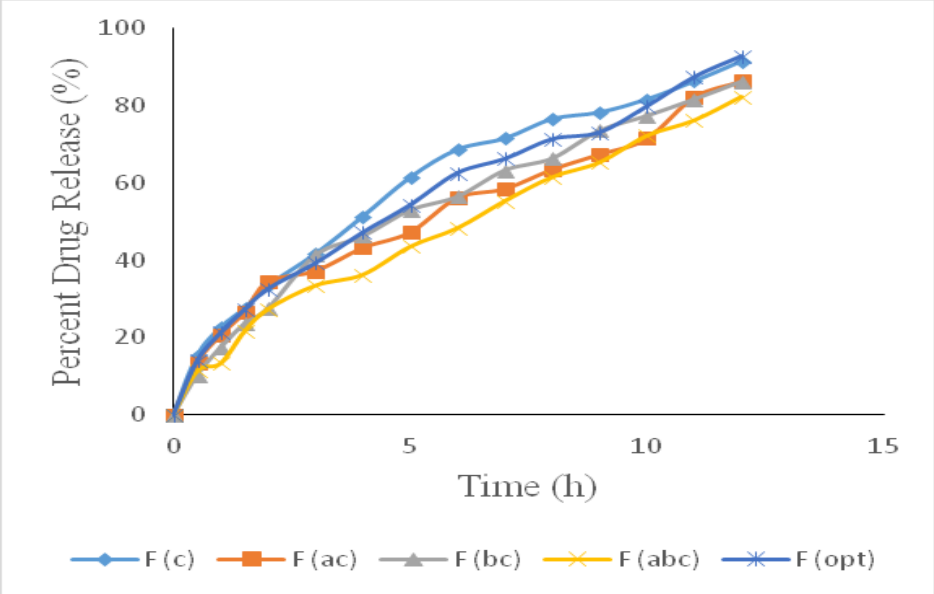

Fig.2: Drug Release Profiles of Valsartan Floating Tablets Prepared (F_c, F_{ac}, F_{bc}, F_{abc}) and optimized formulation (F_{opt})

Optimization:

Optimization of valsartan floating tablet formulation was done taking floating lag time as the parameter for optimization. For optimization, floating lag time was taken as response (Y) and level of sodium bicarbonate as (X_1), level of bees wax as (X_2) and level of starch acetate as (X_3). The polynomial equation describing the relationship between the response, Y and the variables, X_1, X_2 and X_3 based on the observed data was found to be

Y = 8.996 - 8.596 (X1) + 2.396 (X2) – 2.431 (X1 X2) + 0.561 (X3) - 0.521 (X1 X3) + 0.396 (X2 X3) - 0.271 (X1 X2 X3).

The magnitude of the coefficients of the variables in the polynomial equation indicate the relative strength of the variables in influencing the response involved. In the above polynomial equation, the coefficients of variables X_1 (sodium bicarbonate) is much higher when compared to the coefficients of other variables. As such the results indicate that the floating lag time is much influenced by the sodium bicarbonate levels in the formulation.

Based on the above polynomial equation, the optimized valsartan floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (160 mg/tablet), beeswax (28 mg/tablet) and starch acetate (10 mg/tablet). To verify valsartan floating tablets were formulated employing the optimized levels of sodium bicarbonate, beeswax and starch acetate as per the formula given in Table 1. The optimized valsartan floating tablet formulation was prepared and evaluated for floating and drug release characteristics. The optimized formulation exhibited a floating time of 14 h with a lag time of 21 seconds fulfilling the target floating lag time set. This result also indicated validity of the optimization technique employed. The optimized formulation exhibited a slow release of Valsartan over 12h.

Overall, formulations F_{opt} and F_{ab} prepared exhibited excellent floating characteristics (floating over 13-14 h with a lag time of 21 and 12 seconds respectively) and good sustained release of valsartan over 12 . As such, formulations F_{opt} and F_{ab} are considered as the best floating tablet formulations of valsartan suitable for b.i.d administration.

CONCLUSIONS:

1. Valsartan floating tablets prepared as per 2^3 factorial design were non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids and were of good quality with regard to drug content, hardness, friability and suitable for controlled release.
2. The individual effects of sodium bicarbonate (Factor A) and starch acetate (Factor C) and their combined effect (AC) on the floating lag time were significant ($P < 0.05$).Whereas the individual effect of bees wax (Factor B) and all other combined effects of the three factors involved were not significant in influencing floating lag time of the tablets.
3. Formulations Fa, Fab, F_{ac} and F_{abc} exhibited excellent floating over >12 h with a floating lag time in the range 12-40 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time.
4. Valsartan release from the floating tablets prepared except formulation F_a was slow and spread over 12 h and dependent on the composition of the tablets. Drug release from formulation F_a was very rapid.
5. Valsartan release from the floating tablets was by non-fickian diffusion mechanism in all the cases except F_a. In the case of formulation F_a that gave rapid release of drug fickian diffusion was the drug release mechanism.
6. Optimization of valsartan floating tablet formulation was done taking floating lag time as the parameter for optimization. For optimization, floating lag time was taken as response (Y) and level of sodium bicarbonate as (X_1), level of bees wax as (X_2) and level of starch acetate as (X_3).
7. The polynomial equation describing the relationship between the response, Y and the variables, X_1 , X_2 and X_3 based on the observed data was found to be **$Y = 8.996 - 8.596 (X1) + 2.396 (X2) – 2.431 (X1 X2) + 0.561 (X3) - 0.521 (X1 X3) + 0.396 (X2 X3) - 0.271 (X1 X2 X3)$.**
8. Based on the polynomial equation developed, the optimized valsartan floating tablet formulation with a floating lag time of 20 seconds could be formulated employing sodium bicarbonate (160mg/tablet), beeswax (28mg/tablet) and starch acetate (10mg/tablet).
9. The optimized formulation (F_{opt}) exhibited a floating time of 12-14 h with a lag time of 21 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed.
10. Formulations F_{opt} and F_{ab} prepared exhibited excellent floating characteristics (floating over 12 with a lag time of 21 and 12seconds respectively) and good sustained release of valsartan over 12– 14h.
11. Formulations F_{opt} and F_{ab} are considered as the best floating tablet formulations of valsartan suitable for b.i.d administration.

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