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Optimization of Valsartan SR Floating Tablet Formulation by 2^2 Factorial Design and Multiple Regression Technique

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Abstract**—***The objective of the present study is optimization of valsartan SR floating tablet formulation by 2^2 factorial design. SR floating tablets of valsartan (80 mg) were formulated employing HPMCK100M (factor A) as matrix forming polymer, sodium bicarbonate (factor B) as gas generating agent and beeswax and ethyl cellulose 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 2^2 factorial design employing HPMCK100M (factor A) and sodium bicarbonate (factor B). The 2 levels of factor A are 20 and 60 % of the tablet weight and the 2 levels of factor B are 10 and 20% of the tablet weight. The Valsartan floating SR tablets were prepared by wet granulation method and were evaluated.*

Valsartan SR floating tablets prepared as per 2^2 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. The individual effect of sodium bicarbonate (factor B) and combined effect of HPMCK100M and sodium bicarbonate (AB) on the floating lag time are significant ($P < 0.05$). Formulations F_b and F_{ab} exhibited excellent floating over >12 h with a floating lag time in the range 15-45 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time. Valsartan release from the floating tablets prepared was slow and spread over 12 h and dependent on the composition of the tablets. Valsartan release from the floating tablets prepared was by non-fickian diffusion mechanism in all the cases.

Optimization of valsartan sustain release 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 HPMCK100M as (X_1) and level of sodium bicarbonate as (X_2). The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data obtained by multiple regression was found to be $Y = 123.75 - 31.25 (X1) – 93.75 (X2) +16.25 (X1 X2)$. Based on the polynomial equation developed, the optimized valsartan sustain release floating tablet formulation with the desired floating lag time could be formulated employing HPMCK100M (200 mg/tablet) and sodium bicarbonate (101 mg/tablet). The optimized formulation (F_{opt}) exhibited a floating time of > 12 h with a lag time of 24 seconds and gave a release rate (K_0) of 7.85 mg/hr fulfilling the target floating lag time set indicating validity of the optimization technique employed. The release rate (K_0) of the optimized formulation (7.85 mg/hr) was very close to the desired release rate (K_0) of Valsartan (7.4 mg/hr) based on its pharmacokinetics. The optimized formulation (F_{opt}) exhibited a slow release of Valsartan over 12h. As such, formulation F_{opt} is considered as the best floating tablet formulation of valsartan suitable for b.i.d administration.

Keywords**—** *Formulation development, Floating tablets, Valsartan, Optimization, Factorial design, Multiple regression, Sustained release.*

I. 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

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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 HPMCK100M, as matrix forming polymer, sodium bicarbonate as gas generating agent and beeswax and ethyl cellulose 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 sustain release floating tablets was optimized by 2^2 factorial design.

II. Materials and Methods

Materials

Valsartan and HPMCK100M were gift samples from M/s Micro Labs Ltd, Pondicherry. , sodium bicarbonate, dicalcium phosphate (DCP), ethyl cellulose and beeswax were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

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 0.8% and 1.2% respectively. No interference from the excipients used was observed.

Formulation of Floating Tablets

Matrix tablets each weighing 500 mg and containing 80 mg of valsartan were formulated employing HPMCK100M as matrix forming polymer, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers. Valsartan floating tablets were formulated as per 2^2 factorial design. The two factors involved in the 2^2 factorial design are HPMCK100M (factor A) and sodium bicarbonate (factor B). The two levels of factorA (HPMCK100M) are 20 % and 60 % of the tablet weight. The two levels of factor B (sodium bicarbonate) are 10% and 20 % of the tablet weight. Four valsartan floating tablet formulations were prepared employing selected combinations of the levels of the two factors as per 2^2 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 2^2 factorial design and optimized formulation.

Ingredient (mg/tab)	F (1)	F (a)	F (b)	F (ab)	F (opt)
Valsartan	80	80	80	80	80
HPMCK100M	100	300	100	300	200
Sodium bicarbonate	50	50	100	100	101
Ethyl Cellulose	10	10	10	10	10
Bees wax	10	10	10	10	10
DCP	250	50	200	-	99
Total weight (mg)	500	500	500	500	500

The required quantities of valsartan, HPMCK100M, Sodium bicaronate, Ethyl Cellulose and DCP 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 tablet granules were then compressed into 500mg 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.

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[9] and Korsemeyer - Peppas[10] equation models to assess drug release kinetics and mechanism from the floating tablets prepared.

III. 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

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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 HPMCK100M as matrix forming polymer, sodium bicarbonate as gas generating agent and ethyl cellulose and beeswax as floating enhancers. Valsartan floating tablets were formulated as per 2^2 factorial design. The two factors involved in the 2^2 factorial study are HPMCK100M (factor A) and sodium bicarbonate (factor B). The two levels of HPMCK100M (factor A) are 20 % and 60 % of the tablet weight and the two levels of sodium bicarbonate (factor B) are 10 % and 20 % of the tablet weight. Four valsartan floating tablet formulations were prepared employing selected combinations of the levels of the two factors as per 2^2 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 2^2 factorial design and optimized formulation.

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (mg/tablet)	Floating lag time (sec)	Floating Time (h)
F_1	4.5	0.85	80.25	265	>12
F_a	5.5	0.45	80.65	170	>12
F_b	5.0	0.58	79.85	45	>12
F_{ab}	4.5	0.50	79.60	15	>12
F_{opt}	5.0	0.75	80.50	24	>12

Hardness of the tablets was in the range of 4.5-5.5 Kg/cm^2.Weight loss in the friability test was in the range of 0.45 % – 0.85 % 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 15 to 265 seconds. 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 two factors HPMCK100M and sodium bicarbonate on the floating characteristics of the tablets prepared. The results of ANOVA indicated that the individual effect of sodium bicarbonate (factor B) and combined effect of HPMCK100M and sodium bicarbonate (AB) on the floating lag time are significant ($P < 0.05$). The order of increasing floating lag time observed with various floating tablets prepared was $F_{ab} < F_b < F_a < F_1$. Formulations F_{ab} and F_b exhibited excellent floating more than 12 h with a floating lag time in the range 15-45 seconds. Sodium bicarbonate at 20 % strength gave less floating lag time than at 10 % strength. Formulations F_{ab} and F_b 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 coefficient of determination (R^2) values in the analysis of release data as per different kinetic models are given in Table 3. The drug release plots are shown in fig. 1.

TABLE 3. Coefficient of determination (R^2) 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	0.9570	0.9487	0.9869	0.9792
F_b	0.9328	0.9837	0.9928	0.9879
F_{ab}	0.9497	0.9673	0.9978	0.9978
F_{opt}	0.9718	0.9516	0.9821	0.9853

Valsartan 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 - 0.58 in all the cases indicating 'non-Fickian diffusion' as the release mechanism from these floating tablets.

TABLE 4. Release parameters of valsartan floating tablets prepared as per 2^2 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	5.7	6.31	0.1392	0.53
F_b	2.8	10.25	0.2985	0.57
F_{ab}	3.9	7.32	0.1920	0.52
F_{opt}	3.9	7.85	0.1995	0.57

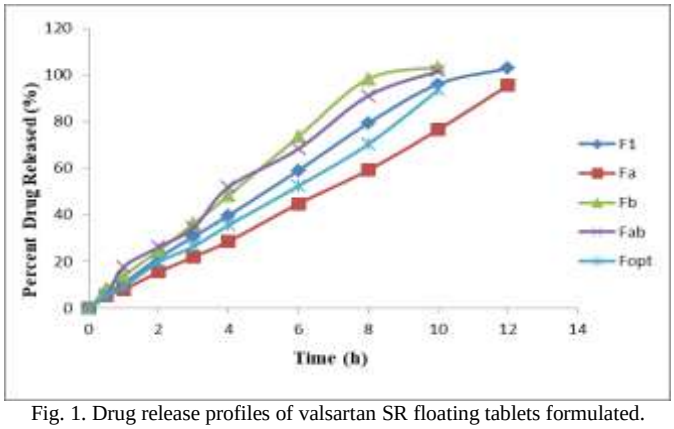

Fig. 1. Drug release profiles of valsartan SR floating tablets formulated.

Optimization:

Optimization[11] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite

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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 2^2 factorial design.

Optimization of valsartan sustain release 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 HPMCK100M as (X_1) and level of sodium bicarbonate as (X_2). The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be Y = 123.75 - 31.25 (X1) – 93.75 (X2) +16.25 (X1 X2) by multiple regression analysis.

The magnitude of the coefficients of the variables in the polynomial equation indicates the relative strength of the variables in influencing the response involved. In the above polynomial equation, the coefficient of variable X_2 (Sodiumbicarbonate) 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 Sodiumbicarbonate level in the formulation.

Based on the above polynomial equation, the optimized valsartan SR floating tablet formulation with the desired floating lag time could be formulated employing HPMCK100M (200 mg/tablet) and sodium bicarbonate (101 mg/tablet). To verify valsartan SR floating tablets were formulated employing the optimized levels of HPMCK100M and sodium bicarbonate as per the formula given in Table 1. The optimized valsartan SR floating tablet formulation was prepared and evaluated for floating and drug release characteristics. The optimized formulation exhibited a floating time of > 12 h with a lag time of 24 seconds and gave a release rate (K_0) of 7.85 mg/hr fulfilling the target floating lag time of 25 sec set. The desired release rate (K_0) was estimated as K_0 = 7.4 mg/hr based on the pharmacokinetics of Valsartan[6]. The release rate (K_0) of the optimized formulation (7.85 mg/ hr) was very close to the desired release rate (K_0) of Valsartan (7.4 mg/ hr) based on its pharmacokinetics. Hence the optimized formulation exhibited the desired floating lag time and also gave a release rate needed for valsatan SR tablets. The results, thus, indicated validity of the optimization technique employed. The optimized formulation exhibited a slow release of Valsartan over 12h.

As such, formulation F_{opt} is considered as the best floating tablet formulation of valsartan suitable for b.i.d administration.

IV. Conclusions

1. Valsartan SR floating tablets prepared as per 2^2 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 effect of sodium bicarbonate (factor B) and combined effect of HPMCK100M and sodium bicarbonate (AB) on the floating lag time are significant ($P < 0.05$).
3. Formulations F_b and F_{ab} exhibited excellent floating over >12 h with a floating lag time in the range 15-45 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time.
4. Valsartan release from the floating tablets prepared was slow and spread over 12 h and dependent on the composition of the tablets.
5. Valsartan release from the floating tablets prepared was by non-fickian diffusion mechanism in all the cases.
6. Optimization of valsartan sustain release 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 HPMCK100M as (X_1) and level of sodium bicarbonate as (X_2).
7. The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data obtained by multiple regression was found to be Y = 123.75 - 31.25 (X1) – 93.75 (X2) +16.25 (X1 X2).
8. Based on the polynomial equation developed, the optimized valsartan sustain release floating tablet formulation with the desired floating lag time could be formulated employing HPMCK100M (200 mg/tablet) and sodium bicarbonate (101 mg/tablet).
9. The optimized formulation (F_{opt}) exhibited a floating time of > 12 h with a lag time of 24 seconds and gave a release rate (K_0) of 7.85 mg/hr fulfilling the target floating lag time set indicating validity of the optimization technique employed.
10. The release rate (K_0) of the optimized formulation (7.85 mg/ hr) was very close to the desired release rate (K_0) of Valsartan (7.4 mg/ hr) based on its pharmacokinetics.
11. The optimized formulation (F_{opt}) exhibited a slow release of Valsartan over 12h. As such, formulation F_{opt} is considered as the best floating tablet formulation of valsartan suitable for b.i.d administration.

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