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FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM FLOATING TABLETS: OPTIMIZATION BY 2^3 FACTORIAL DESIGN

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ABSTRACT

The objective of the present study is optimization of Losartan Potassium floating tablet formulation by 2^3 factorial design. Floating tablets of losartan potassium (50 mg) were formulated employing HPMC K15M (50 %) as matrix forming polymer, sodium bicarbonate as gas generating agent and beeswax and ethyl cellulose as floating enhancers. Losartan Potassium 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 ethyl cellulose (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 ethyl cellulose (Factor C) are 5% and 10%. Eight losartan potassium floating tablet formulations were prepared employing selected combinations of the levels of the three factors as per 2^3 factorial design. All the floating tablets prepared were evaluated for drug content, hardness, friability, disintegration time, floating lag time, floating time and drug release characteristics. Losartan Potassium 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. ANOVA indicated that the individual effects of sodium bicarbonate (Factor A), bees wax (Factor B) and ethyl cellulose (Factor C) and the combined effects of sodium bicarbonate and bees wax (AB), sodium bicarbonate and ethyl cellulose (Factor AC) on the floating lag time are highly significant ($P < 0.01$).Formulations F_{abc}, F_{ac}, F_{ab} and F_a exhibited excellent floating over 24 h with a floating lag time in the range 9-48 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time. Losartan potassium 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. Losartan Potassium release from the floating tablets was by non-fickian diffusion mechanism. Optimization of losartan potassium 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 ethyl cellulose 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 $Y = 12.96 - 13.09 (X_1) + 7.70 (X_2) – 7.86 (X_1 X_2) -2.92 (X_3) - 3.08(X_1 X_3) + 0.32 (X_2 X_3) - 0.18(X_1 X_2 X_3)$. Based on the polynomial equation developed, the optimized losartan potassium floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (100mg/tablet), beeswax (17.5mg/tablet) and ethyl cellulose (37.5mg/tablet). The optimized formulation (F_{opt}) exhibited a floating time of 24 h with a lag time of 16-20 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed. Formulations $F_{opt,}$ $F_{ab,}$ F_{ac} and F_{abc} prepared exhibited excellent floating characteristics (floating over 24h with a lag time in the range 09 to 48 seconds) and good sustained release of losartan potassium over 12 h. As such, these formulations are considered as the best floating tablet formulations of losartan potassium suitable for b.i.d administration.

KEYWORDS: Floating tablets, Losartan potassium, Optimization, Factorial design, Sustained release.

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.[2,3] 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.[4, 5] Several approaches are currently used to retain the dosage in the stomach. These include bioadhesive systems,[6] swelling and expanding systems,[7,8] floating systems[9,10] and other delayed gastric emptying devices.[11,12]

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, ethyl cellulose 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 losartan potassium were formulated employing HPMC K15M (50 %) as matrix forming polymer, sodium bicarbonate as gas generating agent and beeswax and ethyl cellulose as floating enhancers. Losartan potassium is an affective antihypertensive drug which is a highly specific Angiotensin II AT1 receptor antagonist. It is readily absorbed from the gastro intestinal tract, having oral bioavailability of 33% and plasma elimination half life of 1.5 to 2.5 hours. Upper small intestine is the major site of absorption of losartan potassium. These characteristics made it suitable for floating drug delivery.[13,14] A dose of 50 mg 2 or 3 times daily is required. Floating tablets of losartan potassium 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 losartan potassium over 10-12h is aimed in addition to good floating characteristics. Formulation of losartan potassium floating tablets was optimized by 2^3 factorial design.

Optimization[15] 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 losartan potassium floating tablet formulation by 2^3 factorial design.

EXPERIMENTAL

Materials

Losartan Potassium was a gift sample from M/s Micro Labs Ltd, Pondicherry. HPMC K15M, ethyl cellulose (50 cps), sodium bicarbonate, dicalcium phosphate (DCP) and beeswax were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Estimation of Losartan Potassium

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 250 nm in 0.1 N HCl was used for the estimation of losartan potassium. The method obeyed Beer-Lambert's law in the concentration range of 0-10 µm/mL. When a standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.85% and 1.25%, respectively. No interference from the excipients used was observed.

Formulation of Floating Tablets

Matrix tablets each containing 50 mg of losartan potassium were formulated employing HPMC K15M (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and ethyl cellulose and beeswax as floating enhancers. Losartan Potassium 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 ethyl cellulose (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 ethyl cellulose (Factor C) are 5% and 10%. Eight Losartan Potassium 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.

The required quantities of losartan potassium, HPMC K15M, ethyl cellulose, DCP 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 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 ± 0.5^0C, 0.1 N HCl (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[16] and Korsemeyer – Peppas[17] 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 losartan potassium were designed based on gas generating principle. The objective of the present study is optimization of formulation of losartan potassium floating tablets based on gas generating principle.

Matrix tablets each containing 50 mg of losartan potassium were formulated employing HPMC K15M (50%) as matrix forming polymer, sodium bicarbonate as gas generating agent and ethyl cellulose and beeswax as floating enhancers. Losartan potassium 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 ethyl cellulose (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 ethyl cellulose (Factor C) are 5% and 10%. Eight losartan potassium 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.Hardness of the tablets was in the range 4.0-5.0 Kg/cm^2.Weight loss in the friability test was less than 0.85% in all the cases. All the tablets prepared contained losartan potassium within 100±3% 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 9 seconds to 49 minutes. Floating time was in the range 20-24 hours with various floating tablets. 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 ethyl cellulose on the floating characteristics of the tablets prepared. The results of ANOVA (Table 3) indicated that the individual effects of sodium bicarbonate (Factor A), bees wax (Factor B) and ethyl cellulose (Factor C) and the combined effects of sodium bicarbonate and

bees wax(AB), sodium bicarbonate and ethyl cellulose(Factor AC) on the floating lag time are highly significant ($P < 0.01$).Whereas the combined effect of bees wax and ethyl cellulose (Factor BC) and combined effects of the three factors involved (Factor ABC)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 $F_{abc} < F_{ac} < F_{ab} < F_a < F_1 < F_c < F_b < F_{bc}$. Formulations F_{abc}, F_{ac}, F_{ab} and F_a exhibited excellent floating over 12-24 h with a floating lag time in the range 9-48 seconds. Sodium bicarbonate at 20 % strength gave less floating lag time than at 10 % strength. Formulations F_{abc}, F_{ac}, F_{ab} and F_a are considered as the best floating tablets formulated based on the floating characteristics.

Losartan potassium release from the floating tablets prepared was studied in 0.1N HCl. The drug release profiles of floating tablets prepared are shown in Fig.1. Drug release parameters of the tablets prepared are summarized in Table 5.Losartan potassium release from the floating tablets prepared was slow and spread over 12 h and depended on the composition of the tablets. The release data were analysed 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 various kinetic models are given in Table 4. Drug release from all the floating tablets prepared followed zero order kinetics. ANOVA of release rate (K_1) values (Table 6) indicated that individual and combined effects of all the three factors except the combined effect of sodium bicarbonate and ethyl cellulose (AC) are highly significant ($P < 0.01$) in influencing release rate of drug from the floating tablets.

Formulations F_{ab}, F_{ac} and F_{abc} exhibited excellent floating characteristics and good sustained release of losartan potassium over 10-12 h. As such these formulations are considered as the best floating tablet formulations of losartan potassium suitable for b.i.d administration.

Drug release from all the floating tablets prepared was diffusion controlled as indicated by the linear Higuchi plots. When the release data were analysed as per Korsemeyer- Peppas equation, the release exponent ‘n’ was found to be in the range 0.631-1.007 in all the cases indicating ‘non-Fickian diffusion’ as the release mechanism from these floating tablets.

Optimization of losartan potassium 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 ethyl cellulose 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 $Y = 12.96 - 13.09 (X_1) + 7.70 (X_2) – 7.86 (X_1 X_2) -2.92 (X_3) - 3.08(X_1 X_3) + 0.32 (X_2 X_3) - 0.18(X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized Losartan Potassium floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (100 mg/tablet), beeswax (17.5mg/tablet) and ethyl cellulose (37.5mg/tablet). To verify Losartan Potassium floating tablets were formulated employing the optimized levels of sodium bicarbonate, beeswax and ethyl cellulose as per the formula given in Table 1. The optimized Losartan Potassium floating tablet formulation was prepared and evaluated for floating and drug release characteristics. The optimized formulation exhibited a floating time of 24 h with a lag time of 16-20 seconds fulfilling the target floating lag time set. This result also indicated validity of the optimization technique employed. The optimized formulation (Fopt) gave slow and gradual release of Losartan Potassium over 12 h.

Overall, formulations $F_{opt,}$ $F_{ab,}$ F_{ac} and F_{abc} prepared exhibited excellent floating characteristics (floating over 24h with a lag time in the range 09 to 48 seconds) and good sustained release of losartan potassium over 12 h. As such, these formulations are considered as the best floating tablet formulations of losartan potassium suitable for b.i.d administration.

Table 1: Formulae of Losartan Potassium Floating Tablets Prepared as Per 2^3 Factorial Design.

Ingredient (mg/tab)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}	Fopt
Losartan potassium	50	50	50	50	50	50	50	50	50
Sodium bicarbonate	50	100	50	100	50	100	50	100	100
Bees wax	10	10	25	25	10	10	25	25	17.5
Ethyl cellulose	25	25	25	25	50	50	50	50	37.5
HPMC K15M	250	250	250	250	250	250	250	250	250
Dicalcium phosphate	95	45	80	30	70	20	55	5	25
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight (mg)	500	500	500	500	500	500	500	500	500

Table 2: Physical Parameters of Losartan Potassium Floating Tablets Prepared as per 2^3 Factorial Design.

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (mg/tablet)	Floating lag time (min- sec)	Floating Time (h)
F_1	4.0	0.68	49.9	5-36	24
F_a	4.5	0.59	49.22	0-48	20
F_b	5.0	0.78	51.3	35-40	24
F_{ab}	4.5	0.85	50.2	0-13	24
F_c	4.2	0.60	49.2	16-19	24
F_{ac}	4.0	0.75	48.9	0-13	24
F_{bc}	4.5	0.69	48.6	48-08	24
F_{abc}	4.0	0.72	49.5	0-9	24
Fopt	4.0	0.75	49.4	16 to 20 sec	24

Table 3: ANOVA of Floating Lag time Values of Losartan Potassium Tablets Prepared as per 2^3 Factorial Design.

Source of Variation	DF	SS	MSS	F-ratio
Total	23	11676.3	507.66	-
Treatment	7	11665.6	1666.51	2491.98
Error	16	10.7	0.66	-
F_a	1	4082.56	4082.56	6104.76
F_b	1	1406.07	1406.07	2102.53
F_{ab}	1	1466.71	1466.71	2193.22
F_c	1	198.14	198.14	296.29
F_{ac}	1	221.31	221.31	330.93
F_{bc}	1	2.80	2.80	4.18
F_{abc}	1	1.04	1.04	1.55

$F_{0.05}(1, 16) = 4.49$; $F_{0.05}(7, 16) = 2.66$ $F_{0.01}(1, 16) = 8.53$; $F_{0.01}(7, 16) = 4.03$

Table 4: Coefficient of determination (R^2) Values in the Analysis of Release Data of Losartan potassium Floating Tablets Prepared as per Different Kinetic Models.

Formulation	Zero order	First order	Higuchi	Korsemeyer –Peppas
F1	0.985	0.982	0.977	0.991
Fa	0.923	0.839	0.820	0.960
Fb	0.989	0.965	0.961	0.991
Fab	0.988	0.963	0.993	0.985
Fc	0.996	0.938	0.970	0.993
Fac	0.996	0.939	0.960	0.993
Fbc	0.977	0.947	0.994	0.995
Fabc	0.983	0.945	0.938	0.973
Fopt	0.989	0.975	0.960	0.977

Table 5: Release Parameters of Losartan Potassium Floating Tablets Prepared as per 2^3 Factorial Design.

Formulation	T_{50} (h)	Release Rate		Release Exponent (n)
		K_0 (mg/h)	$K_1(h^{-1})$	
F1	4.2	4.89	0.282	0.822
Fa	4.5	7.47	0.474	1.007
Fb	8.0	3.13	0.102	0.785
Fab	6.4	5.0	0.274	1.006
F_c	5.0	4.72	0.258	0.901
F_{ac}	5.6	4.85	0.265	0.974
F_{bc}	4.3	3.77	0.157	0.631
F_{abc}	5.6	4.75	0.237	1.005
Fopt	6.0	4.04	0.155	0.986

Table 6: ANOVA of Release Rates (K_1) of Losartan Potassium Floating Tablets Prepared as per 2^3 Factorial Design.

Source of Variation	DF	SS	MSS	F-ratio
Total	23	1.039	0.04	-
Treatment	7	1.037	0.14	1069.92
Error	16	0.002	0.0001	-
F_a	1	0.009	0.009	71.03
F_b	1	0.018	0.018	130.21
F_{ab}	1	0.045	0.045	325.29
F_c	1	0.002	0.002	17.90
F_{ac}	1	8.82	8.82	0.63
F_{bc}	1	0.00	0.00	5.08
F_{abc}	1	0.01	0.01	108.27

$F_{0.05}(1, 16) = 4.49$; $F_{0.05}(7, 16) = 2.66$ $F_{0.01}(1, 16) = 8.53$; $F_{0.01}(7, 16) = 4.03$

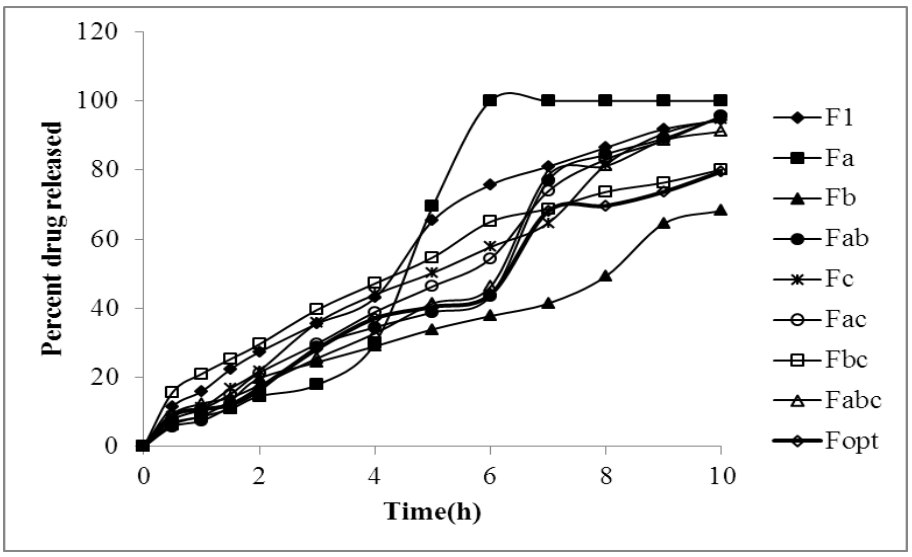

Fig 1: Drug Release Profiles of Losartan Potassium Floating Tablets Prepared as per 2^3 factorial design.

CONCLUSIONS

1. Losartan potassium 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. ANOVA indicated that the individual effects of sodium bicarbonate (Factor A), bees wax (Factor B) and ethyl cellulose (Factor C) and the combined effects of sodium bicarbonate and bees wax(AB), sodium bicarbonate and ethyl cellulose(Factor AC) on the floating lag time are highly significant ($P < 0.01$).
3. Formulations $F_{abc,}$ F_{ac}, F_{ab} and F_a exhibited excellent floating over 24 h with a floating lag time in the range 9-48 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time.
4. Losartan potassium 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. Losartan potassium release from the floating tablets was by non-fickian diffusion mechanism.
6. Optimization of losartan potassium 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 ethyl cellulose 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 $Y = 12.96 - 13.09 (X_1) + 7.70 (X_2) – 7.86 (X_1 X_2) -2.92 (X_3) - 3.08(X_1 X_3) + 0.32 (X_2 X_3) - 0.18(X_1 X_2 X_3)$.
8. Based on the polynomial equation developed, the optimized losartan potassium floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (100mg/tablet), beeswax (17.5mg/tablet) and ethyl cellulose (37.5mg/tablet).
9. The optimized formulation (F_{opt}) exhibited a floating time of 24 h with a lag time of 16-20 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed.
10. Formulations $F_{opt,}$ $F_{ab,}$ F_{ac} and F_{abc} prepared exhibited excellent floating characteristics (floating over 24h with a lag time in the range 09 to 48 seconds) and good sustained

release of losartan potassium over 12 h. As such, these formulations are considered as the best floating tablet formulations of losartan potassium suitable for b.i.d administration.

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