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FORMULATION AND EVALUATION OF CAPTOPRIL 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 captopril floating tablet formulation by 2^3 factorial design. Floating tablets of captopril (100 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. Captopril is an ACE inhibitor and is widely prescribed for the treatment of hypertension and congestive heart failure. It has been reported, however, that the duration of antihypertensive action after a single oral dose of Captopril is only 6 – 8 h. Clinical use requires a daily dose of 30 – 60 mg to be taken 2 - 3 times a day. It is most stable at PH 1.2 and as the PH increases, it becomes unstable and undergoes a degradation reaction. Captopril 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 captopril 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.

Captopril 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, and friability and suitable for controlled release. 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 $F_{ab,}$ F_{ac} and F_{abc} exhibited excellent floating over 12-14 h with a floating lag time in the range 10-35 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time. Captopril 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. Captopril 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 captopril 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 $\mathbf{Y = 3.19 - 5.68(X_1) + 0.56\ (X_2) + 2.27\ (X_1\ X_2) - 0.38\ (X_3) + 0.37(X_1\ X_3) - 0.08\ (X_2\ X_3) + 0.25(X_1\ X_2\ X_3)}$. Based on the polynomial equation developed, the optimized captopril floating tablet formulation with a floating lag time of 20 seconds could be formulated employing sodium bicarbonate (140mg/tablet), beeswax (28mg/tablet) and starch acetate (60mg/tablet). The optimized formulation (F_{opt}) exhibited a floating time of 12-14 h with a lag time of 20-22 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed. Formulations F_{opt} and F_{ac} prepared exhibited excellent floating characteristics (floating over 13-14h with a lag time of 20 and 35seconds respectively) and good sustained release of captopril over 12 – 14h. Formulations F_{opt} and F_{ac} are considered as the best floating tablet formulations of captopril suitable for b.i.d administration.

KEY WORDS: Floating tablets, Captopril, 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 inc1lude 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, 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 captopril 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. Captopril is an ACE inhibitor and is widely prescribed for the treatment of hypertension and congestive heart failure. It has been reported, however, that the duration of antihypertensive action after a single oral dose of Captopril is only 6 – 8 h. Clinical use requires a daily dose of 30 – 60 mg to be taken 2 - 3 times a day.[13] It is most stable at pH 1.2 and as the pH increases, it becomes unstable and undergoes a degradation reaction.[14] Sustained release dosage form of captopril improved bioavailability as well as prolonged the duration of action.[15] Floating tablets of captopril 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 captopril over 10-12h is aimed in addition to good floating characteristics. Formulation of captopril floating tablets was optimized by 2^3 factorial design.

Optimization.[16] 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 captopril floating tablet formulation by 2^3 factorial design.

EXPERIMENTAL

Materials

Captopril 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

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 85^{o}C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

FORMULATION OF FLOATING TABLETS

Matrix tablets each containing 60 mg of captopril 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. Captopril 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 captopril 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 captopril, 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 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 CAPTOPRIL

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 215 nm in 0.1N HCl was used for the estimation of captopril. 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 0.65% and 0.95%, 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^{0}C. 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 215 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[17] and Korsemeyer – Peppas[18] 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 captopril were designed based on gas generating principle. The objective of the present study is optimization of formulation of captopril floating tablets based on gas generating principle.

Matrix tablets each containing 100 mg of captopril 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. Captopril 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 captopril 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 4.5-5.5 Kg/cm^2. Weight loss in the friability test was less than 0.90% in all the cases. All the tablets prepared contained captopril 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 10 seconds to 14 min 20 seconds. Floating time was in the range 10-14 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 starch acetate on the floating characteristics of the tablets prepared. The results of ANOVA (Table 3) 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 $F_{ab} < F_{ac} < F_{abc} < F_a < F_c < F_1 < F_{bc} < F_b$. Formulations $F_{ab,}$ F_{ac} and F_{abc} exhibited excellent floating over 12-14 h with a floating lag time in the range 10-35 seconds. Sodium bicarbonate at 20 % strength gave less floating lag time than at 10 % strength. Formulations $F_{ab,}$ F_{ac} and F_{abc} are considered as the best floating tablets formulated based on the floating characteristics.

Captopril 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. Captopril 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 drug release plots are shown in Figs 1 – 2. Drug release from all the floating tablets prepared followed first order kinetics. The R^2 values were higher in the first order model than in the zero model in all the cases.

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 0.532 - 0.595 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 0.150 indicating fickian diffusion as the drug release mechanism.

OPTIMIZATION

Optimization of captopril 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 $\mathbf{Y = 3.19 - 5.68(X_1) + 0.56\ (X_2) + 2.27\ (X_1\ X_2) - 0.38\ (X_3) + 0.37(X_1\ X_3) - 0.08\ (X_2\ X_3) + 0.25(X_1\ X_2\ X_3)}$.

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 captopril floating tablet formulation with a floating lag time of 20 seconds or 0.33 min could be formulated employing sodium bicarbonate (140 mg/tablet), beeswax (28 mg/tablet) and starch acetate (60 mg/tablet). To verify captopril 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 captopril 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

20 - 22 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 Captopril over 12-14 h.

Overall, formulations F_{opt} and F_{ac} prepared exhibited excellent floating characteristics (floating over 13-14 h with a lag time of 20 and 35 seconds respectively) and good sustained release of captopril over 12 - 14 h. As such, formulations F_{opt} and F_{ac} are considered as the best floating tablet formulations of captopril suitable for b.i.d administration.

Table 1: Formulae of Captopril 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)
Captopril	100	100	100	100	100	100	100	100	100
Sodium bicarbonate	80	160	80	160	80	160	80	160	140
Bees wax	16	16	40	40	16	16	40	40	28
Starch acetate	40	40	40	40	80	80	80	80	60
Starch Urea Borate	400	400	400	400	400	400	400	400	400
Lactose	144	64	120	40	104	24	80	-----	52
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

Table 2: Physical Parameters of Captopril Floating Tablets Prepared as per2^3 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	0.85	99.20	11-00	15
F_a	5.0	0.65	99.85	0-55	10
F_b	4.5	0.90	100.12	14-20	11
F_{ab}	5.5	0.35	100.20	0-10	12
F_c	5.0	0.45	99.45	10-10	12
F_{ac}	5.0	0.45	99.63	0-35	13
F_{bc}	4.5	0.55	100.25	12-10	15
F_{abc}	4.5	0.65	99.35	0-30	14
F_{opt}	5.5	0.70	100.25	0-21	14

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

Source of Variation	DF	SS	MSS	F-ratio
Total	23	2787.46	121.194	---
Treatment	7	2684.08	383.44	59.34
Error	16	103.37	6.461	---
F_a	1	1184.13	1184.13	183.27
F_b	1	23.72	23.72	3.67
F_{ab}	1	24.60	24.60	3.80
F_c	1	37.90	37.90	5.86
F_{ac}	1	34.56	34.56	5.34
F_{bc}	1	5.07	5.07	0.786
F_{abc}	1	6.04	6.04	0.934

$F_{0.05(7, 16)} = 2.66$; $F_{0.05(1, 16)} = 4.49$.

Table 4: Release Parameters of Captopril 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	2.5	7.449	0.271	0.553
F_a	0.25	94.62	1.156	0.150
F_b	4.6	7.19	0.163	0.552
F_{ab}	5.0	6.385	0.137	0.577
F_c	3.4	6.987	0.202	0.532
F_{ac}	5.0	6.252	0.149	0.568
F_{bc}	4.2	6.734	0.165	0.595
F_{abc}	5.0	6.355	0.138	0.563
F_{opt}	2.8	6.947	0.251	0.562

Table: 5 ANOVA of Release rates (K_1) Values of Captopril FloatingTablets Prepared as per 2^3 Factorial Design.

Source of Variation	DF	SS	MSS	F-ratio
Total	23	0.152	0.007	-
Treatment	7	0.148	0.021	84.0
Error	16	0.004	0.00025	-
F_a	1	0.012	0.012	48.0
F_b	1	0.058	0.058	232.0
F_{ab}	1	0.024	0.024	96.0
F_c	1	0.025	0.025	100.0
F_{ac}	1	0.016	0.016	64.0
F_{bc}	1	0.032	0.032	128.0
F_{abc}	1	0.019	0.019	76.0

$F_{0.05(7, 16)} = 2.66$; $F_{0.05(1, 16)} = 4.49$.

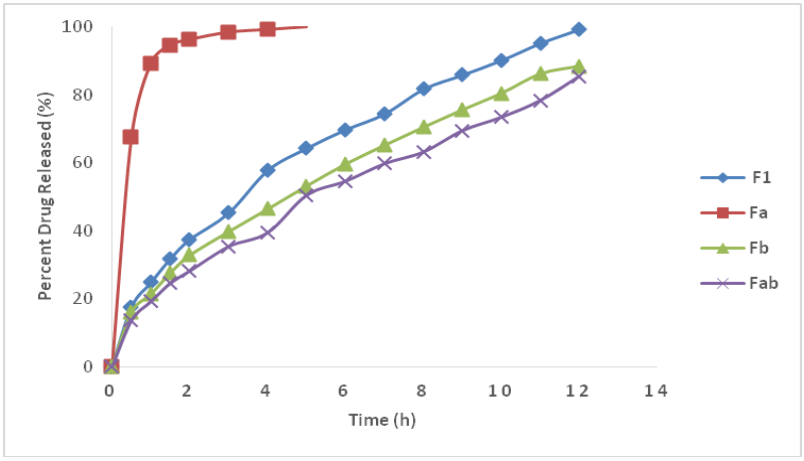

Fig. 1: Drug Release Profiles of Captopril Floating Tablets Prepared (F_1, F_a, F_b, F_{ab}).

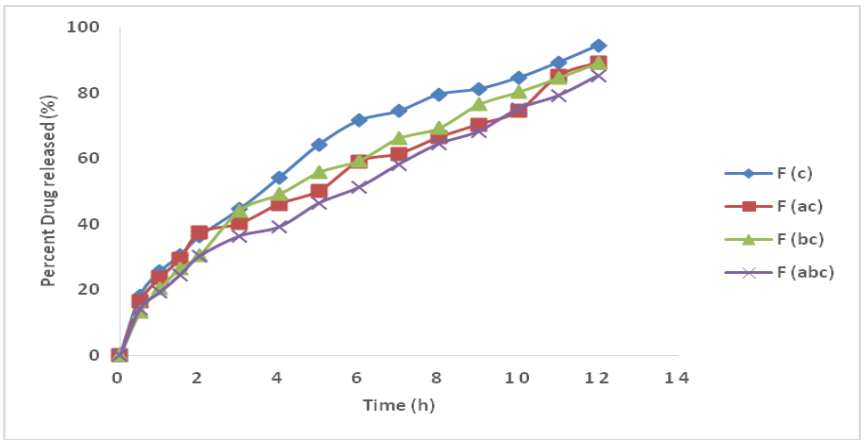

Fig.2: Drug Release Profiles of Captopril Floating Tablets Prepared (F_c, F_{ac}, F_{bc}, F_{abc}).

CONCLUSIONS

1. Captopril 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 F_{ab}, F_{ac} and F_{abc} exhibited excellent floating over 12-14 h with a floating lag time in the range 10-35 seconds. Higher levels (20 %) of sodium bicarbonate gave shorter floating lag time.

4. Captopril 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. Captopril 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 captopril 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 $\mathbf{Y = 3.19 – 5.68(X_1) + 0.56\ (X_2) + 2.27\ (X_1\ X_2) - 0.38\ (X_3) + 0.37(X_1\ X_3) – 0.08\ (X_2\ X_3) + 0.25(X_1\ X_2\ X_3)}$.
8. Based on the polynomial equation developed, the optimized captopril floating tablet formulation with a floating lag time of 20 seconds could be formulated employing sodium bicarbonate (140mg/tablet), beeswax (28mg/tablet) and starch acetate (60mg/tablet).
9. The optimized formulation (F_{opt}) exhibited a floating time of 12-14 h with a lag time of 20-22 seconds fulfilling the target floating lag time set indicating validity of the optimization technique employed.
10. Formulations F_{opt} and F_{ac} prepared exhibited excellent floating characteristics (floating over 13-14h with a lag time of 20 and 35seconds respectively) and good sustained release of captopril over 12 – 14h.
11. Formulations F_{opt} and F_{ac} are considered as the best floating tablet formulations of captopril suitable for b.i.d administration.

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