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Research Article

DESIGN AND OPTIMIZATION OF FLOATING MATRIX TABLETS OF FAMOTIDINE BY CENTRAL COMPOSITE DESIGN

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ABSTRACT

The aim of present study was to develop controlled release floating type gastroretentive tablets using famotidine as a drug and HPMC K15M as a polymer. This targeted delivery of the drug provides an effective and safe therapy with reduced dose and duration of therapy. A floating controlled-release drug delivery system of famotidine was developed by effervescent approach using varying concentrations of HPMC K15M and sodium bicarbonate. The matrices are fabricated using sodium bicarbonate ($NaHCO_3$) and citric acid as gas formers so that upon contact with gastric fluid, carbon dioxide is liberated that is entrapped in the jellified hydrocolloids, which produces an upward motion of the dosage form and maintain its buoyancy. Central composite design(2-factor, 3-level) was used to optimize the formulation. A total number of thirteen formulations were prepared as per the standard experimental design protocol using Design Expert Software (Version 8.0.5, Stat- Ease Inc, Minneapolis, MN). Independent variables such as the amount of polymer –HPMC K15M (X_1) and the amount of gas forming agent- Sodium bicarbonate (X_2) were optimized. Floating lag time and the time required for 50% drug release (t_{50}) were taken as the dependent/response variables.Tablets containing HPMC K15M (30mg) and sodium bicarbonate (20mg) showed satisfactory results with respect to floating lag time, total floating duration and sustained drug release rates. This results in an increased gastric residence time and also controls the fluctuations in plasma drug concentration in better way. It can be concluded from the study that the problem of short gastric residence time encountered with an oral controlled release formulation can be overcome with the floating matrix tablets of famotidine for treatment of gastric ulcers.

Keywords: Controlled Release, Famotidine, Effervescent Approach, Central Composite Design.

INTRODUCTION

Gastroretentive drug delivery system provides continuous release of the drugs for longer duration of time and proposes advantage to the drugs for local action in stomach and drugs primarily absorbed in the stomach. Drug absorption from oral controlled release (CR) dosage forms is often limited by the short gastrointestinal retention time, available for absorption [1].Gastroretentive drug delivery systems can be retained in the stomach, and thus can help improve the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems facilitate continuous release of a drug before it reaches the absorption window, thus ensuring optimal bioavailability [2].

Several approaches can be used to prolong gastric retention time, including floating drug delivery systems (i.e., hydrodynamically balanced systems), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric-emptying devices [3-10]. In floating drug delivery system, the bulk density of the dosage form is less than the gastric fluid so that it remain buoyant and release the drug slowly and consistently [11].

Two classes of floating drug delivery systems are available, first is non effervescent system and the second is effervescent (gas generating) system. Non effervescent system includes colloidal gel barrier system, microporous compartment system, alginate beads and hollow microspheres/microballons. These systems swell due to imbibition and do not exit from stomach due to increased size. In gas generating system, the matrics is prepared with the swellable polymer and effervescent components like sodium bicarbonate, citric acid or tartaric acid [12].Carbon dioxide generating components may be either coated over the tablet or intimately mixed in the matrix of the tablet [13]. When the system comes in contact with stomach, it react in the presence of aqueous medium and carbon dioxide is released resulting in floating of the system in stomach [12]. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs [14, 15].FDDS offers important advantages like they are less prone to gastric emptying resulting in reduced intra and inter subject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and increased patient compliance, reduced Cmax and prolonged drug levels above the minimum effective concentration and improved safety profile for drugs with side effects associated with high Cmax[16].

Famotidine is a histamine H_2-receptor antagonist used in the treatment of gastric ulcers/peptic ulcer (PUD), duodenal ulcers, Zollinger-Ellison syndrome, and gastroesophageal reflux disease in doses ranging from 10 to 80 mg [17].

Famotidine has less bioavailability (20-66%), due to its poor solubility in acidic pH e.g. stomach (aqueous solubility of 0.1%w/v at 20^oC) [18]. The oral treatment of gastric disorders with an H_2 receptor antagonist such as famotidine in combination with antacids promotes local delivery of these drugs to the receptor of parietal cell wall. Therefore, in this investigation attempt has been made to prepare floating matrix tablets of famotidine, so that tablets are retained in the stomach for a longer period of time and local delivery increases the bioavailability of the stomach-wall receptor site and increases the efficacy of drugs to reduce acid secretion. Hence, this principle may improve systemic as well as local delivery of famotidine, which would efficiently reduce gastric-acid secretion [19]. Moreover, the short half life (2.5-4hrs.) and undesirable side effects make famotidine a good candidate for formulation in a sustained release dosage form [20, 21]. Constant administration of the short half life drug can cause toxicity. The recommended adult oral dosage of famotidine is 20 mg twice daily or 40 mg once daily. The effective treatment of erosive esophagitis requires administration of 20 mg of famotidine 4 times a day. A conventional dose of 20 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 40 mg leads to plasma fluctuations; thus a sustained release dosage form of famotidine is desirable. This article describes the development of gastroretentive matrix tablets of famotidine to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance. A floating drug delivery system can be designed by incorporating at least one porous structural element that is less dense than gastric juice .The release of the drug from the matrix is influenced by ratio of polymer and drug, compression pressure, particle size of drug, pH of matrix, entrapped air in tablet, molecular size of drug, solubility of drug, presence of excipients or additives and the mode of corporation of substances. Content of polymer and its viscosity are the dominant

factors which influence the release of the drug from the matrix [22]. The polymer HPMC K15M is used in the matrix system which enables the slow release of drug from the matrix system. Various concentrations (10, 20, 30 mg) of the polymer are used in the floating tablets to check the effect of the concentration of the polymer on release characteristics. Sodium bicarbonate is also used in different concentrations to check the effect of the CO_2 forming agents.

In the present investigation floating tablets of famotidine were prepared by effervescent approach using HPMC K15M and Sodium bicarbonate in different concentrations. The aim of the work was to evaluate the effect of gel-forming polymer, HPMC K15M on floating properties and release characteristics of famotidine tablets.

MATERIALS AND METHOD

Material

Famotidine was obtained from Fourrts India Pvt Ltd (Chennai). HPMC K15M, Sodium bicarbonate, citric acid and microcrystalline cellulose were purchased from S. D. Fine Chemicals Ltd (Mumbai, India).All other ingredients were of analytical reagent grade.

Preparation of Floating Tablets of Famotidine

Tablets containing 40mg Famotidine were prepared by direct compression with different proportions of release-retarding polymer (HPMC K15 M) and gas-forming agent ($NaHCO_3$). After passing through sieve no. 20, separately, mixing of powders were carried out using a pestle and mortar for 10 min. Microcrystalline cellulose and lubricants were then added to the mixed powders. Mixing was continued for another 3 min. Finally, tablets were prepared using single punch tablet machine equipped with flat-faced punches. The composition of different formulations of famotidinefloating tablets is shown in Table 1.

Central composite design (face-centered) was used in this study and 2 factors were evaluated, each at 3 levels; experimental trials were performed at all 13 possible combinations. The amount of HPMC K15 M (X_1) and Sodium bicarbonate (X_2) were selected as independent variables. Floating lag time and the time required for 50% (t_{50}) were taken as the dependent/response variables. All other formulation and processing variables were kept invariant throughout the study. The central point (0, 0) was studied in quintuplicate. The resulting data were fitted into Design Expert Software (Version 8.0.5, Stat- Ease Inc, Minneapolis, MN) and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of HPMC K 15 M and Sodium bicarbonate on dependent variables. Table 2 Summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study.

Table 1: Formulation of Famotidine floating tablets using different ratios of polymer and effervescent agents.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Famotidine	40	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K15M	10	20	30	10	20	30	10	20	30	20	20	20	20
Sodium Bicarbonate	10	10	10	15	15	15	20	20	20	15	15	15	15
Citric Acid	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
MCC	135	125	115	130	120	110	125	115	105	120	120	120	120
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Factor Combination as per the Chosen Experimental.

Formulation Code	Coded Factor Levels	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1
F10	0	0
F11	0	0
F12	0	0
F13	0	0
Translation of coded levels in actual units		
Coded level	***-1***	***0*** ***+1***
X_1: HPMC K 15 M (mg)	10	20 30
X_2: Sodium bicarbonate (mg)	10	15 20

Design Experimental Design.

Evaluation of Tablet Properties

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa *et al.,* 1994[23]. The tablets were placed in a 100-mL beaker containing 0.1 N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time (TFT).

In Vitro Dissolution Studies

The release rates of famotidine from floating tablets were determined using *United State Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37° ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance of these solutions was measured at 265 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

RESULTS AND DISCUSSION

In Vitro Buoyancy Studies

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies.

It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate was essential to achieve optimum in vitro buoyancy (i.e floating lag time of sec and floating duration of hours). Further increase in concentration of sodium bicarbonate does not show any significant effect on floating behaviour. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in

pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release.

Table 3: Response Parameters of various Formulations Prepared as per the Experimental Design.

Formulation Code	Floating lag time (sec)	t_{50} (hrs)
F1	39	8
F2	24	6.1
F3	15	5.5
F4	23	7.2
F5	11	5.8
F6	9	4.9
F7	28	6.5
F8	7	5
F9	5	4.3
F10	10	5.6
F11	9	5.9
F12	12	5.7
F13	11	5.5

In Vitro Dissolution Studies

In vitro dissolution studies of all the formulations of floating tablets of famotidine were carried out in 0.1N HCl. The study was performed for 8 hours and cumulative drug release was calculated for every one hour time interval. In vitro dissolution studies of all the formulations are shown in Figure no. 1 to 3. HPMC K15M and sodium bicarbonate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern.

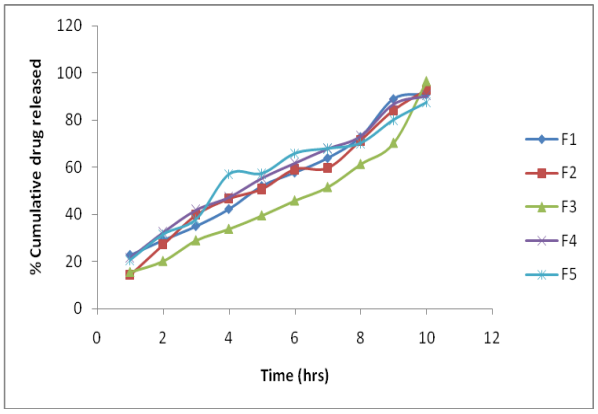

Figure no. 1. HPMC K15M and sodium bicarbonate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern as shown in F1 to F5.

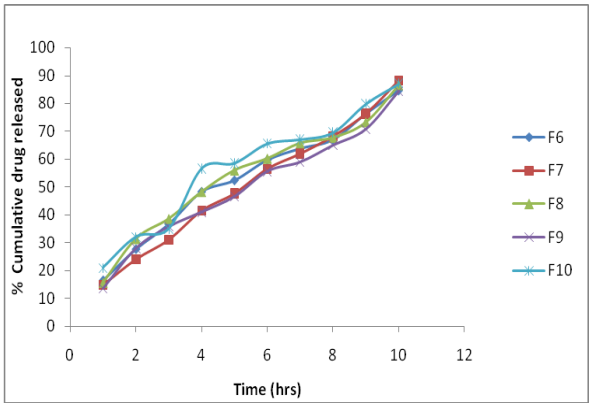

Figure no. 2. HPMC K15M and sodium bicarbonate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern as shown in F6 to F10.

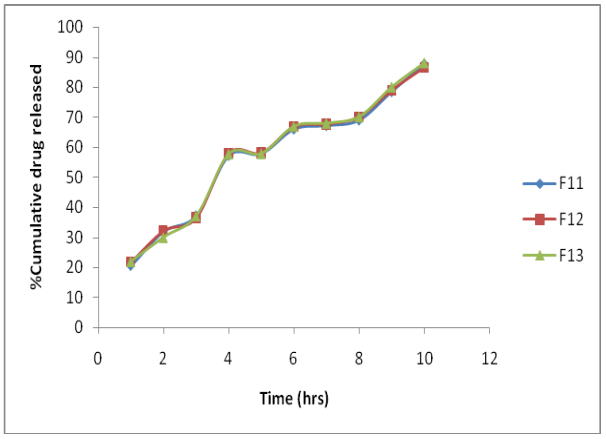

Figure no. 3. HPMC K15M and sodium bicarbonate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern as shown in F11 to F13.

Experimental Design- Central Composite Design

Central composite design (face-centered) was applied using Design Expert Software (Version 8.0.5, Stat- Ease Inc, Minneapolis, MN) to study the effect of amount of HPMC K15M and sodium bicarbonate on the floating lag time and the drug release (t_{50}) from matrix tablets of famotidine.

The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor in Equation (i) to (iv) reveal that HPMC K 15M individually, has rather more pronounced effect on the values of floating lag time and time required for 50% drug release, t_{50}. At a given set of factor levels, however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

Mathematical Modeling:

Final Equation in Terms of Coded Factors

$$\text{Floating lag time} = +10.48 - 10.17X_1 - 6.33X_2 + 0.25X_1X_2 + 5.81X_1^2 + 5.31X_2^2 \quad \text{(i)}$$

Final Equation in Terms of Actual Factors

Floating lag time= +122.35-3.41 HPMC K15M -7.73 Sodium bicarbonate +5.00 HPMC K15M Sodium bicarbonate +0.05 HPMC K15M^2+0.21 Sodium bicarbonate^2 (ii)

Final Equation in Terms of Coded Factors

$$t_{50} = +5.33 - 1.17X_1 - 0.63X_2 + 0.075X_1X_2 + 0.64X_1^2 + 0.14X_2^2 \quad \text{(iii)}$$

Final Equation in Terms of Actual Factors

t_{50}= +13.85-0.39 HPMC K15M -0.32 Sodium bicarbonate+1.50 HPMC K15M Sodium bicarbonate +6.41 HPMC K15M^2 +5.65 Sodium bicarbonate^2 (iv)

Table 4 Shows ANOVA for dependent variables, which indicated that response surface models developed for floating lag time and t_{50} were significant and adequate, without significant lack of fit.

It can be observed from Table 5 that R^2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2 value is in good agreement with the adjusted R^2 value, resulting in reliable models.

Table 4: ANOVA – Influence of formulation variables on the response factors.

Response factor	Model F-value	Prob> F	Lack of fit F-value	Prob> F
Floating Lag Time	31.93	<0.0001 Significant	0.38	0.5694 Nonsignificant
Response in Time, t_{50}	4.55	0.0362 Significant	0.020	0.9954 Nonsignificant

Table 5: Model Summary Statistics - Influence of formulation variables on the response factors.

Response Factor	Std. Dev.	R^2	Adjusted R^2	Predicted R^2
Floating Lag Time	1.07	0.9952	0.9885	0.9448
Response in Time, t_{50}	0.73	0.7648	0.5967	0.6330

Response Surface Analysis

The results of multiple linear regression analysis showed that both the coefficients X_1 and X_2 bear a negative sign. Therefore, increasing the concentration of either HPMC K 15M or Sodium bicarbonate is expected to decrease the floating lag time and time required for 50% drug release (t_{50}). It may be due to interaction between gas generating agent ($NaHCO_3$) and dissolution medium (0.1N HCl) which reduces FLT, and hydrophilic nature of HPMC produces easy swelling of tablets. Figure 4 to Figure 7 shows the 3D surface plots of the amount of HPMC K 15M and the amount of Sodium bicarbonate.

However, the effect of HPMC K 15M seems to be more pronounced as compared with that of Sodium bicarbonate in both cases,floating lag time and time required for 50% drug release (t_{50}), as revealed by the response surface and the mathematical model.

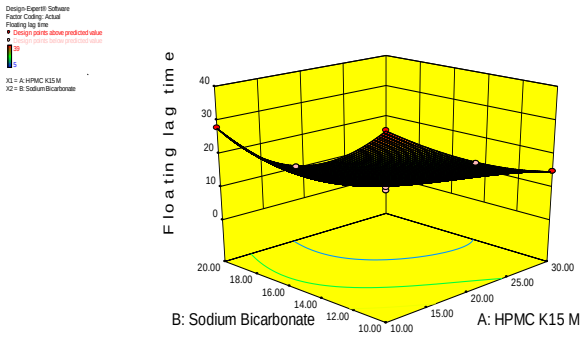

Fig. 4: Response surface plot (3D) showing the effect of amount of HPMC and amount of sodium bicarbonate on floating lag time.

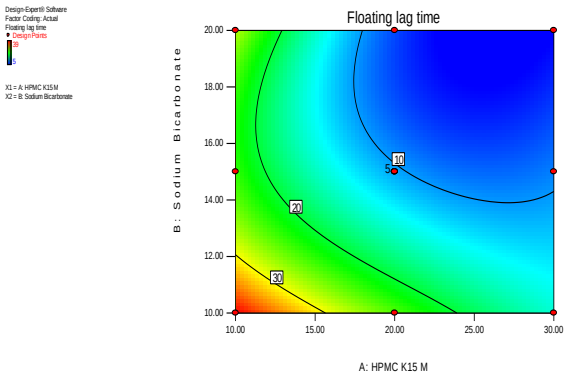

Fig. 5: Contour plot showing the effect of amount of HPMC and amount of sodium bicarbonate on floating lag time.

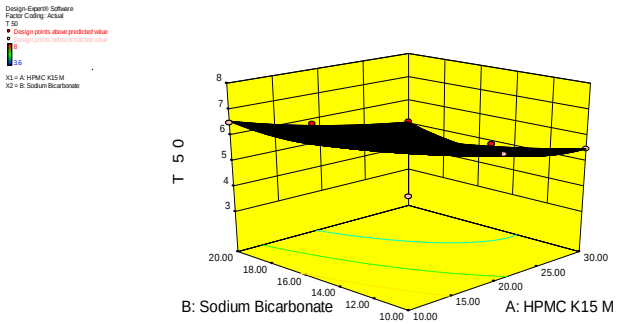

Fig. 6: Response surface plot (3D) showing the effect of amount of HPMC and amount of sodium bicarbonate on time required for 50% drug release (t_{50}).

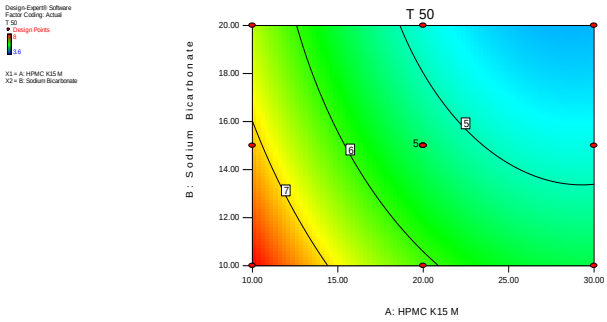

Fig. 7: Contour plot showing the effect of amount of HPMC and amount of sodium bicarbonate on time required for 50% drug release (t_{50}).

CONCLUSION

It is concluded from the present investigation that effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using gel-forming polymer HPMC (K15M) and gas-generating agent sodium bicarbonate. HPMC (K15M) containing floating matrix tablet of famotidine was promising controlled release systems for peptic ulcers. The optimized formulation gives the best result in terms of the required lag time (5 seconds) and floating duration of 10 hours with sustained drug release rates. A central composite design was applied to investigate the combined effect of three formulation variables. Results of multiple regression analysis indicated that moderate level of all three independent variables is useful for development of gastroretentive drug delivery system.

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