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Studies on development of famotidine floating tablets using three grades of Methocil®

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ABSTRACT

Aim: The aim of the study was to design, formulate and characterize famotidine floating matrix tablets employing three grades of Methocil (HPMC) i.e., K4M, HPMC K15M and HPMC K100M.

Materials and methods: Controlled release floating matrix tablets were prepared using wet granulation method employing drug and polymers in four ratios (1:0.5; 1:1; 1:5 and 1:2). Characterization was done on prepared formulations, such as drug-excipient interaction, *in vitro* buyoncy, swelling, *in vitro* dissolution and accelerated stability studies.

Results: FTIR, DSC and XRD studies on the formulations showed no interaction of famotidine with the polymers employed in the study. Most of the tablet formulations showed values within the official limit upon pre and post-compression evaluation. The type of polymer affected the drug release rate and the mechanism. Polymer swelling was crucial in determining the drug release rate flotation. A lesser FLT could be achieved by increasing the concentration and increasing the viscosity grade of the polymer. The optimized formulation (FS4) offered best controlled release along with floating lag time of 1min and total floating time of >14 h. Good stability was observed for 3 months during accelerated stability studies.

Conclusion: The optimized formulation FS4 employing famotidine:HPMC K4M in the ratio of 1:1 showed sufficient release for prolonged period, the dose could be reduced and the possible incomplete absorption of the drug could be avoided.

KEY WORDS: HPMC, K4M, K15M, K100M, Gastroretentive, Famotidine, Matrix tablets, *In vitro* studies.

INTRODUCTION

Prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract [1] and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. [2,3] In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size [4,5].

Gastroretentive drug delivery systems of famotidine were reported for HPMC K100M [6], HPMC K4M [7,8], Carbopol 934P [9], HPMC K4M, HPMC K15M and HPMC K100M [10], chitosan [11] . However in the present study we tried to reduce the concentration of gas generating agent by introducing microcrystalline cellulose there by minimizing the adverse effects of gas generating agents.

MATERIALS AND METHODS

Famotidine was gift sample from Sreenivasa Pharmaceuticals Pvt. Ltd. Hyderabad, India. Methocil (HPMC grades of K4M, K15M and K100M) were obtained from ColorCon Asia Pvt. Ltd, Goa, India. HCl, Microcrystalline cellulose, Citric acid, Sodium bicarbonate, talc and magnesium stearate were purchased from S.D.Fine Chemicals, Mumbai, India. All other ingredients used were of analytical grade.

SPECTRAL (FTIR) STUDIES

The FTIR spectra (400 to 4000 cm^{-1} and resolution of 4 cm^{-1}) of the pure famotidine and polymers were measured by preparing dispersion in dry KBr using Shimadzu FTIR 8400S (Perkin-Elmer 1615 Series or Bruker, Germany). The transmission minima (absorption maxima) in the spectra obtained with these polymers were compared. The presence of additional peaks corresponding to the functional groups was noted [12].

THERMOGRAPHIC (DSC) STUDIES

The heat characteristics of famotidine and polymers were analyzed using a Shimadzu DSC-60 (Shimadzu, Kyoto, Japan). The behavior under heat was studied by heating the samples (2 mg) in an aluminium pan from 25 to 300°C at a heating rate of 10°C/min under a flow of nitrogen at 10 cm^3/min using an empty pan as a point of reference.

CRYSTALLOGRAPHIC (XRD) STUDIES

Powder XRD was conducted using an automatic diffractometry (XRD 7000, Schimadzu, Kyoto, Japan) with a voltage of 40 kV and a current of 30 mA. The sweep measurements of 2θ angle were carried out at a scanning rate of 4^o min^{-1} over a range of 10 to 80^o. The results were interpreted using the computer program (XRD 7000, Schimadzu, Kyoto, Japan). The highest peak of diffraction was measured for crystallinity of the sample.

PRE-COMPRESSION EVALUATION OF POWDER BLENDS

The drug and polymer powders blends of different combinations as per table no were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures [13]. The obtained values after testing are compared with the standard values and inferences were drawn.

PREPARATION OF FLOATING TABLETS USING METHOCIL [14]

In the present investigation, wet granulation technique was employed to prepare tablets of HPMC of different viscosity grades (K4M, 4,000 cps; K15M, 15,000 cps; and 1,00,000 cps) at different drug to polymer ratios as per the composition given in Tables 1. Microcrystalline cellulose was used as diluent along with sodium bicarbonate and citric acid as gas generating agents. PVP K30 dissolved in sufficient isoprpyl alcohol was used as granulating agent (binder). Magnesium stearate was used as lubricant and talc as a glidant. Punch of 8 mm size with corsoponding dies were used for tablet compression the tablets employing Cadmach Press.
The granules were prepared by wet granulation method using warm purified water (50-55 ^oC). The wet mass was prepared by taking the calculated amount of mentioned ingredients as per above composition tables. The ingredients along with water were mixed to make a dough and passed through #20 standard sieve and dried at 60 ^oC in hot air oven for 1 h. The dried granules were sifted through #22 sieve and lubricated with mixture of magnesium stearate and talc (pre-sifted through sieve #80). The mixed granules were compressed in tablet press using suitable punches as stated above.

Table 1: Formulation of famotidine floating tablets prepared using different grades of Methocil

Ingredients (mg)	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8	FS9	FS10	FS11	FS12
Famotidine	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K4M	20	40	60	80	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	20	40	60	80	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	20	40	60	80
Micro crystaline cellulose	80	69	49	29	89	69	49	29	89	69	49	29
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20
Citric acid	15	15	15	15	15	15	15	15	15	15	15	15
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

IN VITRO BUOYANCY STUDIES

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT). The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.*[15]**.** The tablets were placed in a 250 mL beaker containing 100 mL of 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

SWELLING STUDIES [11]

Formulated tablets were weighed individually (W_0) and placed separately in a petri dish containing 50 mL of 0.1N HCl. The Petri dishes were placed in an incubator maintained at 37±0.5ºC. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula

$$\% W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where: W_U – Water uptake, Wt – Weight of tablet at time t, Wo – Weight of tablet before immersion.

IN VITRO DISSOLUTION STUDIES [15]

The release of famotidine from the prepared floating tablets was studied using USP-Type II paddle apparatus (Electrolab TDT 08L, dissolution tester, U.S.P.). Drug release profile was carried out in 900 mL of 0.1N HCl maintained at 37±0.5°C temperature at 100 rpm. 5 mL of samples were withdrawn at regular time intervals up to 12 h. The samples were replaced by equivalent volume of dissolution medium and were filtered through 0.45 µm Whatman filter paper. The samples were suitably diluted and analyzed at 265.5 nm, using (Shimadzu UV 1700) UV spectrophotometer.

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi and Koresmeyer-Peppas equations. Based on the obtained R^2 values, the best-fit model was selected [16-18].

Anomalous diffusion or non-fickian diffusion refers to a combination of both diffusion and erosion controlled rate release. The *Korsmeyer Peppa's equation* is used to deteremine whether the drug release mechanism is Fickian or non-Fickian[19].

STABILITY STUDIES OF OPTIMIZED FLOATING MATRIX TABLETS [20, 21]

The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 40±5ºC/75% RH for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated. The drug content, floating lag-time and drug dissolution profile of the exposed samples were determined.

Student t-test is used to compare the means of two related (paired) samples analyzed by reference and test methods. It gives answer to the correctness of the null hypothesis with certain confidence such as 95% or 99%. If the number of pairs (n) are small than 30, the condition of normality of x is required or atleast the normality of the difference (d_i). This test, also known as Welch's t-test, is used only when the two population variances are not assumed to be

equal (the two sample sizes may or may not be equal) and hence must be estimated separately. The t statistic to test whether the population means are different is calculated as:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}$$

Where, $\bar{X}_1$ = mean of first set of values, $\bar{X}_2$ = mean of second set of values, S_1= standard deviation of first set of values, S_2= standard deviation of second set of values, n_1= total number of values in first set and n_2= total number of values in second set.

Significance of difference for floating lag time and assay values of the optimized formulation before and after accelerated stability testing was calculated based on Student's t-test.

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100 [21]. The dissolution profiles of products were compared using f_2 which is calculated from the following formula,

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{j=1}^{n} | R_j - T_j |^2]^{-0.5} \times 100\}$$

Where, n is the dissolution time and Rj and Tj are the reference and test dissolution values at time t. The similarity factor (f_2) was calculated for comparison of the dissolution profile before and after stability studies in the present study [22].

RESULTS AND DISCUSSION

DRUG-POLYMER COMPATIBILITY STUDIES

The development of a successful formulation depends only on a suitable selection of excipients. Hence the physical states of pure famotidine and the polymers (HPMC grades of K4M, K15M and K100M) individually and the combination of drug and polymers used for the preparation of formulations were studied by FTIR spectroscopy to know the drug-polymer compatibility. The results are shown in Fig. 1.

Famotidine showed different peaks at N–H symmetric stretching : 3395, 3240; C–H stretching: 2970; C=N stretching : 1636; N–H bending: 1595; –SO2–sulphonyl :1326 (s), 1159 (s) cm^{-1} which confirms the purity of famotidine. The same bands were also found in the spectra of the formulations of famotidine using various polymers, which indicated that there was no drug-polymer interaction.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The DSC thermograms of pure drug, polymer and the composition of drug –polymers were recorded in DSC analyzer at a heating rate of 20°C per min from 0 to 350°C in the nitrogen environment. The DSC thermograms showed well defined peaks for famotidine in individual and combination with polymers. The drug showed one sharp endothermic peak occurred at 233.07°C. Formulations of famotidine using HPMC K4M, HPMC K15M and HPMC K100M showed similar endothermic peaks at 226.0, 230.7 and 232.2°C respectively which indicated that there was no significant interaction between the drug and polymers employed in the study. The obtained DSC thermograms are shown in the Fig. 2.

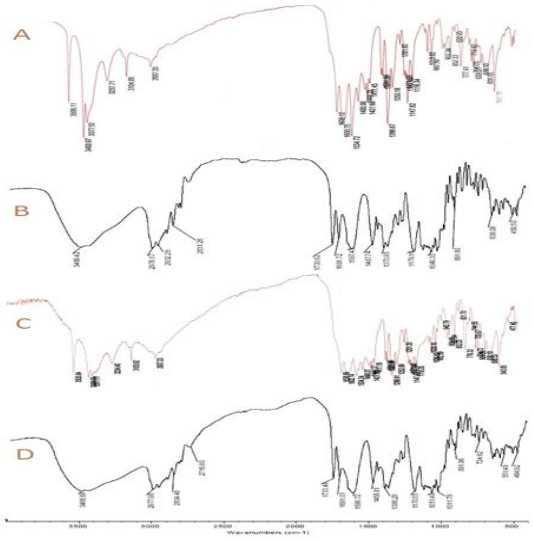

Fig. 1: FTIR spectra of famotidine (A) and formulations of HPMC K4M (B), HPMC K15M (C) and HPMC K100M (D)

Thus, from IR spectra studies and DSC thermograms we can draw a conclusion that the drug remains in its normal form without undergoing any interaction with the polymers evidenced by no additional peaks in FTIR and DSC.

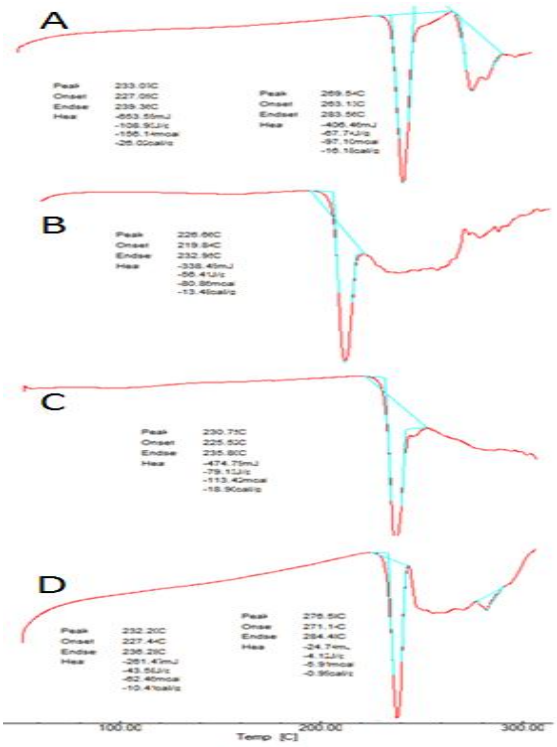

Fig. 2: DSC thermograms of famotidine (A) and formulations of HPMC K4M (B), HPMC K15M (C) and HPMC K100M (D)

CRYSTALLOGRAPHY (X-RAY DIFFRACTION, XRD)

XRD analysis was carried out to confirm formation of a new solid state which provides the information regarding the degree of crystanality and crystal lattice arrangements of the compound. The non crystalline portion simply scatters the X-ray beam to give continuous background, while the crystalline portion causes diffraction lines that are not continuous. The diffractogram of famotidine exhibited a series of intense peaks at 11.56, 20.00, 20.80, 24.00, 30.30, 32.22 and 35.10, 38.64 and 48.57 which were indicative of crystalline nature of famotidine. As compared to famotidine and different formulations using polymers employed in the study showed insignificant diffraction pattern of peaks and their intensity which indicated that there was no variation in the crystanality of formulations as compared to the famotidine alone.

PRE-COMPRESSION FLOW PROPERTIES OF POWDER BLEND

The drug and polymer powders blends of different combinations were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures [13] and consistency in data obtained as indicated by their standard deviation values shown in Table 2.

Bulk density and tapped density

Bulk density and tapped densities showed good packing ability of the powdered blend for compression process. Bulk and tapped densities of different formulations were calculated. The results of bulk density ranged from 0.425±0.45 to 0.488±0.85 gm/cm^3 and tapped density from 0.496±0.09 to 0.580±0.67 gm/cm^3.

Carr's index (Compressibility index)

Carr's index of the powder of all formulations ranged from 6.15% to 20.69%. Formulation FS8 showed lowest Carr's index indicating good compressibility.

Haunsner's ratio

Hausner's ratio ranged between 1.261 and 1.193. The powder blend of formulation FS1 showed lowest Hausner's ratio indicating good flow. Blend of FS8 had an excellent angle of flow as compared to those of other formulations.

Angle of repose

All the powder blends showed excellent flow ability as expressed in terms of angle of repose whose values were found in the range 21.07±1.76^o to 27.76±1.16^o. The powder blend of FS12 had the lowest value among all formulations composition showing excellent flow. As per pharmacopoeial standards the powder blend of FS4, FS11 and FS12 showed an excellent flowabilty, where as those of other formulation were within the range of good flow properties (25–30^o).

The obtained values of all the derived properties of powder combinations were within the limits, indicating that the powder blends poseessed the required flow property for tablet compression.

Table 2: Pre-compression flow properties of powder blends

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)±SD
FS1	0.462±0.98	0.580±0.67	20.69	1.261	27.76±1.16
FS2	0.47±0.99	0.575±1.98	18.26	1.223	25.90±1.01
FS3	0.452±0.98	0.568±2.90	20.42	1.257	25.41±0.16
FS4	0.486±1.98	0.557±1.98	12.75	1.146	22.29±2.16
FS5	0.46±0.90	0.540±1.45	16.21	1.193	26.11±1.96
FS6	0.474±0.70	0.540±0.43	12.22	1.190	25.39±0.13
FS7	0.455±0.87	0.537±2.23	15.27	1.180	25.30±1.14
FS8	0.488±0.85	0.521±1.78	6.15	1.066	23.09±0.16
FS9	0.425±0.45	0.496±0.09	14.31	1.167	25.11±1.59
FS10	0.472±0.53	0.524±2.56	9.61	1.156	23.01±1.10
FS11	0.465±0.09	0.555±2.56	16.22	1.144	22.17±1.18
FS12	0.445±0.12	0.542±0.90	17.59	1.310	21.07±1.76

Table 3: Post-compression physicochemical evaluation of famotidine floating tablets

Formulation	Hardness(kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	FLT (min)	TFT(h)
FS1	4.5±0.13	204.16±0.33	0.62±0.01	99.40±0.65	1.8	>14
FS2	4.5±0.11	208.71±0.77	0.63±0.02	99.62±0.12	1.6	>14
FS3	4.6±0.07	210.71±0.98	0.55±0.01	100.85±0.54	1.4	>14
FS4	4.7±0.04	204.61±0.02	0.58±0.01	99.07±0.86	1.0	>14
FS5	4.3±0.05	198.51±0.66	0.72±0.02	97.45±0.76	1.2	>14
FS6	4.7±0.05	210.23±0.76	0.68±0.02	98.62±0.86	1.6	>14
FS7	4.9±0.04	212.11±0.94	0.62±0.01	99.15±0.78	1.4	>14
FS8	4.9±0.05	200.93±0.28	0.65±0.01	100.42±0.87	1.5	>14
FS9	4.7±0.06	195.08±0.16	0.56±0.02	99.72±1.21	2.0	>14
FS10	4.8±0.03	205.05±0.85	0.54±0.01	99.25±0.85	1.40	>14
FS11	4.9±0.04	188.30±0.05	0.58±0.02	99.50±0.94	1.18	>14
FS12	5.0±0.02	199.90±0.10	0.65±0.018	98.97±0.80	1.10	>14

FLT, floating lag time; TFT, total floating time

FORMULATION OF FAMOTIDINE FLOATING TABLETS

All the tablets were prepared by effervescent approach. The concentration of all the three selected semi-synthetic polymers (HPMC) was decided on trial and error basis. Sodium bicarbonate (10%) and citric acid (7.6%) in the ratio of 1.0:0.76, were incorporated as a gas-generating agents based on earlier studies [23]. PVP-K30 (5%) and MCC (14.4%–44.4%) were used as binder and diluent respectively.Talc (1%) was used as lubricant and magnesium stearate (2%) was employed as glidant to improve the flow of the powder. FTIR study showed that all the polymers used were compatible with famotidine.

From the earlier literature it was evident that HPMC (Methocel K15M) is a good polymer for floating drug delivery system as it is a matrix forming and low density polymer [24].

POST-COMPRESSION EVALUATION OF FAMOTIDINE FLOATING TABLETS

The formulated floating tablets were subjected for post compressional evaluation such as visual inspection, hardness, weight variation, friability, uniformity of drug content, *in vitro* buoyancy, swelling, *in vitro* dissolution, stability and similarity studies. The results are summarized in Table 3.

Visual inspection

The prepared tablets were inspected visually for general tablet deformities. The tablets were smooth with uniform in size, shape and colour. There was no lamination or chipping was observed in all the tablets which indicated that the tablet-instrumentation was compatible with the powder blends and resulting in good tablet characteristics.

Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Hardness in the prepared tablets was found to be in the range of 4.3±0.05–5.0±0.02 kg/cm^2. Hardness of the tablets was found to increase with an increasing of polymer concentration. The floating tablets prepared using HPMC K15M was found to be less harder than those prepared using HPMC K4M and K100M. Similar pattern of results was observed in the study done by Chauhan *et al*, [25].

Weight variation

The weight variation of prepared formulations was found in the range of 195.08±0.16–212.11±0.094 mg. All the batches of tablets were found to pass the weight variation test. The percentage deviation of the individual tablet weights from the average tablet weight was found to be within the I.P. limits of ±7.5 %.

Friability test

The friability loss of prepared tablets was found to be between 0.54% and 0.72 % when tested using Roche friabilator. All batches of tablets passed the test and were within the limits which indicated that the tablets were mechanically stable.

Drug content uniformity

The drug content uniformity of the prepared tablets was examined as per I.P. specification and was found compliant. The drug content of the formulations was in the range 98.62±0.86% to 100.85±0.54% showing the uniformity of drug distribution in the prepared tablets [26]. None of the individual drug content values were outside the average content values of 90% to 110% as per IP.

IN VITRO BUOYANCY STUDIES

In the present study the floating tablets were formulated with sodium bicarbonate ($NaHCO_3$) and citric acid in an optimized ratio (1.0:0.76) as gas forming mixture [27, 23]. This ratio was used in order to provide the shortest possible floating lag time and floating duration of up to 14 h. The floating lag time found for the prepared tablets was 1–1.2 min and the total floating time was found over 14 h for all the formulations (Table 3). Sodium bicarbonate has induced carbon dioxide generation in the presence of dissolution medium (0.01N HCl). Further, sodium bicarbonate induced the effervescence that leads to pore formation and consequently, rapid hydration of the floating tablets. The gas generated was trapped and protected within the gel, which was formed by hydration of HPMC polymer, thus decreasing the density of the tablets. As the density of the tablet falls below 1 g/mL, the tablet becomes buoyant [28].

The floating tablets with low-viscosity grade HPMC K4M exhibited shortest floating lag time of 1 min and floated for longer duration (>14 h) as compared to those containing high viscosity grades of HPMC K15M and K100M polymers. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer (HPMC) influenced the *in vitro* buoyancy. An increase in HPMC concentration in the formulations decreased the floating lag time. Therefore polymer type and concentration affected the *in vitro* buyoncy of floating tablets which was in agreement with the previously reported study by [29].

SWELLING STUDIES

Swelling index is a parameter which describes the ability of the formulation to swell and float in the dissolution medium. Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating and drug dissolution. To obtain floating, the balance between swelling and water acceptance must be restored. The swelling index of floating tablets of FS1–FS12 is shown in Figs. 3–5. Floating tablets prepared using HPMC K4M and HPMC K15M (F1 to F8) swelled rapidly at the beginning in 0.1 N HCl and could not remain their matrix integrity up to 8 h. The swelling index was increased with concentration of HPMC since this polymer gradually absorbs buffer due to hydrophilic nature. The HPMC grade affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M and HPMC, K100M. HPMC K100M exhibited low swelling index which could be due to its high viscosity and high water retention property.

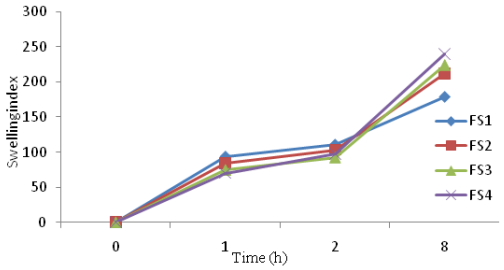

Fig. 3: Swelling studies of famotidine floating tablets formulated with HPMC K4M

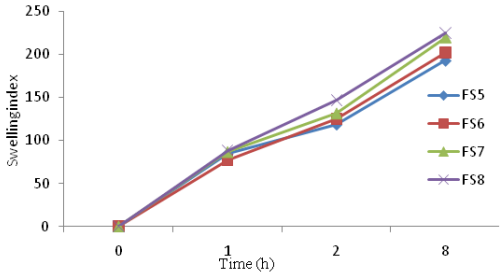

Fig. 4: Swelling studies of famotidine floating tablets formulated with HPMC K15M

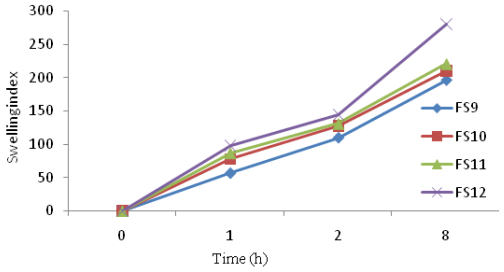

Fig. 5: Swelling studies of famotidine floating tablets formulated with HPMC K100M

IN VITRO DISSOLUTION STUDIES

In vitro dissolution studies of famotidine floating tablet were evaluated in 0.1 N HCl (pH 1.2) for 12 h. The cumulative percentage of drug released from the tablets containing three viscosity grades of HPMC (K4M, K15M and K100M) in specified ratios (1:0.5;1:1;1:1.5 and 1:2) was compared.

The curves of cumulative percentage of drug released vs. time (h) for all the formulations were plotted and are depicted in Figs. 6–8.

Famotidine release was found to decrease with an increase in polymer concentration. Drug release was maximum (99.45±0.10%) for formulation FS4 which was constituted with low viscosity HPMC K4M. The increased density of polymer at higher concentration results in an increased diffusional pathlength, which leads to an overall decrease in release of the drug. Although composition of HPMC K15M and HPMC K100M sustains the drug release for a longer period of time up to 15 h, this controlled release of drug from FS12 could be attributed to the formation of a thick gel structure that delays the drug release from the tablet matrix.

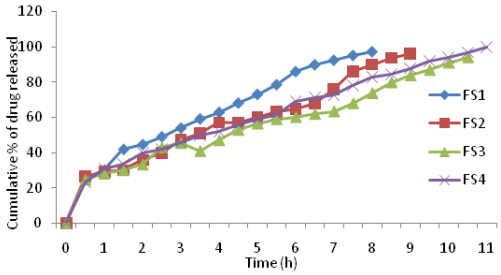

Fig. 6: *In vitro* drug release profiles of famotidine floating tablets of HPMC K4M

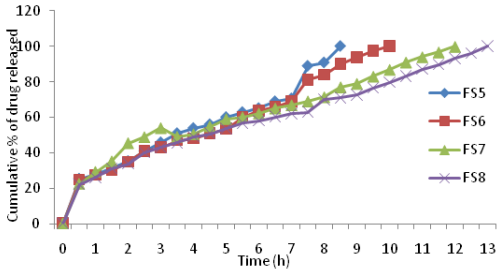

Fig. 7: *In vitro* drug release profile of famotidine floating tablets of HPMC K15M

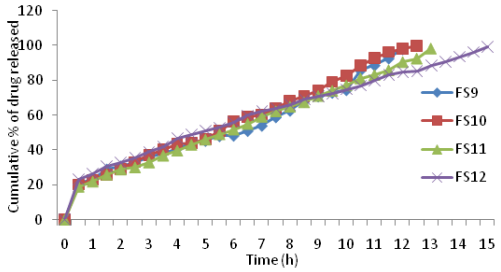

Fig. 8: *In vitro* drug release profile of famotidine floating tablets of HPMC K100M

DRUG RELEASE KINETIC STUDIES

The mechanism of drug release for the above formulations was determined by calculating the correlation coefficient (R^2 value) for the kinetic models, viz., zero-order, first-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation. The results of the kinetic models are summarized in Table 4. For most of the formulations the R^2 value of Korsmeyer–Peppas and zero-order model was nearer to one than those of other kinetic models. Thus, it could be drawn from the results that the drug release follows zero-order and Korsmeyer–Peppas model mechanisms.

The 'n' values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was found to be non-Fickian diffusion or anomalous diffusion for the formulations tested. The time required for dissolution of 50% (T_{50}) and 90% (T_{90})

were determined. The results of drug release kinetics are shown in Figs. 12.

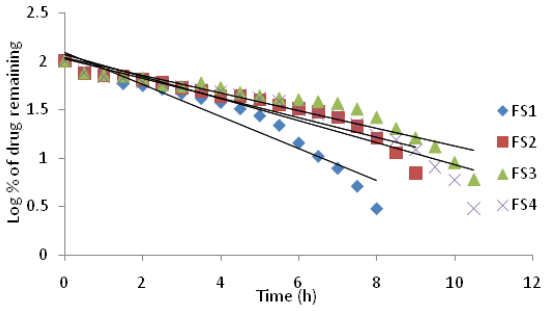

Fig. 9: First order plots of famotidine floating tablets of HPMC K4M

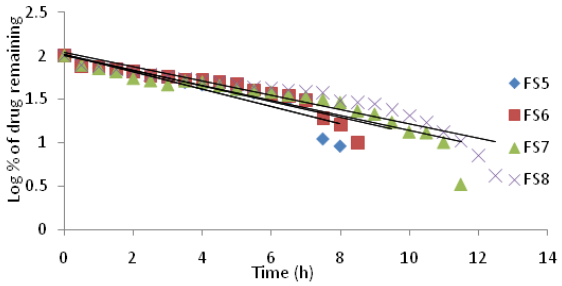

Fig. 10: First order plots of famotidine floating tablets of HPMC K15M

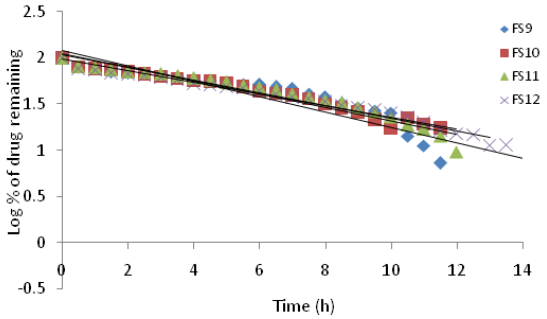

Fig. 11: First order plots of famotidine floating tablets of HPMC K100M

Formulation FS4 (drug-polymer in 1:2 ratio) showed a minimum lag time (1 min) and maximum floating time (> 12h) with maximum drug release (100.02%±0.12% in 11 h). It also showed good linearity (R^2 of 0.996) which indicates zero order release with non-Fickian diffusion mechanism. Therefore, formulation FS4 could be considered as optimized formulation from this set of twelve formulations prepared by three different grades of HPMC polymers. Similar conclusions were also drawn by earlier researchers who worked in the development of floating delivery systems [30, 31].

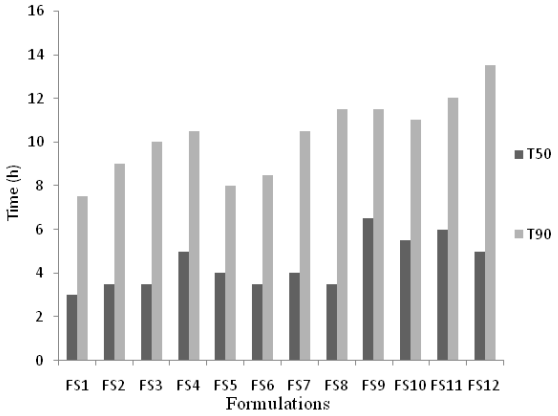

Fig. 12: T_{50} and T_{90} values of famotidine floating tablets

STABILITY STUDIES

Based on floating lag time, floating time and *in vitro* drug release kinetics data, the formulation FS4 was optimized. The tablets of batch FS4 were packed in an aluminum pouch and subjected to accelerated stability studies at 40°C and 75% RH for 3 months in a humidity chamber. The drug content, floating lag-time and drug dissolution profile of the exposed samples were determined. The similarity factor (f_2) was calculated for comparison of the dissolution profile before and after stability studies.

Table 3 shows the results of drug content and floating lag time of the formulation FS4 before and after the accelerated stability studies. Student t-test was conducted on drug content and floating lag time and the values obtained were 0.08 and 1.09 respectively which were lesser than the table value of 2.57 at 95% confidence limits. There was no significant difference observed in the drug content uniformity and floating lag-time before and after the stability studies. The results of *in vitro* dissolution data of formulation FS4, before and after stability studies are shown in Table 5.

SIMILARITY STUDIES

Similarity factor (f_2) for FS4 optimized formulations compared before and after stability testing was found to be 88.64, which was between 50 and 100. This indicates existing of a close similarity between the dissolution profiles of the tested formulation before and after stability studies.

Hence, these results confirm that the developed formulation was stable under tested conditions.

Table 4: *In vitro* drug release kinetics of famotidine floating tablets formulated with HPMC

Formulation	T_{50} (h)	T_{90} (h)	Zero order		First order		Higuchi	KorsmeyerPeppas	
			R^2	K_0 ($mg.h^{-1}$)	R^2	K_1 (h^{-1})	R^2	R^2	N
FS1	3	7.5	0.959	11.15	0.914	0.380	0.988	0.985	0.469
FS2	3.5	9	0.992	7.793	0.903	0.230	0.977	0.979	0.469
FS3	3.5	10	0.984	7.117	0.873	0.207	0.961	0.957	0.588
FS4	5	10.5	0.996	6.769	0.887	0.260	0.957	0.979	0.525
FS5	4	8	0.950	9.284	0.825	0.228	0.938	0.957	0.520
FS6	3.5	8.5	0.985	8.125	0.869	0.205	0.947	0.957	0.489
FS7	4	10.5	0.972	5.913	0.846	0.198	0.972	0.956	0.560
FS8	3.5	11.5	0.992	5.787	0.871	0.189	0.979	0.982	0.680
FS9	6.5	11.5	0.966	6.578	0.829	0.166	0.927	0.939	0.485
FS10	5.5	11	0.995	6.813	0.968	0.145	0.954	0.973	0.526
FS11	6	12	0.987	6.444	0.930	0.157	0.963	0.975	0.645
FS12	5	13.5	0.994	5.056	0.707	1.911	0.989	0.988	0.760

Table 5: Stability studies of optimized formulation FS4

Storage conditions	Drug content (%±sd)	FLT (min±sd)
Reference (FS4)	99.04±0.86	1.0±0.25
Test (40±2^0 C/75±5% RH, 3 months)	99.01±0.63	1.1±0.20
t-test value	0.08	1.09

FLT, floating lag time; n=3

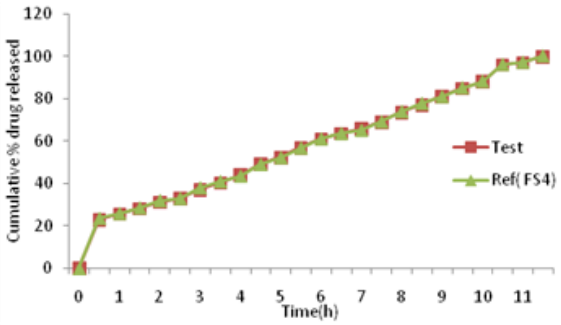

Fig. 13: Cumulative % of drug released vs time plots of formulation FS4 before and after stability studies

CONCLUSIONS

This study discusses the preparation of floating tablets of famotidine using HPMC polymers of different grades K4M, K15M and K100M in different ratios (1:0.5; 1:1; 1:5 and 1:2) respectively as drug-retarding polymers along with sodium bicarbonate and citric acid in 1:0.76 ratio as gas generating agents.

The type of polymer affected the drug release rate and the mechanism. Polymer swelling was crucial in determining the drug release rate flotation. A lesser FLT could be achieved by increasing the concentration and increasing the viscosity grade of the polymer.

The order of drug release with respect to selected polymers was found as HPMC K4M > HPMC K15M > HPMC K100M.

The optimized formulation (FS4) offered best controlled release along with floating lag time of 1min and total floating time of >14 h. Good stability was observed for 3 months during accelerated stability studies.

Since the formulation showed sufficient release for prolonged period, the dose could be reduced and the possible incomplete absorption of the drug could be avoided.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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