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Formulation and characterization of lafutidine floating matrix tablets employing three grades of HPMC polymers

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ABSTRACT

Aim: The aim of the study was to formulate and evaluate lafutidine floating matrix tablets employing three grades of 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 lafutidine 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 (LS2) offered best controlled release along with floating lag time of 1 min 10 sec and total floating time of >14 h. Good stability was observed for 3 months during accelerated stability studies.

Conclusion: The optimized formulation LS2 employing lafutidine 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, Lafutidine, Matrix tablets, *In vitro* studies.

INTRODUCTION

Grater therapeutic effect of the drug substances can be achieved by prolonging the gastric retention of a delivery system. This is more applicable to the drugs those are absorbed in stomach region [1] and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the 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 lafutidine were reported for HPMC K4M [6], HPMC K15M [7,8], sodium alginate [9], HPMC K4M [10], xanthan gum and karaya gum [11] . However in the present study we tried to reduce the concentration of gas generating agent by introducing microcrystalline cellulose thereby minimizing the adverse effects of gas generating agents.

MATERIALS AND METHODS

Lafutidine was gift sample from Ajanta Pharma Ltd, Mumbai, India. Methocel (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 lafutidine 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 lafutidine 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 HPMC POLYMERS[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 corresponding dies were used for tablet compression the tablets employing Cadmach Press.
The granules were prepared by wet granulation method using PVP K30 in sufficient isopropyl alcohol. The wet mass was prepared by taking the calculated amount of mentioned ingredients as per above composition tables. The ingredients 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 lafutidine floating tablets prepared using different grades of HPMC

Ingredients(mg)	LS1	LS2	LS3	LS4	LS5	LS6	LS7	LS8	LS9	LS10	LS11	LS12
Lafutidine	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K4M	10	20	30	40	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	10	20	30	40				
HPMC K100M	-	-	-	-	-	-	-	-	10	20	30	40
Microcrystalline cellulose	119	109	99	89	119	109	99	89	119	109	99	89
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±0.5°C. 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 lafutidine 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 279 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±5°C/75% RH for three months and 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 lafutidine 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.

FTIR spectra of pure lafutidine showed characteristic sharp peaks of alkene stretching (=C–H and CH_2) vibration at 3323.07–2941.33 cm^{-1} and alkane stretching (–CH_3, –CH_2 and –CH) vibration at 2863.82 cm^{-1}. Also exhibited C=O stretch at 1688.13 cm^{-1} due to saturated ketone and C=O–NH stretching at 1648.61 cm^{-1}. A selective stretching vibration at 1562.10 cm^{-1} and 1524.46 cm^{-1} for primary and secondary amine was also observed. For functional groups like S=O stretch and –C–S stretch showed vibrations at 1031.83 cm^{-1} and 727.16 cm^{-1} respectively. Most of the peaks are observed in the spectral region 748.83–881.38 cm^{-1}, 623.17–727.16 cm^{-1}, and 817.70–1031.83 cm^{-1} are due to stretching (bending =C–H and =CH_2), –CH deformation and –CH bending. The same bands were also found in the spectra of the formulations of lafutidien 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 lafutidine in individual and combination with polymers. The DSC thermograms showed well defined peaks for lafutidine in individual and combination with polymers. Drug showed one sharp endothermic peak occurred at 112°C. Formulations of lafutidine using HPMC K4M, HPMC K15M and HPMC K100M showed similar endothermic peaks at 102, 103 and 106°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.

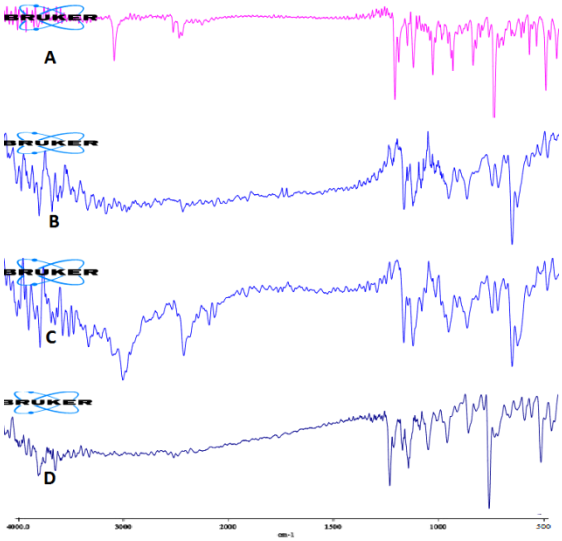

Fig.1: FTIR spectra of LAF (A) and formulations of HPMC K4M (B), HPMC K15M (C) and HPMC K100M (D)

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.

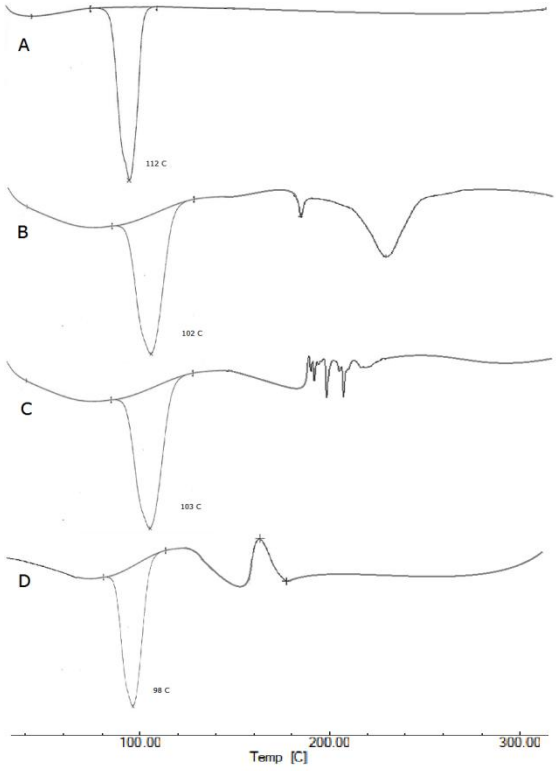

Fig. 2: DSC thermograms of lafutidine (A) and formulations of HPMC K4M (B), HPMC K15M (C) and HPMC K100M (D)

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 lafutidine exhibited a series of intense peaks at 10.23, 12.82, 13.12, 15.14, 17.81, 18.12, 19.24, 21.52, 22.34, 23.45, 24.44, 25.62, 27.12, 28.22 and 31.88 which were indicative of crystalline nature of lafutidine. As compared to lafutidine 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 lafutidine 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 0.346±0.87 to 0.490±0.32 gm/cm^3 and tapped density from 0.400±0.67 to 0.582±0.32 gm/cm^3.

Carr's index (Compressibility index)

Carr's index of the powder of all formulations ranged from 8.54% to 21.55%. Formulation LS8 showed lowest Carr's index indicating good and passable compressibility.

Haunsner's ratio

Hausner's ratio ranged between 1.14 and 1.20. The powder blend of formulation LS5 showed lowest Hausner's ratio indicating good flow. Blend of LS8 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 22.39±0.45° to 29.21±1.21°. The powder blend of LS5 had the lowest value among all formulations composition showing excellent flow. As per pharmacopoeial standards ranged in (25–30°) [23].

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

Table 2: Pre-compression flow properties of powder blends

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)±SD
LS1	0.490±0.32	0.582±0.32	15.81	1.19	27.92±0.32
LS2	0.472±0.54	0.568±0.54	16.90	1.20	29.21±0.21
LS3	0.425±0.67	0.512±0.21	16.99	1.20	27.42±0.12
LS4	0.420±0.89	0.535±0.23	21.50	1.27	26.11±0.33
LS5	0.440±0.90	0.495±0.34	11.11	1.13	22.29±0.24
LS6	0.452±0.21	0.512±0.54	11.72	1.13	28.37±0.54
LS7	0.406±0.32	0.500±0.65	18.80	1.23	25.25±0.76
LS8	0.439±0.34	0.480±0.76	08.54	1.09	24.69±0.65
LS9	0.375±0.45	0.478±0.88	21.55	1.27	22.39±0.45
LS10	0.386±0.56	0.465±0.89	16.99	1.20	28.99±0.34
LS11	0.394±0.67	0.450±0.09	12.44	1.14	29.10±0.23
LS12	0.346±0.87	0.400±0.67	13.50	1.16	28.00±0.12

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

Formulation code	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	FLT (min)	TFT (h)
LS1	4.1±0.02	201.12±0.24	0.20±0.010	100.14±0.13	1.08	>14
LS2	4.2±0.00	200.05±0.08	0.34±0.088	100.78±0.05	1.10	>14
LS3	4.2±0.025	210.55±0.28	0.36±0.078	100.78±0.15	1.12	>14
LS4	4.2±0.092	199.93±0.34	0.42±0.084	99.56±0.11	1.23	>14
LS5	4.3±0.022	199.03±0.91	0.28±0.011	99.99±0.10	1.18	>14
LS6	4.4±0.00	202.33±0.31	0.65±0.064	99.16±0.12	1.16	>14
LS7	4.5±0.025	200.55±0.28	0.55±0.098	99.78±0.15	1.18	>14
LS8	4.3±0.025	200.58±0.20	0.34±0.008	101.78±0.10	1.22	>14
LS9	4.3±0.092	199.03±0.04	0.40±0.054	98.96±0.91	1.63	>14
LS10	4.4±0.022	204.03±0.01	0.42±0.044	99.16±0.12	1.78	>14
LS11	4.5±0.032	200.93±0.34	0.51±0.024	99.56±0.11	2..12	>14
LS12	4.6±0.022	200.33±0.31	0.60±0.024	100.16±0.12	2.15	>14

FLT, floating lag time; TFT, total floating time

FORMULATION OF LAFUTIDINE 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 (7.5%) in the ratio of 1.0:0.7, were incorporated as a gas-generating agents. PVP-K30 (5%) and MCC (44.5%–59%) 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 lafutidine [24].

POST-COMPRESSION EVALUATION OF LAFUTIDINE 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 4.1±0.02 to 4.6±0.022 kg/cm^2. Hardness of the tablets was found to increase with an increasing of polymer concentration. 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 199.03±0.04 –204.03±0.01 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 0.28±0.011% and 0.60±0.024 % when tested using Roche friabilator. All batches of tablets passed the test and were within the limits of less than 1% 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 98.96±0.91 % to 101.78±0.10 % 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 (1.0:0.75) as gas forming mixture. Floating lag time of all formulations was found to be within the range 1.08–2.15 min and results are given in Table No.3. All formulations floated in the 0.1N HCl for more than 14 h showing good matrix integrity during this extended period of time. The results showed that as the concentration of HPMC polymer increased, the floating lag time decreased due to the increasing hydrophilic nature of the polymer allowing penetration of liquid through pores formed on the surface of the tablet. Sodium bicarbonate and citric acid reacts with acid to liberate CO_2, which gets trapped within the gel formed by hydration of polymer thus decreasing the tablet density to below 1 g/cm^3 [27].

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 LS1–LS12 is shown in Figs.3-5. Floating tablets prepared using HPMC K4M and HPMC K15M (LS1 to LS8) swelled rapidly at the beginning in 0.1 N HCl and could 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. The swelling index was calculated with respect to time. As time increases, the swelling index also increased, this is because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. The direct relationship was observed between swelling index and polymer concentration (HPMC), and as polymer concentration increases, swelling index was found to increase. Similar fashion was also reported by [28].

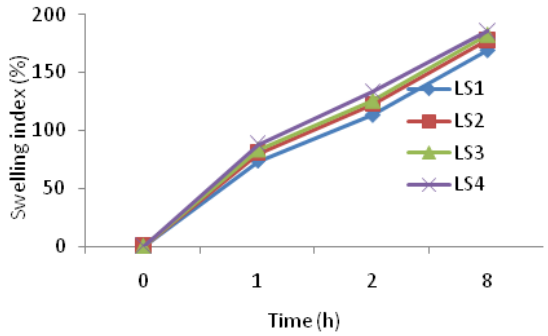

Fig. 3: Swelling studies of lafutidine floating tablets formulated with HPMC K4M

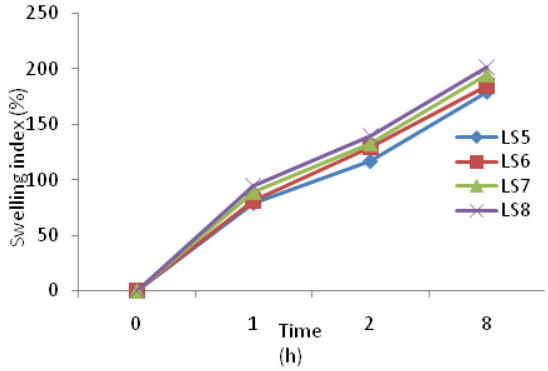

Fig. 4: Swelling studies of lafutidine floating tablets formulated with HPMC K15M

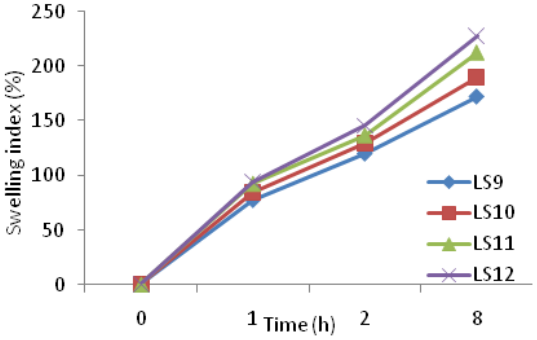

Fig. 5: Swelling studies of lafutidine floating tablets formulated with HPMC K100M

***IN VITRO* DISSOLUTION STUDIES**

In vitro dissolution studies of lafutidine floating tablet were evaluated in 0.1 N HCl (pH 1.2) for 8.5 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.

As the concentration of polymer HPMC was increases, the rate of release of drug from tablets were decreases. When concentration of HPMC was lower (10 mg) it released maximum drug but as concentration of HPMC increases (upto 40 mg) the rate of release drug consistently decreases at a constant time period. The amount HPMC in formulation was also found to be a key factor in terms of controlled drug release rate. It is widely known that high HPMC contents usually retard drug release by forming a viscous gel layer which will not only increase the diffusion path length but also the resistance to diffusion [29]. Thus, HPMC concentration was found to play a key role in modifying the drug release.

HPMC K4M floating tablet LS4 showed release of 99.36%, while HPMC K15M (LS8), HPMCK100M (LS12) formulated in the same concentration exhibited 96.99% and 94% drug release respectively at 8.5 h. This indicates there was also an influence of polymer viscosity on the release rate of the drug. High viscosity grade HPMC contents results in a greater amount of gel being formed. This gel increases diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug.

Formulation LS2 gave 98.92% drug release at 8.5th h fulfilling the aim of study and, hence, was selected as optimized batch.

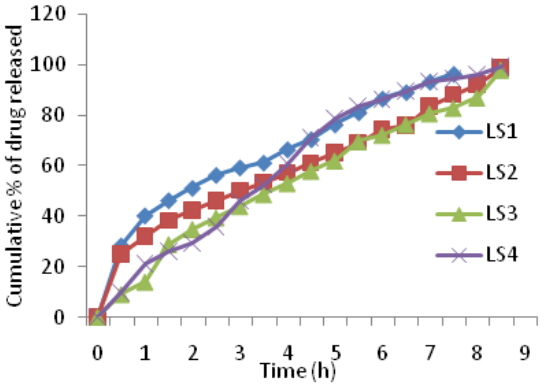

Fig. 6: *In vitro* drug release profiles of lafutidine floating tablets of HPMC K4M

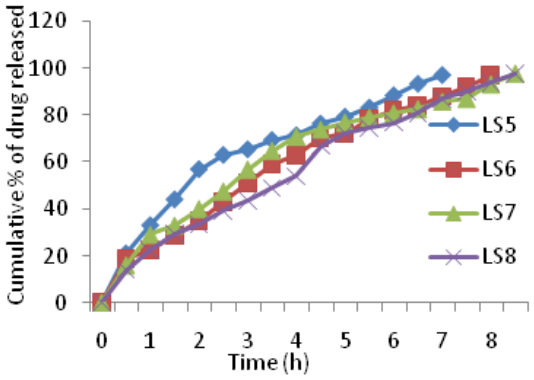

Fig. 7: *In vitro* drug release profile of lafutidine floating tablets of HPMC K15M

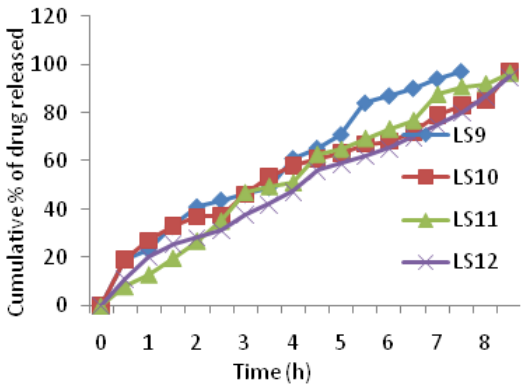

Fig. 8: *In vitro* drug release profile of lafutidine floating tablets of HPMC K100M

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.

Formulation LS2 (drug-polymer in 1:1 ratio) showed a minimum lag time (1 min 10 Sec) and maximum floating time (> 14h) with maximum drug release (98.99%±0.65% in 8.5 h). It also showed good linearity (R^2 of 0.995) which indicates zero order release with non-Fickian diffusion mechanism. Therefore, formulation LS2 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].

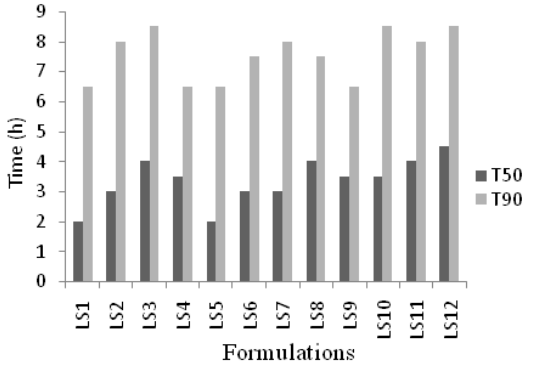

Fig. 12: T_{50} and T_{90} values of lafutidine floating tablets

STABILITY STUDIES

Based on floating lag time, floating time and *in vitro* drug release kinetics data, the formulation LS2 was optimized. The tablets of batch LS2 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.

Student t-test was conducted on drug content and floating lag time and the values obtained were 1.87 and 0.18 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 LS2, before and after stability studies are shown in Table 5 and Fig.13.

SIMILARITY STUDIES

Similarity factor (f_2) for LS2 optimized formulations compared before and after stability testing was found to be 50 (~ 70.088) 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.

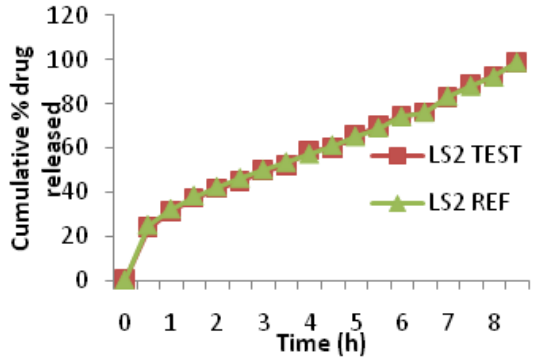

Fig. 13: Cumulative % of drug released vs time plots of formulation LS2 before and after stability studies

Table 5: Stability studies of optimized formulation LS2

Storage conditions	Drug content (%±sd)	FLT (min±sd)
Reference (LS2)	100.78±0.05	1.10±0.20
Test (40±2^0 C/75±5% RH, 3 months)	100.10±00.89	1.11±0.12
t-test value	1.87	0.18

FLT, floating lag time; n=3

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

Formulation Code	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
LS1	2.0	6.5	0.986	11.687	0.925	0.318	0.974	0.988	0.454
LS2	3.0	8.0	0.995	08.492	0.899	0.258	0.937	0.990	0.490
LS3	4.0	8.5	0.980	10.179	0.976	0.245	0.939	0.992	0.471
LS4	3.5	6.5	0.961	11.687	0.955	0.405	0.927	0.976	0.636
LS5	2.0	6.5	0.935	10.330	0.945	0.345	0.983	0.953	0.516
LS6	3.0	7.5	0.979	10.679	0.969	0.316	0.980	0.964	0.714
LS7	3.0	8.0	0.933	09.343	0.972	0.295	0.979	0.964	0.568
LS8	4.0	7.5	0.985	10.493	0.937	0.320	0.980	0.993	0.705
LN9	3.5	6.5	0.986	11.631	0.899	0.337	0.963	0.986	0.725
LN10	3.5	8.5	0.983	08.699	0.965	0.212	0.988	0.989	0.588
LN11	4.0	8.0	0.984	11.254	0.930	0.212	0.959	0.981	0.759
LN12	4.5	8.5	0.993	09.729	0.929	0.212	0.958	0.989	0.664

CONCLUSIONS

Preformulation studies reveals that the lafutidine and HPMC polymers are compatible, precompresion results are excellent to proceed further for formulation development of lafutidine floating tablets, post compression evaluation parameters evidenced the benchmark results for the LS2 formulation prepared with (1:1 drug : polymer) (2:1 ; sodium bicarbonate:citric acid-gas generating agent) ratios with a zero order kinetics with % drug released at 8.5th h was found to be 98.99±0.65, drug contenet 100.78±0.05. The swelling index to the optimized formulation was 194 % with floating lag time 1.10 and total floating time >12 h. Henceforth from this part of the research it can be concluded that LS2 with a similarity factor f_2 70.088 after stability study can be further evaluated in vivo for it robustness in the biological systems then scaled up to validate its industrial applicability and as a promising floating drug delivery system.

Micro Crystalline Cellulose (Avicel PH 101), in this formulation is used as a diluent, it also imparts superior flow properties and enhances powder compaction in during compression. Moreover it is reported that microcrystalline cellulose is capable of swelling in contact with aqueous fluids due to its water soluble property, it also imparts in pore formation in the tablets disc that leads to entry of aqueous fluid then the increased released at a short time, therefore the maximum release of drug in this investigation was at 8.5h due to increase amount of MCC in the formulations.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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