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FORMULATION AND EVALUATION OF FLOATING TABLET OF FAMOTIDINE BY SOLID DISPERSION METHOD

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Abstract: The present study reports the development and in vitro evaluation of gastro retentive floating tablets of Famotidine. The formulations were developed using cellulose derivatives such as HPMC K4M, HPMC K15M in different ratios with gas generating agents and other excipients by of solid dispersion method (solid dispersion formulate by melting method). The formulations were subjected to various evaluation parameters in vitro, viz., hardness, friability, uniformity of drug content, in vitro floating studies, in vitro dissolution studies, All the formulations were good in appearance and showed better physical and mechanical properties. Formulation F6 containing HPMC K4M 2.023 gm, Sodium bicarbonate 0.225 gm and carbopol 1.25 gm was found to be the best formulation in terms of drug release and in vitro buoyancy time and was subjected to stability studies and IR spectroscopy .The results indicate that the formulation was stable and there was no chemical interaction between the polymer and the drug.

Keywords: Famotidine, solid dispersion, buoyancy, IR spectroscopy.

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INTRODUCTION

Famotidine is a histamine-2 blockers. Famotidine works by decreasing the amount of acid the stomach produces. Famotidine is used to treat and prevent ulcers in the stomach and intestines. It also treats conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome. Famotidine also treats gastroesophageal reflux disease (GERD) and other conditions in which acid backs up from the stomach into the esophagus, causing heartburn. This system is particularly important for the drugs which have higher absorption rate in a particular region of gastrointestinal tract[1]. Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol. A dosage form which can retain Famotidine at its absorption site for an extended period will increase its absorption and bioavailability[2].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability.

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Ranbaxy Laboratories Pvt Ltd, Gurgaon. Carbopol-934 Gifted by Colorcon Asia Pvt Ltd, Verna, Goa India. HPMC K4 100 Gifted by Colorcon Asia Pvt Ltd, Verna, Goa. PEG 4000- CDH, India. Ethanol, propanol, butanol, methanol, chloroform, sodium hydroxide, potassium hydroxide, sodium bicarbonate and all other required chemicals obtaine from CDH India.

Method

Solid dispersion method: Preparation of solid dispersion by melting method

In melting or fusion method of preparation, polymer PEG 4000 at 55 ^{0}C in china-dish was heated to a temperature. Just above melting point and then drug was incorporated into matrix. The mixture was then cooled with constant stirring in ice bath, to disperse the drug throughout the matrix homogenously. The solidified mass of drug-polyethylene glycol polymer system was often found to require storage of one or more days in vacuum desiccators for hardening and case of powdering. The final mass is then crushed, pulverized and sieved by 40no. mesh.

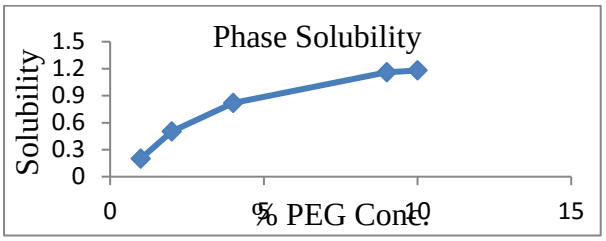
S.NO	Preparation	Drug content	Polymer PEG conc./Ratio
1	Melting method	1	1
2	Melting method	1	2
3	Melting method	1	3
4	Melting method	1	9

Table 1: Different formulation prepared of solid dispersion.

Characterization of Solid Dispersion

1. **Phase Solubility:**

Figure 1: Phase solubility curve for the drug.



2. Drug Content Estimation:

S.NO.	Formulation code	% Drug content
1	FS-0	99.71±0.89
2	FS-1	98.31±0.76
3	FS-2	99.67±1.25
4	FS-3	97.12±0.11
5	FS-4	96.46±0.36
6	FS-5	96.32±0.29

[a]Mean ± S.D. (n=3)

Table 2 : % Drug Content in solid dispersion.

Characterization of solid dispersion formulation

1. Differential Scanning Calorimetric (DSC) Study:

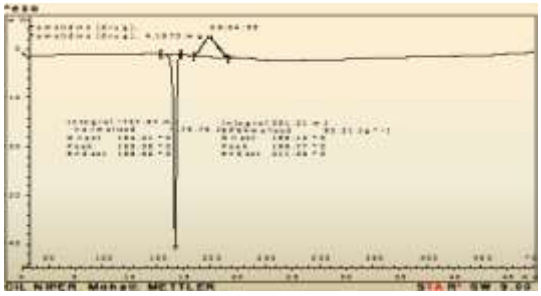


Figure: DSC analysis of Famotidine

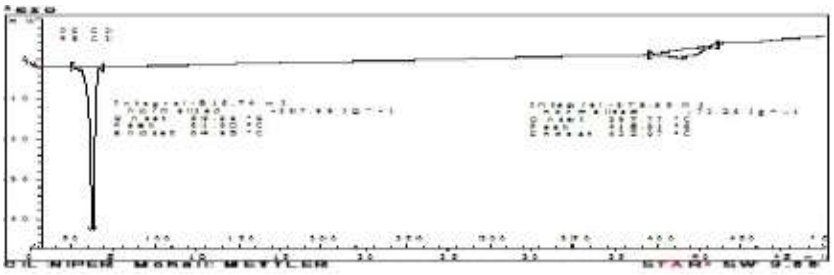
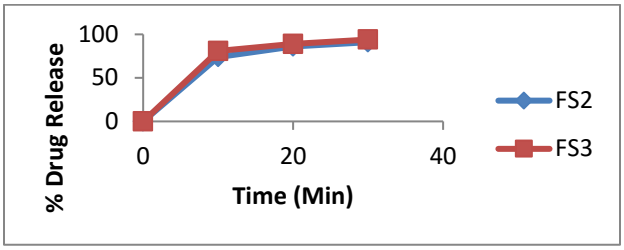


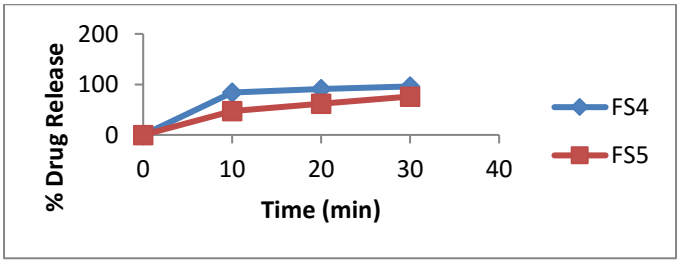
Figure: DSC analysis of polymer PEG 4000.

S.NO.	DSC	Peak Observed
1	Famotidine	168ċ
2	PEG 4000	62ċ
3	Formulation	168ċ, 62ċ

Dissolution Studies:

S.NO.	Time (min)	FS 0	FS 1	FS 2	FS 3	FS 4	FS 5
1	0	0	0	0	0	0	0
2	10	24.21±1.43	71.28±1.98	74.21±1.98	81.78±1.56	84.68±1.56	47.38±2.32
3	20	32.3±2.31	84.45±3.12	86.75±2.35	89.78±2.34	91.68±3.12	62.32±2.13
4	30	42.45±2.13	89.03±2.34	91.45±3.12	94.89±2.56	96.78±3.12	76.47±2.13





EVALUATION OF GRANULES:

Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plan.

$$\tan\theta = H / R$$

$$\theta = \tan^{-1}(H / R)$$

Flow Rate: Flow rate of a powder has been defined as the rate at which the particular mass emerges through the office of funnel of a suitable diameter

$$\text{Flow Rate} = \frac{\text{Weight of granules}}{\text{Time in seconds}}$$

Bulk Density: The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. It was calculated by using equation below-

$$D_f = M/V_p$$

Where

D_f = bulk density

M = weight of samples in grams

V_p = final volumes of granules in cm^3

Tapped density: The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. It was calculated by using equation given below:

$$D_o = M/V_p$$

Where

D_o= bulk density

M = weight of samples in grams

V_p = final volumes of granules in cm^3

Carr's Index: An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\% \text{ compressibility} = \frac{D_f - D_o}{D_f} \times 100$$

Where,

D_f = Fluff or Poured bulk or bulk density.

D_o = Tapped or Consolidated bulk density. .

S.No.	Formulation Code	Angle of repose [a]	Flow Rate[a]	Bulk Density [a]	Tapped Density [a]	Carrs Index [a]
1.	FS-1	33.69±.20	1.21±.01	0.68±.04	0.83±.06	21.86
2.	FS-2	34.77±.30	1.17±.02	0.83±.03	0.93±.04	12.05
3.	FS-3	35.67±.20	0.94±.02	0.76±.02	0.89±.06	16.70
4.	FS-4	34.80±.30	0.97±.08	0.72±.01	0.91±.O5	24.72
5.	FS-5	32.45±.10	1.17±.02	0.87±.02	0.93±.03	7.58
6.	FS-6	35.10±.20	0.94±.02	0.68±.02	0.98±.O5	23.57

[a]Mean ± S.D.(n=3)

Table : Evaluation of solid dispersion granule

Preparation of floating tablet by solid dispersion:

For each formulation (Fl to F6), solid dispersion. The homogenous blend of granule was then compressed[2] in to tablets on a single punch tablet press.

S. NO.	Ingredients (gm)	FL-1	FL-2	FL-3	FL-4	FL-5	FL-6
1	Solid dispersion	1.6	1.6	1.6	1.6	1.6	1.6
2	HPMC K4M	2.023	4.063	-	2.023	-	4.063
3	HPMC 15M	2.023	-	4.063	2.023	4.063	-
4	Carbopol 934	0.938	0.938	0.938	1.25	1.25	1.25
5	Lactose	0.938	0.938	0.938	0.938	0.938	0.938
6	Sodium bicarbonate	0.025	0.025	0.025	0.025	0.025	0.025

*Each formulation contains Magnesium Stearate 25mg & Talc 2%.

Table: Different formulation of floating tablet.

Evaluation of Tablets:

Weight variation [4,5]Tablet Thickness and Diameter:

Thickness and diameter were measured using Verniers Calipers.

S. No.	Formulation code	Average weight [a]	Thickness [a]	Diameter [a]
1.	FL-1	258.13±1.32	5.96±0.46	9.00±0.002
2.	FL-2	252.8±1.73	6.08±0.02	9.03±0.004
3.	FL-3	253.4±1.72	6.00±0.12	9.03±0.004
4.	FL-4	251.6±0.04	5.93±0.50	9.02±0.003
5.	FL-5	250.4±0.86	5.61±0.11	9.03±0.003
6.	FL-6	250.2±0.50	5.80±0.08	9.02±0.001

[a]Mean ± S.D. (n=3)

Table: *In-vitro* evaluation of the tablet.

Tablet Hardness:

The hardness of tablet of each formulation was measured by Monsanto Hardness Tester. The hardness was measured in items of kg/cm^2.

S.No	Formulation code	Hardness [a]
1.	FL-1	**4.6±0.74**
2.	FL-2	**5.5±0.82**
3.	FL-3	**5.6±0.46**
4.	FL-4	**4.8±0.31**
5.	FL-5	**4.7±0.41**
6.	**FL-6**	**4.6±0.28**

[a]Mean ± S.D. (n=3)

Friability:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure

S.No	Formulation code	Friability [a]
1.	FL-1	0.04± .002
2.	FL-2	0.03± .003
3.	FL-3	0.05± .029
4.	FL-4	0.08± .059
5.	FL-5	0.06± .052
6.	FL-6	0.03± .016

[a]Mean ± S.D. (n=3)

Table: Friability of different formulation.

Uniformity of Content:

This test was applicable to tablets that contain less than 10 mg or less than 10% w/w of active ingredient.

S.NO	Formulation code	% Drug content [a]
1.	FL-1	98.03±1.22
2.	FL-2	98.41±1.32
3.	FL-3	98.68±.962
4.	FL-4	98.69±1.68
5.	FL-5	98.73±.255
6.	FL-6	97.27±.316

[a]Mean ± S.D. (n=3)

Table: % Drug content of different formulation.

Floating Time[6]:

Floating time was the time, the tablet floats in dissolution medium including floating lag time.

S.No	Formulation Code	Tablet Floating Time(hrs) [a]
1.	FL-1	25.3±1.69
2.	FL-2	29.5±2.86
3.	FL-3	23.8±1.27
4.	FL-4	24.2±1.93
5.	FL-5	23.2±1.62
6.	FL-6	31.3±1.94

[a]Mean ± S.D. (n=3)

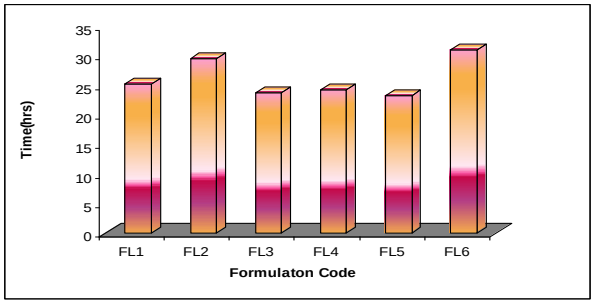


Figure: Floating time of different formulation.

Swelling Characteristics:

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution medium, in 900 ml of 0.1 N HCl at 37± 0.5^{0}C. The tablets were removed periodically from dissolution medium. After draining free water these measured for weight gain, thickness and diameter. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation,

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the table}} \times 100$$

Formulation Code	Avarage weight	Thickness	Diameter	Final weight	Final Thickness	Final Diameter	Swelling Index
FL1	258.13±2.13	5.96± 0.56	9.00±0.10	595.46±5.67	7.10±2.33	16.40±1.43	130.62
FL2	252.16±2.32	6.08±0.12	9.03±.015	611.47±3.98	7.21±1.78	16.43±1.66	142.46
FL3	253.13±2.13	6.00± 0.19	9.03±0.11	510.45±4.56	7.26±2.33	16.12±3.52	98.65
FL4	251.87± 2.18	5.93± 0.34	9.02± 0.015	576.90±5.23	6.99±2.77	16.39±3.19	129.60
FL5	250.98± 2.17	5.61± 0.23	9.03±0.02	537.20±5.56	7.12±3.23	16.35±2.12	114.80
FL6	250 .67± 3.12	5.80±0.50	9.02±0.01	611.23±4.66	7.02±2.65	16.48±2.13	153.20

a Mean ± S.D. (n=3)

Table: Final weight, thickness, diameter, swelling index of different formulation

Dissolution Studies[7]:

The release rate of Famotidine from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5^{0}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these

solutions was measured at 266 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

S.No	Requirement	Specification
1.	Apparatus	USP Type II
2.	Volume of medium	900 ml
3.	Temperature	37^0C
4.	Paddle Speed	50 rpm
5.	Dissolution medium used	0.1 N HCl
6.	A liquid taken at each time interval	10 ml

Table: Details of Dissolution Test:

Stability Testing of Floating Tablet[8,9]:

The stability of prepared tablet from formulation FL-1 toFL-6 containing solid dispersion, HPMC of different grade, K4M, K15M, carbopol, lactose, sodium bicarbonate, magnesium stearate ,talc was investigated at 40 ^{0}C in both opened and closed HDPE bottles for 30 days. The release rate of Famotidine was calculated for both conditions.

S. No.	Formulation	%Drug content [a] Closed Container(FC)	%Drug content [a] Open Container(FO)
1.	FL-1	94..41± 1.32	93.90±1.92
2.	FL-2	94.79± 0.92	94.02±1.39
3.	FL-3	93.21± 1.68	92.80±1.60
4.	FL-4	94.73±0.25	93.68±2.16
5.	FL-5	92.67±3.10	92.11±1.12
6.	FL-6	92.83±1.79	92.27±1.97

[a]Mean ± S.D. (n=3)

Table: % Drug content after 30 days in container.

CONCLUSION

In conclusion a single unit, floating drug delivery system has been developed, which is based on simple lipid Carbopol 934,HPMCK4M, HPMC 15M,. It's *in vitro* floating performance and the ability to control drug release over prolonged periods of times have been demonstrated. The drug release patterns can effectively be adjusted by varying sample formulation parameters, tablet thickness and diameter, type of matrix forming polymer, addition of water-soluble and water in-soluble fillers, and the use of polymer blends. Thus, desired release profile adapted was achieved in sustaining the effervescent based floating drug delivery in gastro retentive dosage form of famotidine.

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