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Design and Characterization of Famotidine Effervescent Gastric Floating Matrix Tablets

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ABSTRACT

The present study was done to increasing gastric residence time; the objective of present study was to formulate a floating tablet of famotidine by using the different polymers carbopol, HPMC and chitasan by direct compression method. Fourier transformation infra-red studies are indicating that, there are no drug interactions. Solubility profile of famotidine indicating that freely soluble in glace acetic acid. The floating tablets are evaluated for the bouncy, in vitro dissolution, drug content and stability studies. The optimized formulation showing good floating lag time 51 sec and physical property and "floating" time about 12 hours. Effect of the polymers and drug release from tablet pattern was studied. The drug release from the F_8 formulation with HPMC, carbapol and chitason. The drug released from tablet was 99.85% and zero order 99.85% was conformed. Stability, dissolution profile in 3 months was conformed.

Key words: *Famotidine, Carbopol, HPMC, and Chitason*

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached [1].

Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease [5].
Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form[2], making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine [3].

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MATERIALS AND METHODS

The drug was brought from Zydus Cadila Pharmaceuticals, polymer brought from Comprime Laboratories and analytical grade chemicals were used for the study [6].

Preformulation Studies:

Colour and Appearance, Melting Point, Solubility, UV Spectral Analysis (Water, 0.1Hcl, Phosphate buffer pH 7.4, Phosphate buffer pH 6.8 containing rat caecal contents) Infrared Spectrum and Loss on drying. Drug - Polymers Compatability Studies (FTIR and DSC). Evaluation of Micromeritic Properties of Granules (Angle of Repose, Bulk Density and Tapped Bulk Density, Carr's Compressibility Index and Hausner's ratio).

Formulatin and Evaluation Methods:

Formulation of Tablets (Wet granulation method). Evaluation of Tablets Properties of Tablets – Appearance, Size and Thickness, Hardness, Friability, Weight variation, Content uniformity, floating Index of Tablets, *In-vitro* Drug Release Studies , Kinetics of *In-vitro* Drug Release (Zero order, First order, Higuchi and Korsmeyer Peppas) and Stability Studies.

1. Drug and polymers pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add diluents and other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 10 mm round punches.

RESULTS AND DISCUSSION

Color appearance:

The drug colour is "white to yellow powder" as same as the reported reference.

Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed melting point is 161-163 ºC.

Result:

The value of compressibility index above 25%, 15-25%, less than15% indicates poor flow ability, optimum flow ability and

high flow ability respectively. As Famotidine value is more than 25% it exhibits good flow.

Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

Table No. 1: Composition of Famotidine Floating Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	20 mg	20mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Chitosan	20 mg	40 mg	---	---	---	---	---	20 mg	20 mg
Carbopol 934	---	---	20 mg	40 mg	---	---	20 mg	---	20 mg
HPMC K15 M	---	---	---	---	20 mg	40 mg	20 mg	20 mg	---
Sodium bi- carbonate	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25mg	25 mg	25 mg
Micro Crystalline Cellulose	80 mg	60 mg	80 mg	60 mg	80 mg	60 mg	60 mg	60 mg	60 mg
Megnesium stearate	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Talc	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Total Weight	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

Table No. 2: List of Micromeritic properties of directly compressible powder

Formulation	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Angle of repose(θ)	Carr's Index (%)	*Hausner's* ratio
F1	0.40	0.47	21.5	14.89	1.17
F2	0.41	0.46	20.1	12.1	1.12
F3	0.41	0.47	19.6	12.7	1.14
F4	0.41	0.45	20.1	8.8	1.09
F5	0.39	0.45	21.3	13.3	1.15
F6	0.38	0.46	19.5	17.3	1.21
F7	0.37	0.43	19.2	13.9	1.16
F8	0.41	0.46	17.5	10.8	1.12
F9	0.40	0.45	21.9	11.1	1.12

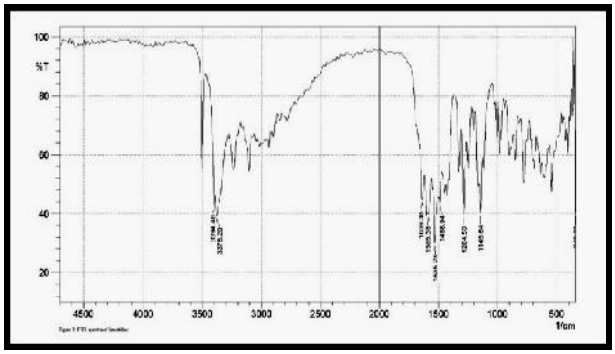

Fig. 1: FT-IR Sample for Famotidine (Pure Drug)

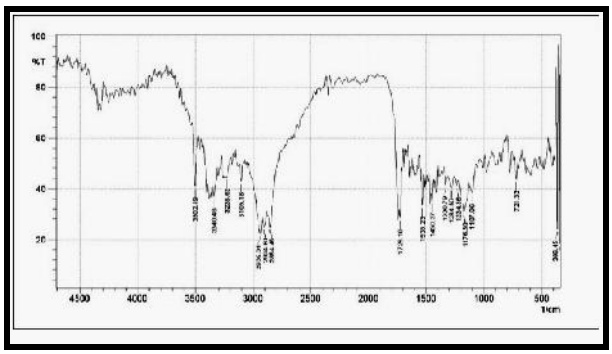

Fig. 2: FT-IR Sample for Optimized Formulation F-1

Calibration of Standard Graph of Famotidine:

Construction of Calibration curve of model drugs by UV-Visible spectroscopy:

Preparation of Standard stock solutions:

Famotidine equivalent to 100 mg was weighed and transferred to 100 ml volumetric flask, dissolved in methanol and the final volume was made upto 100ml with 0.1N HCL. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as "stock solution A". From the stock solution A, 1 ml was pipette out in 10ml volumetric flask and the final volume was made up to 10ml with 0.1N HCL. The resulted solution had the concentration of 0.1mg/ml (100µg/ml) which was labeled as "stock solution B". This stock solution B is used as working stock solution for further study. Further dilutions were prepared from the same solution [6].

Preparation of Standard solutions:

From the stock solution B, further dilution was made with 0.1N HCL in 10 ml volumetric flasks to get the solutions in the range of 2-10 µg/ml concentration and absorbance was recorded at 265nm against suitable blank using UV-Spectrophotometer (UV-1601, Shimadzu, Japan). A calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10µg/ml. The Regression equation and correlation coefficient was determined.

Table No. 3: Standard graph of Famotidine in 0.1 N HCl at λ_{max}= 265nm

S. No.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.130
3	4	0.250
4	6	0.380
5	8	0.510
6	10	0.640

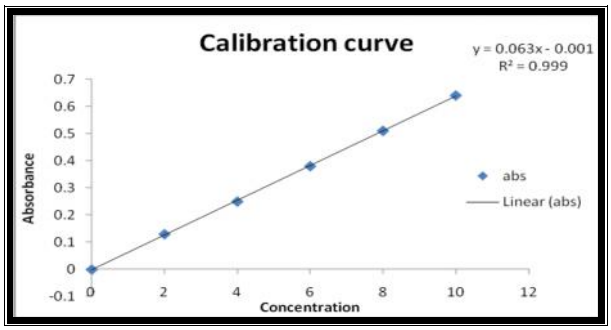

Fig. 3: Standard graph of Famotidine

Evaluation of the Prepared Tablets for Physical Parameters:

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeia limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table No. 4: Results for Evaluation parameters of all formulations

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	150± 0.004	149± 0.005	148± 0.004	150± 0.005	150± 0.004	149± 0.004	150± 0.005	149± 0.004	150± 0.004
Thickness (mm)	1.5±0.4	1.6±0.4	1.3±0.4	1.6±0.4	1.5±0.4	1.5±0.3	1.5±0.4	1.5±0.1	1.5±0.2
Hardness (kg/cm²)	8.9±1.4	7.4±1.2	8.2±1.2	6.9±0.9	8.4±1.9	8.1±1.7	8.2±1.5	8.3±1.6	8.2±1.4
Friability	0.22% ±0.2	0.26% ±0.23	0.25% ±0.19	0.25% ±0.26	0.25% ±0.22	0.22% ±0.1	0.21% ±0.4	0.21% ±0.5	0.21%± 0.7
Assay	99.68% ±0.2	99.84% ±0.4	99.87% ±0.3	98.88% ±0.2	99.88% ±0.3	99.89% ±0.2	99.88% ±0.2	99.91% ±0.2	99.88% ±0.2
Floating lag time (sec)	39	42	43	34	42	41	36	51	41

Floating lag time:

The floating tablets of Famotidine were prepared by using Chitosan, HPMC K15M, and Carbopol 934. Nine different formulations were prepared using different ratios of polymers the floating lag time of the optimized formulation F-8 was 51 sec.

In vitro Dissolution studies:

The dissolution conditions used for studying the drug release from tablet of Famotidine are:

Apparatus : USP apparatus II (Paddle)
Agitation speed (rpm) : 50rpm
Medium : 0.1N HCl
Volume : 900 ml
Temperature : 37.0 ± 0.5 C
Time : 1, 4, 6, 8, 10, 12 hrs.
Wavelength : 265nm

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 265nm.

Table No. 5: Results of Dissolution profile for F1-F9

Time (Hrs)	%Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	23.49	18.65	17.98	15.56	21.24	18.57	19.66	18.78	21.89
4	45.78	34.92	26.91	23.68	35.78	34.67	39.73	37.94	34.78
6	49.48	47.93	51.24	56.98	46.48	47.89	49.48	64.68	53.48
8	83.18	89.72	73.97	79.97	73.18	77.89	81.18	87.98	82.18
10	95.94	95.92	98.92	96.15	97.94	97.96	96.94	94.59	92.94
12	99.36	98.83	99.13	98.99	98.56	99.34	99.16	99.85	99.32

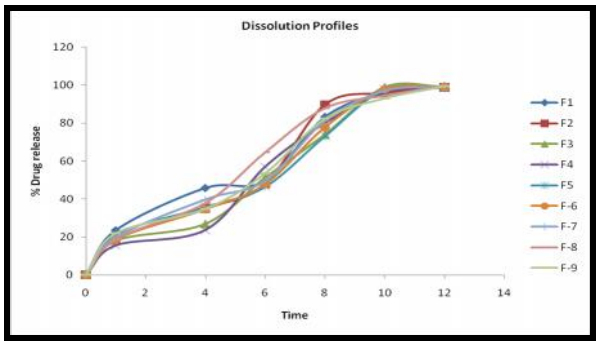

Fig. 4: Standard graph of Dissolution profile for F1-F9

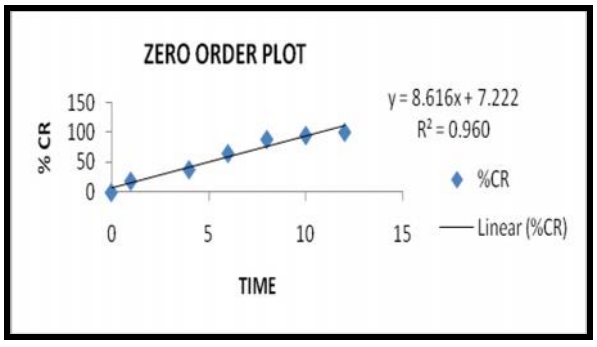

Fig. 5: Zero Order Plot for Optimized Formulation

Kinetic Models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table No. 6: Zero-Order Kinetics

S. No.	TIME (Hrs)	%CR
1	0	0
2	1	18.78
3	4	37.94
4	6	64.68
5	8	87.98
6	10	94.59
7	12	99.85

Table No. 7: First order kinetics

S. No.	TIME (Hrs)	LOG% DRUG RETAINED
1	0	2
2	1	1.909663
3	4	1.792812
4	6	1.548021
5	8	1.079904
6	10	0.733197
7	12	-0.82391

Fig. 6: First Order Plot for Optimized Formulation

Table No. 8: Higuchi Model

S. No.	Square root of Time	%CR
1	0	0
2	1	18.78
3	2	37.94
4	2.44949	64.68
5	2.828427	87.98
6	3.162278	94.59
7	3.464102	99.85

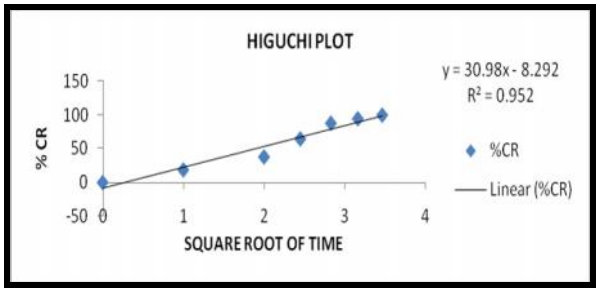

Fig. 7: Higuchi Plot for Optimized Formulation

Table No. 9: Kore smayer Peppas equations

S. No.	log T	log %CR
1	#NUM!	0
2	0	1.273696
3	0.60206	1.579097
4	0.778151	1.81077
5	0.90309	1.944384
6	1	1.975845
7	1.079181	1.999348

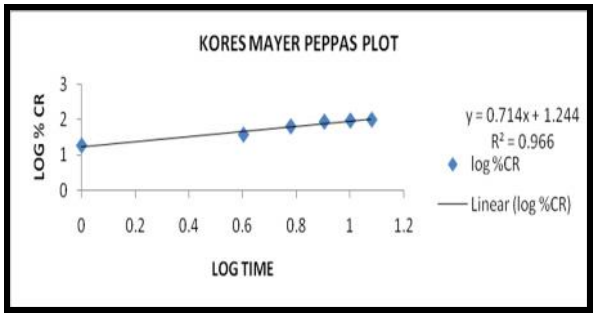

Fig. 8: Kores Mayer Peppas Plot for Optimized Formulation

Table No. 10: Hixon Crowell erosion equation

S. No.	TIME	CUBE ROOT OF %DRUG REMAINING
1	0	4.641
2	1	4.33
3	2	3.95
4	4	3.281
5	8	2.29
6	10	1.755
7	12	0.531

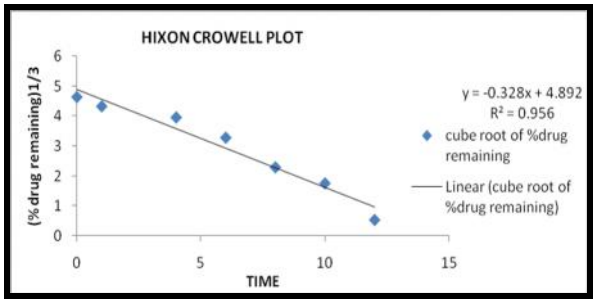

Fig. 9: Hixon Crowell Plot for Optimized formulation

Stability Study:

There was no significant change in physical and chemical properties of the tablets of formulation F-8 after 3 Months. Parameters quantified at various time intervals were shown;

Table No. 11: Results of stability studies of optimized formulation F-8

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F8	**25⁰C/60%RH % Release**	99.85	99.84	99.84	99.83	Not less than 85 %
F8	**30⁰C/75% RH % Release**	99.85	99.84	99.83	99.83	Not less than 85 %
F8	**40⁰C/75% RH % Release**	99.85	99.84	99.84	99.83	Not less than 85 %
F8	**25⁰C/60% RH Assay Value**	99.91	99.89	99.89	99.89	Not less than 90 % Not more than 110 %
F8	**30⁰C/75% RH Assay Value**	99.90	99.89	99.89	99.89	Not less than 90 % Not more than 110 %
F8	**40⁰C/75% RH Assay Value**	99.92	99.89	99.89	99.89	Not less than 90 % Not more than 110 %

Table No. 12: Stability dissolution profile of F-8 for 1st, 2nd & 3rd months

S .No.	TIME(Hrs)	F-8 1M	F-8 2M	F-8 3M
1	**0**	0	0	0
2	**1**	18.76	18.76	18.75
3	**4**	37.94	37.94	37.93
4	**6**	64.68	64.68	64.68
5	**8**	87.97	87.96	87.96
6	**10**	94.57	94.54	94.53
7	**12**	99.84	99.84	99.83

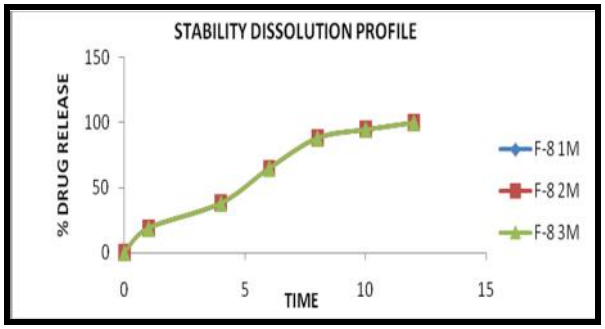

Fig. 10: Stability dissolution profile of F-8 for 1st, 2nd& 3rd months

SUMMARY AND CONCLUSION

The objective of the present study is to develop Floating tablets of Famotidine. In this present study an attempt was made to increase the GI residence time of Famotidine, as the drug is having less gastric residence time, by formulating in to Floating tablets.

Systematic studies were conducted using different concentration of rate releasing polymer HPMC, carbopol and chitosan for extending the drug release in upper GIT. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, pre formulation studies to find out the micromeritic properties to assess flow ability, compressibility properties and solubility studies. And all the formulations gave good results for above pre formulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, buoyancy, content uniformity, all the formulations were found within the permissible range.

Finally it was concluded that:

Among all the formulations (F1-F9), it was observed that formulation-8 has shown better buoyancy and dissolution profile. So Formulation-8 was found to be the best formulation among others.

The kinetic treatment of the drug release data of the prepared formulations followed first order drug release; the prepared formulations followed Hixon Crowell profile. It indicated that drug release was dissolution controlled and directly proportional to cube root of time. Hence ***F8*** was considered as formulation extending **99.85%** of drug was released at the end of 12 hrs. The stability studies were carried out for period of 3 months as per ICH guidelines and were in acceptable limits.

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