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Research Article

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Formulation and evaluation of famotidine floating microsphere in cost effective and simple technique

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Abstract
The purpose of this research was to prepare a floating drug delivery system of famotidine. The floating microspheres can be prepared for the improvement of absorption and bioavailability of famotidine by retaining the system in the stomach for prolonged period of time. Floating microspheres of Famotidine were prepared using different polymers like ethyl cellulose, hydroxypropyl methylcellulose, eudragit by emulsion solvent evaporation / emulsion solvent diffusion method. These formulations were subjected to various evaluation parameters in vitro, viz, hardness, friability, uniformity of content, in vitro floating studies, in vitro dissolution studies, all the formulations were good in appearance and showed better physical and mechanical properties. Formulation F4 containing Poly ethylene oxide and famotidine in the ratio of 1:2 and also the Formulation F10 containing Eudragit & Famotidine in the ration of 1:2 was found to be the best formulation in terms of drug release and was subjected for IR and stability studies.The results indicated that the significant effect was observed of increased polymer concentration, on said parameters in each case. The results indicated that the significant effect was observed of increased polymer concentration, on said parameters in each case.
Key words: Famotidine, Eudragit, floating microspheres Poly ethylene oxide, In vitro dissolution studies, IR spectroscopy.

Introduction

One of the most viable approaches for achieving a prolonged and predictable drug delivery in the Gastro intestinal tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form which reside in the stomach for a longer period of time than conventional dosage forms[1]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydro dynamically balanced systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.[2] Microspheres drug delivery systems made from the natural, biodegradable polymers have attracted several researchers for last decade in sustaining the drug delivery3. Microspheres have varied applications and are prepared using various polymers. However, the success of microspheres is limited due to their short residence time at the site of absorption/action4. High density microspheres provide an increased residence time by making them to sink in gastric fluid. This can be achieved by coupling high density materials which has higher density than gastric fluid5. High density systems have advantages like increased gastric residence time and specific targeting of drugs at the absorption site, efficient absorption and enhanced bioavailability6,7.

Gastro retentive floating drug delivery technology is one of the promising approach for enhancing the bioavailability and controlled delivery of drugs that exhibit narrow absorption window 8. These drug delivery systems have been shown to possess better efficacy in controlling the release rate for drugs with site specific absorption 9. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach and involve the mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract[10-12]. Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage

forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism. [13,14] . Famotidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease (dose is 20 mg by mouth twice daily for 6 to 12 weeks). The low bioavailability (40-45%) and short biological half life (2.5-4.0 hours) of famotidine, following oral administration favors development of a sustained release formulation[15-20]

Materials and Methods

Materials:

Famotidine was received as a gift sample from Vasava Pharma Private Limited, Hyderabad.Poly Ethylene Oxide & Eudragit are purchased from Merk. All other ingredients, reagents and solvents were of analytical grade.

Methods:

Floating microspheres of Famotidine were prepared using different polymers like ethyl cellulose, hydroxypropyl methylcellulose, eudragit by emulsion solvent evaporation / emulsion solvent diffusion method using Eudragit as a polymer. Drug and polymer in the proportion of 1:1, 1:2, 1:3, 1:4 and 1:5 were dissolved in 1:1 mixture of solvent system of ethanol and dichloromethane. This solution is dispersed in a solution of distilled water (200ml) and span 80 (0.02%) which was maintained at a temperature of 40 degrees and stirred for 30 mins. the microspheres were separated by filtration and were washed with water twice and were dried.Table 1 gives the details of the various formulations.

Evaluation of microspheres:

Preformulation Studies

1) Flow Properties determination: Certain methods are used to measure granulation and powder characteristics in order to monitor granulation suitability for tableting. Good flow properties are essential for the transport of the material through the hopper into and through the feed frame and in to dies.

2) Angle of repose: The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the granules and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

$$\tan \theta = h/r$$

Therefore $$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Determination of Bulk Density, tapped density:15 gms of Drug-x was taken in 50 ml measuring cylinder which was placed in Electro lab Tapped Density Apparatus(method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tapings were repeated. No difference was noted between the volumes between two tapings (500 and 750). The final volume (V) was considered after completion of 750 taps. The values obtained are reported in the table

Post Formulation Studies:

a) Shape of tablets :

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet.2

b) Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier calliper. Three tablets of each formulation were picked randomly and thickness was measured individually.11

c) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester .It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.16

d) Friability Test:

The friability of tablets was determined by using vergo friabilator. It is expressed in percentage (%). It is expressed in percentage (%). Ten tablets were initially weighed (wI) and transferred into friabilator. The friabilator was operated at 25 rpm or run up to 100 revolutions. The tablets were weighed again(wF).The friability was then calculated by

%F=100(1-W I/W F)

% Friability of tablets less than 1% was considered acceptable.20

e) Weight variation Test :

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopeia. The following percentage deviation in weight variation was allowed.9,38

f) Floating Time Studies:

The buoyancy lag- time of the tablets was studied at 37±0.5°C, in 100 ml of 0.1N HCl. The time required for the tablet to rise to the surface and float was taken as the buoyancy lag- time. The duration of floating is known as floating time.4

g) In Vitro Dissolution studies:

Apparatus: Dissolution apparatus IP Type II(paddle)

Speed :5o rpm

Min. temp : 37 ± 0.5°c

Sample preparation:

One tablet each were placed in 6 – dissolution bowls. Then the apparatus was runned and the sample was withdrawn from each bowl at regular intervals and the solution was filtered through 0.45 micron memebrane filter. The filterate was collected after discarding first few ml of the filterate.11

Buffer: 0.1N HCl

Preparation of 0.1N HCl: Dissolve 8.5 ml of HCl in 1000 ml of water.

h) Drug-polymer interaction by FT-IR

Drug polymer interaction was studied by taking FT-IR. Infrared spectra of Famotidine, Eudragit RS100 and Famotidine floating microspheres were carried out by using KBR pellet technique and were recorded on a shimadzu FT-IR spectrometer.

Table.1

Formulation code/ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug: polymer (PEO)	01:00.5	1:01	01:01.5	1:02	01:02.5	1:03						
Drug : polymer(eudragit)							01:00.5	1:01	01:01.5	1:02	01:02.5	1:03

Table. 2

Batch code	Bulk density	Tapped density	Carr's index	Hausners's ratio	Angle of repose
F1	0.41	0.47	1.14	12.76	28.94
F2	0.39	0.44	1.12	11.36	29.48
F3	0.55	0.64	1.16	14.06	26.21
F4	0.53	0.61	1.15	13.11	25.74
F5	0.5	0.58	1.16	13.79	25.02
F6	0.49	0.56	1.14	12.5	27.51
F7	0.47	0.54	1.15	12.96	29.68
F8	0.46	0.53	1.15	13.2	28.82
F9	0.462	0.591	1.25	21.8	26.06
F10	0.469	0.561	1.19	21.39	25.42
F11	0.46	0.55	1.19	16.36	26.62
F12	0.59	0.68	1.15	13.04	29.19

Table 3

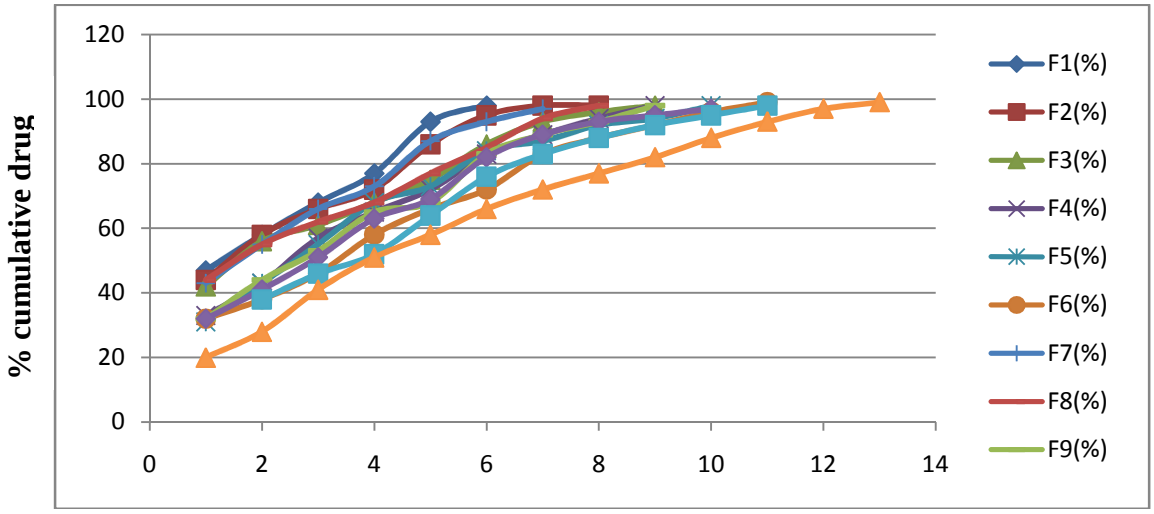
Formulation code/ingredients	Particle size
F1	127.7
F2	139.2
F3	140
F4	128.6
F5	122.5
F6	132.4
F7	150.6
F8	220.4
F9	278.9
F10	250.9
F11	246.7
F12	271.6

Table.4

Formulation code/ingredients	% yield	% Boyancy studies	% Drug entrapment
F1	73.2	68	86.24
F2	85.6	72	88.63
F3	74.9	74	84.78
F4	69.8	73	79.24
F5	86.4	66	77.68
F6	91.2	84	81.51
F7	88.7	81	77.47
F8	82.9	77	78.24
F9	76.9	83	83.46
F10	78.6	74	89.42
F11	91.8	69	90.69
F12	92.7	73	92.48

Comparision of dissolution profiles:

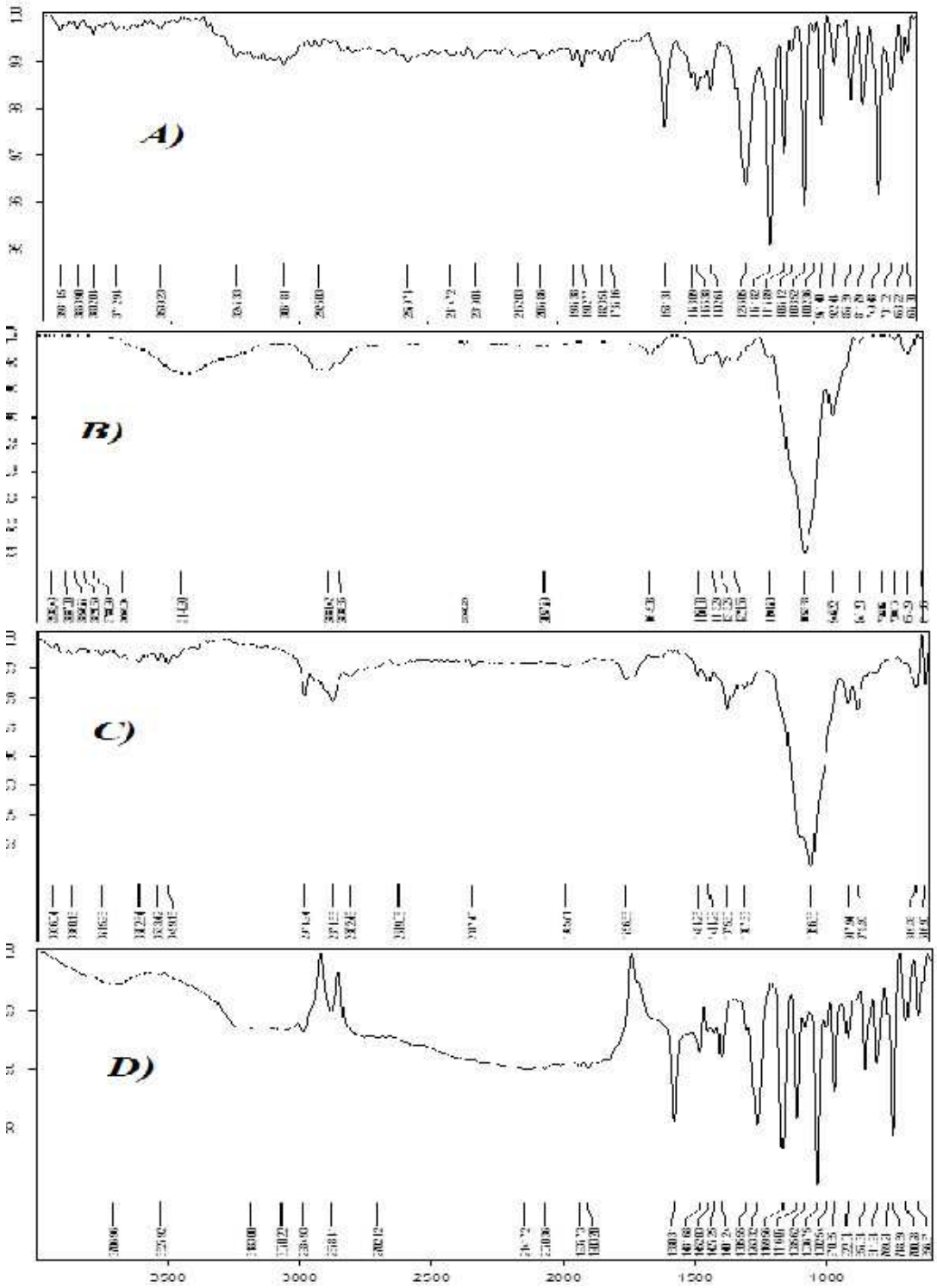
Formulation code/parameter	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11 (%)	F12(%)
1hr	47	44	42	31	27	32	43	44	32	32	22	20
2 hr	58	58	56	43	38	38	55	55	44	41	38	28
4 hr	68	66	61	55	43	46	66	62	53	51	46	41



Time in hrs

Results and Discussion

Drug – Excipient FT-IR studies: Fig No:7



Discussion

The development of floating drug delivery systems would clearly be advantageous. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease dose requirements. Thus, an attempt was made in this investigation to use Eudragit RS 100 as polymer to prepare Stavudine (antiviral drug) floating microspheres. Drug–polymer interaction was studied using FTIR analysis. The results showed that there were no changes in the IR spectra of pure Famotidine in the presence of Eudragit RS 100 (Figures 1 to 3). Thus revealing compatibility of the selected drug with the polymer. The Percentage yield of the developed fomulations of Famotidine floating microspheres (F1 to F12) were found to be in the range of 82.47 to 93.11%. The mean particle size of the developed formulations (F1 to F12) of floating microspheres were

found to be in the range of 23.87- 44.43µm.Which indicates the percentage yield and particle size were increased with increasing the polymer concentration. The drug loading of Famotidine floating microspheres decreased with increase in the concentration of polymer and drug entrapment efficiency of Famotidine floating microspheres increased with increase in the concentration of polymer. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy (%) for Famotidine floating microspheres was (F1-F12): 71.19 – 78.67%. Among the different Famotidine floating microspheres formulations, the formulation F2 was selected as the ideal formulation, based on its micromeritic properties, spherical in shape, floating behavior, drug loading, drug entrapment efficiency and percentage of drug released for a prolonged period over 12h, for further studies such as release kinetics and stability studies. The in vitro release data obtained from Formulation-F2 was fitted to kinetic models. The zero order plots were found to be fairly linear as indicated by high regression value of 0.981 for A1. The stability studies at room temperature and 45°C/75%RH for selected Famotidine floating microspheres formulations F2 was carried out. There were no significant changes in their physical appearance, average weight of capsule and FTIR pattern. The drug contents of the samples were analyzed after 10, 20 and 30 days of storage and there were no significant changes in the drug content. The drug release profile indicated that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed Famotidine floating microspheres were stable and retained their pharmaceutical properties over a period of1 month.

Conclusion

The present study reported the development of Famotidine loaded floating microspheres using polymer Eudragit RS100 by emulsion solvent evaporation method. Floating microspheres indicated different micromeritic properties, floating behavior, drug content, drug entrapment efficiency and drug release by varying the polymer concentration. The floating microspheres prepared were found to be spherical and free flowing. All the formulated floating microspheres remained buoyant for more than 12h. *In vitro* Famotidine release data showed that all the prepared formulations released Famotidine in a controlled manner for over 12 h. Based on the results obtained it can be concluded that F2 was found to be the ideal formulation considering its micromeritic properties, drug content, drug entrapment efficiency, floating behavior and release profile. The mechanism of drug released was found to be diffusion controlled. They are thus may be reduce frequency of dosing, thereby minimizing the occurrence of side effects, increase residence time in stomach and increase the effectiveness of the drug.

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