

Formulation and Evaluation of Famotidine Floating Tablets

M. Jaimini, A.C. Rana and Y.S. Tanwar*

Bhupal Nobles' College of Pharmacy, Udaipur-313001, Rajasthan, India

Abstract: The purpose of this investigation was to prepare a gastroretentive drug delivery system of famotidine. Floating tablets of famotidine were prepared employing two different grades of methocel K100 and methocel K15M by effervescent technique; these grades of methocel were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The effect of citric acid on drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration. A combination of sodium bicarbonate (130mg) and citric acid (10mg) was found to achieve optimum *in vitro* buoyancy. The tablets with methocel K100 were found to float for longer duration as compared with formulations containing methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Keywords: Famotidine, floating tablets, *in vitro* buoyancy.

INTRODUCTION

Famotidine is a histamine H₂-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bedtime, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastroesophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40 mg twice daily for a similar period. For the short term symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellison syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary; dose up to 80 mg daily have been employed [1]. 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.

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [2].

It has been reported that the oral treatment of gastric disorders with an H₂ receptor antagonist like famotidine or ranitidine used in combination with antacids promotes local delivery of these drugs to the receptor of parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases efficacy of drugs to reduce acid

secretion. Hence this principle may be applied for improving systemic as well as local delivery of famotidine, which would efficiently reduced gastric acid secretion [3].

In the present investigation floating tablets of famotidine were prepared by effervescent approach using two different grades of methocil (K100 and K15M). The aim of the work was to evaluate the effect of gel-forming polymer methocil on floating properties and release characteristics of famotidine tablets.

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Alembic Limited, Vadodara, India. Methocel K100 (100 cPs apparent viscosity as a 2% solution) and methocel K15M (15,000 cPs apparent viscosity as a 2% solution) were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Magnesium stearate, hydrochloric acid, sodium bicarbonate and citric acid anhydrous (hereafter referred to as citric acid) were purchased from S.D. Fine-Chem Ltd, Ahmedabad, India. Polyvinyl pyrrolidone K-30 (PVP K-30) was procured from Ottokemi, Mumbai, India. Lactose and purified talc were purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Methods

Preparation of Floating Tablets of Famotidine

The composition of different formulations of famotidine floating tablets is shown in Table 1. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granules (40 mesh) were dried in conventional hot air oven at 45°C. Drying of the granules was stopped

*Address correspondence to this author at the Bhupal Nobles' College of Pharmacy, Udaipur-313 001, Rajasthan, India; Telefax: +91-294-2413182(O); E-mail: yuveraj2000@yahoo.co.in

Table 1. Composition of Floating Tablets of Famotidine

Ingredients (mg per tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Famotidine	40	40	40	40	40	40	40	40	40	40
Methocel K100	90	90	90	80	70	-	-	-	-	-
Methocel K15M	-	-	-	-	-	90	90	90	80	70
Sodium bicarbonate	130	130	130	130	130	130	130	130	130	130
Citric acid	20	15	10	10	10	20	15	10	10	10
PVP K-30	50	50	50	50	50	50	50	50	50	50
Lactose	153	153	153	153	153	153	153	153	153	153

when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3%, as measured by a moisture balance at 105°C. The dried granules were sized through 40/60 mesh, lubricated with magnesium stearate (0.5%w/w) and purified talc (0.5%w/w) and then compressed on a single punch tablet machine (Cadmach Machinery Ltd., Ahmedabad, India). The tablets were round and flat with an average diameter of 12.0 ± 0.1 mm and a thickness of 3.2 ± 0.2 mm.

Flow Properties of Granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio [4]. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \tan^{-1} of the (height of the pile / radius of its base) gave the angle of repose.

Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were calculated. Hausner ratio (H_R) and Carr index (I_C) were calculated according to the two equations given below:

$$H_R = \rho_t / \rho_b$$

$$I_C = (\rho_t - \rho_b) / \rho_t$$

Evaluation of Floating Tablets

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets [5], hardness (Monsanto tester) [6], friability using 10 tablets (Roche type friabilator) [6], drug content, *in vitro* buoyancy [7] and *in vitro* dissolution studies. The results are expressed as mean \pm S.D. (n=5).

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al.* [7]. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. 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.

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45 μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 265nm using 0.1 N hydrochloric acid as blank.

The release rate of famotidine from floating tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method; Veeco Scientific, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 μ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 265 nm using a Thermospectronic-1 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Flow Properties of Granules

The granules prepared for compression of floating tablets were evaluated for their flow properties (Table 2). Angle of repose was in the range of 24.512 to 27.528 $^\circ$ with granules containing methocel K100 and 24.462 to 29.653 $^\circ$ with methocel K15M. Bulk density ranged between 0.561 to 0.582 gm/cm 3 with granules containing methocel K100 and 0.593 to 0.624 gm/cm 3 with methocel K15M. Tapped density ranged between 0.634 to 0.680 gm/cm 3 with granules containing methocel K100 and 0.667 to 0.692 gm/cm 3 with methocel K15M. Carr index was found to be 0.089 to 0.154 and Hausner ratio ranged from 1.098 to 1.182 for granules of different formulations. These values indicate that the prepared granules exhibited good flow properties.

Table 2. Flow Properties of Granules

Code	Angle of repose (θ)	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Hausner ratio (H _R)	Carr index (I _c)
F1	27.528±0.235 ⁰	0.561±0.032	0.634±0.043	1.130	0.115
F2	24.512±0.290 ⁰	0.567±0.045	0.660±0.057	1.164	0.141
F3	27.210±0.352 ⁰	0.574±0.058	0.652±0.083	1.135	0.119
F4	27.050±0.252 ⁰	0.582±0.026	0.674±0.048	1.158	0.136
F5	24.625±0.374 ⁰	0.575±0.048	0.680±0.061	1.182	0.154
F6	28.561±0.380 ⁰	0.624±0.043	0.691±0.053	1.107	0.096
F7	24.840±0.972	0.607±0.057	0.667±0.063	1.098	0.089
F8	29.653±0.784 ⁰	0.605±0.086	0.682±0.049	1.127	0.113
F9	28.462±0.850 ⁰	0.611±0.048	0.679±0.057	1.111	0.100
F10	27.389±0.674 ⁰	0.593±0.053	0.692±0.075	1.167	0.130

Evaluation of Floating Tablets

The floating tablets of famotidine were prepared by effervescent technique using methocel (K100, K15M), sodium bicarbonate, citric acid and PVP K-30. The magnesium stearate and talc were used as lubricant and glidant, respectively. The results of the physico-chemical characterization are shown in Table 3.

The weight of the tablet varied between 481 mg to 488 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeial specifications [5]. The hardness for different formulations was found to be between 4.05 to 5.25 kg/cm² indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content varied between 39.26 to 39.92 mg in different formulations with low coefficient of variation (C.V.< 1.0%), indicating content uniformity in the prepared batches.

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies.

All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased the floating lag time and tablets were found to float for longer duration. The tablets with low-viscosity grade methocel

K100 exhibited short floating lag time and floated for longer duration as compared with formulations containing high-viscosity grade methocel K15M. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer methocel influenced the *in vitro* buoyancy. Reduction in methocel level in the formulations F4, F5, and F9, F10 prolonged the floating lag time and shortened the total floating time. Thus a combination of sodium bicarbonate (130mg) and citric acid (10mg) with methocel (90mg) was found to achieve optimum *in vitro* buoyancy and floatability.

The pH of the stomach is elevated under fed condition (~3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; more over citric acid has a stabilizing effect on famotidine formulation. The effect of two different grades of methocel in the tablet with varying proportion of citric acid and sodium bicarbonate was studied on the release characteristics.

It is evident from the *in vitro* dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to of excess carbon dioxide, disturbing the monolithic tablet. The citric acid level in the formulations greatly influenced the drug release, irrespective of methocel grade. The drug release from floating tablets was found to be 85.72 to 98.37% for F1 to F5 with methocel K100. The drug release from formulations containing high-viscosity grade methocel K15M (F6 to F8) varied between 85.10 to 95.07%. The prepared formulations sustained the drug release for a period of 8-10 hours. Comparing the two different grades of methocel (K100 and K15M), it was found that low-viscosity grade methocel K100 provided better-sustained release characteristics with excellent *in vitro* buoyancy.

Formulations containing sodium bicarbonate and citric acid in ratio of 13:1 with varying amount of methocel were studied for their effect on release profile of famotidine. It was observed that the release of famotidine from such formulations increased on decreasing the proportion of

Table 3. Physico-Chemical Characterization of Famotidine Floating Tablets

Code	Uniformity of weight (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (mg)	Floating lag time (s)	Total floating time (h)
F1	482.1±0.25	4.25±0.11	0.57±0.06	39.26±0.15	34.01±1.65	9.25 ±0.03
F2	484.5±0.20	5.00±0.07	0.54±0.09	39.61±0.35	39.02±2.40	9.75±0.05
F3	487.6±0.29	4.25±0.19	0.70 ±0.05	39.80±0.12	47.52±1.53	10.05±0.06
F4	483.2±0.45	5.25±0.08	0.68±0.07	39.42±0.20	70.53±1.19	8.35±0.01
F5	481.3±0.55	5.25±0.15	0.45±0.05	39.92±0.42	71.57±1.15	7.50±0.06
F6	482.5±0.48	4.20±0.20	0.63±0.05	39.34±0.25	42.51±3.36	7.30±0.02
F7	488.3 ±0.56	5.25±0.10	0.71±0.02	39.78±0.45	51.05±2.28	7.40±0.05
F8	487.4±0.43	4.50±0.25	0.67±0.05	39.30±0.39	57.50±1.70	9.19±0.02
F9	482.5±0.32	5.01±0.10	0.72±0.09	39.80±0.18	62.52±2.36	8.15±0.04
F10	484.2±0.29	4.05±0.15	0.61±0.08	39.49±0.27	68.59±3.09	6.06±0.07

methocel in the formulation but duration of floating decreased.

The data obtained from *in vitro* dissolution studies were fitted in different models viz. zero order, first order and Korsmeyer's equation (Table 4). The zero order plots were found to be fairly linear (Fig. 1) as indicated by their high regression values ($r^2 = 0.979$ to 0.996). To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsmeyer's equation [8,9]. Regression analysis was performed and regression values ' r^2 ' were 0.982 to 0.998 for different formulations. Slope values ($0.5 < n < 1.0$)

suggest that the release of famotidine from floating tablets followed non-Fickian transport mechanism.

CONCLUSION

The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer methocel (K100 and K15M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve *in vitro* buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Table 4 Kinetics of *In Vitro* Famotidine Release from Floating Tablets

Code	Zero Order		First Order		Korsmeyer Model	
	k_0 (mg.h ⁻¹)	r^2	k_1 (h ⁻¹)	r^2	n	r^2
F1	9.984	0.988	-0.237	0.959	0.737	0.982
F2	7.494	0.979	-0.186	0.938	0.680	0.998
F3	8.459	0.990	-0.117	0.975	0.897	0.992
F4	9.458	0.995	-0.122	0.959	0.853	0.989
F5	10.312	0.989	-0.131	0.953	0.804	0.994
F6	11.609	0.991	-0.168	0.941	0.793	0.986
F7	11.01	0.996	-0.134	0.954	0.842	0.987
F8	9.225	0.989	-0.119	0.950	0.853	0.983
F9	8.927	0.982	-0.133	0.947	0.771	0.982
F10	9.063	0.980	-0.123	0.968	0.807	0.987

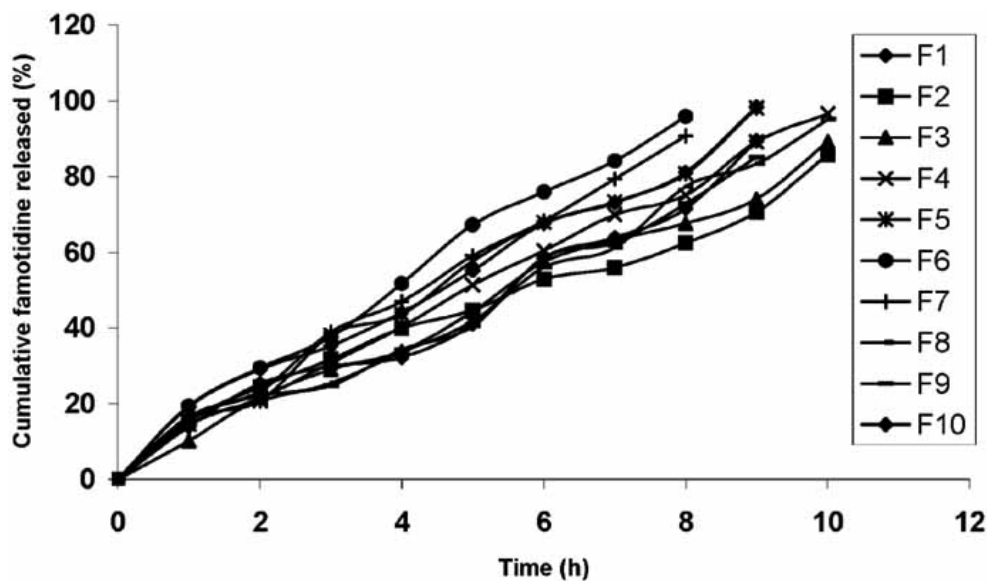


Fig. (1). *In vitro* dissolution profile of famotidine floating tablets.

REFERENCES

- [1] Reynolds, J.E.F. *Martindale The Extra Pharmacopoeia*, The Royal Pharmaceutical Society: London, **1996**, pp.1218-20.
- [2] Singh, B; Kim, K. *J. Control. Release*, **2000**, *63*, 235-59.
- [3] Coffin, M; Parr, A. US Patent 5 407 687, April 18, **1995**.
- [4] Sinha, V.R.; Agarwal, M.K.; Kumria R. *Curr. Drug Deliv.*, **2005**, *2*, 1-8.
- [5] Indian Pharmacopoeia, The Controller of Publications: Delhi, **1996**, Vol. II, pp.734-36.
- [6] Banker, G.S.; Anderson, N.R. In *The Theory and Practice of Industrial Pharmacy*, Lachmann, L., Liberman, H.A.; Kaing, J.L. Eds. Varghese Publishing House: Bombay, **1987**, pp. 297-99.
- [7] Rosa, M.; Zia, H.; Rhodes, T. *Int. J. Pharm.*, **1994**, *105*, 65-70.
- [8] Ritger, P.L.; Peppas, N.A. *J. Control. Release*, **1987**, *5*, 37-42.
- [9] Rao, V.; Shyale, S. *Turk. J. Med. Sci.* **2004**, *34*, 239-46.