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Design, development and optimization of famotidine gastroretentive drug delivery system

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ABSTRACT

Famotidine (FMT) gastroretentive (GR) controlled release system was formulated to increase gastric residence time leading to improved drug bioavailability. Novel combinations of carbopol 940 P, Sodium Alginate, Guar Gum and Kollidon SR were selected for the present study. Floating lag time (Flag) and diffusion exponent as dependent variables revealed that the amount of carbopol 940 P, Sodium Alginate, Guar Gum and Kollidon SR have a significant effect ($p < 0.05$) on famotidine release and Flag. FMTGR tablets were prepared and evaluated for mass, thickness, hardness, friability, drug content and floating property. Tablets were studied for dissolution for 12 h and exhibited controlled release of FMT with floating for 12 h. The release profile of the optimized batch F2 (carbopol 940 P Sodium Alginate) and F6 (carbopol 940 P, Kollidon SR) fitted zero- -order kinetics.

Keywords: Famotidine, gastroretention, floating tablets, release kinetics, controlled release.

INTRODUCTION

Gastric retention will provide advantages such as delivery of drugs with narrow absorption windows in the small intestinal region, namely proximal parts of the gastrointestinal tract (stomach and/or duodenum). Pharmaceutical dosage for FMT which remain in stomach for a prolonged period of time after oral administration and release the active ingredient in a controlled manner are important for the delivery of a wide variety of drugs (1-3).

Famotidine (FMT) is a H_2-receptor Antagonist, Antiulcerative. Orally administered famotidine is incompletely absorbed from gastrointestinal tract, and it undergoes minimal first-pass metabolism. The main limitations of the therapeutic effectiveness of Famotidine is its low bioavailability (20 to 66%), short biological half life (~3 to 4 h). Since the half-life of FMT is ~3 to 4 h, multiple doses are needed to maintain a constant plasma concentration for a good

therapeutic response and improved patient compliance. FMT is recommended for the short-term treatment of acute duodenal ulcer, gastric ulcer and gastroesophageal reflux and soluble in stomach pH. It is therefore a suitable candidate for gastroretentive floating monolithic system (4).

The present study involves the design and optimization of a novel gastroretentive, floating, swellable, controlled release tablet by combining three polymers with different concentrations: carbopol 940 P, Sodium Alginate and Guar Gum– gel forming agent. Kollidon SR – rapidly hydrating, rate controlling polymers. Furthermore sodium bicarbonate (SBC) as a gas generating agent was also used. The combined effect of these polymers on the floating behaviour and on in vitro release pattern of the FMT has also been evaluated. (5)

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Zim laboratories, India. Sodium Alginate, Kollidon SR and carbopol 940 P were received as a gift sample from Zim Laboratories, Nagpur and Guar Gum was received as a gift sample from Colorcon asia pacific, goa, India. SBC, talc and Magnesium Stearate was purchased from S.D. Fine-Chem Ltd., India. All the other chemicals used were of analytical grade.

Methods

Calibration curves of FMT were determined in 0.1 M HCl at l = 266 nm (R = 0.9932), using a UV-Visible spectrophotometer (Shimadzu, Japan). The calibration curve in 0.1 M HCl was used for dissolution studies.

Preparation of FMTGR tablets

FMTGR tablets were prepared according to the composition of optimized batches (Table I) FMTGR tablets (300 mg) were prepared by the direct compression method. Initially, all ingredients were sieved through sieve no. 80, weighed and mixed for 10 min. The drug was mixed with carbopol 940 P (CP), Sodium Alginate (SA), Guar Gum (GG), Kollidon SR (KSR). SBC, talc and MCC. Finally, the FMT was added as a lubricant and mixed for additional 2–3 min. Tablets were compressed on a tabletting machine (10 stations, Cadmach Machinery, Mumbai. India) fitted with a 10mm circular shaped standard concave punch. (6)

Fourier Transform Infrared (FTIR) Spectroscopy

IR spectrum of drug was measured in the solid state (Drug: Excipient ratio 1:1) as potassium bromide dispersion. The bands have been assigned for drug, polymer and formulations. The powder of mixture of drug and polymer were mixed with potassium bromide (Merck) in 1:100 proportions and dried at 40^{o}C. The mixture was compressed to a 12 mm semi transparent disk by applying a pressure of 10 tons (KBr press, tsi, Mumbai) for 2 min. The FTIR spectra over the wavelength range 4000–400 cm^{-1} were recorded using a FTIR spectrometer (8400S, Shimadzu, Japan). (7)

Characterization of FMTGR tablets

The prepared FMTGR tablets were tested for physical characteristics, viz., weight variation, thickness (measured using a Screw gauge), hardness (measured with a hardness tester, Monsanto, Dolphin Ltd., Mumbai, India) and friability (determined using a Roche friabilator, Mumbai, India).(8)

Table I. FMTGR tablet composition

Batch	Formulation (CP) (%)	(SA) (%)	GG) (%)	(KSR) (%)
F1	40.0	-	-	-
F2	33.3	6.6	-	-
F3	26.6	13.3	-	-
F4	33.3	-	6.6	-
F5	26.6	-	13.3	-
F6	33.3	-	-	6.6
F7	26.6	-	-	13.3
F8		40.0	-	
F9		-	40.0	
F10		-	-	40.0

CP – carbopol 940 P, SA – Sodium Alginate, GG – Guar Gum, KSR – Kollidon SR.
All batches contain - 39.43 % microcrystalline cellulose, Talc, 16.6 % SBC and 1 % magnesium stearate. Total tablet mass is 300.0 mg.

Drug content

Accurately weighed FMTGR tablets (10 tablets) were crushed to form a fine powder. An accurately weighed quantity equivalent to 40 mg of FMT was transferred to a 100-mL volumetric flask. To this, 50 mL 0.1 N HCl was added and sonicated for 15 min. Volume was made up to the mark with 0.1 N HCl. The solution was filtered through a 0.45-mm filter and 1 mL of this solution was diluted to 50 mL with 0.1 N HCl. Absorbance was measured at 266 nm. (9)

In vitro dissolution studies

The release rate of FMTGR tablets (n = 3) was determined with a USP dissolution apparatus- II (paddle method) using 100 rpm speed and 900 mL of 0.1 N HCl as dissolution medium at 37 ± 0.5 °C (11). A sample 5 mL of the solution was withdrawn from the dissolution apparatus (DBK Instruments Ltd., Mumbai, India) at regular time intervals up to 12 h (2, 4, 6, 8, 10 and 12 h) and replaced with the same volume of fresh dissolution medium. The samples were filtered through a 0.45-mm membrane filter and diluted to a suitable concentration with 0.1 N HCl and the absorbance of these solutions was measured at 266 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve. (10)

In vitro buoyancy studies

The *in vitro* buoyancy studies were performed by measuring the floating lag times. The tablets were placed in a 100-mL beaker containing 0.1 M HCl. The time required for the tablet to rise to the surface and float was defined as the floating lag time (Flag). (11)

RESULTS AND DISCUSSION

Physical characterization of the tablets

Tablet weight of all the formulations was found to be 300.0 ± 15.0 mg. Tablet thickness was found to be 4.25 ± 0.1 mm. The hardness of the formulation was 5 to 6 kg/cm^2, indicating satisfactory mechanical strength. Percentage mass loss in the friability test was 0.34 to 0.5 % in all cases, which was an indication of good mechanical resistance of the tablet. Tablets of all the prepared batches containing FMT were found to be within 100.0 ± 5.0 % of the labelled content, indicating content uniformity of the prepared formulations.

FTIR spectroscopy study

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. It can be concluded that there was no interference in the functional group as the principle peaks of the FMT was found to be unaltered in the drug-polymer physical mixtures, indicating they were compatible.

In vitro buoyancy studies

The results of in vitro buoyancy studies showed quick floating of the tablet within 2 min after placing the tablet in dissolution medium. Studies showed that no single polymer individually was sufficient to produce buoyancy and integrity of the tablet. Flag varied between 45 s to 15 min (Table II). Buoyancy mainly depended upon the quantity of SBC. SBC of 16.6 % was found optimal with optimum integrity and controlled release profile of the drug from the tablet. CP produces swelling of the tablet while SBC has the ability to generate gas in the presence of hydrochloric acid, which gets entrapped in the tablet. This leads to reduction in the density of the tablet, thereby producing floating.

In vitro dissolution studies

By using pharmacokinetic parameters of famotidine, the theoretical drug release for a 12h dosage form was calculated. An effective drug plasma concentration was maintained when the sustained release formulation released the required quantity of drug with predetermined kinetics. To achieve this, floating tablets should be formulated so that they release the drug in a predetermined and reproducible manner.

The release of famotidine from effervescent floating tablets was analyzed by plotting the cumulative percent drug release against time. The in vitro drug release studies revealed that formulations F1, F8, F9 and F10 (Fig. 2) containing 40% Carbopol 940 P, sodium alginate, guar gum and kollidon SR alone respectively, were able to sustain the drug release for 12, 8, 12 and 6 h, respectively are shown in Fig. 2. In F1, 40 % of Carbopol 940 P was sufficient to sustain the drug release for 12 h. Sodium alginate and kollidon SR polymers alone were unable to retard the famotidine release for 12 hrs. Hence both the polymers alone were unsuitable for sustained release of drug. Total buoyancy was 10 to 12 h and tablet integrity was good for Carbopol 940 P and guar gum formulations. Floating lag time was 98 seconds.

Drug release profiles of formulations F2 to F7 containing 33 % Carbopol 940 P and 6.6 and 13.2 % of sodium alginate (F2 and F3) , guar gum (F4 and F5) and kollidon SR (F7 and F8) each , are shown in Fig. 1. For F2 and F3, 100 % of the drug was released after 12 and 8 hours

respectively. 77.9 % and 82.61 % of drug was released from formulations F4 and F5, respectively, after 12 h. Formulation F3, F7, F8 and F10 underwent swelling and erosion, resulting in faster drug release. This variation was considered to be due to different polymers and their concentrations. Release of the drug was faster with kollidon SR may be due to lower gel strength, less entanglement and smaller diffusion path length compared to Carbopol 940 P. In all the formulations, polymer concentration greatly affected the release of the drug. The drug release rate was inversely proportional to the polymer concentration present in the matrix. It was observed that when the polymer concentration was increased, the drug release rate decreased.

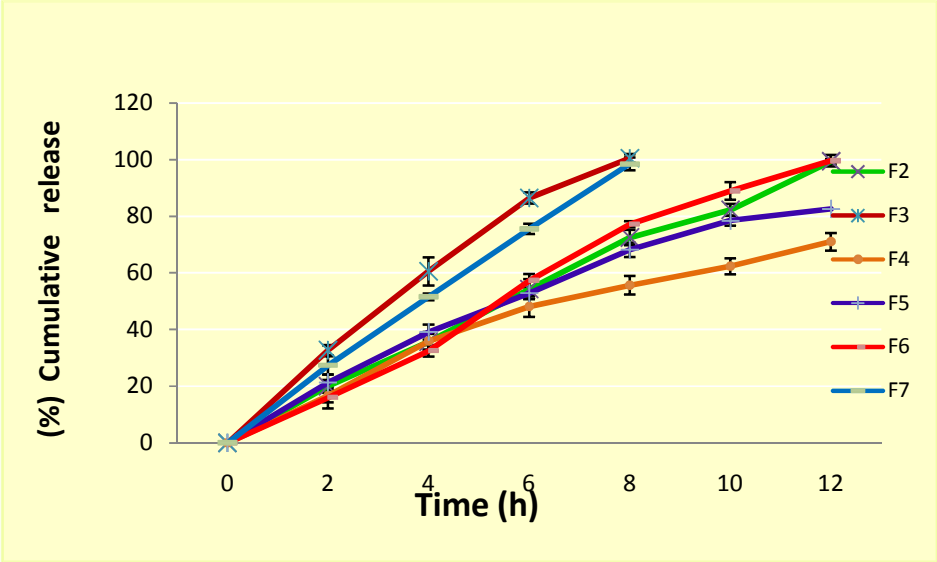

Fig. 1. FMTGR tablets dissolution profile of batches F2 to F7. Mean ± SD, n = 3.

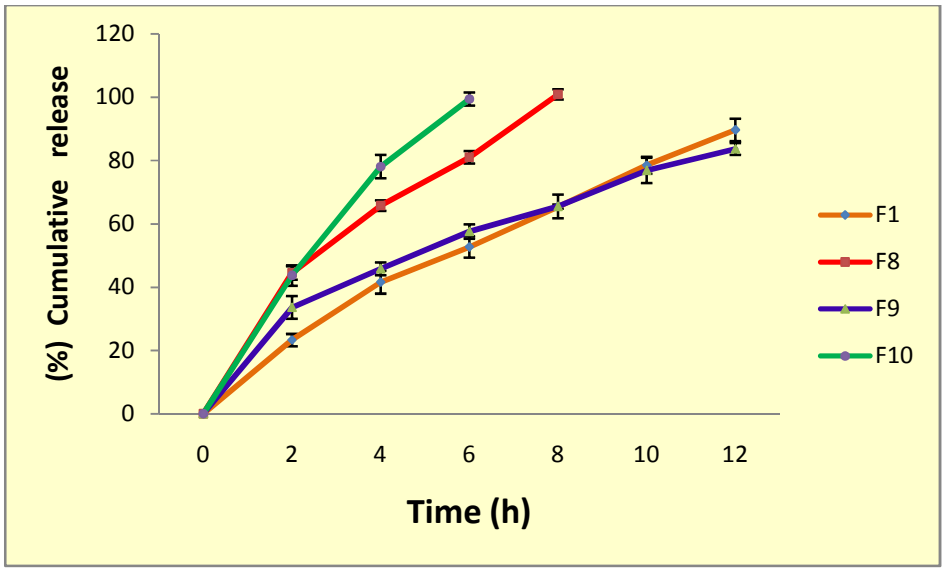

Fig.2. FMTGR tablets dissolution profile of batches F1 and F8 to F10. Mean ± SD, n = 3.

Drug release kinetics

The results of kinetic models for famotidine release from floating matrix tablets are shown in Table II. The coefficient of determination (R^2) was used as indicator of the best fitting for each of the models considered. To explore the mechanism of drug release, the results of in vitro data were fitted into the first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The results revealed that formulations F1, F2, F4 – F7 and F10 of floating matrix tablets fitted best the zero-order model. Formulations F8 and F9 were fitted best for the Higuchi and Formulations F3 showed First Order kinetics.

The release profile of the optimized batches F2 and F6 were fitted best to the zero-order showing least floating lag time of 45 s and 63 s; for these reasons, batches F2 and F6 were considered the best among all the formulations.(10)

Table II. In vitro release kinetics of Famotidine effervescent floating tablets

	R^2			
Batch Code	Zero order	First order	Higuchi	n value
F1	0.983	0.964	0.969	0.76
F2	0.987	0.946	0.962	0.958
F3	0.993	0.996	0.957	0.828
F4	0.987	0.987	0.961	0.881
F5	0.992	0.627	0.863	0.813
F6	0.998	0.962	0.933	1.105
F7	0.987	0.946	0.962	0.924
F8	0.939	0.998	0.999	0.548
F9	0.925	0.984	0.997	0.508
F10	0.978	0.837	0.978	0.758

R^2 – coefficient of determination, n – release exponent of Korsmeyer-Peppas

CONCLUSION

The present study involved the design of a novel gastroretentive floating and swellable, controlled-release, tablet of FMT. It comprised the release-rate-controlling hydrophilic polymers, in different concentrations, a release modulator and a gas generating agent. Upon administration, the FMTGR tablet was hydrated and swelled rapidly due to imbibition of the gastrointestinal fluid; subsequent gas generation helped the system buoyancy and the desired release profile. Optimized batch formulation F2 and F6 showed buoyancy with Flag time less than one min (63 s) and remained floating for 12 h. Minimum floating lag time and higher percentage of swelling of the F2 and F6 formulations are required to increase their residence time in the stomach and eventually improve the extent of bioavailability. The present study confirmed the test of the suitability of gastroretentive platform technology developed for the FMTGR tablet without changing any excipients and process parameters. The optimized batches F2 and F6 were prepared by using novel combinations of Carbopol 940 P and Sodium Alginate (F2) Carbopol 940 P and Kollidon SR (F6) and and SBC, can be successfully employed as a twice-a-day oral controlled release drug delivery system.

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