International Journal of Advances in Pharmaceutics
ISSN: 2320–4923; DOI: 10.7439/ijap
Volume 4 Issue 4 [2015]
Journal home page: http://ssjournals.com/index.php/ijap

Research Article

Fabrication of gastro retentive floating swellable matrices for oral controlled and sustained release of Famotidine

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Keywords:
Famotidine,
Guar Gum,
Psyllium Husk,
Rosin floating tablets,
Controlled and sustained release

Abstract

Gastroretentive (GR) swellable controlled and sustained release system of Famotidine (FMT) was formulated to increase gastric residence time of drug. A combination of Guar Gum, Psyllium Husk and Rosin were selected for the present study. Floating lag time (Flag) and diffusion exponent as dependent variables revealed that the amount of Guar Gum, Psyllium Husk and Rosin have a significant effect ($p < 0.05$) on Famotidine release and Flag. FMTGR tablets were prepared and evaluated for weight variation, 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 G3 (Famotidine and Guar Gum in a ratio 1:2.5) fitted zero- -order kinetics.

1. Introduction

Drug absorption from the gastrointestinal tract is a complex process and is subject to many physiological variables. Gastric emptying time (GET) is one of them which is the time taken for stomach contents to be passed into the duodenum and in humans it's normally averages 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine. The short GET can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.[1]

In order to overcome such limitations many scientist contributes their valuable support to make an ideal oral drug delivery system for those drugs that have narrow absorption window and poor bioavailability. One of the main hurdles is the poor gastric residence time (GRT) of drug. The average time required for a dosage unit to traverse the GIT is 3–4 h, although slight variations exist among various dosage forms.[2]

The gastro retentive floating drug delivery system can remain in the gastric region for several hours via float on the gastric contents and hence significantly prolong the gastric residence time of drugs. The pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of those drugs with narrow absorption window. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.[3-4]

2. Experimental

2.1 Materials

Famotidine was received as a gift sample from Themis Laboratories, Mumbai. Rosin and Psyllium husk were received as a gift sample from Zim laboratories, India. Guar Gum was received as a gift sample from Colorcon asia pacific, Goa, India. SBC, Talc and Magnesium Stearate were purchased from S.D. Fine-Chem Ltd., India. All the other chemicals used were of analytical grade.

2.2 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.

2.3 Preparation of Famotidine gastroretentive tablets (FMTGR)

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. Famotidine was mixed with Guar Gum (GG), Rosin and Psyllium husk alone and in combination. Sodium Bicarbonate (SBC), Talc and MCC were added. Finally, the magnesium stearate was added as a lubricant and mixed for additional 2–3 min as shown in table 1. Tablets were compressed on a tablet machine (10 stations, Cadmach Machinery, Mumbai. India) fitted with a 10mm circular shaped standard concave punch.

Table 1: Famotidine and Guar gum alone and in combinations with various other polymers (Formulations G1- G8)

Ingredient (mg)	BATCH CODE							
	G1	G2	G3	G4	G5	G6	G7	G8
Famotidine	40	40	40	40	40	40	40	40
Guar Gum	60	80	100	120	100	80	100	80
Psyllium Husk	-	-	-	-	20	40		
Rosin							20	40
Sodium Bicarbonate	50	50	50	50	50	50	50	50
Mg Stearate	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6
MCC	141	121	101	81	81	81	81	81
Total weight	300	300	300	300	300	300	300	300

2.4 Evaluation of Tablets [5-8]

Sustained release floating matrix tablets were developed using release retarding, gel forming polymers like Guar Gum, Rosin, and Psyllium Husk (PH) etc and gas forming agent like $NaHCO_3$ and evaluated for following parameters.

Formulations G1 to G4 prepared with guar gum started floating after 126 sec, 143 sec, 164 sec and 176 sec and remained buoyant for more than 12h till they were completely eroded except formulation G1. On the other hand, formulation G5-G6 prepared with combination of guar gum and PH showed decrease in floating lag time 105 sec and 102 sec and increased floating duration (>12h). This might be due to high hydrophilicity of polymers PH and GG maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. Result obtained with batches prepared from guar gum and Rosin was similar to FLT of Formulations G1 to G4.

***2.5 In Vitro* Drug Release Study**

The present study was aimed to make the formulation remain in the stomach for longer period of time, gastro retentive dosage form was designed, to release the drug in controlled and sustained manner in gastric fluid.

Table 2: Dissolution data of FMT and Guar gum tablets alone and in combination of various polymers

Time (hr)	G1	G2	G3	G4	G5	G6	G7	G8
2	54.48±2.1	34.60±4.7	23.6±3.61	19. 39±1.87	37.91±2.56	43.72±2.78	33.89±2.92	38.54±2.51
4	65.74±1.67	49.48±3.34	40.81±2.02	25.33±2.68	61.66±2.47	67.57±3.89	45.83±3.56	58.38±2.82
6	81.05±1.95	63.57±3.02	57.57±2.27	33.6±2.61	72.15±3.15	86.47±2.68	63.64±2.74	75.59±3.49
8	100.90±1.6	78.3±2.05	72.52±3.78	39.98±3.49	87.43±2.31	100.2±3.21	82.54±2.18	99.5±3.33
10	-	99.56±0.55	83.68±3.99	51.02±3.59	99.93±0.69	-	99.81±2.17	-
12	-	-	99.21±1.91	67.33±2.63	-	-	-	-

All values are mean ± SD, (n = 3)

***2.6 In-Vitro* Dissolution Studies of Formulations G1 to G8**

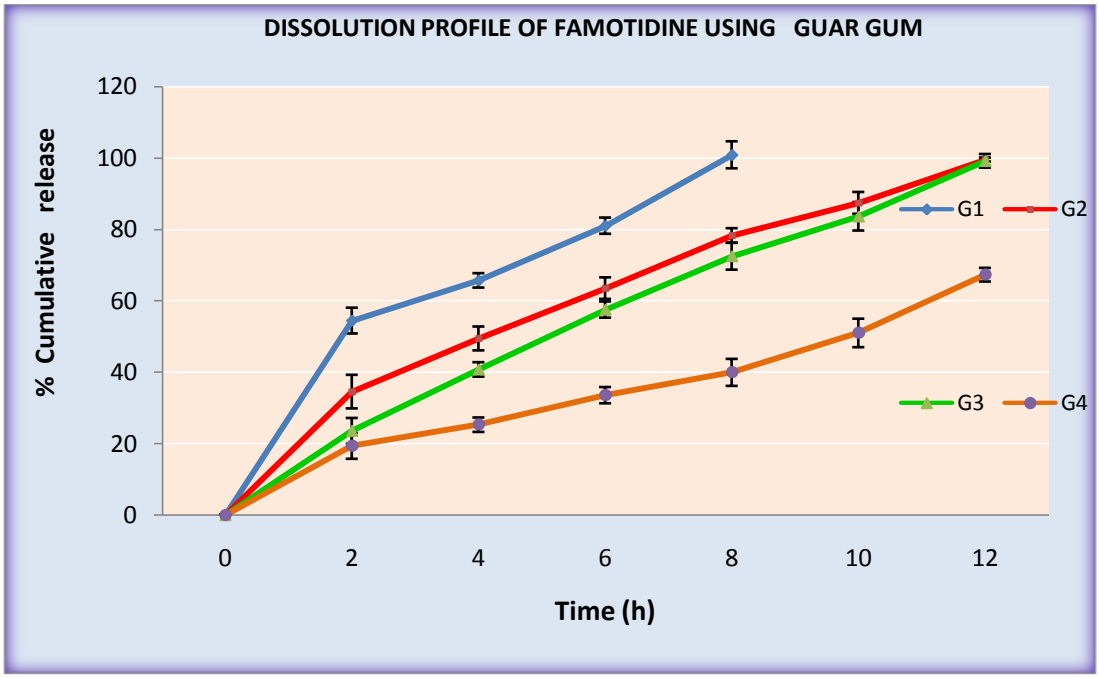

Fig. 1a: Effect of guar gum conc. on *in vitro* release of Famotidine (Mean ± SD, n=3)

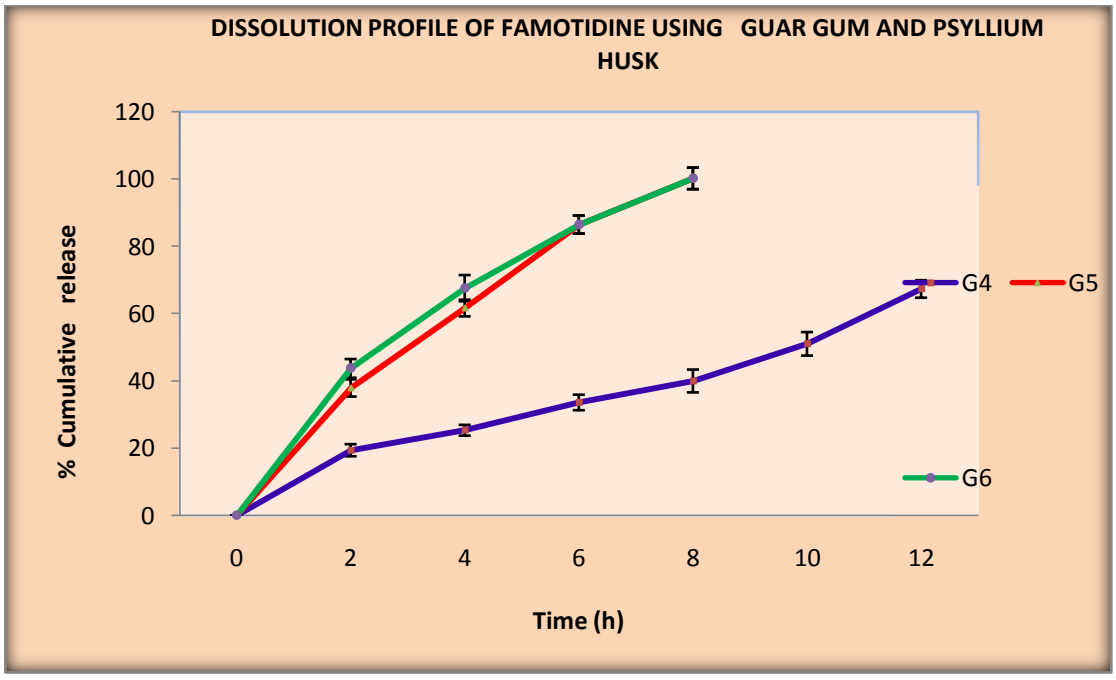

Fig. 1b: Effect of psyllium husk conc. in combination with guar gum on *in vitro* release of Famotidine (Mean ± SD, n=3)

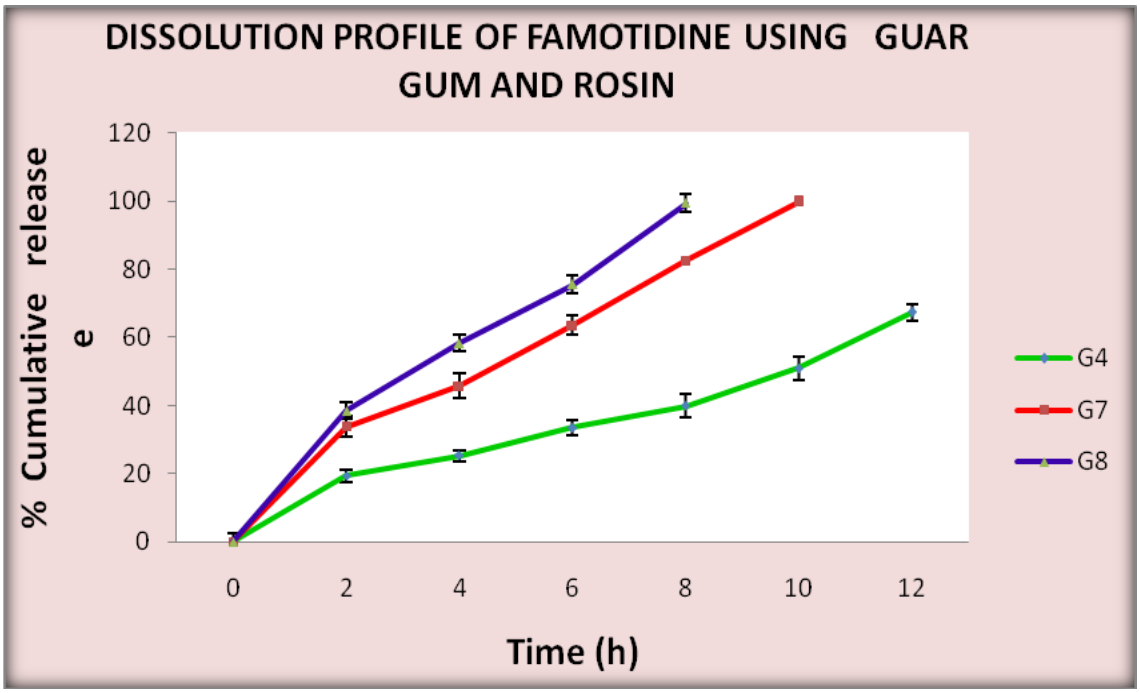

Fig. 1c: Effect of Rosin conc. in combination with guar gum on *in vitro* release of Famotidine (Mean ± SD, n=3)

The *in vitro* drug release study revealed that formulations G1, G2, G3 and G4 containing 20% , 26.67%, 33% and 40% guar gum, respectively releases drug 100% for 8 h, 99.36 for 10 h, 83.68 and 67.33 for 12h. Total buoyancy was 4 to 12h and tablet integrity was poor for guar gum formulations. Formulations G1 underwent swelling and erosion, resulting in faster drug release. Formulation G2 containing 26.67% of GG was sufficient to sustain the drug release for 12 h on increasing the quantity of GG up to 40%, the release of the drug was too slow and only 67.33% of drug was released. It was observed that when the polymer concentration was increased, the drug release rate was decreased. In vitro release data for batches G1, G2, G3 and G4 showed that the release of FMT decreased with the increase in concentration of guar gum showing initial burst release in acidic medium (pH 1.2) during first 2 hours such that 54% in formulation G1. Famotidine and guar gum in a ratio 1:2.5 can reduced initial burst release (G3) with CPR 100 % /12 hour and less floating lag time with buoyancy for 12 hrs. But guar gum in a ratio 1:3 can reduce initial burst release (G4 with CPR 67 % /12 hour). This clearly indicated that guar gum is able to sustain the drug release in the acidic medium itself therefore, overall extent of drug release at the end of 8 hour. Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the water soluble drug (FMT) from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules and also may be due to alkaline nature of FMT. The release kinetics data from table 3 showed that batch GG followed nearly Korsemeyer peppas kinetics with maximum regression coefficient of 0.998 and non fickian diffusion mechanism (n>0.5). It was observed that penetration of water into the guar gum based sustained release tablets resulted into formulation of gel layer on the tablet surface that swelled up initially and controlled the release thereafter. Formulations G5-G8 composed of Guar Gum and various polymers like psyllium husk (formulations G5 and G6), Rosin (formulations G7 and G8), Formulations G1, G6 and G8 showed 100% drug release for 8 h. Formulations G2, G5 and G7 for 10 h and Formulations G3 showed 100% and G4 showed 67% drug release for 12 h as shown in Fig. 1. This variation was considered to be due to different polymer types and their concentrations. The *in vitro* drug release from the matrices containing hydrophilic polymers at various conc. was shown in Fig.1. The influence of Guar Gum -Psyllium Husk ratio on the release of Famotidine from floating tablets in 0.1N HCl (pH 1.2) at 37±0.5°C was shown in Fig. 2. Effect of different concentrations of Psyllium husk on *in vitro* release of Famotidine was studied. As the conc. of Psyllium husk increases, initial burst drug release as well as drug release in the later hours increases. Drug associated with the surface of tablet matrix could have also contributed to the initial burst release. The gel like networks surrounding these matrices upon contact with aqueous media would produce strong surface barriers that would effectively reduce the burst drug release in case of various earlier mentioned polymers in combination with guar gum in a ratio 1:5.

Fig.1b and 1c demonstrate the effect of guar gum on the release of Famotidine from dosage form containing guar gum and other various polymers. Guar gum provides slow release in the stomach. Guar gum has the most homogeneous gel structure and there are very few channels through which the drug may diffuse hence guar gum have the slowest release rate in buffer of pH 1.2. Formulations without guar gum exhibited a much higher burst effect likely due to the fact that guar gum when contacted with water it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of drug from the floating drug delivery system. The initial burst drug dissolution normally seen in tablets is primarily due to the quick penetration of water into pore of polymer matrix and diffusion of the drug through these pores prior to complete gel formation.

17% of sodium bicarbonate (of total tablet weight) was incorporated in the Floating Matrix Tablets produced an optimized batch. Sodium bicarbonate generates CO_2 in the presence of a dissolution medium. The generated gas is trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1g/cm^3, the tablet becomes buoyant.

The swelling studies revealed that formulations G1, G2, G3 and G4 containing 20%, 24%, 33% and 40 % Guar Gum, respectively, were able to show maximum swelling for 5 to 8 h. Formulations G4 and G5 showed greater than 200% swelling after 8 h and 6 h respectively. Formulations G2 and G3 showed greater than 150% swelling after 5 h and Remaining Formulations showed less than 150% swelling after 5 h. This variation in release of drug was considered to be due to different polymer types and their concentrations.

Table 3: Kinetic modeling of drug release for formulations G1-G8

Batch Code	R^2 Value						Best Fit Models
	Zero order	First Order	Higuchi	Hixon Crowell	Korsmeyer Peppas	n value	
G1	0.903	0.970	0.989	0.805	0.946	0.430	First Order
G2	0.865	0.9924	0.9920	0.984	0.989	0.424	First Order
G3	0.995	0.984	0.997	0.977	0.975	0.508	Zero order
G4	0.963	0.977	0.972	0.976	0.97	0.594	KP
G5	0.973	0.957	0.978	0.867	0.996	0.716	KP
G6	0.948	0.987	0.995	0.875	0.998	0.603	KP
G7	0.982	0.674	0.961	0.870	0.973	0.678	Zero order
G8	0.976	0.997	0.975	0.891	0.990	0.668	First Order

In vitro matrix tablet release data were fitted to Korsmeyer Peppas release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form. The release exponent values thus obtained thus obtained were ranged from 0.6 to 0.86. formulations G4, G5 and G6 exhibited Korsmeyer Peppas release model and followed anomalous (Non Fickian Transport) diffusion mechanism with a value ranging between 0.603 to 0.86 (Table 3). Formulations G3 and G7 showed as highest R^2 values for zero order kinetics indicating the FMT release from these floating tablets were by both diffusion and erosion. Formulations G1, G2 and G8 followed first order drug release kinetics exhibiting values of n in a 0.43 and 0.424 for G1 and G2 while 0.668 was for G8.

Formulation G3 was selected as a most promising formulations for further study depending on its excellent floating behavior (very short floating lag time and prolonged floating duration), sustained drug release characteristics, swelling study, and zero order drug release kinetics. Thus taking into consideration the goal of the work of achieving a compromise between excellent floating behavior (very short floating lag time and prolonged floating duration) and sustained drug release characteristics, formula G3 was chosen for further studies.

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