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DEVELOPMENT OF FAMOTIDINE FLOATING DRUG DELIVERY SYSTEM USING NATURAL POLYMERS

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ABSTRACT

In the present study,FDDS of Famotidine, a copmpetative inhibitor of histamine H_2 receptors were prepared by using natural gums viz. xanthan gum and guar gum at different drug to gum ratio using sodium bicarbonate and citric acid as gas generating agents and lactose as diluent.FDDS tablets were prepared by wet granulation technique using PVP K30 as granulating agent. The prepared FDDS tablets were evaluated for its pre compression characteristics like bulk density, angle of repose, true density and compresibility index and post compression parameters such as hardness, friability, uniformity of drug content, *in vitro* floating studies, *in vitro* dissolution studies. The physical evaluation of all the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. The floating lag time of all the formulations was less than 10 minutes,All the formulations showed good matrix integrity and retarded the release of drug for 10 hours. Formulation X3 containg drug: xantahne gum ratio of 1:3 showed zero order kinetics, the IR spectroscopic studies indicated that the drug was compatible with the polymer and co-excipients and therefore can be a promising alternative to the existing dosage form.

INTRODUCTION: Peptic ulceration, gastroesophageal reflux disease, and hypersecretory conditions such as Zollinger–Ellison syndrome require reduction in gastric acid secretion and need constant monitoring. Famotidine is used as a potent inhibitor of gastric acid secretion acting as a competitive inhibitor at the H2 receptor on the parietal cell [1]. In the management of benign gastric and duodenal ulceration, the dose of Famotidine is 40 mg daily by mouth at bed time, for 4 to 8 weeks. In gastroesophageal reflux disease, the recommended dose is 20 mg by mouth twice a daily for 6 to 12 weeks, where gastro esophagealreflux disease is associated with esophageal ulceration; the recommended dose is 40 mg twice daily for similar period. For symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellision syndrome the initial dose by mouth is 20mg every 6 hours, increased as necessary, dose upto 80 mg daily have been employed. 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 floating 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 gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the

absorption window, thus ensuring optimal bioavailability [2].

Hence, the present study was designed to develop sustained release floating drug delivery system of famotidine using natural gum like xanthan gum and guar gum.

MATERIALS AND METHODS: Famotidine was obtained as a gift sample from Sreenivasa Pharmaceuticals Pvt. Ltd, Hyderabad. Xanthan Gum, Guar Gum, Magnesium Stearate, Talc, Sodium bicarbonate, Citric acid, PVP K30, Lactose were procured from Loba Chemicals, Mumbai, India.

Preparation of Floating tablets of Famotidine: Eight formulations were developed using different ratios of drug and gums as shown in **Table 1**.The drug and gum was blended and granulated by using 1 % PVPK30 solutions. The wet mass was passed through sieve no. 10 and the granules were dried in a hot air oven at not more than 45°C until till constant weight was obtained (until dry).Dried granules were passed through sieve no. 12 lubricated with magnesium stearate,talc and compressed by using 10.0mm diameter, spherical tablet punches on a tablet compression machine[3] (Rimek minipress machinery Co. Pvt. ltd., India) at the hardness of 5 to 6 kg/cm^2. Eight formulations were prepared and coded them from X1 to X8.

TABLE 1: COMPOSITION OF FAMOTIDINE FLOATING TABLETS

Ingredients	Formulation code (Quantity in mg)							
	X1	X2	X3	X4	X5	X6	X7	X8
Famotidine	40	40	40	40	40	40	40	40
Xanthan gum	80	100	120	160	-	-	-	-
Guar gum	-	-	-	-	80	100	120	160
$NaHCO_3$	70.8	70.8	130	130	70.8	70.8	130	130
Citric acid	30	30	30	30	30	30	30	30
Lactose	20	20	40	40	20	20	40	40
PVP K30	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Talc	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Mg.Stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Evaluation of Famotidine Floating Tablets:

Pre Compression Parameters: The flow properties of granules were characterized in terms of angle of repose [4], bulk density, true tapped density [5], Carr's index [6].

Post Compression Parameters: The prepared floating tablets were evaluated for hardness (Monsanto tester), friability (Rochetype friabilator), weight variation [7, 8], drug content estimation, floating lag time and total floating time.

***In vitro* buoyancy studies:** *In- vitro* buoyancy studies were performed for all the eight formulations as per the method described by Rosa *et al* [9]. Randomly selected tablets from each formulation were introduced in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The time for which the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT). The results were depicted in **Table 3**.

Drug Content Estimation: The drug content in each formulation was estimated by triturating 20 tablets. Powder equivalent to 10 mg of famotidine was added in 100ml of 0.1N HCl followed by stirring for 10 minutes. The stock solution was diluted suitably and the absorbance of resultant solution was measured at 265 nm by using Elico-UV-Visible Spectrophotometer (SL-159) 0.1N HCl was used as blank [8].

***In-Vitro* Dissolution Studies:** The release rate of famotidine from floating tablets was determined using USP dissolution apparatus II (Lab Hosp india). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. Aliquots 5ml was collected at predetermined time intervels and replenished with an equivalent volume of fresh medium. The samples were filtered through a 0.45 µm membrane filter and diluted suitably with 0.1N HCl and were analyzed using Elico UV/Visible spectrophotometer at 265 nm [10]. The results are illustrated in **Figure 1**.

TABLE 2: RESULTS OF PRE COMPRESSION PROPERTIES OF FAMOTIDINE FLOATING TABLETS

Formulation code	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's index %
X1	16.75	0.63	0.217	10.16
X2	18.65	0.66	0.258	9.67
X3	22.15	0.74	0.371	6.98
X4	22.76	0.64	0.186	7.35
X5	17.65	0.49	0.211	12.07
X6	19.06	0.50	0.326	8.84
X7	20.87	0.51	0.236	6.52
X8	21.14	0.53	0.368	2.93

TABLE 3: POST COMPRESSION EVALUATION OF FAMOTIDINE FLOATING TABLETS

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Weight variation (%)	Drug content (%)	Floating lag time (min)	Total floating time (Hr)
X1	4±0.2	0.409	2.526	100.09±0.020	3.54±0.045	>24
X2	4±0.6	0.417	2.482	100.26±0.687	2.27±0.976	>24
X3	4±0.3	0.550	2.205	99.06±0.698	1.48±0.098	>24
X4	4±0.8	0.560	2.611	98.66±1.689	1.31±0.098	>24
X5	4±0.5	0.510	1.872	100±0.482	3.26±0.096	>12
X6	4±0.8	0.440	1.896	100.6±0.276	2.49±0.096	>12
X7	4±0.6	0.560	2.340	99.6±1.059	2.47±0.076	>12
X8	5±0.2	0.628	2.700	98.6±1.068	1.55±0.075	>12

RESULTS AND DISCUSSION: The Pre compression parameters were in the prescribed range exhibiting good flow properties formulation containing drug and xanthan gum showed the angle of repose in the range of 16.75 to 22.76 where as formulations containing drug and guar gum showed 17.65 to 21.14 indicating both the compositions having acceptable flow properties. The other pre compression parameters such as bulk density, tapped density, Carr's index were also within the prescribed range as indicated in Table 2.

Post compression characteristics such as hardness, friability, weight variation, drug content estimation, floating lag time, *in vitro* dissolution studies. The hardness and friability of the formulation was found to be in the range of 4±0.2 to 5±0.2 and 0.417 to 0.628 respectively indicating the sufficient strength of tablet to withstand wear and tear during handling. Weight variation is an important evaluation parameter for tablets any deviation from the prescribed limits may adversely affect the content uniformity of the formulation the prepare formulations were evaluated for weight variation using eagle electronic balance and was found to be within the IP limits.

The floating lag time studies showed that batch containing xanthan gum had less floating lag time compare to those containing guar gum the total floating time for all the formulation was more than 12 hours which is sufficient to be consider as floating dug delivery systems in general it can be concluded that with an increase in the polymer concentration there was an increase in floating time and decrease in floating lag time. *In vitro* dissolution studies were performed for all the batches of FDDS of Famotidine using USP XXIII dissolution test apparatus II at 50 rpm, 900ml of 0.1N HCl used as dissolution media.

The *in vitro* drug release data is shown in **Figure 1** for all eight formulations. The *in vitro* dissolution profiles of all the prepared FDDS formulations of famotidine were found to extend the drug release over a period of 10 hours and the drug release decreased with increase in gum concentration.

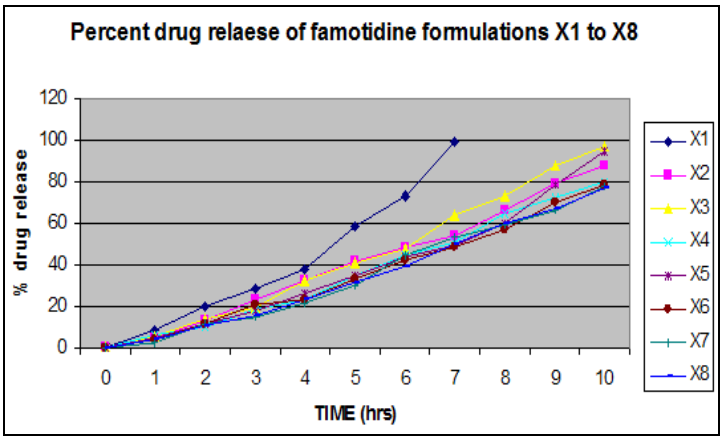
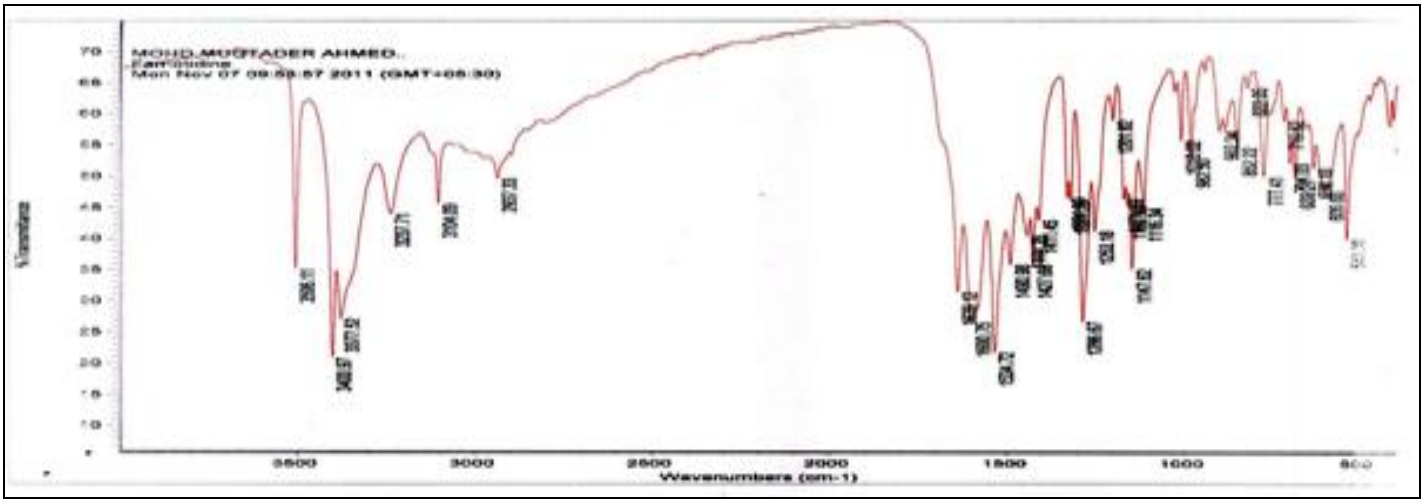


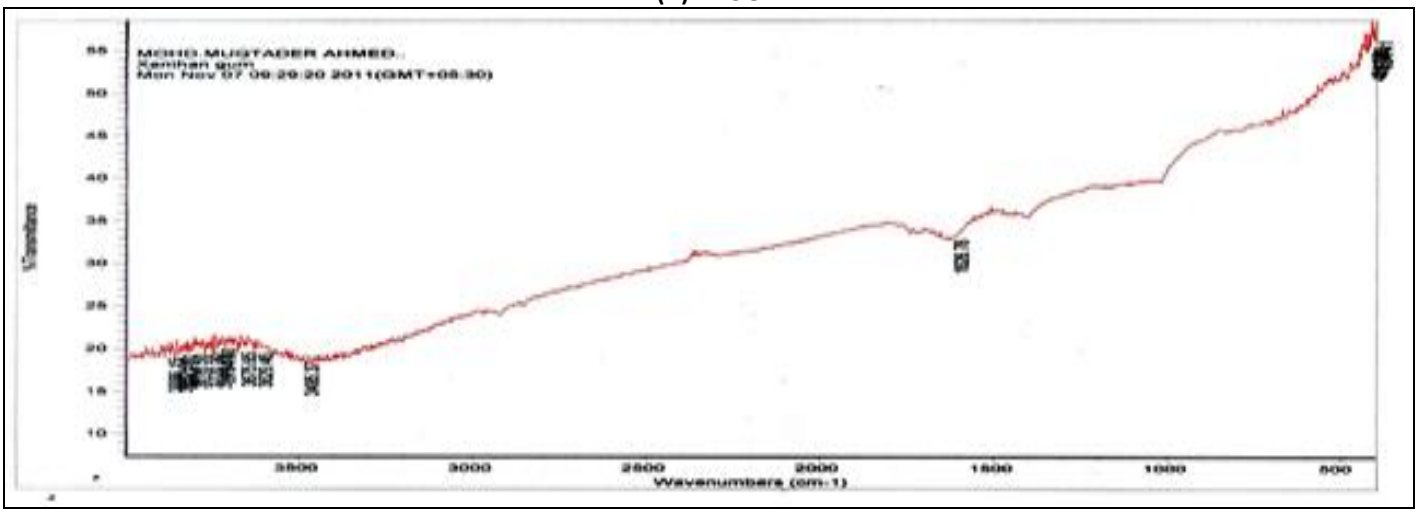
FIGURE 1: *IN VITRO* DRUG RELEASE PROFILE OF FAMOTIDINE FLOATING TABLETS

Among the various FDDS formulations studied, formulation X3 containing drug-gum ratio (1:3) prepared with XG (Xanthan Gum) showed promising results releasing ≈ 96.89% of the drug in 10 hours with a floating lag time of 1.48±0.098 min and floating time of 24 hours has been considered as an ideal formulation.

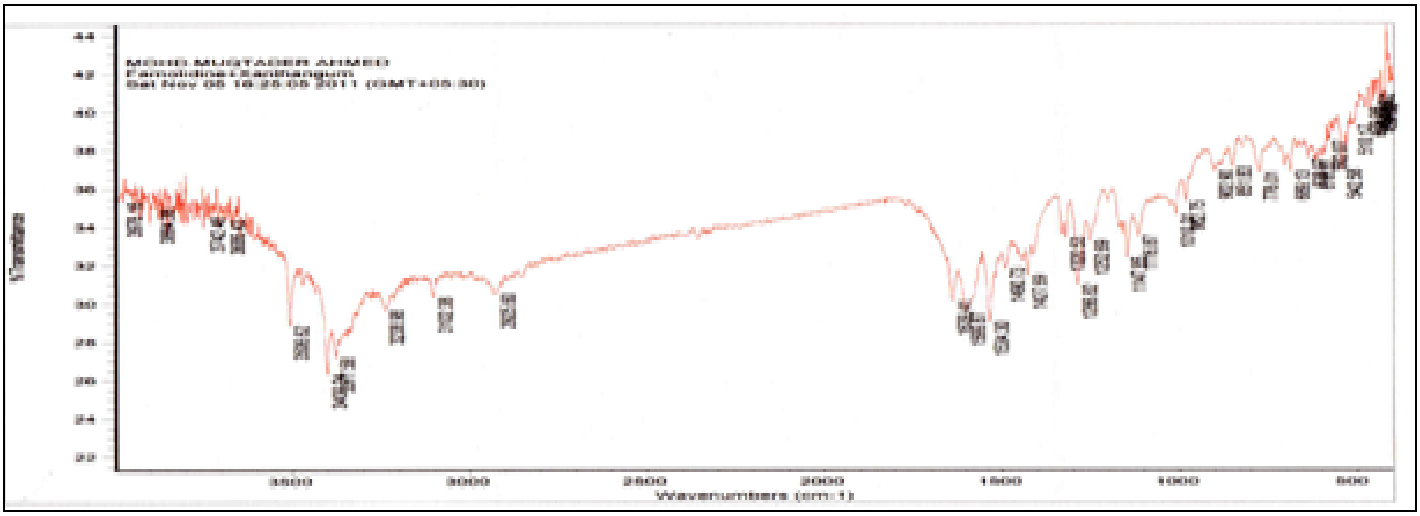
The IR spctra suggest that there was no polymer drug interaction the spectrum is depicted in **Fig. 2**.



(A) DRUG



(B) XANTHAN GUM



(C) FORMULATION X3

FIGURE 2: FT-IR SPECTRA OF (A) DRUG, (B) XANTHAN GUM, (C) FORMULATION X3

CONCLUSION: Floating delivery systems are promising dosage forms which could be a better alternative to the conventional oral dosage froms in order to improve bioavailability by increasing the gastric retention time of the drug. Natural polymers such as xantane gum and guar gum can be used to prepare floating drug delivery systems for drugs like famotidine which has higher absorption at low pH. However, this is to be explored by performing controlled *in vivo* studies.

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