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DESIGN AND DEVELOPMENT OF FLOATING TABLETS OF FAMOTIDINE BY USING NATURAL POLYMERS

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Abstract:

The aim of present research work is to prepare and evaluate controlled release floating tablet of Famotidine in view to enhance bioavailability and to reduce the dosing frequency. The tablets were prepared by using wet granulation technique employing PVP K 30 as binder and isopropyl alcohol as granulating fluid. The granules were evaluated for flow properties. 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. All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. Based on the release rate constant and % of drug release the formulations prepared with Aeglemarmelos gum shown prolonged retarding nature compared with the formulations prepared with Tamarind kernel Powder mucilage. Among all the formulations, F_6 formulation containing drug and Aeglemarmelos gum in 1:1.5 ratio was found to be optimized formulations.

Key words: *Famotidine, Aeglemarmelos gum, Tamarind kernel Powder mucilage, Sodium bicarbonate*

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INTRODUCTION:

Famotidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastro esophageal reflux disease [1].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 gastro esophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastro esophageal 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-Ellision syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary; dose up to 80 mg daily have been employed [2].The low bioavailability (40-45%) and short biological halflife (2.5-4.0 hours) of famotidine following oral administration favors development of a sustained release formulation [3]. All these factors highlight the need to develop sustained release dosage forms of Famotidine. It is also reported that oral treatment of gastric disorders with an H_2 - receptor antagonist like Famotidine, used in combination with antacids, promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery of these drugs also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion [4]. This principle may be applied for improving systemic as well as local delivery of Famotidine, which would efficiently reduce gastric acid secretion.

The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs. There is a need to investigate a number of indigenously available retardant materials to make the concept of controlled release drug delivery more viable for the drug industry at more economical way. In the present study, natural polymers such as Aeglemarmelos gum and Tamarind kernel Powder mucilage were selected for the preparation of floating tablets of Famotidine. Sodium bicarbonate was used as gas generating agent. Tablets were prepared by wet granulation method using these polymers.

MATERIALS AND METHODS:

Famotidine was obtained as a gratis sample from Hetero labs, Hyderabad. Aegle marmelos gum and Tamarind kernel Powder mucilage were purchased from Yucca enterprises, Mumbai. PVP K 30, Isopropyl alcohol and Sodium bicarbonate were purchased from Qualigens fine chemicals, Mumbai. All other ingredients were of analytical grade.

Preparation of Famotidine floating tablets

Famotidine was mixed with required quantities of Tamarind kernel Powder mucilage / Aeglemarmelos gum, Sodium bicarbonate and Citric acid by geometric mixing. The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. Magnesium stearate and talc were used as lubricant and glidant respectively. The final blend was compressed into tablets using 12 mm punches and corresponding dies on rotary tablet compression machine [6].The composition of each formulation was given in Tables 1.

Table 1: Composition of Famotidine floating tablets formulated with different natural polymers.

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)
Famotidine hydrochloride	40	40	40	40	40	40
Tamarind kernel Powder mucilage	20	40	60			
Aeglemarmelos gum				20	40	60
Micro crystaline cellulose	95	75	55	95	75	55
Sodium bicarbonate	20	20	20	20	20	20
Citricacid	10	10	10	10	10	10
Poly Vinyl pyrolidine	10	10	10	10	10	10
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	200	200	200	200	200	200

Evaluation Parameters

Flow properties of granules:

The granules were evaluated for the bulk density, Tapped density, Carr's index, Hausner's ratio and angle of repose [7].

Evaluation of Famotidine floating tablets

a) Hardness:

The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force [8]. The hardness was measured in terms of kg/cm^2.

b) Weight variation:

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated [8]. The percent weight variation was calculated by using the following formula.

$$\%\ \text{Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} X 100$$

c) Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty two pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula [8].

$$\text{Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X 100$$

d) Swelling Index:

Formulated tablets were weighed individually (W_0) and placed separately in Petri dish containing 50 ml of 0.1N Hydrochloric acid. The Petri dishes were placed in an incubator maintained at 37±0.5ºC. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula [9]:

$$\%\ W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where:

W_U – Water uptake

Wt – Weight of tablet at time t

Wo – Weight of tablet before immersion

e) In vitro buoyancy study:

This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N Hydrochloric acid at paddle rotation of 100 rpm at 37 ± 0.5^0 C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time [10].

f) Drug content:

20 tablets were weighed and powdered the powder weight equivalent to 40mg of Famotidine was dissolved in 100ml of 0.1N Hydrochloric acid and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated at 266nm by UV spectrophotometer [11].

g) In vitro dissolution test:

The release of Famotidine from the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N Hydrochloric acid maintained at 37 ± 0.5°C temperatures at 100 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples was replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm Whatman filter paper and analyzed at 266 nm by UV spectrophotometer [12].

Drug Excipient Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with Tamarind kernel Powder mucilage / Aeglemarmelos gum in tablet formulations [13].

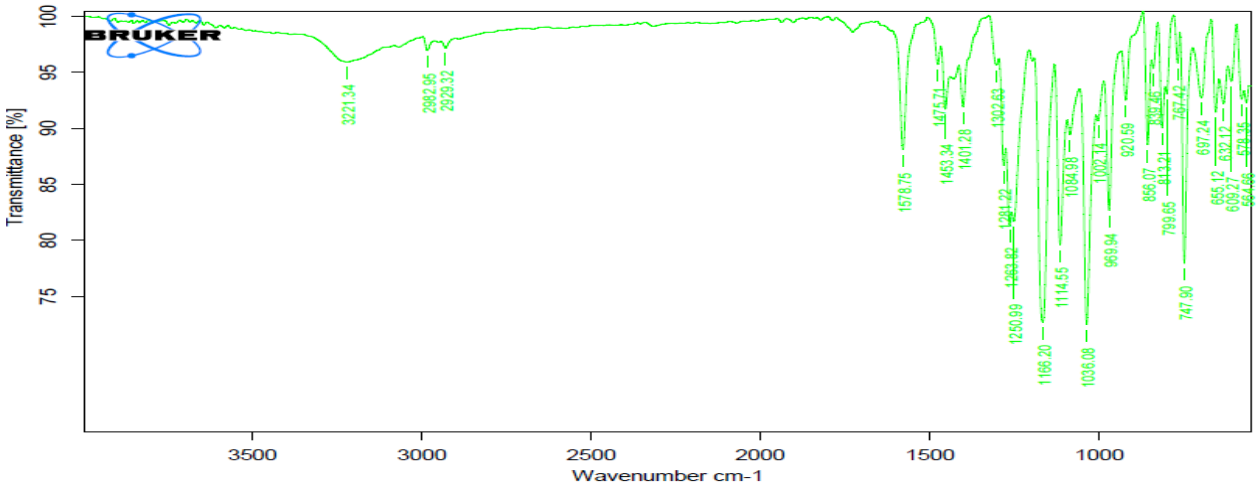


Fig 1: FTIR spectrum of Famotidine

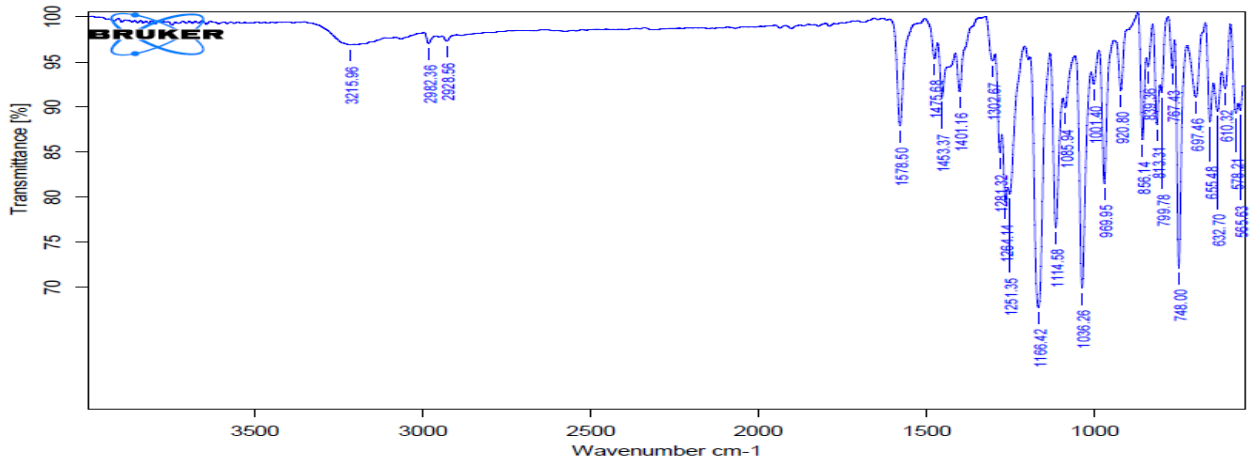


Fig 2: FTIR spectrum of Famotidine floating tablet prepared with Tamarind kernel Powder mucilage

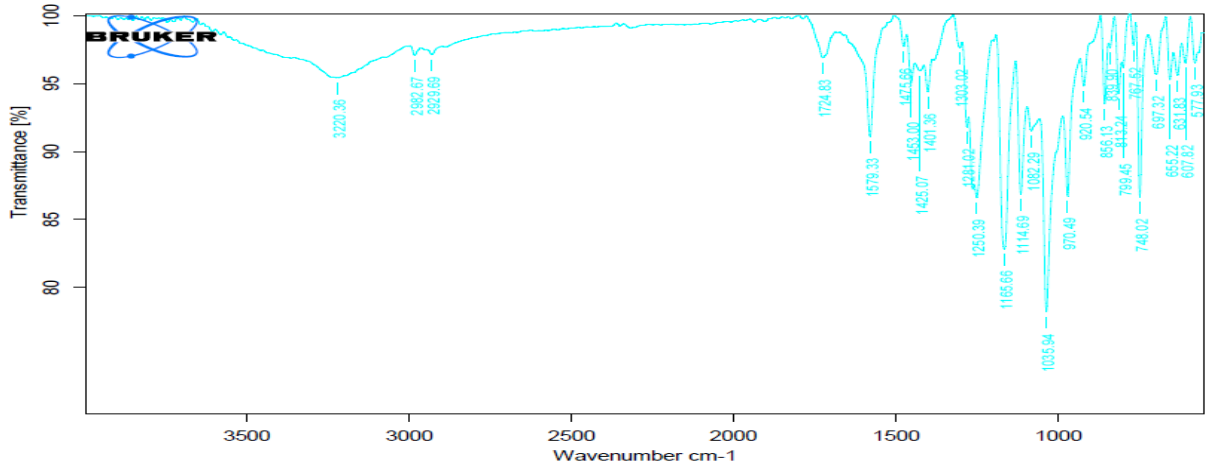


Fig 3: FTIR spectrum of Famotidine floating tablet prepared with Aeglemarmelos gum

Stability studies of optimized floating matrix tablets:

The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 25±5ºC/60% RH and 40±5ºC/75% RH respectively for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated[14].

RESULTS AND DISCUSSION:

Floating tablets of Famotidine were prepared by varying the concentration of Tamarind kernel Powder mucilage (F_1-F_3) and Aeglemarmelos gum (F_4-F_6) . The formulated granules were evaluated for various flow properties. The bulk density for all the formulations ranged from 0.522 to 0.527. The angle of repose for all the formulations was found to be in the range of $25^0\ 73^l$-$26^0\ 52^1$. The Carr's index for all the formulations ranged from 15.67 – 15.27%. The value of bulk density indicates good packing characters. The value of angle of repose (25^0-30^0) for all the formulations indicates good flow property. The value of Carr's index (10-16%) indicates free flowing material. The values of Hausner's ratio were found to be between 1.180-1.185. The powder blend with Hauser's ratio of 1.25 has good flow properties. So the values indicate that the granules had acceptable flow properties. The flow properties were shown in table 2.

Table 2: Micromeritic properties of granules of Famotidine floating tablets formulated with different concentrations of natural polymers.

Formulation code	Angle of repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F_1	27.91	0.527	0.627	15.94	1.189
F_2	27.63	0.530	0.629	15.73	1.187
F_3	26.45	0.532	0.630	15.55	1.185
F4	26.52	0.522	0.619	15.67	1.185
F5	26.14	0.524	0.620	15.48	1.183
F6	25.73	0.527	0.622	15.27	1.180

Table 3: Physical properties of Famotidine floating tablets formulated with different concentrations of natural polymers.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_1	4.3±0.012	200.13±0.15	0.66±0.007	99.87±0.16	2.28 min	>14
F_2	4.4±0.009	200.16±0.12	0.52±0.011	99.89±0.13	2.13min	>14
F_3	4.5±0.011	199.97±0.16	0.43±0.012	99.95±0.11	1.94 min	>14
F_4	4.4±0.016	200.18±0.14	0.57±0.010	100.44±0.06	2.19 min	>14
F_5	4.5±0.018	200.23±0.12	0.38±0.018	99.36±0.13	2.04 min	>14
F_6	4.6±0.019	199.34±0.19	0.16±0.024	99.29±0.14	1.56 min	>14

Table 4: *In vitro* drug release kinetic data of Famotidine floating tablets formulated with different concentrations of natural polymers

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9926	0.7407	0.9089	0.9941	4.48	0.8882	4.5	8.0
F_2	0.9968	0.7705	0.9197	0.9960	4.16	0.8804	4.8	8.6
F_3	0.9990	0.7991	0.9278	0.9971	3.92	0.8750	5.2	9.2
F4	0.9988	0.6859	0.9271	0.9968	3.95	0.8732	5.1	9.1
F5	0.9983	0.8085	0.9352	0.9983	3.61	0.8651	5.5	9.9
F6	0.9965	0.7450	0.9355	0.9989	3.31	0.8594	6	10.8

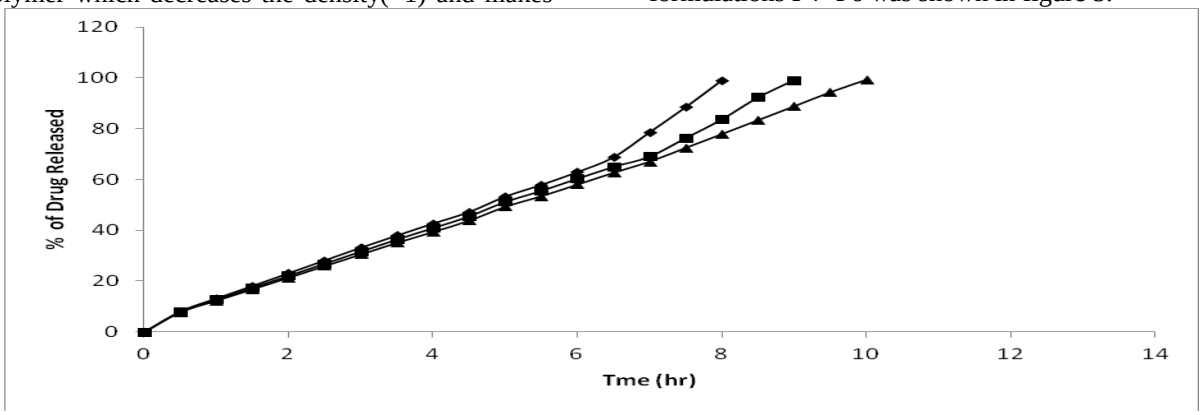
Table 5: Swelling index values of Famotidine floating tablets formulated with different concentrations of natural polymers

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_1	15.46	25.12	65.36
F_2	19.24	39.17	79.74
F_3	21.37	48.16	87.63
F_4	23.45	33.82	75.20
F_5	26.72	49.44	89.68
F_6	30.67	57.13	97.47

Floating matrix tablets were evaluated for hardness and friability. The hardness was found to be in between 4.4 – 4.6 kg. The tablets satisfied friability requirement, as the % friability values were less than 1%.The drug content estimations showed values in the range of 99.29 to 100.44%, which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ±5% of the weight. 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.

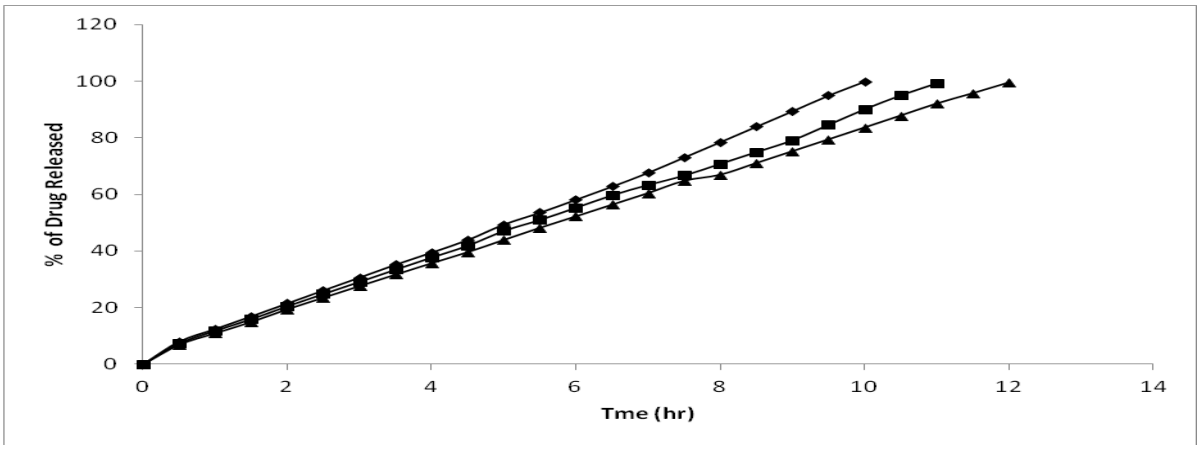
All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The results of various physical properties and *invitro* buoyancy studies were tabulated in table 3.

In vitro dissolution studies of all the formulations of floating matrix tablets were carried out in 0.1N HCl. The study was performed for 12 hrs and the cumulative drug release was calculated. All the formulations remained floating and intact throughout the dissolution studies. The formulations (F_1-F_3) containing Tamarind kernel Powder mucilage showed decrease in drug release with increase in concentration of Tamarind kernel Powder mucilage. The drug release from formulation F_3 containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 9.2 hours. The dissolution profile for the formulations F1- F3 was shown in figure 4. The formulations (F4-F6) containing Aeglemarmelos gum showed decrease in drug release with increase in concentration of Aeglemarmelos gum. The drug release from formulation F_6 containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 12 hours. The dissolution profile for the formulations F4- F6 was shown in figure 5.



(-♦-)Floating tablets formulated with drug and Tamarind kernel Powder in 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Tamarind kernel Powder in 1:1 ratio
(-▲-) Floating tablets formulated with drug and Tamarind kernel Powder in 1:1.5 ratio

Fig 4: Comparative *in vitro* drug release profile of Famotidine floating tablets formulated with different concentrations of Tamarind kernel Powder mucilage



(-♦-)Floating tablets formulated with drug and Aeglemarmelos gum in 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Aeglemarmelos gum in 1:1 ratio
(-×-) Floating tablets formulated with drug and Aeglemarmelos gum in 1:1.5 ratio

Fig 5: Comparative *in vitro* drug release profile of Famotidine floating tablets formulated with different concentrations of Aeglemarmelos gum

To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. The in-vitro drug release kinetic data was shown in Table 4.The swelling index studies showed a gradual increase with increase in concentration of natural polymer and was shown in Table 5.

The characteristics peaks confirmed the structure of Famotidine. The same peaks were also reported in all drug loaded matrix tablet. There were no change or shifting of the characteristic peaks in matrix tablets suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations. Drug release from optimized formulations before and after storage under varying conditions was evaluated periodically at the regular interval of every month. The drug release profiles of all the formulations did not change significantly after storage at 25±2° C/60±5% RH and 40±2° C/75±5% RH for a period of 3 months. There is no significant difference in the drug content and release rate constants. The results indicated that the drug releases from the optimized formulations were found to be quite stable.

CONCLUSION:

From the above results, it is clearly evident that the invitro release of Famotidine from the floating tablet was influenced by nature of natural polymer. Based on the release rate constant and % of drug release the formulations prepared with Aeglemarmelos gum shown prolonged retarding nature compared with the formulations prepared with Tamarind kernel Powder mucilage. Among all the formulations, F_6formulation containing drug and Aeglemarmelos gum in 1:1.5 ratio was found to be optimized formulations.

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