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Research

Hydrodynamically Balanced Systems using Famotidine: Influence of natural and synthetic polymers

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Abstract

This study focuses on the development and evaluation of floating sustained-release tablets of Famotidine using the Hydrodynamically Balanced System (HBS) approach to prolong gastric retention and enhance bioavailability for the management of peptic and duodenal ulcers. Floating tablets were formulated via wet granulation employing both synthetic (HPMC 15cps, HPMC 100M, Carbopol) and natural polymers (Chitosan, Psyllium husk), along with gas-generating agents to achieve buoyancy. All prepared formulations were assessed for drug-polymer compatibility, pre-compression parameters, and post-compression characteristics, including in-vitro buoyancy and drug release. Infrared spectroscopy confirmed the compatibility between Famotidine and the polymers. The synthetic polymer-based formulations demonstrated superior performance compared to those with natural polymers. Among all, formulation SPF5, containing HPMC 15cps, was identified as the optimized batch. It exhibited an excellent floating lag time of 15 seconds, a total floating time of over 23 hours, a high swelling index (68.38%), and sustained drug release over 12 hours in simulated gastric fluid. The drug release from SPF5 followed zero-order kinetics (R^2=0.964) and the Higuchi model, indicating a diffusion-based, Non-Fickian release mechanism. Stability studies confirmed the formulation's robustness over time. In conclusion, the successful development of Famotidine HBS tablets presents a promising strategy for controlled drug delivery, offering improved therapeutic efficacy over conventional dosage forms.

Keywords: Hydrodynamically Balanced System, Floating tablets, Floating lag time, swelling index, Drug release.

INTRODUCTION

Oral drug delivery remains the most convenient and preferred route of drug administration due to its ease of use, patient compliance, and flexibility in dosage design. However, one of the major limitations associated with conventional oral dosage forms is the unpredictable gastric emptying time, which can significantly influence drug absorption, bioavailability, and therapeutic efficacy. To overcome this challenge, gastroretentive drug delivery systems (GRDDS) have been developed to prolong the residence time of dosage forms in the stomach, thereby improving the absorption of drugs that exhibit site-specific absorption in the upper gastrointestinal tract. Among various GRDDS approaches, the Hydrodynamically Balanced System (HBS), also known as the floating drug delivery system, has gained considerable attention for its ability to remain buoyant on the gastric contents and release the drug in a controlled manner over an extended period.

The Hydrodynamically Balanced System functions by incorporating low-density polymers or excipients that enable the dosage form to float on the gastric fluid without affecting the gastric motility. Upon contact with gastric fluids, the system swells and forms a gel barrier, entrapping air within the matrix to maintain buoyancy. This floating property ensures prolonged gastric retention, enhanced drug absorption window, and improved bioavailability for drugs that are preferentially absorbed from the stomach or upper small intestine. Moreover, the sustained release characteristics of HBS contribute to minimizing dosing frequency, reducing fluctuations in plasma drug concentration, and improving patient adherence to therapy[1].

Famotidine, a potent histamine H_2-receptor antagonist, is widely used in the management of peptic ulcers, gastroesophageal reflux disease (GERD), and Zollinger–Ellison syndrome. Despite its clinical efficacy, Famotidine exhibits poor bioavailability of approximately 40–45%, primarily due to its limited absorption window in the upper gastrointestinal tract and short biological half-life of about 2.5–4 hours. Conventional dosage forms of Famotidine require multiple daily dosing to maintain therapeutic plasma concentrations, which may lead to poor patient compliance and inconsistent therapeutic outcomes. Therefore, developing a hydrodynamically balanced system for Famotidine presents a promising strategy to overcome these limitations by retaining the dosage form in the stomach for an extended duration, ensuring sustained drug release, and improving systemic absorption.

The formulation of Famotidine-loaded Hydrodynamically Balanced Systems aims to achieve prolonged gastric residence, controlled drug release, and enhanced bioavailability, ultimately improving therapeutic effectiveness. This study focuses on the formulation and evaluation of HBS containing Famotidine using suitable polymers and excipients that impart buoyancy and controlled release characteristics. The developed system is expected to optimize drug release kinetics, enhance patient compliance, and provide a more effective therapeutic approach for acid-related gastrointestinal disorders[2].

MATERIALS AND METHODS

Famotidine is a gift sample from Dr. Reddy's Lab Ltd, Hyderabad, Carbopol 934P purchased from Sigma Aldrich, HPMC procured from Titan Biotech Ltd, Psyllium husk purchased from Amazon.in, PVP-K30 and Chitosan purchased from S.D. Fine Chem Ltd.

FT-IR studies

The drug and polymer interactions were studied by Fourier Transform Infrared (FTIR) Spectroscopy[4] by KBr disc method. A thin and transparent pellet wasprepared by applying 2000 psi pressure. The spectra were recorded for pure drug,polymer and the physical mixture of drug and polymer in the ratio 1:1 at the scanningrange of 400-4000 cm^{-1} using FT-IR-8400 S, spectrophotometer (SHIMADZU, Japan).

Formulation development of Famotidine buoyant tablets

Floating tablets of Famotidine were prepared by wet granulation technique using different polymers in varied combination and ratios with citric acid and sodiumbicarbonate as effervescent agents. The composition of synthetic and natural polymersformulations were given in table 1 and 2 respectively. All the powders were passed through 60 mesh sieve. Weighed quantities of drug andpolymers were mixed homogenously using mortar and pestle. PVP-K30 solution insufficient isopropyl alcohol was used as granulating agent. Granules were prepared by passing wet coherent mass through a BSS # 12 sieve. The obtained granules were dried at 40^{o}C temperature for 60 minutes. The dried granules were sieved through BSS # 16, sodium bicarbonate and citric acid were mixed and blended with magnesium stearate and talc. Lubricated granules were compressed into tablets using 10 station single rotary punching machine (Rimek mini press-II) with 11 mm punches and dies to obtain tablets of desired specifications.

Table 1: Composition of Famotidine floating tablets made by synthetic polymers

Ingredients	Quantity (mg)								
	SPF1	SPF2	SPF3	SPF4	SPF5	SPF6	SPF7	SPF8	SPF9
Famotidine	40	40	40	40	40	40	40	40	40
HPMC15CPS	100	-	-	50	60	-		50	40
HPMC K100M	-	100	-	-	-	50	60	50	40
Carbopol 934P	-	-	100	50	40	50	40	-	20
PVP K-30	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citricacid	10	10	10	10	10	10	10	10	10
MCC	70	70	70	70	70	70	70	70	70
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Total weight	300	300	300	300	300	300	300	300	300

Table 2: Composition of Famotidine floating tablets made by natural polymers

Ingredients	Quantity (mg)					
	NPF1	NPF2	NPF3	NPF4	NPF5	NPF6
Famotidine	40	40	40	40	40	40
Psyllium husk	100	-	100	50	50	50
Chitosan	-	100	50	100	150	50
PVP k-30	30	30	30	30	30	30
Sodium bicarbonate	50	50	50	50	50	50
Citric acid	10	10	10	10	10	10
MCC	55	55	55	55	5	55
Magnesium stearate	5	5	5	5	5	5
Talc	10	10	10	10	10	10
Total weight	300	300	300	300	300	300

EVALUATION STUDIES

Weight variation test

The weight of the tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. The IP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the IP test if not more than 2 tablets are outside the percentage limits[5].

Hardness

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness[6]. The instrument measures the force required to break the tablet when the force generated by anvils to the tablet. Tablet hardness is defined as the load required crushing or fracture a tablet placed on its edge. The hardness of the tablets was determined using Monsanto hardness tester. Three tablets were randomly picked and hardness of the tablets was determined and expressed in kg/cm^2.

Friability Test

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tabletingredients. Initial weight of ten tablets were recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the final weight was recorded[7]. Percentage friability was calculated by using the formula,

$$\text{Percent friability} = \frac{Initial\ weight\ of\ tablets - Final\ weight\ of\ tablets}{Initial\ weight\ ot\ tablets} \times 100$$

Drug content

This test is used to ensure that every tablet contains the same amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, this test is performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equivalent to average weight of tablet was dissolved in 0.1 N HCl in 100 ml volumetric flask. The sample solution was further diluted and the absorbance was measured at 266 nm using 0.1N HCl as blank[8].

Swelling studies

Swelling of tablet involves the absorption of a liquid resulting in an increase inweight and volume. Liquid uptake by the particle may be due to saturation of capillaryspaces within the particles or hydration of macromolecule. The liquid enters the particlesthrough pores and bind to large molecule, breaking the hydrogen bond and resulting in swelling of particles. The extent of swelling can be measured in terms of percentage weight gain by the tablet. Swelling studies were carried out for formulations and from each formulae, one tablet was weighed and placed in a petri dish containing 10 ml of 0.1N HCl After each hour the tablet was removed from petri dish and weighed again up to 5 h. The percentage weight gain by the tablet was calculated by using the formula[9].

Swelling index (S.I) = {(Wt-Wo) / Wo} x 100

Where, S.I. = swelling index, Wt = Weight of tablet at time t, Wo = Weight of tablet before immersion.

***In-vitro* buoyancy determination**

Floating time was determined using USP XXIII dissolution apparatus-II at 50 rpm using 900ml. of 0.1 N HCl. and temperature was maintained at 37±0.5°C, throughout the study. Theduration of floating (floating time) is the time the tablet floats in the dissolutionmedium(including floating lag time which is the time required for the tablet to rise to the surface) ismeasured by visual observation. The results are summarized in table no.5.5 and 5.6 forsynthetic and natural polymers respectively[10].

***In-vitro* dissolution studies**

Invitro dissolution studies of HBS of Famotidine was studied in USPXXIII tablet dissolution test apparatus-II (Electrolab), employing a paddle stirrer at a speed of 50 rpm using 900ml 0.1N HCl as dissolution medium at 37±0.5°C. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 266 nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicates. The results are given in tables 5.9 to 5.10 for synthetic and natural polymer formulations respectively.

Mathematical modeling of drug release profile

The prepared formulations were evaluated to determine the order of drug release from the niosomes using Zero order Vs First order and mechanism of drug release using Higuchi and finally the drug release mechanism was confirmed using Korsmeyer-Peppas model.

Stability study

The optimized formulation was examined for stability study. The formulations stored at 40±2°C/75±5%RH for a period of three months and at predetermined interval the samples were evaluated.

RESULTS AND DISCUSSION

FT-IR Study

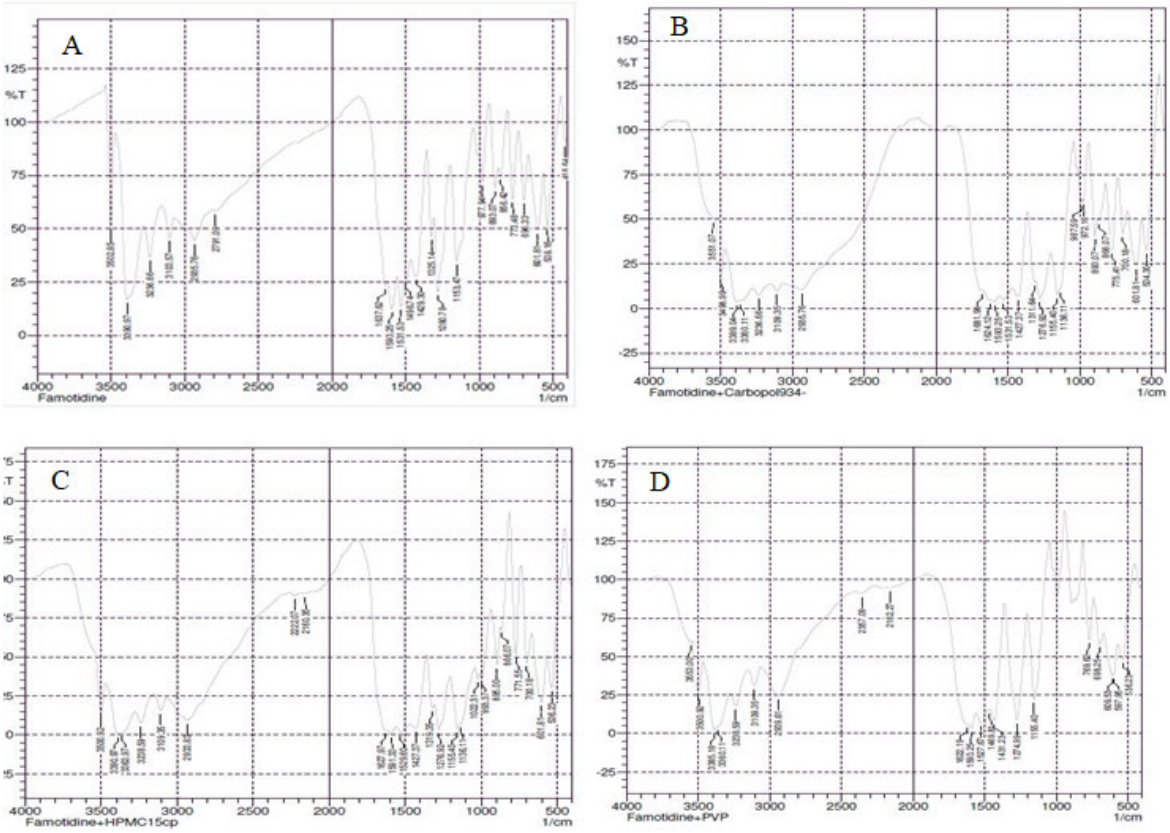

Fig 1: Drug – Polymer compatibility study (A- Famotidine; B- Famotidine and Carbopol; C- Famotidine and HPMC; D- Famotidine and PVP)

Table 3: Interpretation of Infra Red absorption spectra (Fa -combination of famotidine with Carbopol 934P, Fb- combination of famotidine with HPMC100M, Fc- combination of famotidine with PVP)

Groups	Vibrations	Standard intensity range cm^{-1}	Observed Intensity range cm^{-1}
Hydrocarbon chromophore	C-H bending CH2-alkane	1300-1500	Fa-1427 Fb-1427 Fc-1431
Amines	N-H stretching N-H bending	3000-3700 1500-1700	Fa-3498 Fb-3500 Fc-3500 Fa-1593 Fb-1591 Fc-1591
Unsaturated nitrogen groups	C=N stretching	1600-1700	Fa-1624 Fb-1627 Fc-1622
Aromatic substitution one hydrogen atom	C-H bending	880-900	Fa-893 Fb-895 Fc-895

From the above Figure 1 and Table 3, it was observed that there were no changes in the main peaks in IR spectra of drug, which show there were no physical interactions because of some bond formation between drug and polymers. This indicates that the drug was compatible with the formulation components.

Post-compression Evaluation

Table 4: Post-compression results of synthetic polymer formulations

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability Test (%)	Drug content (%)	Floating lagtime (sec)	Total floating time(h)
SPF1	5.5±0.25	3.1±0.04	306±0.5	0.74±0.06	99.49±1.5	15	9
SPF2	5.1±0.25	3.11±0.03	304±0.6	0.71±0.03	98.32±1.23	18	11
SPF3	5.2±0.15	3.1±0.04	298±0.9	0.65±0.07	99.39±1.4	NO	NO
SPF4	4.5±0.32	3.09±0.08	308±0.4	0.59±0.04	98.51±1.3	94	23
SPF5	5.2±0.14	3.08±0.02	296±0.3	0.68±0.06	99.84±1.2	55	21
SPF6	5.3±0.22	3.12±0.06	311±0.8	0.49±0.01	97.98±1.4	12	24
SPF7	4.8±0.19	3.16±0.05	294±0.4	0.42±0.09	98.56±1.0	59	23
SPF8	5.4±0.28	3.12±0.04	303±0.2	0.47±0.06	98.39±1.1	55	23
SPF9	4.7±0.21	3.13±0.03	307±0.7	0.59±0.04	99.56±1.2	64	24

Table 5: Post-compression results of natural polymer formulations

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability Test (%)	Drug content (%)	Floating lagtime (sec)	Total floating time(h)
NPF1	4.2±0.28	3.42±0.0.2	305±0.5	0.84±0.05	98±1.5	98	40.5
NPF2	4.1±0.24	3.11±0.08	305±0.7	0.77±0.07	98.32±1.6	294	7
NPF3	4.5±0.32	3.64±0.01	354±0.6	0.63±0.06	99.39±1.8	122	1.5
NPF4	4.2±0.14	3.71±0.06	351±0.4	0.59±0.04	98.51±1.4	128	3.5
NPF5	4.6±0.03	3.72±0.08	348±0.3	0.68±0.07	97.84±2.1	135	7
NPF6	4.2±0.16	3.16±0.03	302±0.4	0.49±0.03	98.48±2.0	84	2

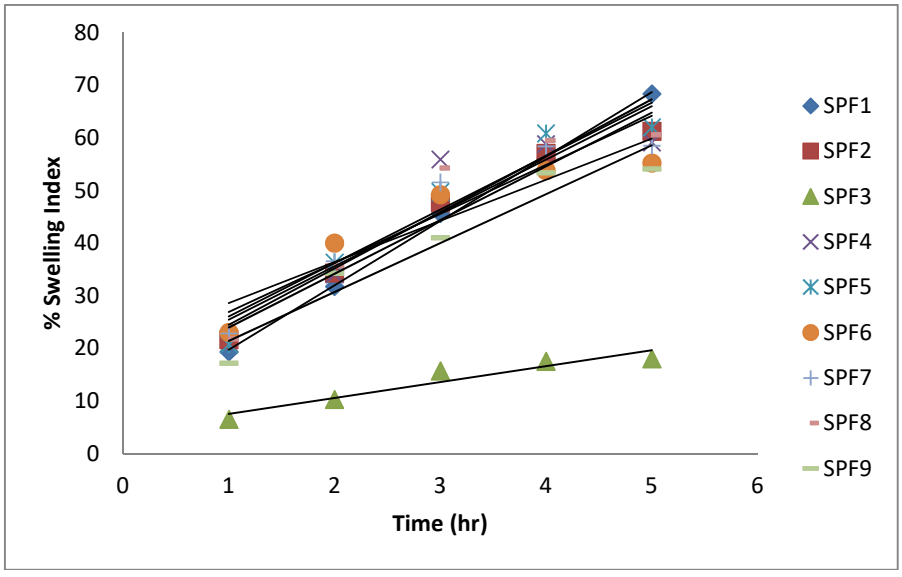

Fig 2: Rate of swelling index of formulation coded with SPF

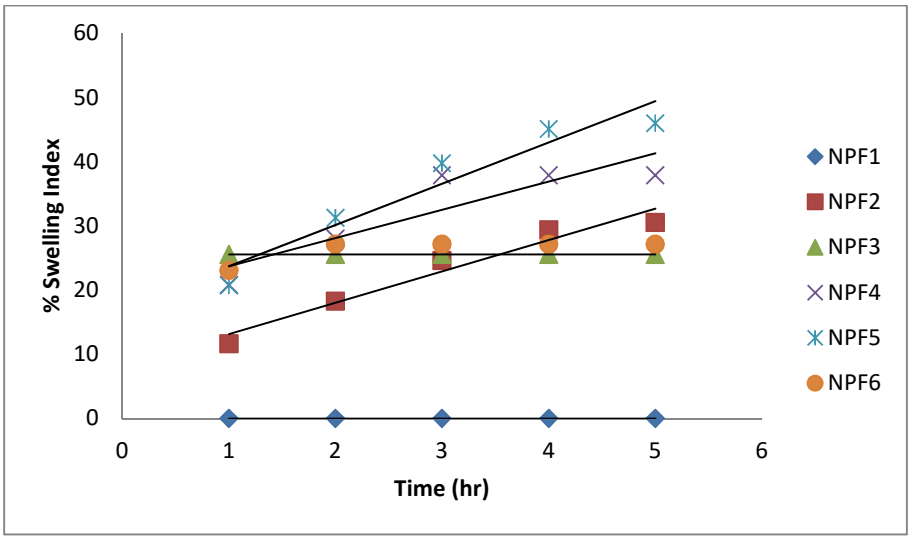

Fig 3: Rate of swelling index of formulation coded with NPF

The thickness, of the tablets were around 3mm. The hardness of the floating tablets ranged between 4.1-5.5 Kg/cm^2 and the percent friability of the prepared tablets was well within acceptable limit (<1 %). No significant weight variation was observed between average weight and individual weights. The results of post-compression parameters aregiven in Table 4 and 5 for synthetic and natural polymers respectively. Content uniformity test showed that the percentage of drug content for all the batches were in between 97.84 -99.84 %.

The tablets are hydrated gradually up to five hours and reached the pleatue andremained almost constant until end of experiment, so swelling index was done up to 5hours. The swelling index results of synthetic polymer formulations were depicted in Figure 2 and 3. From the results it was concluded that swelling index increases as timepasses (up to some extent of time) because the polymer gradually absorb the medium due to hydrophilic nature and swell. In formulations using synthetic polymers swelling was a strong enough to avoid premature disintegration as well as burst effect and retarded the release of drug for a longer period of time. In formulation SPF-3 which is formulated using Carbopol the swelling index remained very low that is 18.0, when compared to other formulations made of synthetic polymers. In formulation SPF-1 which is formulated using HPMC 15cps the swelling index was maximum that is 68.38.

But in formulations made of using natural polymers the swelling index is low. The formulation NPF-1(which is made of using Psyllium husk powder) disintegrated within one hour, so it has no swelling index. The formulation NPF-5 (which is made of using Psyllium husk-50mg and chitosan 150mg) the swelling index was high (53.00) when compared with the other natural polymer formulations. The swelling index results ofnatural polymer formulations were depicted in Figure 3.

In this investigation, the gastric floatation of the tablet was achieved by employing sodium bicarbonate as a gas forming agent dispersed in the tablet matrix. After reacting with hydrochloric acid, sodium bicarbonate liberates carbondioxide whose bubbles were on the surface of the tablets. It was observed that the gas generated was trapped and protected within the gel, formed by hydration of polymers thus decreasing the density of the tablet below 1.0 and thus promoting buoyancy of tablet. Floating lag time of the tablets was found to be directly related to nature of polymer and its concentration.

On immersion in 0.1N HCl solution pH (1.2) at 37ºC, the tablets made of synthetic polymers floated, and remained buoyant without disintegration for long time. Table 4 shows the seconds, while the formulation containing Carbopol alone did not float at all. This may be due t results of buoyancy study. From the results it can be concluded that the batch containing polymers with concentrations of HPMC 15cps showed less buoyancy lag time (BLT) of 15 o the nature of polymer in the present study.

In case of natural polymer formulations the least buoyancy lag time of 45 was achieved by NPF1 which has Psyllium husk but it got disintegrated within 30 minutes. The formulation containing chitosan that is NPF2 showed maximum buoyancy lag time of 294 seconds but remained floating for 7 hours. The formulation NPF5 which contains Psyllium husk 50mg and Chitosan 150mg showed better buoyancy lag time of 135 seconds with more floating time.

***In-vitro* drug release Study**

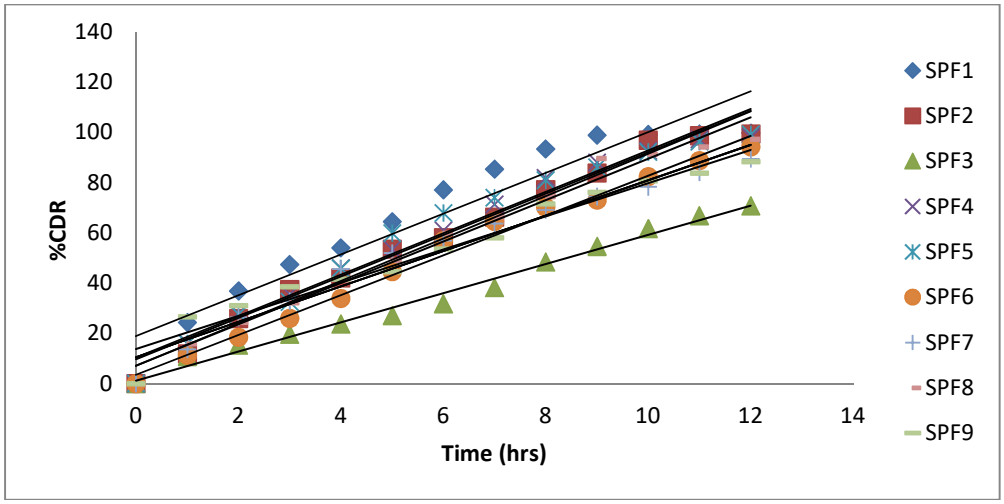

Fig 4: In-vitro drug release profile of formulations coded with SPF

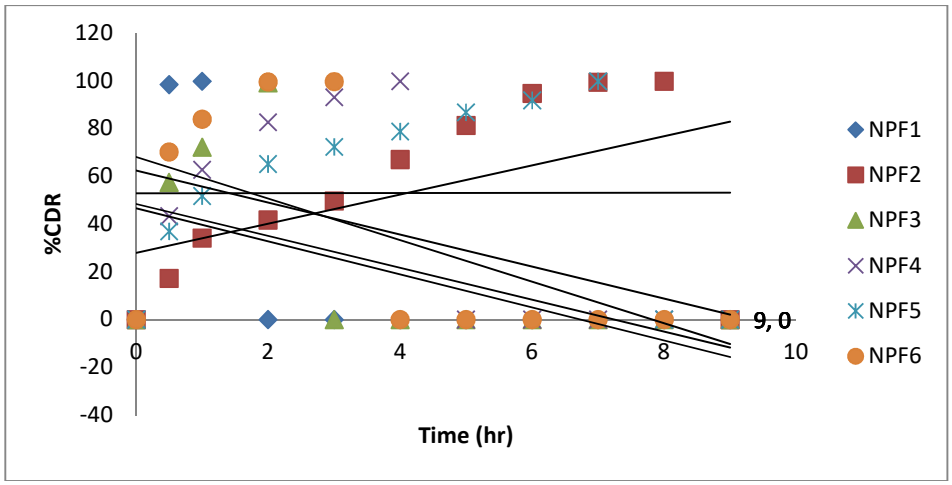

Fig 5: In-vitro drug release profile of formulations coded with NPF

In-vitro dissolution studies all synthetic and natural polymer formulations has shown in table no.5.9 and 5.10 respectively. The synthetic polymer formulations SPF1 and SPF2 has drug release of 98.96 % and 98.72 with in 9 and 11 hours after which they did not float and got dispersed in medium. The formulation SPF5 showed drug release of 99.2% at 12 hours and remained floated for up to 23 hours which is the best formulation when compared to all synthetic formulations and as well as all natural formulations.

The natural polymer formulations NPF-1 has a release of 99.76 at the end of just one hour. The formulation NPF2 and NPF5 had shown released of 99.81 and 99.82 at the end of 8th and 7th hour respectively. Hence it is observed that the formulation containing chitosan remained buoyant for more time (7 hours) but buoyancy lag time is more (294 seconds), But the combination of chitosan 150mg and Psyllium husk powder 50mg the buoyancy lag time was decreased to 135 seconds and floated for 7 hours. The formulationNPF6 which has 1:1 ratio of chitosan and Psyllium husk also got disintegrated just after 2hours. The results shows that the Psyllium husk cannot be used alone for the floating tablets, since it gets disintegrated with short time and cannot retain the shape of tablet. So Psyllium husk should be used in combination of other polymers.

Chitosan if used alone it took more time to float (buoyancy lag time) but remained buoyant for long time (7 hrs) when compared to other natural polymer formulations. So, even chitosan cannot be used alone in floating tablets because it cannot float for more time which is the prerequisite for the floating drug delivery system.

Kinetic Study

Table 6: $R^2$and'n'values for the optimizes formulation SPF5

Zero Order R^2 value	First Order R^2 value	Higuchi R^2 value	Korsmeyer	
			R^2 value	n-value
0.965	0.864	0.970	0.988	0.764

The regression coefficients values for formulation SPF5 of zero order and first order plots were found to be 0.965 and 0.864 respectively which confirms to follow zero order for drug release. Higuchi's plot was almost linear with regression coefficient values of 0.970 for formulation SPF5. The linearity suggests that the release of Famotidine from, formulation SPF5 which contains HPMC K15cps 60mg and Carbopol 40mg was diffusion controlled. Peppas model is widely used when the release mechanism is not well knowor when more than one type of release phenomenon was involved. The 'n' value for SPF5 was found to be 0.764 which is indicates that the release follows non-Fickian diffusion mechanism.

Stability Studies

Table 7: *In-vitro* release data for Accelerated stability study of formulation SPF5

Time (h)	Cumulative Percent Drug release			
	Initial	After one month	After two months	After three months
0	0	0	0	0
1	15.91	15.02	14.75	14.12
2	27.74	27.01	26.31	25.45
3	32.56	32.13	31.82	30.36
4	45.93	45.47	45.07	44.29
5	59.90	59.40	58.8	58.15
6	67.93	67.43	66.91	65.23
7	73.98	72.79	72.31	71.28
8	81.04	80.76	80.23	79.52
9	86.15	85.31	84.87	83.75
10	92.28	91.85	91.30	90.47
11	96.41	96.01	95.49	94.63
12	99.2	98.83	98.31	97.18

Accelerated stability studies were performed for the formulation SPF5. The formulation was stored at 40 ± 2ºC/ 75 ± 5 % RH for 3 months. At an interval of 1, 2 and 3 months the samples were withdrawn and tablet evaluation tests were conducted. There was found to be no appreciable change in the drug content and *in-vitro* drug release rates of the formulation as indicated in the table 7.

CONCLUSION

Hydrodynamically Balanced Systems (HBS) provide an effective approach to enhance gastric retention and control drug release for sustained and site-specific action. In this study, floating tablets of Famotidine were formulated using the wet granulation method with both synthetic polymers (HPMC 15cps, HPMC 100M, Carbopol) and natural polymers (Chitosan, Psyllium husk) along with gas-generating agents such as citric acid and sodium bicarbonate to maintain buoyancy and sustain drug release for 12 hours in simulated gastric fluid. The infrared spectroscopic analysis confirmed drug–polymer compatibility, and all formulations exhibited satisfactory pre- and post-compression characteristics. Synthetic polymer-based formulations performed better than natural polymer ones, with SPF5 (containing HPMC 15cps) showing superior swelling index (68.38), floating lag time (15 seconds), and total floatation duration (23 hours).

The in-vitro release profile of the optimized formulation (SPF5) demonstrated sustained drug release following zero-order kinetics (R^2 = 0.964) and Higuchi's diffusion model, indicating a Non-Fickian release mechanism. Stability studies revealed no significant changes in drug content or release behavior over time, confirming formulation stability. Overall, the developed Famotidine HBS tablets effectively prolonged gastric residence and provided a controlled release pattern, improving bioavailability and therapeutic efficacy for peptic and duodenal ulcer management compared to conventional dosage forms.

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