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Advanced Granulation and Formulation Strategies for Histamine H2 Receptor Antagonists in Peptic Ulcer Disease Management

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ABSTRACT

Present work seeks to formulate floating tablets of famotidine Hydrochloride employing HPMC K4M, HPMC K15M and HPMC K100M polymers. The bulk density of the floating drug delivery systems is lower than the gastric fluid density and therefore has the potential to be suspended in the gastric cavity for long durations of time although the rate of gastric emptying is unaffected. Famotidine is classified as a histamine H2 receptor antagonist and it is on the World Health Organization's Model List of Essential Medicines used for the treatment of peptic ulcer disease (PUD) and gastro oesophageal reflux disease (GERD). Due to its short half-life, short gastric resorption time and multiple dosages any formulator may suggest famotidine as an exceptional drug for formulating floating drug delivery systems. Famotidine floating tablets were developed by using HPMC K4M, HPMC K15M and HPMC K100M by melt granulation technique. The floating tablets were evaluated for following parameters: weight variation, hardness, friability, thickness, drug content, in-vitro buoyancy, drug polymer compatibility (IR study), and in-vitro dissolution studies of tablets. The micromeritic properties were observed to be satisfactory, the tablets were able to remain buoyant in the dissolution medium and the in vitro release studies indicated a good and rapid release nature of the tablets. Formulation F4 of HPMC K100M exhibited good in-vitro buoyancy lag time & floating time in which in lowering the density of all the formulations and in-vitro dissolution showed 96.78% drug release in 12 hrs.

Keywords: *HPMC K4M, HPMC K15M, HPMC K100M, GERD, PUD.*

1. INTRODUCTION

Gastro-retentive drug delivery systems (GRDDS) are dosage forms designed to remain in the stomach for extended periods, enabling controlled drug release at a steady rate. This approach is particularly beneficial for drugs with a narrow absorption window, ensuring they are released at the site where they can be effectively absorbed over a prolonged duration.

Over the past few decades, oral controlled-release (CR) dosage forms have gained significant attention due to their therapeutic benefits, including ease of use, enhanced patient compliance, and formulation flexibility. Despite these advantages, CR systems face physiological challenges, such as inconsistent gastric emptying and motility, which can affect their ability to stay in the desired region of the gastrointestinal (GI) tract. Additionally, the average gastric emptying

time in humans—typically 2 to 3 hours—may limit the amount of drug released and absorbed, particularly in the stomach and upper intestine, which are critical zones for drug absorption. This limitation can lead to suboptimal therapeutic effects [1,2].

To address these challenges, maintaining the drug delivery system in a specific region of the GI tract can provide significant benefits. This is especially true for drugs with limited absorption windows or those prone to degradation in certain GI conditions. By prolonging the gastric retention time, GRDDS can enhance the bioavailability and effectiveness of such medications [3].

Gastric emptying and motility:

Gastric emptying occurs in both fasting and fed states and refers to the process by which substances move from the stomach to the small intestine. This process plays a crucial role in drug absorption, as the small intestine is the primary site for most drug absorption. Rapid gastric emptying can enhance drug bioavailability, especially for drugs that are unstable in the acidic gastric environment and require faster action. On the other hand, delayed gastric emptying can benefit drugs that are poorly soluble, primarily absorbed in the stomach, or in the upper part of the intestine, as it allows more time for their dissolution and absorption [4, 5].

The motility of the gastrointestinal (GI) tract differs between the fasting and fed states. In the fasting state, a cyclic pattern of electrical and muscular activity known as the migrating myoelectric complex (MMC) occurs. This cycle, lasting approximately 2 to 3 hours, consists of four distinct phases [6-9]:

1. **Phase I (Basal Phase):** A period of minimal activity lasting 40 to 60 minutes, characterized by infrequent contractions.
2. **Phase II (Pre-burst Phase):** This phase lasts 40 to 60 minutes and is marked by intermittent contractions and action potentials, with their intensity and frequency gradually increasing as the phase progresses.
3. **Phase III (Burst Phase):** Lasting 4 to 6 minutes, this phase features intense and regular contractions that sweep undigested material from the stomach to the small intestine. It is also referred to as the "housekeeper wave."
4. **Phase IV (Transition Phase):** A brief phase lasting 0 to 5 minutes that marks the transition between Phase III and the next cycle's Phase I.

In the fed state, the motility pattern changes, transitioning from the fasting MMC to the fed or digestive motility pattern. This state is characterized by continuous contractions similar to those in Phase II of the fasting state. These contractions aid in breaking down food particles into smaller sizes (less than 1 mm) and propel them toward the pylorus in suspension form. The onset of the MMC is delayed during the fed state, slowing the gastric emptying rate [10].

Scintigraphy studies assessing gastric emptying rates have demonstrated that controlled-release dosage forms administered orally encounter two significant challenges: limited gastric residence time and variability in gastric emptying rates. These factors can influence the drug's effectiveness and therapeutic outcomes.

Gastric Transit time [11, 12]:

The transit time of a gastrointestinal drug delivery system through the GI tract is a critical physiological factor influencing the development of controlled-release drug delivery systems. The transit pattern varies depending on whether the stomach is in a fasted or fed state, as illustrated in Figure 1.

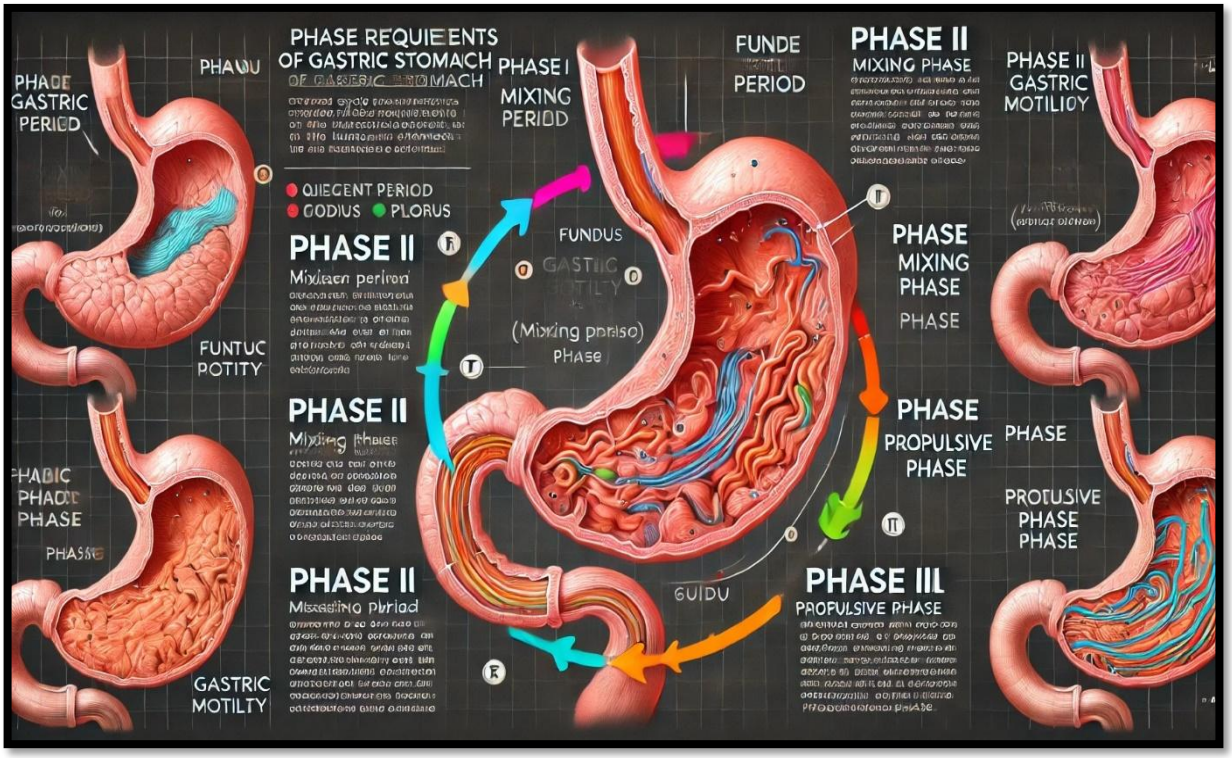


Fig no. 01- Phase cycle Requirements for gastric retention:

For successful gastric retention, certain physiological factors must be considered. To remain in the stomach, the dosage form must meet specific criteria. A primary requirement is its ability to endure the mechanical forces generated by peristaltic waves, as well as the continuous contractions, grinding, and churning actions of the stomach. Additionally, to serve effectively as a gastric retention system, the device must resist premature gastric emptying. Once its function is fulfilled, the system should exit the stomach smoothly without causing discomfort or complications [13-16].

SUITABLE DRUG CANDIDATES FOR GRDDS [17-20]

Controlled-release gastro-retentive drug delivery systems (CRGRDDS) are most suitable for drugs with poor absorption in the colon but better absorption in the upper gastrointestinal tract (GIT). The following categories of drugs are ideal candidates for CRGRDDS:

- **Drugs that act locally in the stomach:** Examples include antacids and medications for *Helicobacter pylori* infection, such as Misoprostol.
- **Drugs primarily absorbed in the stomach:** Examples include Amoxicillin.
- **Drugs with poor solubility in alkaline pH:** Examples include Furosemide, Diazepam, and Verapamil.
- **Drugs with a narrow absorption window:** Examples include Cyclosporine, Methotrexate, Riboflavin, and Levodopa.
- **Drugs rapidly absorbed in the GIT:** Examples include Metronidazole and Tetracycline.
- **Drugs absorbed predominantly in the stomach and upper GIT:** Examples include calcium supplements, Chlordiazepoxide, and Cinnarizine.
- **Drugs that degrade in the colon:** Examples include Ranitidine, Metformin HCl, and Metronidazole.
- **Drugs that disrupt normal colonic microbial flora:** Examples include Amoxicillin trihydrate, an antibiotic effective against *Helicobacter pylori*.

Drugs Unsuitable for GRDDS [21, 22]

Certain drugs are not ideal for gastro-retentive systems due to specific limitations:

- **Drugs with minimal solubility in acidic environments:** For example, Phenytoin.
- **Drugs unstable in gastric conditions:** For example, Erythromycin.

• **Drugs requiring targeted release in the colon:** For example, 5-Aminosalicylic acid and Corticosteroids.

Formulation Considerations for GRDDS [23, 24]

When designing gastro-retentive drug delivery systems, the following factors should be taken into account:

1. The system must achieve effective gastric retention to meet clinical needs.
2. It should have adequate drug loading capacity.
3. The drug release profile must be well-controlled.
4. The system should fully degrade and evacuate once drug release is complete.
5. It should not interfere with gastric motility, including the gastric emptying pattern.
6. The system must not cause adverse local effects in the stomach.

Floating drug delivery systems [25-28]

Floating drug delivery systems (FDDS) are designed to have a lower density than gastric fluids, allowing them to float on the stomach's contents. This floating capability ensures that the system remains in the stomach for an extended period without significantly influencing the gastric emptying rate. While floating, the drug is released gradually at a controlled rate, leading to prolonged gastric residence time (GRT) and more consistent plasma drug concentrations.

For FDDS to function effectively, it must form a cohesive gel barrier and maintain a specific gravity lower than gastric fluids (1.004–1.010). Additionally, the system should dissolve or degrade slowly, ensuring it acts as a drug reservoir for the intended duration.

Types of Floating Drug Delivery Systems [29-32]

FDDS can be categorized based on the mechanism that enables buoyancy. Two primary approaches are used in their design:

1. **Non-Effervescent FDDS:** These systems utilize hydrophilic polymers to form a gel-like structure that traps air or liquid, keeping the dosage form afloat.

2. **Effervescent FDDS:** These systems rely on the generation of gas (such as carbon dioxide) upon reaction with gastric fluids, which helps the dosage form remain buoyant.

FORMULATION INGREDIENTS OF FLOATING DOSAGE FORM [33, 34]

Following types of the ingredients can be incorporated in to floating dosage form,

a) Hydrocolloids

b) Inert fatty materials

c) Release rate accelerants

d) Release rate retardant

e) Buoyancy increasing agents

f) Low density material

g) Miscellaneous

EVALUATION PARAMETERS OF FDDS [35-38]

Various studies in the literature suggest that pharmaceutical dosage forms demonstrating floating behavior in vitro tend to show prolonged gastric residence in vivo. However, it is important to note that good in vitro floating performance does not automatically guarantee effective gastric retention in vivo. The simultaneous presence of food and the complex motility of the stomach can significantly influence the system's behavior, making it challenging to predict in vitro results with certainty. Only well-conducted in vivo studies can definitively confirm whether prolonged gastric residence is achieved.

Key Parameters for Floating Drug Delivery Systems

1. **Floating Time**
2. **Drug Release Profile**
3. **Drug Loading Capacity**
4. **Drug Entrapment Efficiency**
5. **Particle Size Distribution**
6. **Surface Characterization** (for floating microspheres and beads)

Methodology and Formulation Steps: [39, 40]

1. Sieving: Accurately weigh all the ingredients. Famotidine is sieved through mesh size 80, and HPMC K4, HPMC K15, and HPMC K100 are also sieved using mesh size 80.

2. Melting: Melt white beeswax in a China dish.

3. Mixing: Add the Famotidine drug to the molten beeswax and mix thoroughly. Then, incorporate HPMC polymers, sodium bicarbonate, and lactose into the mixture and blend well.

4. Granulation: Allow the mass to cool to room temperature, then scrape it from the China dish. The cohesive mass is passed through sieve no. 20.

5. Lubrication: The granules are mixed with magnesium stearate and talc for lubrication.

6. Compression: The lubricated granules are compressed into tablets using a standard concave punch on a 10-station rotary Proton mini press machine, aiming for an average weight of 200 mg. After compression, tests for weight variation, friability, dissolution, and assay are conducted. The formulations from F1 to F8 are listed in Table 1.

Table no. 01- Formulation of Famotidine tablets

INGREDIENTS (in mg)	FORMULATION BATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
HPMC K4M	0	30	0	0	30	30	0	30
HPMC K15M	0	0	30	0	30	0	30	30
HPMC K100M	0	0	0	30	0	30	30	30
$NaHCO_3$	20	20	20	20	20	20	20	20
Bees wax	30	30	30	30	30	30	30	30
Lactose	98	68	68	68	38	38	38	8
Magnesium stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Average weight	200	200	200	200	200	200	200	200

2. RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies:

Table no. 02- Drug-excipient compatibility

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	

Drug	White powder	No change	No change	Yes
Drug + HPMC K4 M	White powder	No change	No change	Yes
Drug + HPMC K15 M	White powder	No change	No change	Yes
Drug + HPMC K100 M	White powder	No change	No change	Yes

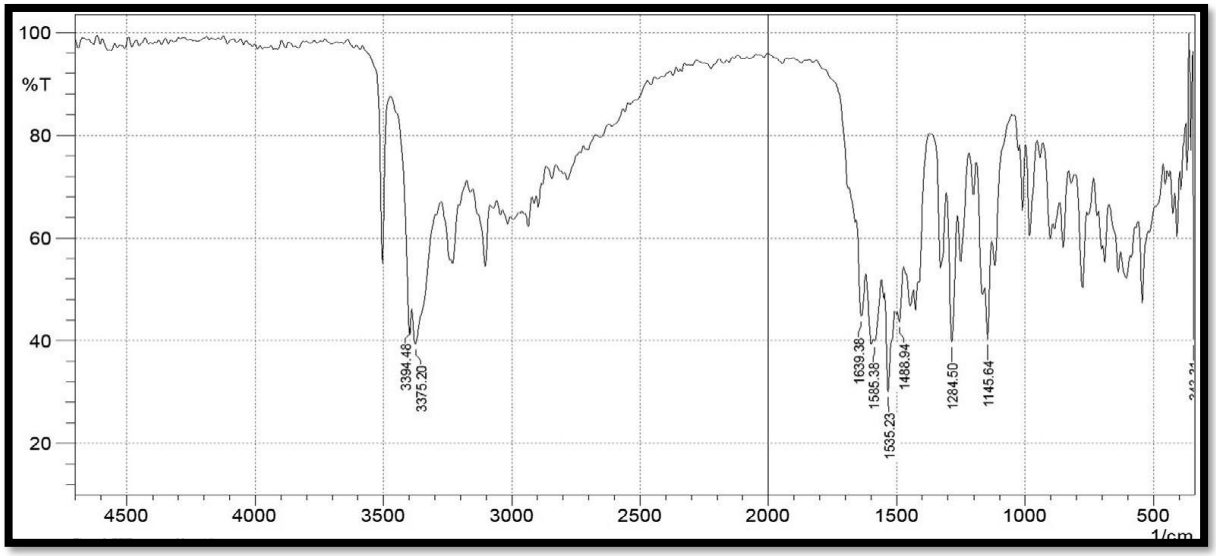


Fig. no. 02- FTIR of Famotidine

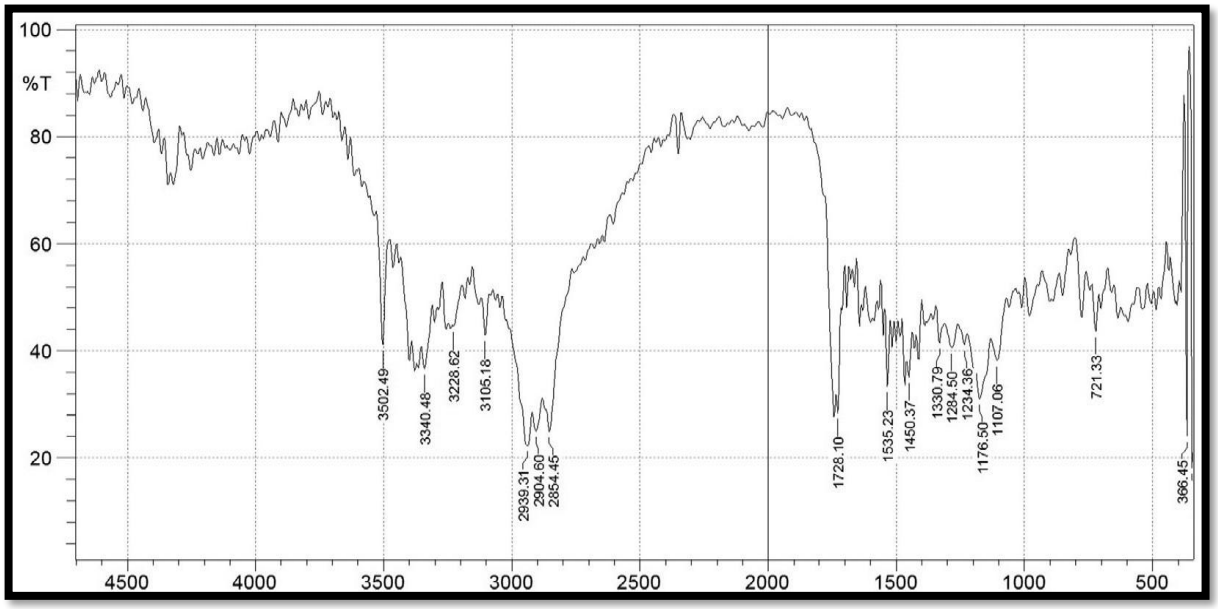


Fig. no. 03- FTIR of Famotidine and Excipients

3. DISCUSSION

The FT-IR spectra demonstrated that there were no significant changes in the peaks, indicating that no interactions occurred between the drug and the excipients. This suggests compatibility between the drug and the polymers used in the formulation. The FT-IR analysis plays an essential role in understanding how the drug and excipients interact, which can affect drug release properties.

Granule Evaluation:

Table no. 03. Showing results of angle of repose, bulk and tapped density, Carr's index, Hausner's ratio

Batch no.	Angle of repose (^{0})	Bulk density (gm/ml)	Tapped density (gm/ ml)	Carr's index (%)	Hausner ratio
F1	26 º 32'	0.2891	0.3503	14.04	1.21
F2	24º 64'	0.2845	0.3394	15.68	1.22
F3	28o 59'	0.2924	0.3349	11.94	1.13
F4	26o12'	0.2875	0.3446	13.96	1.16
F5	23o 62'	0.2862	0.3420	15.13	1.19
F6	24o74'	0.2677	0.3214	13.92	1.15
F7	24 o 77'	0.2743	0.3242	15.42	1.19
F8	26 o 56'	0.2847	0.3177	10.38	1.11

4. DISCUSSION

The angle of repose for the formulations F1-F8 ranged from 23.06° to 28.59°, indicating good flow properties. The compressibility index for the formulations F1-F8 was between 10.38% and 15.6%, suggesting that the blend is suitable for compression with good flow characteristics. These results are summarized in Table 3.

Evaluation of Famotidine Tablets:

Table no. 04- weight variation, Friability, Content Uniformity, Thickness, Hardness, Bouncy Lag Time and Floating Time

Batch no.	Weight variation	Friability	Content uniformity	Thickness (mm)	Hardness (kg/cm^2)	Buoyancy lag time	Total buoyancy time (hrs.)
F1	+ 1.52	0.23	99.65	5.2+0.01	6.2	624	15
F2	±2.37	0.34	99.74	5.1+0.02	7.1	96	3
F3	+ 1.87	0.21	98.34	5.3+0.01	6.5	90	6
F4	+ 1.41	0.27	99.44	5.1+0.03	6.9	84	12
F5	±1.86	0.18	100.38	5.2+0.01	6.3	171	5
F6	±2.56	0.28	99.96	5.3+0.04	7.2	63	10
F7	+2.35	0.29	99.47	5.5+0.01	7.5	44	15
F8	±1.93	0.19	99.35	5.3+0.01	6.4	39	14

5. DISCUSSION

The weight variation of the tablets ranged from +1.23% to +3.09%, which is within the acceptable limits (less than 5%) as per pharmacopoeial standards. The friability was between 0.18% and 0.34%, complying with the pharmacopoeial standard of being less than 1%. The content uniformity of the tablets ranged from 99.37% to 100.38%, meeting the required standards. The thickness of the formulations ranged from 5.1 ± 0.01 mm to 5.5 ± 0.01 mm, and the hardness was between 6.2 and 7.5 kg/cm², indicating satisfactory mechanical strength. Among all the formulations, F1, F4, F7, and F8 exhibited good buoyancy, with all formulations showing buoyancy for up to 12 hours. The data is provided in Table 4.

In-Vitro Release Profile:

Table no. 05- *In-vitro* release profile

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
	8.65	24.79	15.13	7.24	21.32	13.76	5.91	12.25
2	13.12	58.12	34.67	12.09	43.13	24.27	11.64	16.79
3	17.75	90.39	46.21	17.62	67.08	30.14	17.08	22.47
4	25.34		63.90	23.98	91.34	39.51	25.42	26.75
5	29.59		76.39	31.56		46.24	29.32	30.54
6	34.23		92.14	39.34		53.69	31.13	37.67
7	41.09			47.87		67.76	36.41	43.34
8	47.23			55.23		80.09	40.69	49.50
9	53.98			64.42		89.13	46.86	54.71
10	58.14			73.76		92.43	53.63	60.92
11	61.17			84.54			57.20	68.43
12	67.91			96.78			62.32	72.19

6. DISCUSSION

The in-vitro drug release studies for all formulations (F1 to F8) are shown in Table 5. The formulations were designed for sustained drug release, with some formulations like F2, F3, and F5 releasing the drug within 6 hours, while F6 released the drug up to the 10th hour. The desired sustained release formulation was selected based on a target release duration of at least 12 hours. Formulation F4 was chosen as the best formulation because it showed a controlled release profile. The in-vitro release data for F4 is summarized in Table 5, and the release profile is shown in Figure 4.

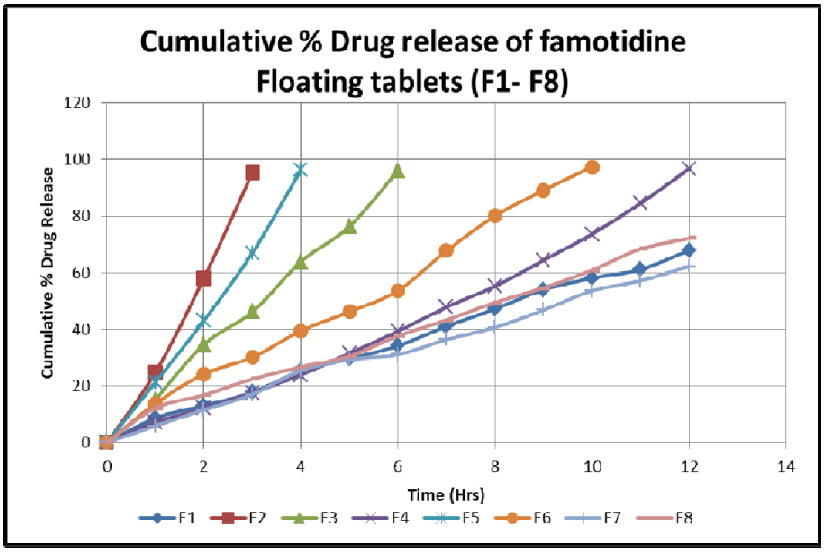


Fig no. 04- Showing in-vitro drug release profile for F1-F8 formulations

In-Vitro Release Profile of Best Formulation (F4):

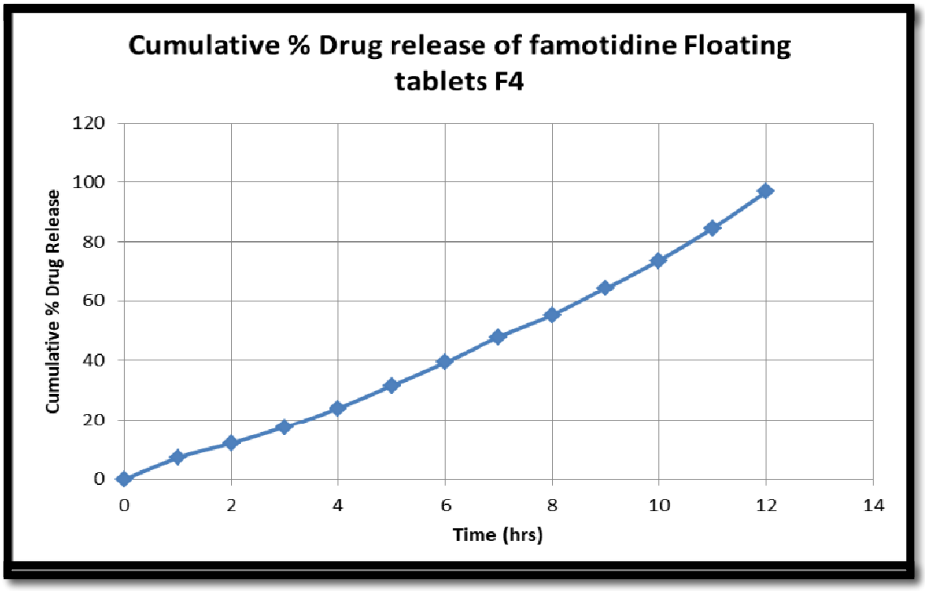


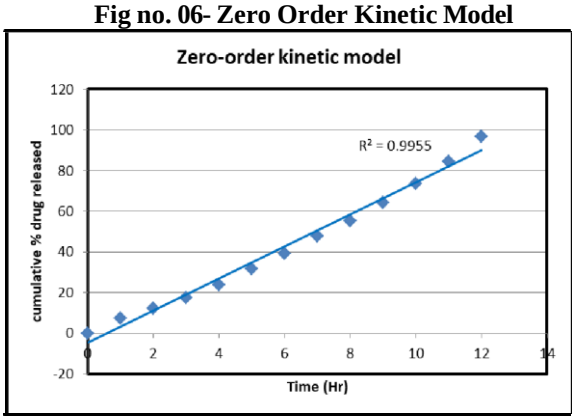
Fig no. 05-In-Vitro Release Profile of Formulation-F4

DRUG RELEASE KINETICS:

Time (Hr.)	Cumulative % Drug released	% Drug remaining	Square root time	Log Cumu % Drug remaining	Log time	Log Cumu % Drug released	% Drug Released
0	0	100	0.000	2.000	0.000	0.000	100
1	7.24	92.76	1.000	1.967	0.000	0.860	7.24
2	12.09	87.91	1.414	1.944	0.301	1.082	4.85
3	17.62	82.38	1.732	1.916	0.477	1.246	5.53
4	23.98	76.02	2.000	1.881	0.602	1.380	6.36
5	31.56	68.44	2.236	1.835	0.699	1.499	7.58
6	39.34	60.66	2.449	1.783	0.778	1.595	7.78
7	47.87	52.13	2.646	1.717	0.845	1.680	8.53
8	55.23	44.77	2.828	1.651	0.903	1.742	7.36
9	64.42	35.58	3.000	1.551	0.954	1.809	9.19
10	73.7	26.3	3.162	1.420	1.000	1.867	9.28
11	84.54	15.46	3.317	1.189	1.041	1.927	10.84
12	96.78	3.22	3.464	0.508	1.079	1.986	12.24

Table. No. 06- Drug release kinetics

Fig no. 06- Zero Order Kinetic Model



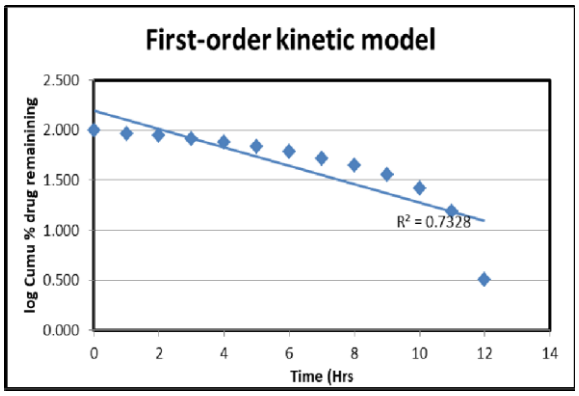


Fig no. 07- First Order Kinetic Model

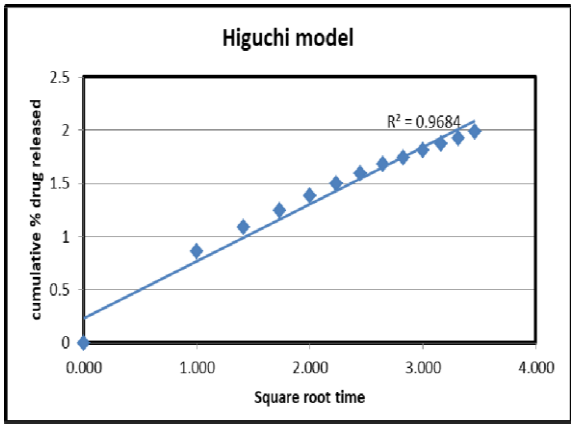


Fig no. 08- Higuchi Model

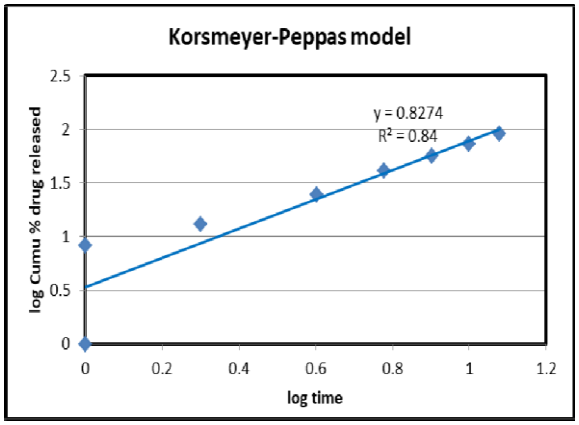


Fig no. 09- Korsmeyer Peppas Model

7. DISCUSSION

The drug release kinetics for formulation F4 were analysed, and the results are presented in Table 6. The drug release followed zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, as shown in Figures 6-9. The release exponent (n) value was 0.8274, indicating that the drug release follows non-Fickian diffusion. This data is further supported by the regression coefficient values provided in Table 7.

Table no. 07- Regression coefficient of F4

Formulation	Regression coefficient (R^2) value			
	Zero-order	First order	Higuchi	Korsmeyer – Peppas (n value)
Famotidine tablets	0.9955	0.7328	0.9684	0.84 (0.8274)

Buoyancy Effect of the Formulation (F4):

Table at 0 mint **Tablet after 01-mint** **Tablet after 05-Mints**

Fig no. 10- Buoyancy table of Formulation F4

Discussion:
The buoyancy of formulation F4 was observed at different time intervals (0, 1, and 5 minutes) and is depicted in Figure 10.

8. SUMMARY

This study focuses on the formulation and evaluation of gastro-retentive drug delivery systems for Famotidine tablets. These systems are designed to prolong the retention of the drug in the stomach by utilizing swelling properties, preventing premature gastric emptying. Preformulation studies, including organoleptic properties, bulk density, Carr's index, Hausner's ratio, melting point, pH, and solubility, were conducted as per the IP specifications. Drug-excipient compatibility studies confirmed no significant interaction between the drug and the excipients. Tablet evaluation for weight variation, friability, hardness, content uniformity, and buoyancy showed that the formulations met the pharmacopoeial standards. In-vitro release studies were carried out using 0.1N HCl, and formulation F4, which used HPMC K100 M, demonstrated the best sustained release profile with drug release up to 12 hours.

9. CONCLUSION

Floating tablets with sustained release properties offer significant advantages, such as site-specific drug delivery, improved absorption, and enhanced efficacy. The technology is simple, easy to adopt, and can be applied to various drugs with poor bioavailability due to limited absorption in the upper gastrointestinal tract. This approach can enhance absorption and improve the bioavailability of these drugs. Furthermore, floating drug delivery systems can be employed in the development of therapies for diseases such as gastric and duodenal cancers, offering a beneficial treatment strategy.

Conflicts of Interest: Nil.

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