



CODEN [USA]: IAJPBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.6635723>Available online at: <http://www.iajps.com>

Research Article

**FORMULATION DEVELOPMENT OF FAMOTIDINE
GASTRORETENTIVE TABLETS BY MELT GRANULATION
TECHNIQUE****H. Padmalatha**

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Article Received: May 2022**Accepted:** May 2022**Published:** June 2022**Abstract:**

The aim of the present study is to formulate and evaluate gastro retentive tablet of famotidine for the treatment of peptic ulcer, thus the action would be specifically in the stomach. Preformulation studies which include Organoleptic properties, Bulk and Tapped densities, Carr's index, Hausner's ratio, Melting point, P^H , Solubility, were carried out as per IP specifications. Drug-excipient compatibility studies were performed which shows that there is no interaction between drug and polymers. Evaluation studies have been performed for tablets include friability, hardness, weight variation, content uniformity, buoyancy studies are as per IP specifications. Drug release studies have been performed by using 0.1N Hcl for 12 hrs. These studies have shown that the formulation F4 gave better drug release upto 12 hrs. which is formulated with HPMC K100 M. Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development to treating various diseases. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

KEYWORDS: Famotidine, Gastroprotective Tablets, Melt Granulation Technique, Kinetic Study**Corresponding author:****H. Padmalatha,**

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Please cite this article in press **H. Padmalatha, Formulation Development Of Famotidine Gastroretentive Tablets By Melt Granulation Technique., Indo Am. J. P. Sci, 2022; 09(6).**

INTRODUCTION

Oral drug delivery systems have dominated other drug delivery systems for human administration due to their various advantages including ease of administration, flexibility in formulation, cost-effectiveness, easy storage and transport, and high patient compliance. However, oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensal flora, gastric retention time of the dosage form, surface area, and enzymatic activity [1]. Conventional drug delivery systems may not overcome the issues imposed by the gastrointestinal tract (GIT) such as incomplete release of drugs, decrease in dose effectiveness, and frequent dose requirement. Therefore, the failure of conventional drug delivery systems to retain drugs in the stomach may lead to the development of GRDDS. These systems offer several benefits such as prolonged gastric residence time (GRT) of dosage forms in the stomach up to several hours, increased therapeutic efficacy of drugs by improving drug absorption, and suitability for targeted delivery in the stomach. In addition, GRDDS can enhance the controlled delivery of drugs by continuously releasing the drug for an extended period at the desired rate and to the desired absorption site until the drug is completely released from the dosage form [1,2].

GRDDS are feasible for drugs that have low absorption in the lower part of the GIT, are unstable and poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine for eradication of *Helicobacter pylori* [3,4,5,6,7,8,9,10,11,12,13,14,15]. Several formulation strategies have been used to design successful controlled release GRDDS including superporous hydrogel, bio/mucoadhesive, raft-forming, magnetic, ion-exchange, expandable, and low- and high-density systems [3,4,5,6,7,8,9].

Various formulation-related factors such as polymer types (nonionic, cationic, and anionic polymers), polymer composition in dosage form, viscosity grade, molecular weight of the polymer, and drug solubility can affect the quality of the gastroretentive dosage form [9]. Moreover, the physicochemical nature of excipients plays an important role in various GRDDS. For instance, density of excipients and composition of effervescent agents are critical factors in effervescent floating systems. In the case of superporous hydrogel systems, high swelling excipients such as crospovidone and sodium carboxymethylcellulose are required to form a super

porous hydrogel [9,16]. Likewise, process variables can also influence the quality of the gastroretentive dosage form, as the density of a tablet can be altered by the compression pressure during tableting [9].

Famotidine is a histamine H2 receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Famotidine is available in different dosage forms, like tablets, solutions and injections. The dose of 20mg, 40 mg is available. Half-life of famotidine is around 2.5 to 3.5 hr; therefore, it is used for floating sustained release of the drug is possible.

The aim of the present study is to formulate and evaluate gastro retentive tablet of famotidine for the treatment of peptic ulcer, thus the action would be specifically in the stomach.

MATERIALS AND METHOD:

Chemicals and reagents are taken from different suppliers such as Famotidine from Molecules India Pvt.Ltd, HPMC K4M, HPMC K15M, HPMC K100M from Sooriyan pharmaceuticals, Bees wax, Sodium bicarbonate, Talc from Fine Chem, industries, Magnesium stearate from Advance labs.

PREFORMULATION [13-17]

Preformulation studies are carried out in order to evaluate the physical and chemical properties of the drug alone and in the combined form with the excipients. These studies are important to predict the physical and chemical properties and stability of the drug and excipients.

PREPARATION OF STANDARD CURVE

Preparation of 0.1 M Hydrochloric acid:

Accurately measure 8.5 ml of hydrochloric acid and sufficient water to make upto 1000 ml.

Preparation of stock solution:

Accurately weigh 100 mg of Famotidine and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl.

Preparation of standard solution:

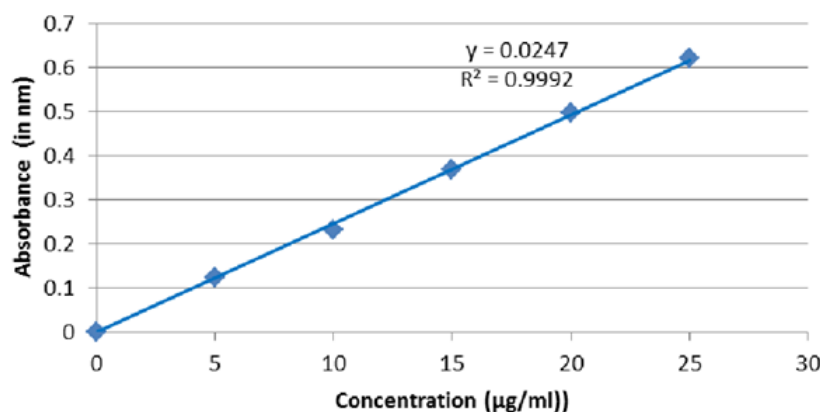
Pipette out 10 ml of the above solution and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl. Then from the standard stock solution withdraw 2ml, 4ml, 6ml, 8ml, and 10ml into five 100 ml different volumetric flasks. Then make up the volume to 100 ml with 0.1M Hcl to get 2, 4, 6, 8, 10 µg/ml concentration.

CALIBRATION CURVE OF FAMOTIDINE:

The absorbance of the prepared stock solutions was measured at 266 nm in an UV spectrophotometer. Plot a graph between concentration (in μ g/ml) vs absorbance (in nm) on X-axis and Y-axis respectively.

Table 1: Calibration curve of Famotidine

S.no.	Concentration(in μ g/ml)	Absorbance (in nm)
1.	0	0.000
2.	5	0.123
3.	10	0.233
4.	15	0.369
5.	20	0.497
6.	25	0.621
Slope	0.0247	
R ²	0.9992	

Calibration curve of Famotidine**Fig.no.1. Calibration curve of Famotidine****FORMULATION AND DEVELOPMENT OF FAMOTIDINE TABLETS****Table 2: 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

STEPS INVOLVED IN FORMULATION:

Sieving: The ingredients were accurately weighed. Famotidine was sieved from mesh no. 80 then, HPMC K4, HPMC K15, HPMC K100, Sieved through mesh no. 80.

Melting: White bees wax was melted in a China dish.

Mixing: Add Famotidine drug on molten mass and stirred well to mix. Then add HPMC polymer, sodium bicarbonate and lactose and mix it well.

Granulation: Then the mass was allowed to cool to room temperature and then scrapped from China dish. The coherent mass was passed through sieve no. 20.

Lubrication: The resulting granules were mixed with

magnesium stearate and talc.

Compression: The lubricated granules were compressed into tablets using standard concave punch with 10 station rotary Proton mini press machine and keeping average weight of 200 mg. After compression weight variation, Friability, dissolution and assay test were carried out.

RESULTS AND DISCUSSION:**Preformulation studies:**

Organoleptic properties: The tests were performed as per the procedure. The results were tabulated below.

Table 3: organoleptic properties

Test	Specifications/limits	Observations
Colour	White to pale yellow	White powder
odour	Odourless	Odourless

The result complies as per specifications.

Physical properties:**Angle of repose:**

It was determined as per procedure. The results were tabulated below.

Table 4: flow properties

Material	Angle of repose
Famotidine	27.14 ⁰

The results show that the drug having poor flow.

Bulk density and tapped density:

It was determined as per procedure. The results were tabulated below.

Table 5: bulk density and tapped density

Material	Bulk density(gm/ml)	Tapped density(gm/ml)
Famotidine	0.48	0.44

Powder compressibility:

It was determined as per procedure. The results were tabulated below.

Table 6: powder compressibility

Material	Compressibility index	Hausner's ratio
Famotidine	11.27	1.44

Melting point:

It was determined as per procedure. The results were tabulated below.

Table 7: Melting point

Material	Melting point range	Result
Famotidine	163.5 ° C	163 °c

The result indicates that the Famotidine drug was pure one.

SOLUTION PROPERTIES P^H**of the solution:**

It was determined as per procedure. The results were tabulated below.

Table 8: P^H of the solution

Material	test	Specification	observation
Famotidine	P ^H	5-6(1% aqueous solution)	6.22

The result indicates that the Famotidine drug was pure one.

Solubility:

It was determined as per procedure. The results were tabulated below.

Table 9: Solubility

Material	test	Specification	observation
Famotidine	Solubility	Freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.	Complies

The result complies as per specification.

Drug-excipient compatibility studies:**Discussion:**

The FT-IR peaks were observed that there is no change in the spectrum representing that there is no interaction between the drug and polymers and other excipients. These peaks play a vital role with respect to drug release.

Table 10: Drug-excipient compatibility

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

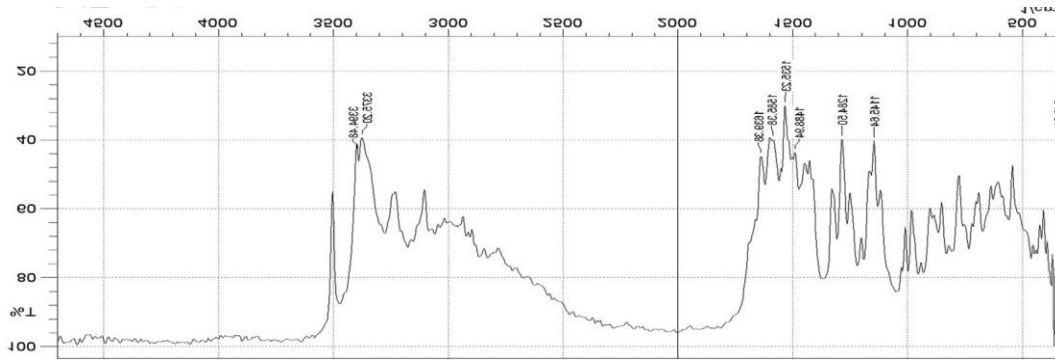


Fig. no. 2. FTIR of Famotidine

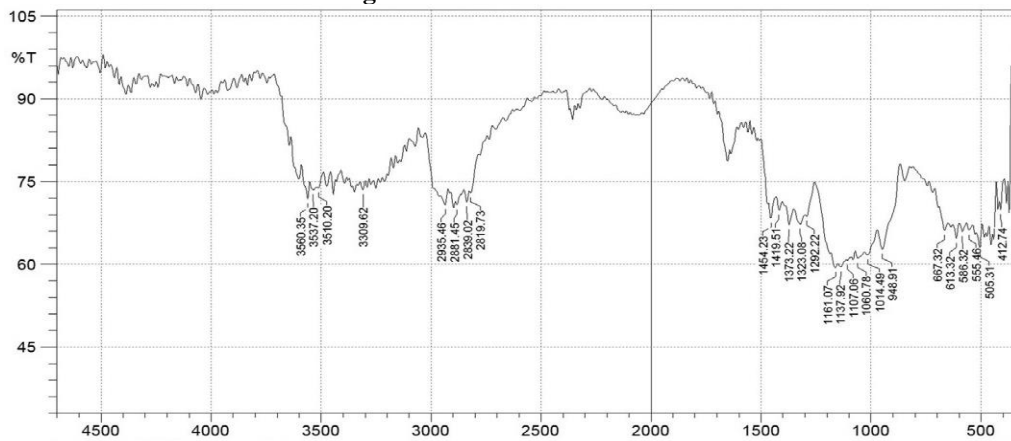


Fig. no. 3. FTIR of HPMC

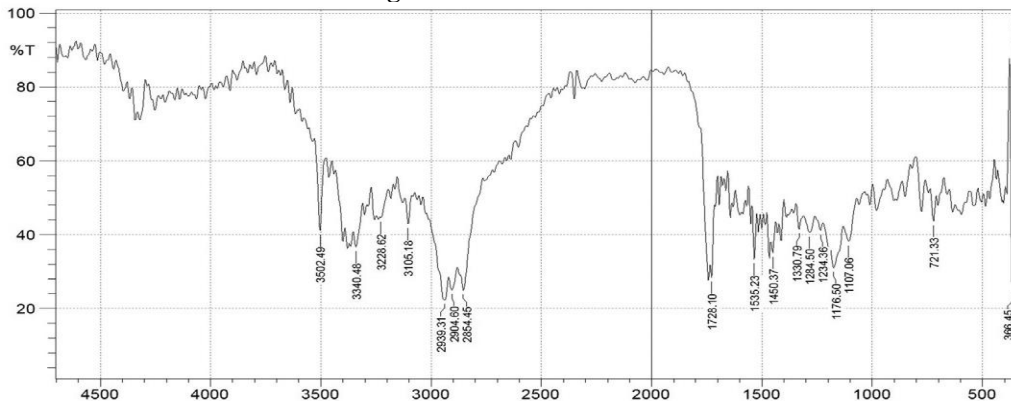


Fig. no. 4. FTIR of Famotidine + excipients

Evaluation of granules:**Table 11: showing results of angle of repose, bulk and tapped density, Carr's index, hausner ratio**

Batch no.	Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner ratio
F1	26 ° 32'	0.2891	0.3503	14.04	1.21
F2	24° 64'	0.2845	0.3394	15.68	1.22
F3	28° 59'	0.2924	0.3349	11.94	1.13
F4	26°12'	0.2875	0.3446	13.96	1.16
F5	23° 62'	0.2862	0.3420	15.13	1.19
F6	24°74'	0.2677	0.3214	13.92	1.15
F7	24 ° 77'	0.2743	0.3242	15.42	1.19
F8	26 ° 56'	0.2847	0.3177	10.38	1.11

Discussion: The angle of repose for the formulations F1-F8 was found to be in the range 23⁰.62' to 28⁰.59' shows good flow. Compressibility index for the formulations F1-F8 found between 10.38% to 15.6% indicating that the blend has good flow property for compression.

EVALUATION OF FAMOTIDINE TABLETS**Table 12: weight variation and friability**

Batch no.	Weight variation	Friability	Content uniformity
F1	± 1.52	0.23	99.65
F2	±2.37	0.34	99.74
F3	± 1.87	0.21	98.34
F4	± 1.41	0.27	99.44
F5	±1.86	0.18	100.38
F6	±2.56	0.28	99.96
F7	±2.35	0.29	99.47
F8	±1.93	0.19	99.35

Discussion: The weight variation of the above tablets are in the range of ± 1.23 to 3.09 % (below 5%) complying with the pharmacopeial standards. The friability of the tablets are in the range of 0.18 % to 0.34% (below 1%) complying with the pharmacopeial standards. The content uniformity of the tablets are in the range of 99.37 to 100.38% complying with the pharmacopeial standards.

THICKNESS AND HARDNESS:**Table 13: Thickness and hardness**

Batch no.	Thickness(mm)	Hardness(kg/cm ²)
F1	5.2±0.01	6.2
F2	5.1±0.02	7.1
F3	5.3±0.01	6.5
F4	5.1±0.03	6.9
F5	5.2±0.01	6.3
F6	5.3±0.04	7.2
F7	5.5±0.01	7.5
F8	5.3±0.01	6.4

Discussion: The thickness of the formulations was found to be in the range of 5.1 ± 0.01 to 5.5 ± 0.01 mm. The hardness of the tablets was found to be in the range of 6.2 to 7.5 kg/cm² indicating a satisfactory mechanical strength.

BUOYANCY LAG TIME AND TOTAL FLOATING TIME

Table 14: Showing buoyancy lag time and total floating time

Batch no.	Buoyancy lag time	Total buoyancy time(hrs)
F1	624	15
F2	96	3
F3	90	6
F4	84	12
F5	171	5
F6	63	10
F7	44	15
F8	39	14

Discussion: From the results formulations F1, F4, F7, F8 shows good buoyancy, all formulations showed buoyancy up to 12 hrs.

In-vitro release profile:

Table 15: *in-vitro* release profile

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	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	95.39	46.21	17.62	67.08	30.14	17.08	22.47
4	25.34	-	63.90	23.98	96.34	39.51	25.42	26.75
5	29.59	-	76.39	31.56	-	46.24	29.32	30.54
6	34.23	-	96.14	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	-	-	73.7	-	97.43	53.63	60.92
11	61.17	-	-	84.54	-	-	57.20	68.43

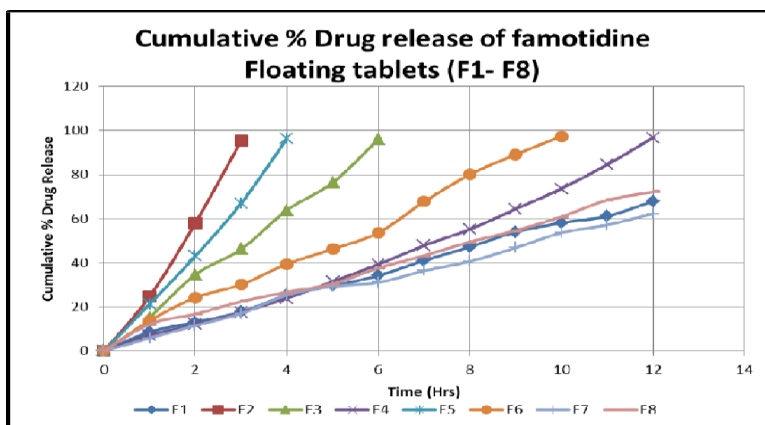


Fig. no. 5. Showing *in-vitro* drug release profile for F1-F8 formulations

From the in-vitro dissolution study of all formulations, formulation F1 gave 84% release at the end of 24th hour, hence F1 have choosen as best formulation.

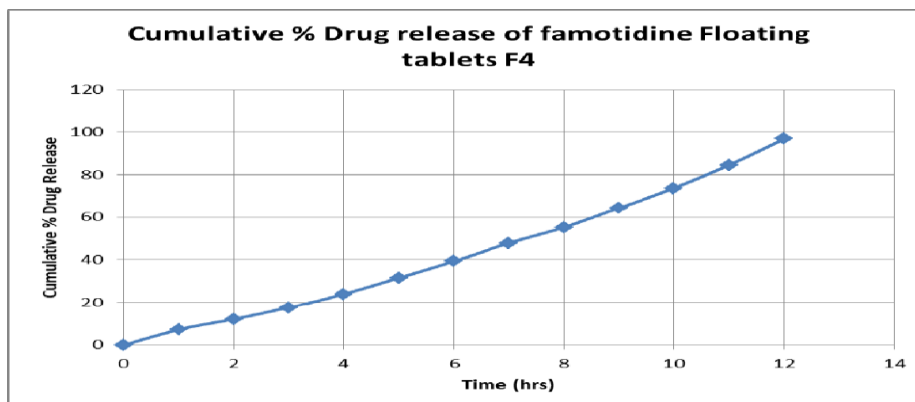


Fig. no. 6. Showing in-vitro release profile of best formulation(F10)

DRUG RELEASE KINETICS:

Table 16: 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

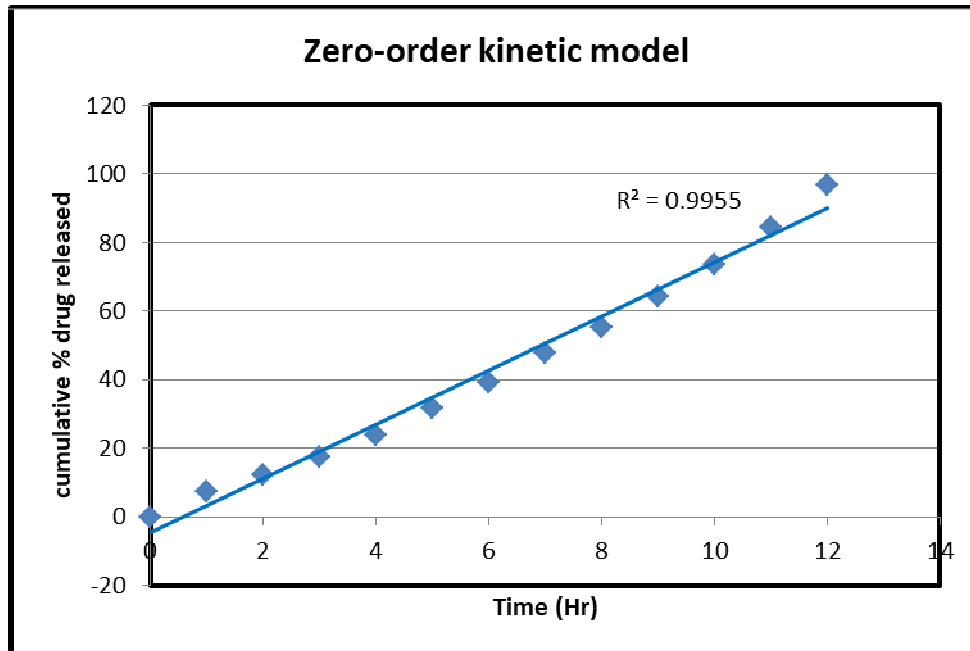


Fig. no 7: Zero Order Kinetic Model

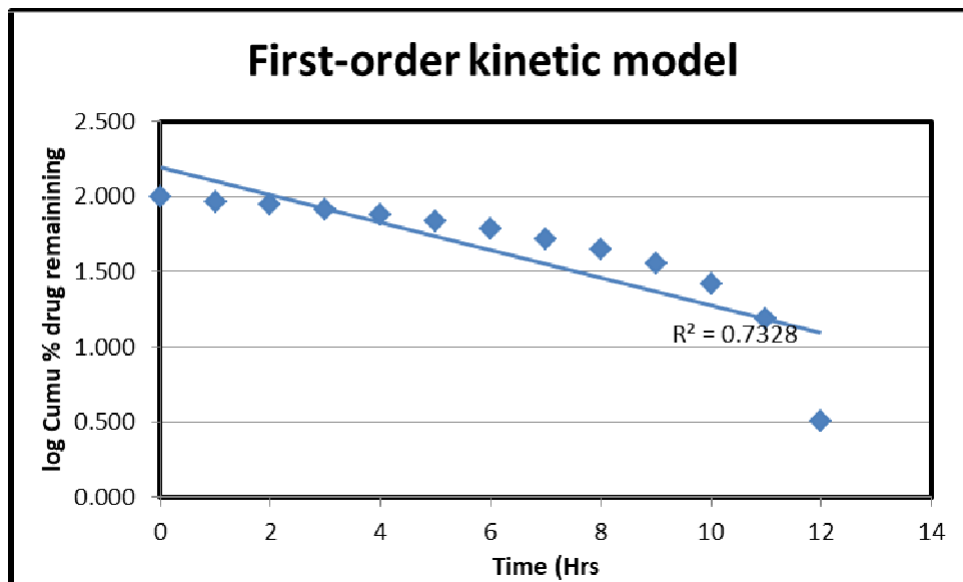


Fig. no. 8: First Order Release Kinetics

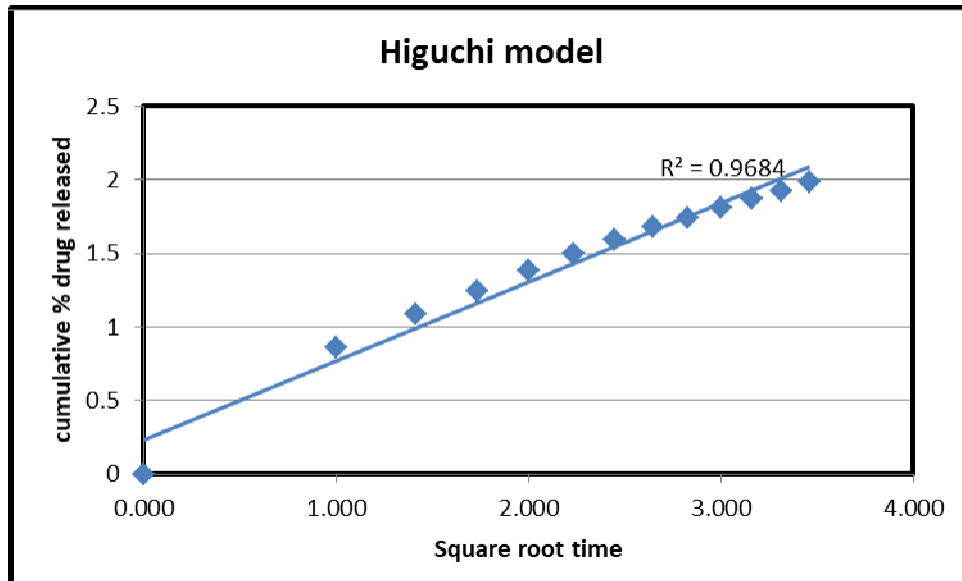


Fig. no. 9: Higuchi model

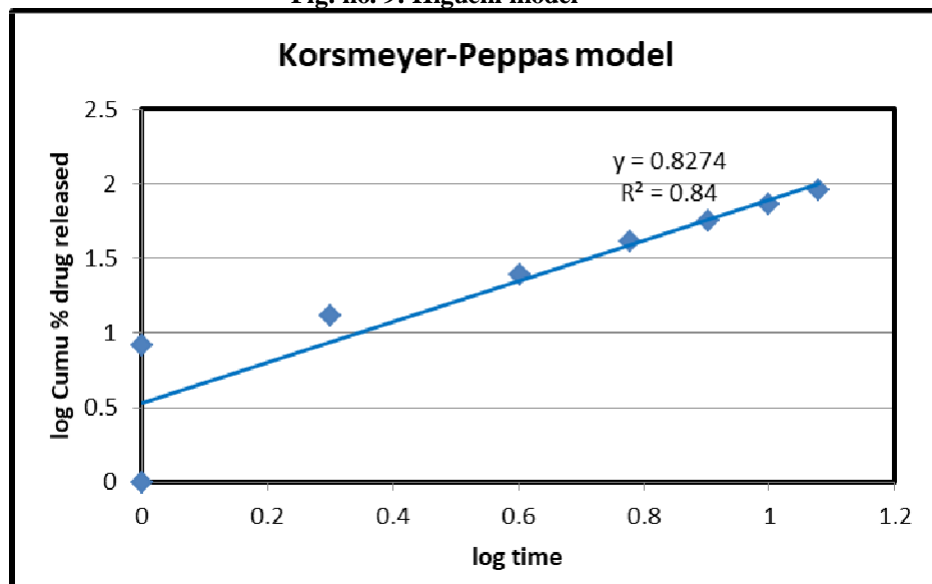


Fig. no. 10: Korsmeyer Peppas Model

Table.No:17. Regression coefficient of F10

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

N value = 0.8274

The regression coefficient values and n values show that the drug releases follow Non - Fickian release.

SUMMARY

The present study involves the formulation and evaluation of gastroretentive drug delivery of Famotidine tablets. This type of drug delivery helps to retain the drug in the stomach. The swelling property of the formulation helps to retain the drug in the stomach, by swelling to such an extent so that cannot pass out of the stomach.

Preformulation studies which include Organoleptic properties, Bulk and Tapped densities, Carr's index, Hausner's ratio, Melting point, P^H , Solubility, were carried out as per IP specifications.

Drug-excipient compatibility studies were performed which shows that there is no interaction between drug and polymers.

Evaluation studies have been performed for tablets include friability, hardness, weight variation, content uniformity, buoyancy studies are as per IP specifications.

Drug release studies have been performed by using 0.1N Hcl for 12 hrs. These studies have shown that the formulation F4 gave better drug release upto 12 hrs. which is formulated with HPMC K100 M

CONCLUSION:

Floating tablets with sustained release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

Moreover, floating mechanism doesn't require any complex technology and hence, easy to adopt. Hence, it can be employed in various developmental studies based on requirement.

Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development to treating various diseases.

Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

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