Formulation and Evaluation of Floating Microspheres Containing Famotidine for Gastro-Retentive Drug Delivery

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Abstract:

The floating drug delivery system, also known as hydro dynamically balanced systems, represents one of the various strategies developed to enhance the gastric retention time of pharmaceuticals. These microspheres are typically free-flowing powders composed of either natural or synthetic polymers, ideally with a particle size of less than 200 μm. When a drug is either dispersed or dissolved within the microsphere matrix, it offers the potential for controlled drug release.[1] Microspheres are classified as multi-particulate delivery systems designed to facilitate the controlled release of medication from the dosage form. This approach aims to improve bioavailability, minimize adverse effects, extend the duration of action, and reduce variability in drug absorption in patients. Additionally, it can decrease the frequency of dosing and mitigate side effects during extended treatment. The formulation of long-acting dosage forms is essential for achieving rapid delivery to effective biological sites. [2,3] Famotidine, an H2 receptor antagonist utilized in the treatment of ulcers, can benefit from being formulated as floating microspheres. This formulation not only allows for targeted action but also enhances sustainability and reduces the dosing interval. The preparation of famotidine as floating microspheres is typically accomplished through the solvent evaporation method, which is a widely favoured technique for creating controlled-release microspheres. This process involves creating an emulsion by introducing a dispersed phase containing the drug, polymer, and suitable dispersing agent into an organic solvent, which is then mixed with a dispersion medium that is immiscible with the dispersed phase. The removal of the solvent from the droplets formed in the emulsion results in the formation of mini matrices.[5,6] The resulting famotidine microspheres undergo various analytical evaluations, including particle size analysis, scanning electron microscopy (SEM) analysis, in vitro dissolution studies, and stability assessments.

Keywords: Famotidine; Floating microspheres; Solvent evaporation; Gastric retentive drug delivery systems; Controlled release, Stability studies

1. Introduction

The oral drug delivery system is favoured due to its ease of administration, high patient compliance, and versatility. To create an effective oral drug delivery system, it is essential to optimize both the duration the system remains in the gastrointestinal tract and the rate at which drugs are released from it. Drugs that are rapidly absorbed in the gastrointestinal tract and possess a short half-life are quickly cleared from the bloodstream, necessitating frequent dosing. To mitigate these challenges, oral controlled release formulations have been developed to facilitate a gradual release of the drug into the gastrointestinal tract, thereby maintaining a stable drug concentration.[1] Dosage forms intended to stay in the stomach are known as gastro-retentive drug delivery systems (GRDDS). These systems possess a lower bulk density than gastric fluids, enabling them to float on the stomach contents and remain there for a prolonged period without affecting the gastric emptying rate.[2] A gastro-retentive drug delivery system (GRDDS) plays a crucial role in improving the bioavailability of drugs that are poorly soluble, unstable at higher intestinal pH or in the colonic environment, and those that are primarily absorbed in the stomach due to a limited absorption window.[3]

Drug Suitable for Gastro-retentive Drug Delivery System

Drugs that are locally active in the stomach include antacids and misoprostol. Some drugs, such as riboflavin and furosemide, have a narrow absorption window in the gastrointestinal tract. Drugs such as ranitidine HCl and captopril are unstable in the colonic environment.

Additionally, certain antibiotics target normal colonic microbes, such as those effective against Helicobacter pylori. Some drugs, including chlordiazepoxide and diazepam, exhibit low solubility at high pH levels.

Drug Unsuitable for Gastro-retentive Drug Delivery System

Drugs that are unsuitable for gastro-retentive drug delivery systems include those with very limited solubility in acidic conditions, such as phenytoin, and those that are unstable in the gastric environment, like erythromycin. Furthermore, drugs designed for selective release in the colon, such as 5-aminosalicylic acid and corticosteroids, also fall into this category. Gastro- retentive dosage forms (GRDF) refer to dosage forms that can be retained in the stomach.

High-Density System

This type of GRDF has a density of approximately 3 g/cm³, allowing it to remain lodged in the stomach's rugae. These systems can be sustained in the lower part of the stomach as long as they do not exceed a maximum threshold density of 2.4-2.8 g/cm³. A significant drawback of this system is the technical challenges associated with manufacturing a large quantity of the drug product.

Swelling and Expandable System

Expandable GRDFs are generally designed in three configurations, with a smaller configuration facilitating easier oral intake. The pyloric sphincter plays a role in the formation of a smaller structure within the stomach, which occurs when retention is no longer required. Swelling typically results from osmosis, while unfolding is attributed to mechanical shape memory.

Mucoadhesive or Bio adhesive System

These systems incorporate bio adhesive agents that facilitate adherence to the stomach walls, thereby preventing gastric emptying. Bio/Mucoadhesive systems attach to the surfaces of gastric epithelial cells or mucin, thereby prolonging gastric retention time (GRT) by 30enhancing the intimacy and duration of contact between the dosage form and the biological membrane.

Super Porous Hydrogel

These swellable systems feature an average pore size exceeding 100μm and can reach equilibrium swelling within a minute due to rapid water absorption through capillary wetting via multiple interconnected open pores. They expand significantly and are expected to possess sufficient mechanical strength to withstand the pressure exerted by gastric contractions.

Magnetic System

Magnetic dosage forms contain a small internal magnet and are controlled by an external magnet to regulate their transit through the gastrointestinal tract. From both formulation and technological perspectives, the Floating Drug Delivery System (FDDS) represents a straightforward and logical approach to developing Gastro-Retentive Drug Formulations (GRDF).

2. Materials and Methods

Table1: Comparison between convention DDs and GRDDs.

Absorption	Convention DDs	GRDDs
Toxicity	Hight risk of toxicity	Low risk of toxicity
Patient compliance	Less	Improves compliance
Durg with narrow absorption window in small intestine	Not much advantageous	Suitable
Drugs having rapid absorption through GIT	Not much advantageous	Very much advantageous
Drugs which degrades in the colon	Not much advantageous	Very much advantageous
Drugs which are poorly soluble at an alkaline pH	Not much advantageous	Very much advantageous
Dose dumping	Hight risk of dose dumping	No risk of dose dumping

Floating Drug Delivery System

FDDS, also known as Hydro-dynamically Balanced Systems (HBS), are low-density systems designed to float on gastric contents, allowing them to remain in the stomach for an extended duration while releasing the drug at a controlled rate. This floating mechanism enhances gastro retention time and

minimizes fluctuations in drug release.[4] Floating microspheres, also known as hollow microspheres, are a type of gastro retentive drug delivery system that employs a non-effervescent mechanism to remain buoyant in the stomach. These microspheres are essentially spherical, empty particles devoid of a core, consisting of free-flowing powders made from proteins or synthetic polymers, typically ranging in size from 1 to 1000 micrometres.[5] Drugs used in the treatment of peptic ulcers are mainly classified into three categories: Antacids, Anticholinergics, H2 receptor antagonists**.** The objective of the present study is to formulate and evaluate Famotidine floating microspheres using a cost-effective and simple technique. Famotidine, an H2-receptor antagonist, is widely used for the treatment of ulcers. By developing it in the form of floating microspheres, the drug can provide targeted action, sustained release, and reduced dosing frequency. This formulation enhances drug absorption and bioavailability by allowing it to remain in the stomach for an extended period, thus improving therapeutic efficacy. A gastro-retentive drug delivery system (GRDDS) is designed to control the pharmacokinetic release of a drug at a specific site to optimize its pharmacological effect.

Basic Gastrointestinal Tract Physiology

The stomach is anatomically divided into three regions: the fundus, body, and antrum (pylorus). Fundus: Proximal part of the stomach. Body: The body functions as a storage site for undigested food material. Pylorus: It is a site for mixing of contents and act as a pump for gastric emptying by propelling actions.

Stomach Physiology

The stomach is a dilated section of the digestive tract located between the oesophagus and the small intestine. In its empty state, the stomach contracts and its mucosa and submucosa form folds called rugae. There are four major types of secretory epithelial cells in the stomach lining and gastric glands: Mucous cells: Secrete alkaline mucus. Parietal cells: Produce hydrochloric acid (HCl). Chief cells: Secrete pepsin, a proteolytic enzyme. G cells: Release the hormone gastrin.

Gastric Emptying Rate

Gastric emptying occurs during both fasting and fed states. During fasting, a cyclic pattern of electrical activity, known as the migrating myoelectric complex (MMC), occurs every 2 to 3 hours. This cycle moves through the stomach and intestines and plays a key role in gastric motility during the fasting state. Floating microspheres containing famotidine were prepared using a combination of excipients, including sodium alginate as the core-forming agent; HPMC K4M, HPMC K15M, and HPMC K100M as rate-controlling agents; calcium carbonate as the gas-generating agent; and calcium chloride as the cross-linking agent. The microspheres were formulated using the ionotropic gelation technique, as detailed in Table1. Initially, a 2% (w/v) sodium alginate solution was prepared by dissolving sodium alginate in distilled water under continuous magnetic stirring. After achieving a clear solution, a specified amount of famotidine was added, along with varying concentrations of HPMC polymers and calcium carbonate. This mixture was stirred at 500 rpm at room temperature to ensure uniform dispersion. To remove entrapped air, the dispersion was sonicated for 30 minutes The resulting homogeneous mixture was then

extruded dropwise through a 20G needle fitted to a 10 ml syringe into 100 ml of 1% (w/v) calcium chloride solution, which was continuously stirred at 100 rpm for 10 minutes to promote gelation. The formed microspheres were collected, washed thoroughly with distilled water, and dried in a hot air oven at 60°C.

Effervescent Floating Drug Delivery Systems (FDDS):

Gas-Generating System:

Utilizes a chemical reaction (typically between citric or tartaric acid and carbonate or bicarbonate salts) to release carbon dioxide which decreases the system's density and allows it to float on gastric fluids.

Volatile Liquid Containing System:

This system includes a floating chamber filled with a volatile liquid, such as cyclopentane or ether, which vaporizes at body temperature, causing the chamber to inflate and enhance buoyancy. Typically, it comprises two compartments: one that holds the drug and another that contains the volatile liquid.

Non-Effervescent Floating Drug Delivery Systems:

Colloidal Gel Barrier System: Forms a gel-like barrier that traps gas and maintains buoyancy. Bi-layer Floating Tablets: Comprises two layers: an immediate-release layer for rapid drug release and a floating layer that maintains the buoyancy of the dosage form. Microporous Compartment System: Contains pores that allow fluid exchange while retaining air, thus maintaining flotation. Floating Beads/Alginate Beads: Made using alginate polymers that trap gas and form beads capable of floating. Micro-balloons/Hollow Microspheres: Hollow, low-density microspheres that remain buoyant because of their air-filled inner core.

Raft-Forming Systems (Effervescent FDDS)

These systems achieve buoyancy through a floating chamber filled with gas (such as CO_2), vacuum, air, or a liquid that vaporizes at body temperature. Buoyancy is often enhanced by an effervescent reaction between organic acids (e.g., citric acid) and carbonates or bicarbonates, generating CO_2 gas. Additionally, swellable polymers like chitosan or other polysaccharides are incorporated to form a matrix that supports flotation.

Gas generation system

This innovative gas generation system employs an effervescent reaction between citric acid or tartaric acid and carbonate or bicarbonate salts to produce CO2, thereby decreasing its specific gravity and enabling it to float over chi.

Volatile liquid storage system

Storage systems for volatile liquids are comprised of an inflatable chamber that contains a volatile liquid, such as cyclopentane or ether, which vaporizes at body temperature to expand the chamber within the stomach. This system includes two chambers: one for the drug and another for the volatile liquid.

Non-Effervescent Floating Drug Delivery Systems (FDDS)

In the gastrointestinal (GI) tract, non-effervescent FDDS operate through mechanisms such as polymer swelling or bio-adhesion to the mucosal lining. The commonly used excipients in these systems include: Hydrophilic gums. Gel-forming or highly swellable cellulose-based hydrocolloids. Polysaccharides and matrix-forming agents such as polymethacrylates, polycarbonates, polystyrenes, and polyacrylates,

along with bio-adhesive polymers like Carbopol and Chitosan, are commonly used in drug delivery systems."

Colloidal Gel Barrier Systems / Single-Layer Floating Tablets

These systems typically consist of one or more highly swellable gel-forming cellulose-type hydrocolloids, polysaccharides, or polymers. Upon contact with gastric fluids, they swell to form a matrix that maintains buoyancy in the stomach.

Bi-Layer Floating Tablets

These tablets are designed with two layers: The immediate-release layer, which provides an initial drug release. The sustained-release layer, which absorbs gastric fluid and swells to form a gel barrier. This barrier lowers the tablet's density, allowing it to float.

Microporous Compartment Systems

In this system, the drug is enclosed within a microporous compartment featuring small openings on the top and bottom walls. This design allows fluid exchange while maintaining buoyancy.

Multi-Particulate Systems

Floating Beads / Alginate Beads: These oral dosage forms consist of numerous small, discrete units. They are typically made using alginate or other polymers that trap gas and enable the beads to float.

Micro-balloons / Hollow Microspheres

Also known as hollow microspheres, these low-density systems float on gastric fluid. When placed in aqueous media, they can maintain buoyancy for up to 12 hours in vitro.

Raft-Forming Systems

Raft-forming systems are frequently utilized for the administration of antacids and treatments for gastrointestinal infections or disorders. When they come into contact with gastric fluid, the gel-forming solution expands to create a dense, viscous gel. This gel traps CO_2 bubbles, forming a floating "raft" on the stomach's contents. The drug is gradually released from this floating layer, providing sustained action in the stomach.

Buoyancy Percentage

The efficiency of buoyancy in microspheres is determined by the formula:

$$\textbf{Buoyancy (\%)} = [Wf / (Wf + Ws)] \times 100$$

Where, Wf represents the weight of the floating microspheres and Ws denotes the weight of the settled microspheres.

Drug-Excipient (DE) Interactions

These interactions are typically analyzed using Fourier Transform Infrared Spectroscopy (FTIR). The appearance of new peaks and/or the disappearance of existing ones in the IR spectrum may indicate potential interactions between the drug and excipients.

Evaluation of Floating Drug Delivery Systems

Bulk Density

The bulk density (Db) is defined as the ratio of the total mass of the powder (m) to its bulk volume (Vo).

$$Db = m / Vo$$

Tapped Density:

Tapped density (Dt) is defined as the ratio of the total mass of the powder (m) to its tapped volume (Vi).

$$Dt = m / Vi$$

Compressibility Index

The flowability of a powder can be assessed by measuring its bulk density (ρ_0) and tapped density (ρt), and observing the rate at which it compacts. The compressibility index is calculated using the following formula:

$$\text{Compressibility Index (\%)} = [(\rho t - \rho_0) / \rho t] \times 100$$

Where, ρ_0 = Bulk density (g/mL), ρt = Tapped density (g/ml)

Hausner's Ratio

Hausner's Ratio is an indicator of powder flow properties, calculated by dividing the tapped density by the bulk density using the formula:

$$\text{Hausner's Ratio} = \rho t / \rho_0$$

Table 2: Specification for Carr's index and Hausner's ratio.

S. no.	Flow ability	Carr's index (%)	Hausner's ratio
1	Excellent	0-10	1.00-1.11
2	Good	10-16	1.12-1.18
3	Fair	16-20	1.19-1.25
4	Possible	21-25	1.26-1.34
5	Poor	26-31	1.35-1.45

Angle of Repose

The assessment of frictional forces in loose powders or granules can be conducted by evaluating the angle of repose. This angle indicates the maximum slope between the surface of a pile of powder or granules and the horizontal plane. To ascertain this angle, the granules are permitted to flow freely through a funnel positioned on a stand at a predetermined height (h). Subsequently, the angle of repose is calculated by measuring the height and radius of the resulting heap of granules.

$$\text{Tan } \theta = (h/r); \ \theta = \tan^{-1}(h/r)$$

Where, θ = Angle of repose h = Height of the heap r = Radius of the heap

Table 3: Relationship Between Angle of Repose and Powder Flow.

Angle of Repose	Power of flow
<25	Excellent
25-30	Good
30-40	Passable

25>40	Very poor

Floating Time

The floating time was determined using a USP Dissolution Apparatus II, operated at 50 rpm in 900 mL of 0.1N hydrochloric acid maintained at 37 ± 0.5°C.The floating time refers to the total duration the tablet remains buoyant in the medium, including the floating lag time the period required for the tablet to rise to the surface. This was observed visually.

Swelling Index

The swelling study was performed on the floating sustained-release tablets. Accurately weighed tablets were placed in a USP Dissolution Apparatus-II containing 900 mL of 0.1N HCl, maintained at 37 ± 2°C. Tablets were allowed to swell until a constant weight was reached. They were then removed, blotted with filter paper, and weighed. The change in weight was recorded in triplicate to calculate the swelling index.

$$\textbf{Swelling index} = (W\text{-}Wo)\ /Wo \times 100$$

Drug Content

Five tablets were randomly selected from each batch, weighed, and powdered. A quantity of powder equivalent to 100 mg of the drug was accurately weighed and transferred to a standard volumetric flask. The volume was made up to the mark with 0.1N HCl. The solution was filtered through a 0.45 µm membrane filter and analyzed using a UV spectrophotometer.

In-vitro Dissolution Studies

The drug release from floating tablets was evaluated using USP Dissolution Apparatus-II (Paddle type) with 900 mL of 0.1N HCl at 37 ± 0.5°C. At hourly intervals over a 12-hour period, 5 mL samples were withdrawn from the dissolution medium. The samples were replaced with fresh dissolution medium and filtered through Whatman filter paper, after which the absorbance of the solutions was measured. For the in-vitro floating potential (buoyancy level), a specific amount of microspheres was spread across the surface of a USP (Type II) dissolution system containing 900 ml of 0.1 N HCl with a certain volume of Tween 80, and agitated at 100 rpm for 12 hours. After this period, the floating and settled layers were separated, dried in a desiccator, and weighed. Buoyancy was then calculated using the following formula.

3. Results and Discussion

The characteristics of the microspheres, including particle size, buoyancy percentage, and micrometric properties, were evaluated through bulk density, tapped density, angle of repose, and Carr's index, as detailed in Table 2. The particle size of the prepared microspheres varied from 50.67 ± 0.13 to 83.34 ± 0.10 µm, with the smallest sizes observed when HPMC K100M was used as the rate-retarding polymer. The bulk density ranged from 0.47 to 0.89 g/ml, while the tapped density varied between 0.51 and 0.83 g/ml. The angle of repose was measured between 20.74˚ and 30.54˚, indicating excellent to good flow

properties. Additionally, the Carr's index for all formulations fell within the range of 7.67% to 14.56%, further suggesting favourable flow characteristics. These findings imply that the microspheres can be handled efficiently during processing. The highest buoyancy percentage (94.23) was recorded in formulation F17, likely due to the slower penetration of the dissolution medium into the microspheres, as HPMC K100M exhibits superior water swell-ability compared to HPMC K4M and HPMC K15M.

Table 4: List of drugs formulated as single and multiple unit froms of floting drug delivery system.

Tablets	Ciprofloxacin, Chlorpheniramine maleate, Theophylline, Furosemide, Captopril, Acetylsalicylic acid, Sotalol. Nimodipine, Amoxycillintrihydrate, Verapamil HCL, Isosorbidedinitrate, Isosorbide mononitrate, Prednisolone, Acetaminophen, Ampicillin, Cinnarizine, Riboflavin 5 Phosphate, Diltiazem, Flurouracil, Piretanide.
Capsules	L. Dopa, Benserazide, Urodeoxycholic acid, Chlordiazepoxide HCL, Furosemide, Nicardipine, Misoprostol, Diazepam, Propranolol.
Microspheres	Aspirin, Griseofulvin, Verapamil, Terfenadine, Tranilast, Ibuprofen. p-Niroaniline, Ketoprofen.
Granules	Diclofenac sodium, Prednisolone, Indomethacin.
Films	Durg Delivery Device, Cinnarizine.
Powders	Several basic drugs.

Table 5: Formulation with HPMCK-4M.

Formulation code	Famotidine (mg)	Sodium alginate (%)	HPMCK100M(mg)	Calcium carbonate (mg)	Calcium chloride (%)
F1	150	2	300	50	1
F2	150	2	250	100	1
F3	150	2	200	150	1
F4	150	2	150	200	1
F5	150	2	100	250	1
F6	150	2	50	300	1

Table 6: Formulation with HPMCK-100M.

Formulation code	Famotidine (mg)	Sodium alginate (%)	HPMCK4M(mg)	Calcium carbonate (mg)	Calcium chloride (%)
F7	150	2	300	50	1
F8	150	2	250	100	1
F9	150	2	200	150	1
F10	150	2	150	200	1

F11	150	2	100	250	1
F12	150	2	50	300	1

Table 7: Formulation with HPMCK-15M.

Formulation code	Famotidine (mg)	Sodium alginate(%)	HPMCK-15M(mg)	Calcium carbonate (mg)	Calcium chloride (%)
F13	150	2	300	50	1
F14	150	2	250	100	1
F15	150	2	200	150	1
F16	150	2	150	200	1
F17	150	2	100	250	1
F18	150	2	50	300	1

Analytical Methods

A suitable analytical method was developed for famotidine using UV spectroscopy, with an analytical wavelength (λ max) identified at 263 nm in a 0.1 N hydrochloric acid solution. A calibration curve was constructed in this medium, demonstrating good reproducibility. The method followed Beer-Lambert's law within the concentration range of 2 to 10 µg/ml in 0.1N HCl solution.

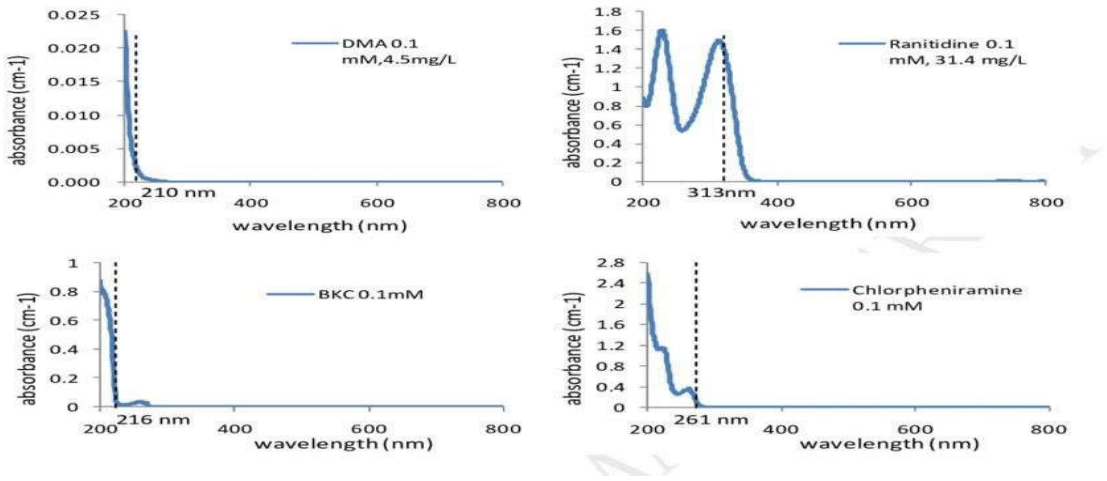


Figure 1: UV spectrum of famotidine.

Equilibrium Solubility Study of Pure Drug

The equilibrium solubility of the pure drug was measured using a UV spectrophotometer in different solvents, including 0.1 N HCl, phosphate buffer (pH 7.4), and distilled water, as presented in Table 4. The drug was found to be practically insoluble in distilled water, with a solubility of only 10 µg/ml at equilibrium. However, in 0.1 N HCl, the solubility significantly increased to 261 µg/ml, indicating that famotidine is highly soluble in acidic media.

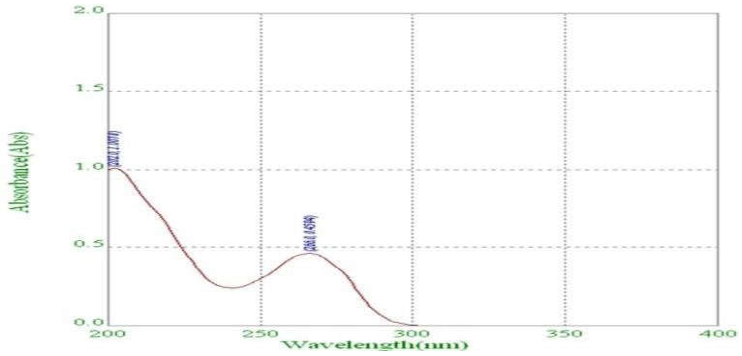


Fig.2: Standard curve of famotidin in 0.1 N HCI at 261 nm.

Table 8: Standard curve of famotidine in 0.1N HCL 263 m.

Concentration	Absorbance
2	0
4	0.071
6	0.138
8	0.212
10	0.276

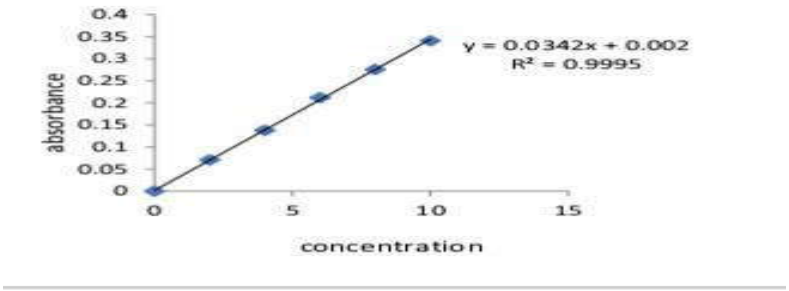


Fig 3: Standard curve of famotidine in 0.1 N HCl at 261 nm.

Drug-Excipient Compatibility Studies Using Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR method is employs to identify the functional groups present in both the pure drug and its compatibility with excipients. FTIR spectra for pure Famotidine and the optimized formulation were obtained using a SHIMADZU FTIR instrument. A specific amount of KBr and excipients were combined in a 100:1 ratio and ground together in a mortar. The resulting mixture was then compressed into pellets under pressure. FTIR spectra were recorded in the range of 4000 to 400 cm−1. For Scanning Electron Microscopy (SEM) studies, the surface characteristics of the microspheres, including their size and shape, were analyzed using a HITACHI S-3700N microscope. Prior to analysis, the microspheres were thoroughly dried, and SEM imaging was conducted at various magnifications.

Stability Studies

The optimized formulation underwent stability testing at 40°C ± 2°C and 75% relative humidity ± 5% for a duration of six months in a stability chamber Samples were collected at specified intervals of 0, 30,

60, 120, and 180 days, following ICH guidelines. Several in vitro parameters, including percentage yield, entrapment efficiency, and drug release profiles, were evaluated. Additionally, FTIR spectra were recorded in the range of 4000 to 400 cm^{-1}, and SEM analysis was conducted to examine the surface morphology, size, and shape of the microspheres.

Pre-formulation studies

Table 9: Bulk density (g/ml) tapped density (g/ml) angle of repose Carr's index (%) Buoyancy.

Formulation code	Particle size	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's Index (%)	Buoyancy (%)
F1	77.22±0.02	0.67	0.72	30°.15	13.95	67.12
F2	75.45±0.09	0.79	0.67	25°.54	10.32	90.17
F3	55.23±0.14	0.68	0.51	22°.91	11.04	65.08
F4	63.22±0.11	0.67	0.79	23°.70	12.34	52.05
F5	83.34±0.10	0.68	0.68	30°.24	12.34	66.74
F6	78.45±0.21	0.67	0.67	22°.91	10.98	87.29
F7	55.04±0.04	0.59	0.58	27°.93	14.56	50.13
F8	60.12±0.08	0.66	0.59	23°.91	9.34	64.42
F9	65.29±013	0.74	0.62	29°.67	8.34	78.42
F10	73.43±0.04	0.76	0.73	30°.54	13.36	69.53
F11	62.35±0.04	0.59	0.57	27°.94	8.12	69.24
F12	79.67±0.09	0.89	0.83	30°.15	9.23	91.24
F13	65.32±0.09	0.82	0.82	25°.54	13.95	70.18
F14	55.23±0.14	0.56	0.63	22°.91	10.32	70.18
F15	73.22±0.11	0.72	0.77	21°.70	8.08	75.30
F16	81.34±010	0.68	0.65	30°.24	7.67	80.47
F17	50.67±0.13	0.47	0.51	20°.74	7.67	94.23
F18	74.35±0.32	0.80	0.72	29°.67	11.43	85.16

Table 10: % yield, % swelling index, and entrapment efficiency of famotidine floating microspheres formulations.

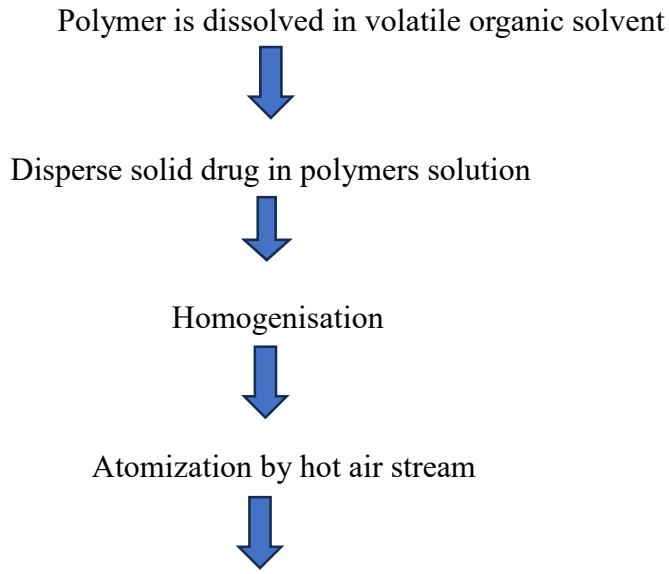
Formulation code	Percentage yield (%)	Swelling index (%)	Entrapment Efficiently (%)
F1	65.45±0.19	65.45±0.19	76.17±0.23
F2	73.16±0.30	74.35±0.17	74.35±0.17
F3	82.93±0.36	65.27±0.24	88.65±0.36
F4	85.31±0.24	78.13±0.15	78.35±0.33
F5	69.27±0.0.19	75.52±0.28	86.98±0.29
F6	89.11±0.33	89.11±0.33	91.23±0.12
F7	90.35±0.12	82.24±0.24	70.23±0.31
F8	84.35±0.35	78.24±0.16	89.14±0.22
F9	77.95±0.27	80.15±0.31	87.63±0.17
F10	92.45±0.21	70.51±0.28	83.45±0.34
F11	68.75±0.32	87.31±0.25	78.29±0.12
F12	83.92±0.28	80.19±0.17	67.83±0.35

F13	62.75±0.25	73.92±0.12	78.25±0.33
F14	82.34±0.31	88.92±0.26	75.16±0.14
F15	76.95±0.11	81.62±0.31	70.19±0.26
F16	85.45±0.24	77.24±0.32	68.10±0.15
F17	95.47±0.36	92.13±0.17	62±0.29
F18	80.42±0.29	19±0.30	84.73±0.13

Table 11: Release order kinetics of optimized formulation Reference Standard.

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korseyer peppas R^2	Peppas value
F1	0.913	0.804	0.949	0.916	0.596
F2	0.939	0.721	0.922	0.951	0.666
F3	0.957	0.807	0.949	0.955	0.647
F4	0.981	0.819	0.933	0.922	0.720
F5	0.977	0.824	0.952	0.970	0.567
F6	0.984	0.785	0.944	0.958	0.679
F7	0.905	0.668	0.911	0.922	0.555
F8	0.911	0.711	0.914	0.933	0.636
F9	0.965	0.815	0.922	0.944	0.587
F10	0.925	0.718	0.922	0.924	0.688
F11	0.954	0.804	0.931	0.944	0.647
F12	0.907	0.709	0.918	0.933	0.599
F13	0.957	0.824	0.919	0.949	0.622
F14	0.944	0.829	0.958	0.971	0.597
F15	0.954	0.819	0.911	0.947	0.711
F16	0.980	0.824	0.957	0.967	0.714
F17	0.989	0.839	0.964	0.976	0.720
F18	0.944	0.816	0.954	0.967	0.711
Marketed product	**0.77**	**0.936**	**0.921**	**0.948**	**0.393**

Fig 4: Schematic representation of microspheres prepared from solvent extraction method.



Small droplet

↓

Evaporation of solvent

↓

Separation of microspheres and vacuum drying to remove traces of solvent

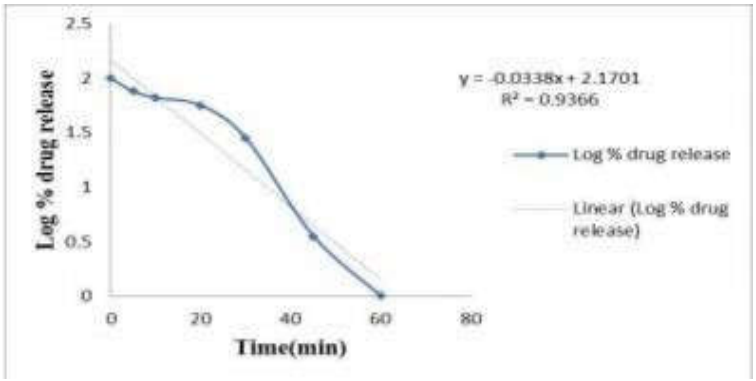


Fig. 5: Zero order plot for Marketed product.

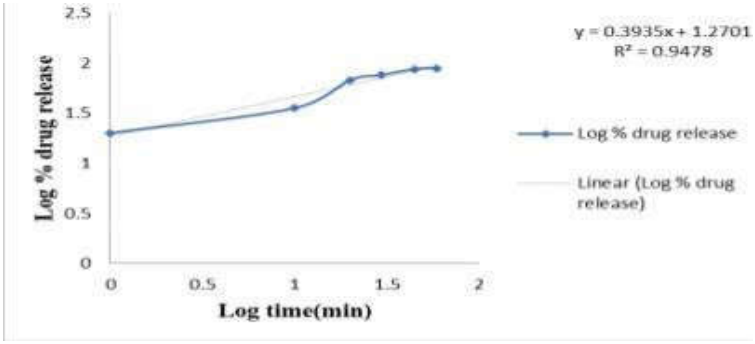


Fig. 6: First order plot for Marketed product.

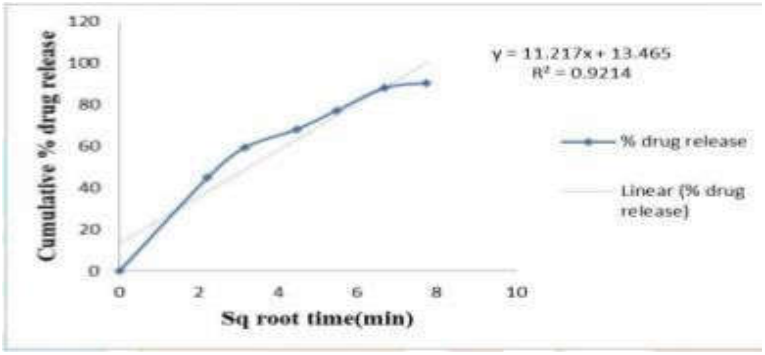


Fig. 7: Higuchi model for Marketed product.

Table 12: Stability studies of optimized floating microspheres.

Retest Time for Optimized formulation	% yield	Entrapment efficiency (%)	In vitro drug release profile (%)
0 days	95.47 ± 0.36	92.13 ± 0.17	96.54 ± 0.72
30 days	94.75 ± 0.242	91.19 ± 0.186	96.25 ± 0.293
60 days	94.28 ± 0.173	91.26 ± 0.153	95.33 ± 0.184
120 days	93.61 ± 0.265	90.87 ± 0.291	94.19 ± 0.253
180 days	93.12 ± 0.321	90.12 ± 0.172	93.33 ± 0.184

In Vitro Drug Release Studies

The release of Famotidine from the floating microspheres was sustained over a 12-hour period. The optimized formulation, F17, demonstrated a cumulative drug release of **96.54 ± 0.72%** at the end of 12 hours, compared to the marketed product, which released **94.53 ± 0.26%** within the same time frame.

SEM Studies of Famotidine Microspheres

Scanning Electron Microscopy (SEM) revealed that the microspheres were spherical with a rough surface, as depicted in Figure 8. The surface roughness was attributed to the high drug concentration, which was uniformly dispersed at the molecular level within the polymer matrix. A humidity level of 75% ± 5% RH, as shown in Table 4. At designated time intervals, samples were gathered and examined for percentage yield, entrapment efficiency, and in vitro drug release.

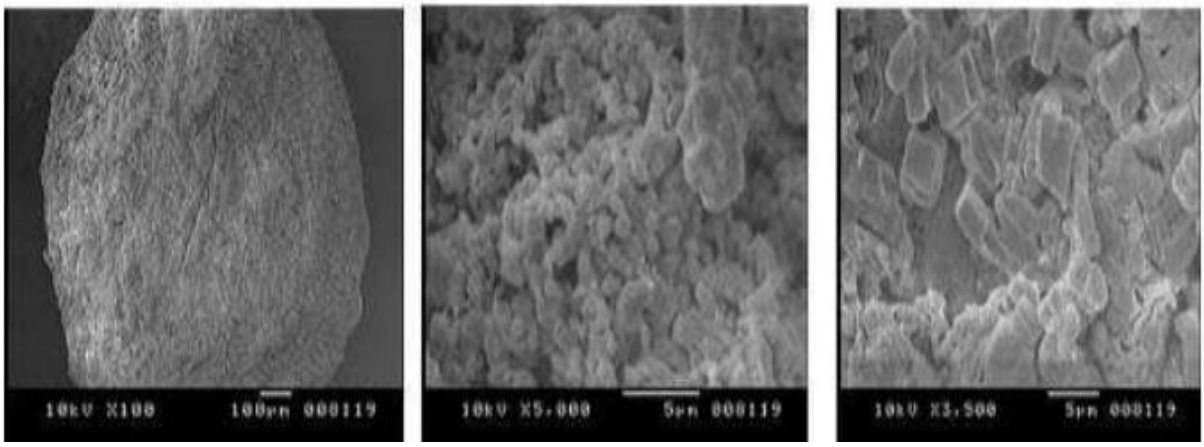


Fig 8: Scanning Electron Microscopy (SEM) of optimized floating microspheres.

FTIR

The FTIR technique is applicable for identifying the functional groups present in the pure drug and assessing drug-excipient compatibility. The FTIR spectra of pure Famotidine and the optimized formulation were recorded using FTIR (SHIMADZU). A weighed quantity of KBr and excipients was taken in a ratio of 100:1 and mixed using a mortar. The samples were then formed into pellets through

the application of pressure. Subsequently, the FTIR spectra were recorded within the range of 4000 - 400 cm−1.

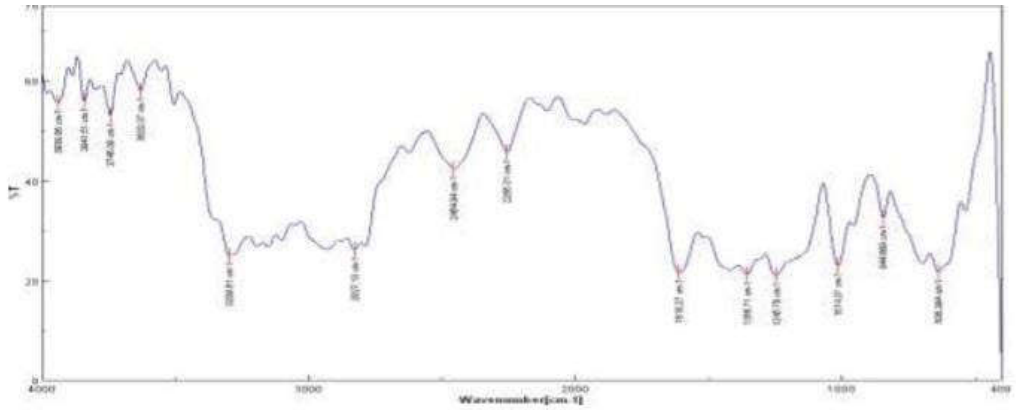


Fig 9: FTIR spectrum of pure drug famotidine.

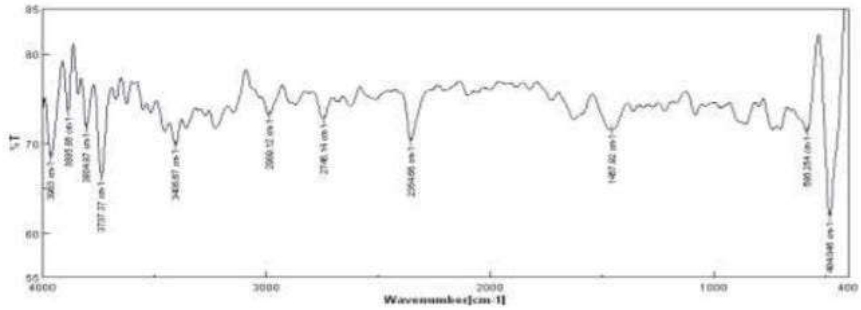


Fig10: FTIR spectrum of Floating famotidine microspheres.

Drug excipient compatibility studies FTIR spectroscopy of Famotidine microspheres

The FTIR spectrum of the pure drug (Figure-09) displayed distinct sharp peaks at 3421 cm-1 (C-N stretch), 2951 cm-1 (C-H stretch), 1436 cm-1 (C=H deformation in NCH, CH), 1500 cm1 (CH & OCH groups), 1587 cm-1 (Conjugated with NO), and 1419 cm-1 for the CH2 bond. No new significant bonds were detected in the pure drug (Figure-09) and the optimized formulation (Figure 10), indicating that there was no interaction observed between the drug and the excipients.

4. Conclusion

Stability studies of optimized Famotidine microspheres, conducted in accordance with ICH guidelines, were performed over a period of 6 months at a temperature of 40°C ± 2°C and relative humidity of 75% ± 5% RH, as presented in Table 4. At specified time intervals, samples were collected and analyzed for % yield, entrapment efficiency, and in vitro drug release. No significant changes were observed in the results before and after the stability studies, indicating that the optimized formulation (F17) was stable. Famotidine-loaded floating microspheres were prepared using the ionotropic gelation method. The results concluded that formulation F17 exhibited satisfactory outcomes in terms of excellent micromeritic properties, with a particle size of 50.67 ± 0.13 µm, a microsphere yield of 95.47 ± 0.36%, an entrapment efficiency of 93.67 ± 0.29%, a buoyancy percentage of 94.23%, a swelling index of 92.13 ± 0.17%, and the highest in vitro drug release of 98.23 ± 5.49% in a sustained manner over an extended

period of 12 hours, compared to the marketed product which showed 95.87 ± 0.31% in the same duration. The compatibility of the drug and excipients was assessed using FTIR. The drug release from Famotidine microspheres adhered to the Zero order and Higuchi models, suggesting that the mechanism of drug release from the microspheres was diffusion-controlled. The prepared microspheres were confirmed to be spherical in shape through SEM analysis. The optimized formulation F17 demonstrated stability. Consequently, the prepared floating Famotidine microspheres may serve as a promising candidate for safe and effective sustained drug delivery, thereby enhancing bioavailability.

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