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Development And Characterization Of Gastroretentive Floating Drug Famotidine

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ABSTRACT

In this study, gastroretentive famotidine microballoons were designed and studied with the purpose of improving the treatment of peptic ulcers by extending the duration of stomach retention and regulating the release of the medicine. With a systematic modification in polymer-drug ratios ranging from 1:1 to 1:3, and stirring speeds ranging from 900 to 1500 revolutions per minute, nine different formulations (F1-F9) were created with HPMC K4M through the process of emulsion solvent diffusion. Excellent micromeritic qualities were demonstrated by the microballoons, as evidenced by appropriate flow characteristics (angle of repose: 22.14°-27.19%; Carr's index: 7.93-13.11%) and sustained buoyancy (>12 hours, 64.17-83.21%), all of which are essential for stomach retention. In order to ensure efficient drug loading, a high drug encapsulation efficiency (63.47-70.34%) was utilised. While FTIR and DSC tests demonstrated that there were no interactions between the medication and the excipient, scanning electron microscopy (SEM) revealed porous spherical structures that made flotation easier. In vitro release experiments demonstrated that the kinetics of the formulation were dependent on the formulation. The formulations F1, F4-F5, and F7-F9 adhered to the Korsmeyer-Peppas model, while F2 and F6 adhered to the Higuchi kinetics. F3 displayed optimal zero-order release (R2=0.9954). Through the maintenance of prolonged therapeutic drug levels in the stomach, this gastroretentive system is able to successfully address the pharmacokinetic limitations of famotidine, particularly its short elimination half-life (2.5-4 hours). Famotidine's therapeutic potential for acid-related illnesses is considerably enhanced by the combination of extended buoyancy and controlled release profile. This combination has the potential to improve treatment efficacy while simultaneously reducing the frequency of dose to minimise adverse effects. Based on these data, it appears that microballoons based on HPMC K4M could be a promising method for the targeted delivery of famotidine to the stomach

Keywords: Famotidine, microballoons, gastroretentive, Korsmeyer-Peppas, HPMC K4M, peptic ulcer.

1. INTRODUCTION

2. BACKGROUNDS

Peptic ulcer disease, often known as PUD, is a common disorder that affects the gastrointestinal tract and is characterised by the development of erosions in the mucosa of the stomach or the duodenum. Clinical manifestations of the condition include symptoms ranging from epigastric pain and bloating to possibly fatal complications such as gastrointestinal haemorrhage .-

Or perforation. The key etiological factors are an infection with Helicobacter pylori and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) over an extended period of time. The current therapeutic approaches have an emphasis on acid suppression as a crucial component of the care of PUD. Histamine H_2-receptor antagonists (H_2RAs), which include famotidine, are an important pharmacological intervention. It is through the competitive inhibition of histamine H2 receptors on parietal cells that famotidine is able to exercise its therapeutic effect, which is achieved by efficiently inhibiting the production of stomach acid. Conventional immediate-release formulations, while their effectiveness, face substantial pharmacokinetic issues. These challenges include a very short elimination half-life (three to four hours) and quick transit through the stomach. Because of these constraints, multiple daily dosage is required, which leads to poor drug concentration profiles and has the potential to compromise whatever therapeutic benefits that may be achieved

3. MATERIAL & METHODS

PREFORMULATION STUDIES OF DRUG FAMOTIDINE

The material under investigation was characterised by means of an exhaustive physicochemical analysis, which provided information regarding the following characteristics: 165-170 degrees Celsius was the melting point range that the compound exhibited, which is an indication of its high purity. Within the analytical range, the UV technique validation exhibited an outstanding linearity (R2=0.999), which was rather impressive. As a result of solubility tests, pH-dependent dissolving characteristics were discovered, and the aqueous solubility of the substance was found to be 1.1 mg/mL under neutral conditions. This finding highlights the necessity of formulation strategies that can improve bioavailability. The combination of these physicochemical features provides conclusive evidence that the material is suitable for use in the creation of pharmaceuticals, in particular for solid dosage forms that require precise control over dissolution and release profiles. The data provide a solid basis for the further formulation optimisation and quality control parameters that will be implemented.

4. DRUG IDENTIFICATION TESTS OF FAMOTIDINE

CHEMICAL TEST

This analytical procedure utilizes a redox-based colorimetric reaction to verify drug identity through characteristic chromophore formation. The test involves sequential reduction and oxidative coupling steps to generate a distinctive colored product.

THIN LAYER CHROMATOGRAPHIC STUDIES (TLC PLATES)

A standard solution of famotidine (0.2 mg/mL in methanol–glacial acetic acid, 100:1) was spotted (5 µL) and developed via ascending chromatography (10 cm run). Plates were dried, visualized with iodine vapor, and Rf values recorded.

5. MELTING POINT MEASURMENT

A small amount of famotidine was packed into a sealed-end capillary tube (~0.5 cm height). The sample-loaded capillary was placed in a melting point apparatus and gradually heated. The temperature range at which the solid completely melted (observed as a clear meniscus formation) was recorded as the melting point (162-164°C), consistent with literature values (Merck Index, 1996).

6. UV SPECTROPHOTOMETERIC STUDIES

UV spectrophotometry is a widely used analytical technique that measures the absorption of ultraviolet (UV) light by a compound to determine its concentration or identity. The method operates based on the Beer-Lambert law, which states that absorbance (A) is proportional to the concentration (c) of the analyte, path length (l), and molar absorptivity.

FOURIER TRANSFORM INFRARED RADIATION

In contrast to the conventional method of dispersive infrared spectroscopy, the technique of FTIR (Fourier transform infrared) makes use of an interferometer to detect all infrared frequencies simultaneously. This results in spectra that are more sensitive, quicker, and have a higher resolution. Passing infrared radiation through a sample is the fundamental principle. This causes particular bonds to absorb characteristic frequencies, which results in the production of a fingerprint spectrum that is only found in that sample.

DETERMINATION OF PARTICLE

In order to conduct the particle size characterisation of the powdered medication, optical microscopy was utilised, and standardised calibration techniques were followed. In order to prevent the particles from aggregating, approximately one hundred of them were suspended in paraffin oil and then equally distributed on a microscope slide for the purpose of measurement. During the process of determining the diameters of the particles, a calibrated eyepiece micrometre was utilised. The calibration was accomplished by comparing the divisions of the eyepiece micrometre to those of a stage micrometre (Martin, 1999). In order to perform the calibration process, it was necessary to align a specific number of eyepiece micrometre divisions (X) with the corresponding stage micrometre divisions (Y). It is important to note that one stage micrometre

division is equal to 10 µm. As a means of assuring precise size determination, the calculation of the value of one eyepiece micrometre division was performed by multiplying (Y ÷ X) by 10 µm. By using this method, exact measurements of individual particles were able to be obtained, and the mean diameter was determined from those measurements in order to depict the overall particle size distribution and its distribution. As a result of the utilisation of paraffin oil, the mobility of particles was reduced, and clear visualisation was made possible under the microscope. The results offered a valid estimation of the powder's particle size characteristics, which is essential for determining dissolution rates, flow properties, and bioavailability. This was accomplished by conducting an analysis on a statistically significant number of particles (n=100). When it comes to pharmaceutical powder characterisation, where particle size plays a significant role in determining product performance and quality, the strategy that has been presented incorporates both simplicity and reproducibility, making it an extremely useful tool.

SOLUBLITY DETERMINATION

At 37°C, the shake-flask method was utilised in order to conduct a comprehensive evaluation of the equilibrium solubility of famotidine under physiologically relevant conditions. In order to imitate the conditions that are found in the gastrointestinal tract, the research was conducted using aqueous systems that included buffered solutions, 0.1N hydrochloric acid, and filtered water. The pH range of these systems was from 1.20 to 6.80. Saturated solutions were made in triplicate, equilibrated for a period of twenty-four hours with continuous agitation, and then filtered through membranes with a thickness of forty-five micrometres in order to separate drug particles that had not been dissolved. At the wavelength of the drug's λmax (265-266 nm), the filtrates were subjected to UV spectrophotometry analysis. The concentrations of the drug were determined by comparing them to the calibration curves of recognised standards that had been validated. Through the use of this methodical methodology, reproducible solubility data were obtained, which is essential for comprehending the dissolving behaviour and bioavailability of bamotidine. In accordance with the medication's weakly basic nature (pKa 6.7-7.1), the findings indicated pH-dependent solubility characteristics. Specifically, the solubility of the drug was much higher in acidic media (0.1N HCl, pH 1.20) compared to circumstances that were close to neutral. The technique adhered to the known pharmaceutical protocols (Lachman et al., 2009), which ensured the collection of trustworthy data for the development of formulations and the classification of biopharmaceuticals.

7. MICROMERITICS PROPERTIES OF DRUG POWDER

BULK DENSITY

The graduated cylinder method was utilised in order to ascertain the powdered drug's bulk density. This method involved carefully pouring a pre-weighed sample into a graduated cylinder in order to record the initial volume. Subsequently, the cylinder was tapped three times from a standardised height of one inch onto a hard surface at intervals of two seconds in order to guarantee uniform packing. Finally, the final volume was measured in order to determine the bulk density. Despite the fact that changes in tapping force or cylinder size may require calibration in order to maintain accuracy across different laboratories, this technique has become a typical practice in preformulation research due to its simplicity and reliability. These findings contribute to the differentiation between cohesive and free-flowing powders, which in turn influences decisions about the selection of excipients and processing procedures in order to maximise the quality of medicinal products.

TAPPED DENSITY

A sample that had been pre-weighed and placed in a graduated cylinder was subjected to controlled mechanical tapping in order to estimate the tapped density of the powdered medical substance. The cylinder was then put on a mechanical tapper and subjected to a standardised sequence of taps (usually 100, 500, or 1250 taps) until no further volume loss was noticed, at which point the final tapped volume was recorded. This was done after the original bulk volume had been measured. Dt equals M divided by Vt Dt is the density that has been tapped. The final tapped volumes of the drug are measured in cm3, and the weight of the samples is denoted by M. The Hausner Ratio Simply dividing the tapped bulk density by the loose bulk density allowed for the calculation of the Hausner ratio, which is an important measure of the flowability of powder. This dimensionless parameter is a reflection of the inter-particulate friction, with values below 1.25 indicating strong flow, values between 1.25 and 1.5 showing moderate flow, and values greater than 1.5 indicating poor flow characteristics. This parameter is essential for forecasting powder behaviour in pharmaceutical operations. Tapped bulk density (Dt) divided by loose bulk density determines the Hauser ratio.

COMPRESSIBITY INDEX

In order to obtain the compressibility index, also known as Carr's Index, a quantitative measure of powder flowability was determined by comparing the bulk density values with the tapped density values. Using the formula that is always used:

Carr's Index (%) = [(Tapped Density - Bulk Density) / Tapped Density] × 100

Table 1 Correlation Between Compression Percentage and Powder Flow Characteristics

Compression Percentage Range	Flow Behavior Description
5-15%	Superior (effortlessly flowing granules)
12-16%	Favorable (easily flowing powdered granules)
18-21%	Moderate (standard powdered granules)
23-28%	Limited (highly mobile powders)
28-35%	Restricted (cohesive particulate systems)
35-38%	Minimal flow capacity
>40%	Exceptionally inadequate flow properties

Angle of Repose (θ): Measured by pouring powder through a funnel onto a flat surface, then calculating θ arctan(h/r) where *h* = pile height, *r* = base radius. Lower θ indicates better flowability.

Table 2: Powder Flow Characteristics Based on Angle of Repose Measurements

Angle of Repose Range (°)	Flow Property Classification
<25	Outstanding flow characteristics
25-30	Satisfactory flow performance
30-40	Considerable flow limitations
>40	Marginal flow capability

Calibration Curve of Famotidine in 0.1 N HCl, pH 1.20

A calibration curve for famotidine was created by utilising standard solutions with concentrations ranging from 5 to 25 µg/mL in 0.1 N HCl with a pH of 1.20. The method was validated using linear regression ($R^2 \geq 0.999$), which was used to determine absorbance at a wavelength of 266 nm using UV spectrophotometry.

8. LINEARITY AND RANGE

An excellent linearity ($R^2 \geq 0.999$) was seen with a regression equation ($y=mx+c$) in the process of establishing the calibration curve. This was accomplished by measuring the absorbance at 266 nm of famotidine standards, which ranged from 5-30 µg/mL, in 0.1N HCl with a pH of 1.20.

Precision

Repeatability (three duplicates), intraday (three measurements in triplicate), and interday (three consecutive days) tests of 5-20 µg/mL concentrations were conducted to verify the precision of the method. The results demonstrated high reproducibility, with relative standard deviation (RSD) less than 2% intraday and less than 3% interday.

In- Vitro Buoyancy Study

For the purpose of conducting the in-vitro buoyancy investigation, the floating tablets were placed in 900 mL of 0.1N hydrochloric acid (pH 1.2, 37±0.5°C) contained within the USP dissolution equipment II (50 rpm). At the same time, the overall floating duration and the floating lag time were visibly recorded.

$$Buoyancy\ (\%) = \frac{Q_f}{Q_f + Q_s} \times 100$$

Where, Q_f is weight of floating microballoons and Q_s is weight of settled microballoons respectively.

In-Vitro Dissolution Study

For the in-vitro dissolution investigation, the USP Apparatus II (paddle) was utilised at a speed of 50 revolutions per minute in 900 millilitres of 0.1N hydrochloric acid with a pH of 1.2 and a temperature of 37±0.5 degrees Celsius. A spectrophotometric analysis was performed at a wavelength of 266 nm on samples that were taken at intervals that had been established.

Kinetic Modeling of Drug Release

For the purpose of determining the drug release kinetics, dissolution data were fitted to a number of different models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The model that yielded the best results was chosen on the basis of its highest correlation coefficient (R2) value.

RESULTS & DISCUSSION

The physical properties of famotidine were characterized using a series of tests, including identification tests, boiling point tenacity, loss on drying, bulk/tapped density measurements, compressibility index, angle of repose, particle size analysis, calibration curve development, and solubility investigations in a variety of environments.

Drug Identification Tests

Chemical Test

Famotidine was determined to be the substance by seeing the formation of a violet-blue colour as a result of the interaction with phenylenediamine dihydrochloride, zinc powder, and ferric ammonium sulphate in an acidic media. This was accomplished in accordance with the usual pharmacopeial identification strategies.

Thin Layer Chromatographic Studies (TLC)

By employing two different solvent systems, namely ethyl acetate, methanol, toluene, and ammonia in the ratio of 40:25:20:2 and chloroform: methanol 9:1, the TLC analysis validated the purity of famotidine with single spots (Rf 0.613±0.036 and 0.569±0.018 respectively), which corresponded to the values found in the literature (Rf 0.539).

`UV Spectrophotometric Studies

The UV spectrophotometric examination of famotidine in phosphate buffers with pH values of 2.50 and 3.50 and 0.1N HCl with a pH of 1.20 revealed the presence of typical λ values ranging from 200 to 400 nm. These values were consistent with the published data, so verifying the appropriate choice of solvent for the analysis.

Table 3: Spectral Analysis of Famotidine in Various Solvent Systems

Entry	Solvent Composition	λ_{max} (nm)
1	Phosphate buffer solution (pH 2.50)	265.5
2	0.1N hydrochloric acid (pH 1.20)	266.0
3	Phosphate buffer solution (pH 3.50)	265.5

Fourier Transform Infrared Radiation

With characteristic peaks that matched reference standards, the FTIR spectrum provided conclusive evidence that famotidine was the substance in question (Fig. 5). Vibrational band analysis was used to confirm the drug's homogeneity and molecular structure, which led to the identification of key functional groups (Table 4).

Table 4: FTIR Spectral Signature Analysis of Famotidine

Peak Position (cm^{-1})	Molecular Vibration Assignment

3506.59, 3398.57, 3240.41	N-H stretching vibrations (amine groups)
3375.43-3240.41	Sulfonamide (SO_2-NH_2) characteristic
2939.52	Aliphatic C-H stretching
1639.49	Aromatic C=C ring stretching
1597.06	N-H out-of-plane deformation
1492.90	Sulfoxide (S=O) stretching
1284.59	SO_2 asymmetric stretching
1149.57	SO_2 symmetric stretching
1203.58	C-H bending modes
1114.86	Thiocarbonyl (C=S) stretching
983.70, 887.26, 779.24	N-H bending vibrations
609.51	=C-H out-of-plane bending

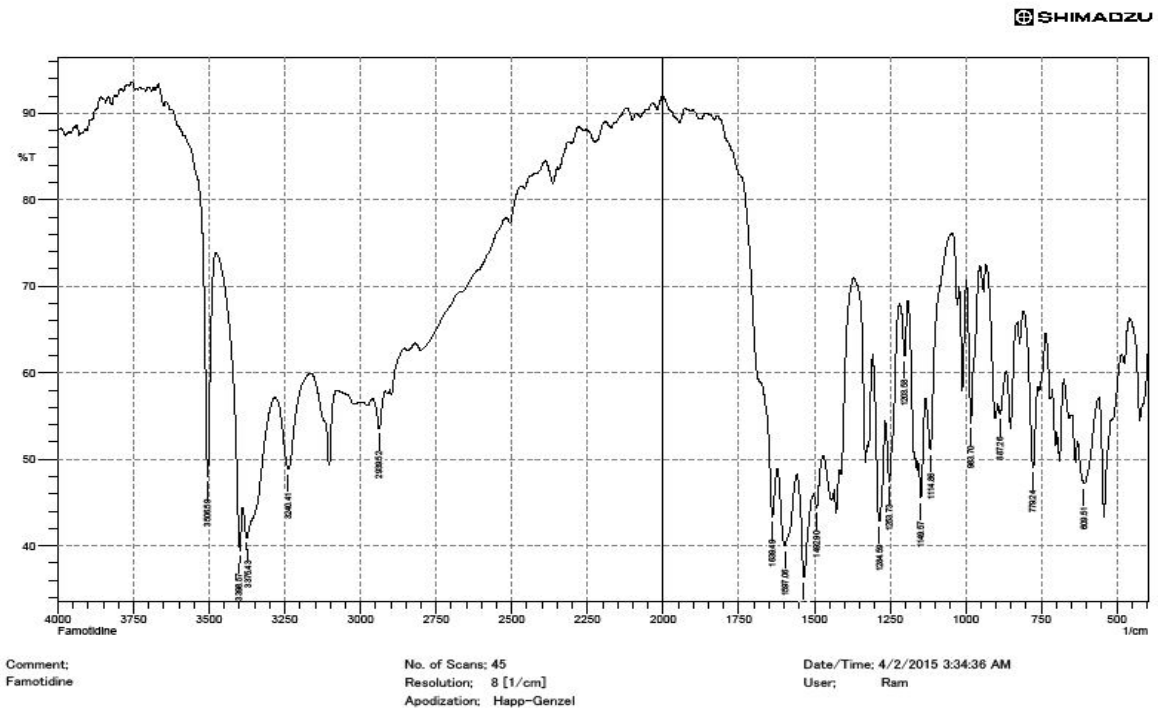

Fig 5: FTIR spectra of famotidine

Loss on Drying

The loss of the drug after drying was 0.096 percent, which was in accordance with the pharmacopeial criteria of less than half a percent. This indicates that the moisture content of the formulation is suitable for processing without compromising its stability or quality.

Determination of Particle Size

In the process of microscope calibration, it was determined that one eyepiece division equals 14 micrometres. The mean particle size of famotidine was measured to be 78.977 µm (0.078977 mm), which supports the utilisation of appropriate micronization techniques for formulation processing.

Solubility Determination

The solubility of famotidine was found to be dependent on the pH of the solution. It was shown to be most soluble in 0.1N hydrochloric acid (pH 1.20, 27.6±1.34 mg/mL), which corresponds to the pH of the stomach and confirms its suitability for gastroretentive formulations. However, the solubility of famotidine was found to be reduced in neutral buffers (pH 6.80).

9. SURFACE MORPHOLOGY

SEM analysis revealed spherical famotidine microballoons with smooth, dense surfaces and highly porous cores (Figs. 6, explaining their excellent buoyancy and controlled drug release properties.

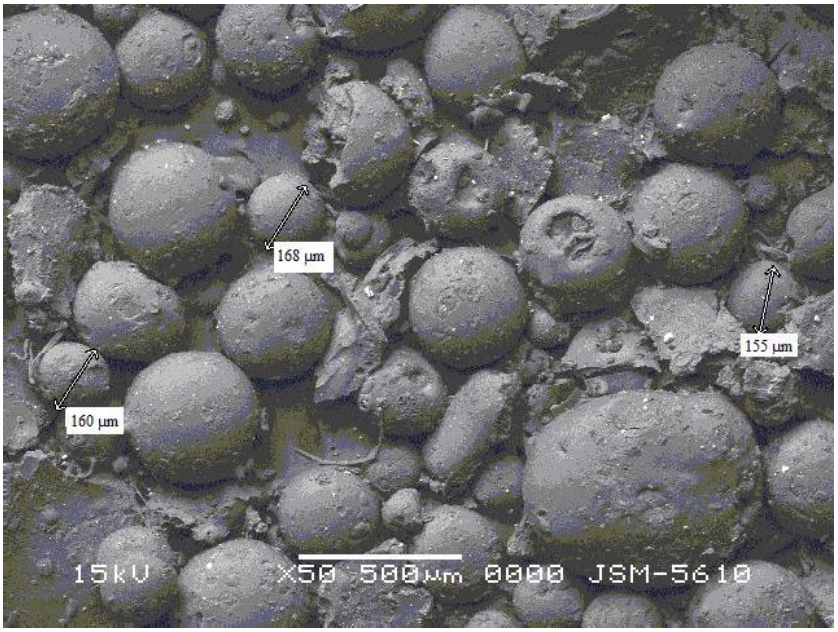

Fig. 6. SEM photographs of range of floating microballoons

In-Vitro Buoyancy Study

All nine famotidine microballoon formulations (F1-F9) demonstrated sustained 12-hour buoyancy (64.17±1.16% to 83.21±1.07%), with buoyancy increasing proportionally with HPMC K4M concentration and particle size (F3: 160.58±0.73µm, 83.21% buoyancy) but inversely with stirring speed.

Table 4 Buoyancy Profile of Famotidine Microballoon Formulations

Formulation	% Buoyancy (Mean ± SD)	Floating Duration (h)	Key Influencing Factor
F1	68.53 ± 1.96	>12	Moderate porosity
F2	75.45 ± 2.14	>12	Optimized density (0.53 g/cm³)
F3	**83.21 ± 1.07**	**>12**	**Highest porosity + large particle size (160.58 µm)**
F4	65.38 ± 1.76	>12	Lower polymer ratio
F5	74.65 ± 1.08	>12	Balanced excipient blend
F6	80.14 ± 1.14	>12	Enhanced cavity formation
F7	64.17 ± 1.16	>12	Smaller particle size (109.43 µm)
F8	70.52 ± 0.96	>12	Intermediate density
F9	78.61 ± 1.59	>12	High HPMC content

All values are expressed as mean ± S.D., n =3

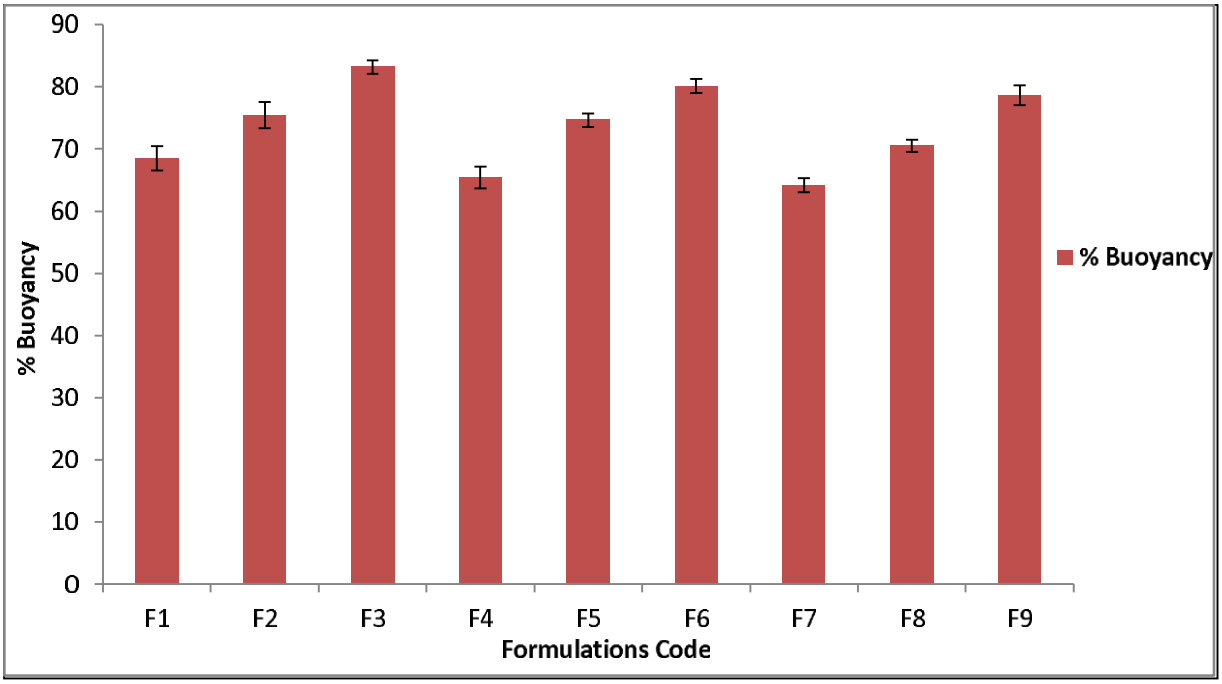

Fig. 7 The graph below presents a comparison of the percentage of buoyancy of several formulations of famotidine microballoons.

Investigation of Dissolution in Vitro

The in vitro drug release of microballoons loaded with famotidine in 0.1N hydrochloric acid (pH 1.20) demonstrated an initial burst release from the surface-associated drug, which occurred within a time frame of less than one hour, followed by a persistent release (Fig. 8). By increasing matrix stiffness and diffusional channel length, higher concentrations of HPMC K4M were able to decrease release rates. On the other hand, lower polymer concentrations resulted in the production of smaller microballoons that would release more quickly due to their larger surface area. When the stirring speed was increased from 900 to 1500 revolutions per minute, the microballoon's integrity was disrupted, which hastened the release but maintained the microballoon's continuous release. Formulations that contained the ideal amount of HPMC K4M (F3: 160.58µm) exhibited a sustained release over a period of twelve hours, thereby demonstrating their gastroretentive ability to be achieved by a combination of buoyancy and controlled release mechanism.

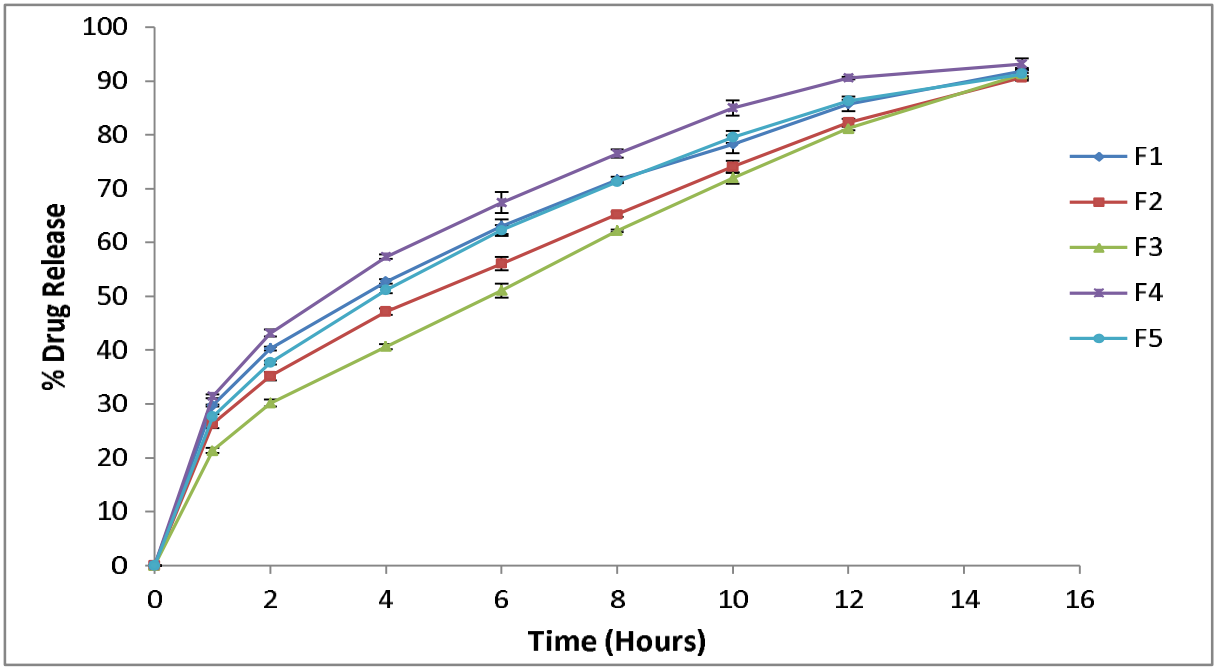

Fig. 8 Microballoons containing famotidine were tested for their drug release profile in vitro for batches F1 to F5.

10. CONCLUSION

Gastroprotective drug delivery systems (GRDDS) for famotidine represent a significant development in the treatment of peptic ulcer disease (PUD) since they are able to overcome the restrictions that are associated with conventional dosage forms. Because of its short half-life and fast transit through the stomach, famotidine must be administered often. This can result in patients not complying with their treatment, which can lead to less-than-ideal therapeutic outcomes. In order to ensure continuous drug release and enhanced bioavailability, famotidine can be kept in the stomach for extended periods of time by the utilization of gastroprotective methods. These strategies include floating systems, mucoadhesive formulations, expandable/swellable matrices, and high-density systems..

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