International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 907-913 www.ijprajournal.com ISSN: 2456-4494

Clinical Investigation and Evaluation of Gastro retentive Drug Tablet: Ranitidine Pure and Its Marketed Formulations: Review Article

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Date of Submission: 10-12-2024 Date of Acceptance: 20-12-2024

ABSTRACT
Drug delivery systems that are gastroretentive are essential for improving the long-term oral administration of drugs that are intended to be absorbed in different parts of the digestive system. Because these systems are meant to stay in the stomach, the medicine can be released continuously before it reaches the absorption window, which guarantees maximum bioavailability. This particular study focuses on creating and evaluating a floating tablet formulation containing ranitidine hydrochloride in vitro. The tablets were made by compressing different grades of polymers (HPMC K4 M and HPMC K100 M) in different concentrations using a direct compression technique. In addition, talc, magnesium stearate, and citric acid—which function as gas-generating agents—were incorporated into the mixture. The pills were thoroughly characterized, with consideration given to variables such medication content, weight fluctuation, lag time, and floating time. In particular, the results showed that the best formulation performance was obtained when a blend of natural and synthetic polymers was used. This novel method has the potential to improve bioavailability and drug release kinetics in gastroretentive drug delivery systems.

I. INTRODUCTION

It is widely acknowledged that oral drug delivery is the most convenient, patient-friendly, and formulation-flexible mode of administration. The development of oral dosage forms, from immediate release to site-specific delivery, has demonstrated notable progress. Recent patentand scientific literature indicate that both academic and industrial research circles are becoming more interested in novel and predictable dosage forms. Constant efforts have been made to improve gastro delivery systems [1]. Over the past three decades, there has been a constant and varied technological advancement in the pursuit and testing of devices intended for retention in the upper portion of the Gastrointestinal Tract (GIT). These devices include floating, scalin, growth and inflammatory systems. Especially advantageous for medications that are intended to work in the upper gastrointestinal tract and have a restricted window for absorption.

The length of drug exposure is greatly increased by gastrointestinal storage systems, which are made to remain in the abdomen region for extended periods of time. Extended stomach retention increases the solubility of medications sensitive to low pH and reduces drug degradation in addition to increasing bioavailability. Additionally, this method makes it easier to administer medication to the small intestine and abdomen.

In order to give patients better access to cutting-edge products, new treatment options, and increased benefits, gastroretention is essential. The discovery of these benefits has prompted the creation of a unique oral dose form with gastroprotective qualities. A viable approach to guarantee consistent and long-term medication delivery to the Gastroretentive Dosage Forms (GRDF) are used in GIT to control Gastric Residence Time (GRT)

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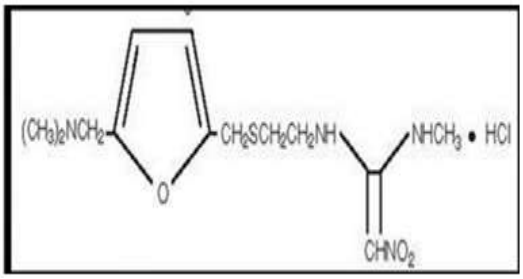

Figure1.Structure of Ranitidine

As an H2 antagonist, ranitidine inhibits the histamine 2 receptor, which lowers the amount and concentration of stomach acid output. Nevertheless, the typical 150 mg dose of ranitidine only lasts for two to three hours, thus repeated administration is required to maintain plasma ranitidine levels. Since the traditional oral dose only shows effects for five hours, developing a controlled release/sustained release formulation becomes essential to get around this restriction. The activity could perhaps last for ten hours if the absorption window is extended.

Because it is expensive to coat tablets with certain coatings, traditional formulation development approaches for controlled release/sustained release tablets provide difficulties with dosage retrieval. The idea behind floating tablets is based on the buoyancy technique, in which low-density materials—like polymers (HPMC, CARBOMERS)—are essential to the production of high-grade floating tablets. Furthermore, the addition of effervescent agents becomes necessary to promote the release of the active medication in the necessary amount within the allotted period.

A variety of ingredients are used in the production of floating tablets, including different ratios of HPMC (15000MW) and Carbopol 934 as gel-forming agents. The addition of citric acid and sodium bicarbonate produces effervescent qualities. When it comes to ranitidine hydrochloride sustained and controlled release formulations, these floating tablets show a better gastroretentive effect.

II. MATERIALS AND METHODS

In the course of this study, specific chemicals and polymers crucial to the formulation, namely Hydroxypropyl Methylcellulose (HPMC K4M and K100M), were thoughtfully provided as gift samples, demonstrating valuable collaboration and support. Additionally, ranitidine was graciously acquired as a complimentary sample, further contributing to the experimental resources.

It is noteworthy that throughout the investigation, only analytical grade chemicals and reagents were employed, ensuring a high standard of purity and precision in the experimental procedures. This commitment to using top-quality materials underscores the reliability and accuracy of the study's findings.

METHODS

Using a pestle and mortar and wet granulation, ranitidine hydrochloride, HPMC (15000), sodium bicarbonate, and citric acid were continuously mixed with carbopol to create the floating tablet. After thoroughly mixing, 2% w/v PVP in isopropyl alcohol was added, and the mixture was swirled until the isopropyl alcohol evaporated completely. After the mixture was run through sieve , wet granules were the result, and they were then put in a hot air oven. The granules were then sent through different sieve. The granules were then treated to lubricants, specifically magnesium stearate and refined talc, before being compressed. The mixture was finally compacted to create the floating tablet.

EVALUATION STUDIES

Angle of repose

The funnel method was used to calculate the angle of repose of the powder blend. A measured portion of the powder mixture was added to the funnel. The funnel's height was changed such that the tip of the funnel barely touched the powder blend's peak. The powder mixture was then let to pour freely through the funnel and onto the surface below. Subsequently, the powder cone's diameter was measured, and the angle of repose was computed by utilizing the following equation: Tan $\theta = h/r$, where 'h' and 'r' stand for the powder cone's height and radius, respectively.

Bulk Density and Tapped Density

The assessment included both tapped bulk density (TBD) and loose bulk density (LBD). Two grams of the powder blend for each formula were added to a 10 milliliter measuring cylinder after it had been shaken to distribute any agglomerates that may have developed. Following the recording of the first volume, the cylinder was let to drop to a hard surface at intervals of two seconds starting at a height of 2.5 cm. We kept tapping until we noticed no further changes in volume.

Weight of powder / bulk volume equals bulk density.

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It shows the proportion of the tapped density to the bulk density, or vice versa, the ratio of the bulk volume to the tapped volume. One of the most important parameters for assessing the flow characteristics of granules and powders is Hausner's ratio. The following formula is used to compute this ratio:

Hausner's ratio= Tapped density/Bulk density

Compressibility Index

The powder blend's compressibility index was calculated using Carr's compressibility index. This test offers a simple evaluation of a powder's tapped bulk density (TBD) and loose bulk density (LBD), showing how likely it is to pack down. The following is the formula for Carr's Index:

Carr's index (%)= (Tapped density-Bulk density) ×100/Tapped density

Weight variation test

Twenty tablets of the formulation were weighed using a Sartorius electronic balance in order to investigate weight variance.

In line with the official procedure.

Hausner's ratio

Flow character	Carr's index (percent)	Hausner's ratio
Excellent	5-15	1.00-1.11
Good	16-18	1.12-1.18
Fair	19-21	1.19-1.34
Poor	22-35	1.35-1.45
Very poor	36-40	1.46-1.59
Extremely poor	>40	>1.60

Drug content

Each of the five tablets was weighed separately, and 0.1 N HCl was used to extract the medication. After that, the mixture was passed through a 0.45-micron membrane filter. After the proper dilution, the absorbance was measured at 315 nm using a UV/Vis double-beam spectrophotometer.

Hardness

The Pfizer hardness tester was used to measure the hardness of five tablets, and the average values were computed.

Friability

The evaluation of friability, serving as a crucial indicator of tablet strength, was carried out utilizing the Roche friabilator. The methodology involved a meticulous procedure, as follows: Twenty tablets were precision-weighed and introduced into the tumbling device. Operating at a consistent speed of 25 rpm, the device facilitated the controlled descent of tablets, dropping six inches with each revolution. After an elapsed time of four minutes, the tablets underwent reweighing, and the percentage decrease in tablet weight was calculated. This comprehensive approach to friability testing ensures a thorough assessment of the tablets' structural integrity and durability, contributing valuable insights into their overall quality.

Floating Lag Time

The floating lag time investigation was conducted in a beaker containing 100 ml of 0.1 N HCl, maintained at a temperature range of 36 to 37 °C as the testing medium. This specific testing environment simulated physiological conditions relevant to the gastrointestinal tract. The floating lag time, a crucial parameter in assessing the performance of the tablet, was precisely defined as the duration required for the tablet to ascend to the surface and achieve buoyancy. This measurement holds significance in understanding the tablet's behavior and responsiveness in a simulated gastric environment, providing valuable insights into its floating capabilities. The meticulous control of temperature and medium composition enhances the reliability and relevance of the experimental results.

Floating Time

The floating time, encompassing the floating lag time, referred to the duration the tablet remained buoyant in the 0.1 N HCl dissolution medium. Upon immersion in the 0.1 N HCl solution with a pH of 1.2 at 37°C, the tablets displayed a remarkable ability to stay afloat without undergoing disintegration. This sustained buoyancy was a noteworthy characteristic indicative of the formulation's effectiveness.

Specifically, one of the formulation , incorporating Xanthan gum, HPMC K4M, and HPMC K100M, exhibited a commendable floating

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time of 48 seconds. The inclusion of these polymers in the formulation played a pivotal role in achieving this desirable floatingcharacteristic. This observation further underscores the significance of polymer selection in formulating tablets with optimal floating properties.

The Swelling Index, another crucial aspect of the study, was examined to evaluate the extent of tablet swelling. This index provides insights into the tablet's ability to absorb fluids, influencing its overall performance. The results of the Swelling Index, as outlined in the investigation, contribute valuable information to the understanding of the formulation's behavior under physiological conditions.

Swelling Index

In the comprehensive examination of swelling index across all batches ,one of the batch stood out with the highest swelling index in the current study. This particular batch, distinguished by the incorporation of a combination of HPMC K4M, HPMC K100M, Xanthan gum, and guar gum, exhibited a notable propensity for swelling. The heightened swelling index in that particular batch underscored the substantial influence of polymer composition on the tablet's behavior under physiological conditions.

The combination of HPMC K4M, HPMC K100M, Xanthan gum, and guar gum in that particular batch suggested a synergistic effect, contributing not only to the tablets' floating capability but also impacting their swelling dynamics and matrix integrity. The viscosity of these polymers emerged as a critical factor influencing the overall performance of the tablets.

These findings, indicating a positive correlation between polymer viscosity and the tablet's floating, swelling, and matrix integrity attributes, propose a linear relationship between the various swelling mechanisms. This observation enhances our understanding of the interplay between formulation components and their collective impact on the tablet's behavior, providing valuable insights for further optimization and development in pharmaceutical formulations.

In vitro Drug Release Study

The assessment of ranitidine HCl release from the floating tablets was conducted using the Dissolution Testing Apparatus . The dissolution test was executed with precision, employing 900 cc of 0.1 N HCl as the dissolution medium. This meticulous procedure unfolded at a controlled temperature of 37 ± 0.5°C, with the paddle rotating at a speed of 50 rpm to ensure standardized conditions.

Throughout the eight-hour duration of the dissolution test, aliquot volumes were systematically withdrawn from the dissolution apparatus at hourly intervals. To maintain consistency, these withdrawn samples were promptly replaced with fresh dissolution medium. The careful handling of the dissolution process aimed to mimic physiological conditions, providing accurate insights into the release kinetics of ranitidine HCl from the floating tablets. Subsequent to the dissolution process, the determination of medication release amounts was accomplished by employing a calibration curve. This involved the crucial steps of filtration and suitable dilution to ensure accurate and precise quantification. This comprehensive methodology adhered to established standards, contributing reliable data on the release profile of ranitidine HCl from the formulated floating tablets.

Table below : Pre-compression parameters of granules, including data on granule size, density, and flow characteristics, provides a comprehensive overview of the physical attributes influencing the subsequent tablet compression process.

Formulation	Bulk density (gm/cm)	Tapped density (gm/cm)	Angle of repose	Hauser's ratio(Hg)	Carr's index
F1	0.467	0.682	24.35	0.146	31.5
F2	0.467	0.614	31.92	1.31	23.9
F3	0.523	0.622	30.98	1.18	15.91
F4	0.55	0.63	29.687	1.14	12.69

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F5	0.456	0.588	24.52	1.28	22.44
F6	0.438	0.601	30.67	1.37	27.12
F7	0.462	0.642	26.58	1.38	28.03
F8	0.418	0.588	28.12	1.40	28.91
F9	0.513	0.617	24.57	1.20	16.85
F0	0.46	0.598	25.6	1.3	23.07

FIGURE below.Graph depicting the Swelling Index and Floating Time of Ranitidine Hydrochloride.

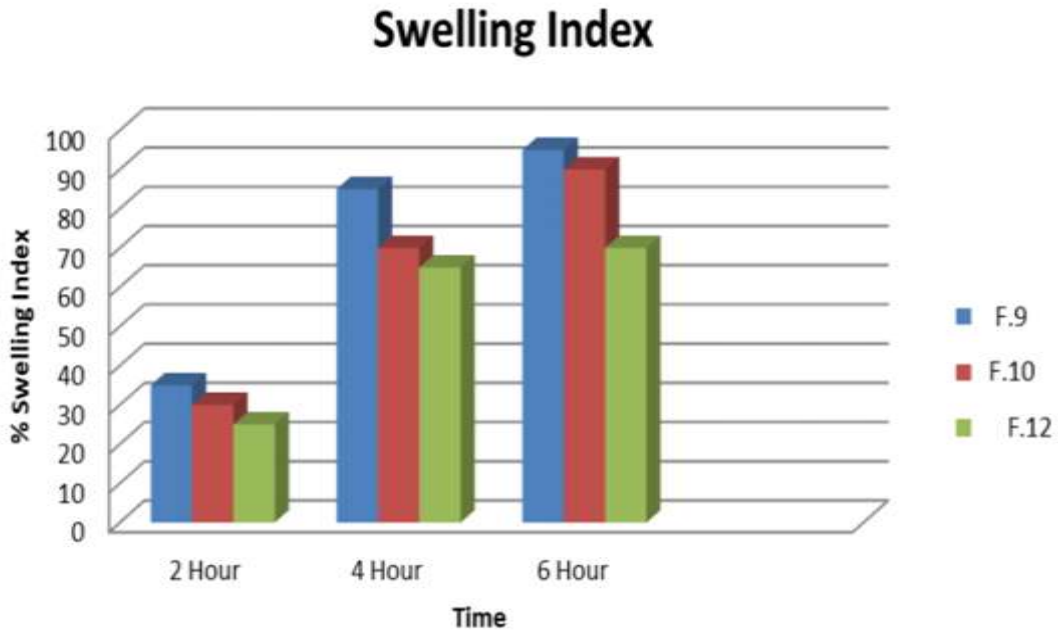

Table below: Results of In Vitro Floating Studies conducted on the floating tablets.

Formulation code	Floating lag time (in sec)	Floating time (in hr)
F1	84	8
F2	99	8
F3	96	8
F4	76	8
F5	45	8
F6	79	8
F7	109	8
F9	125	8
F10	95	8

Figurebelow : Floating Time of Ranitidine Hydrochloride Floating Tablet, visually illustrating the observed durations of buoyancy, serves as a crucial representation in assessing the sustained floating capabilities of the formulated tablets under in vitro conditions

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Figure below :Flow properties and Angle of repose

S.no	Flow properties	Angle of repose
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55
6	Very poor	56-55
7	poorest	More than 66

III. RESULT AND DISCUSSION

This study's main goal was to create and evaluate ranitidine hydrochloride sustained-release floating tablets using HPMC and carbopol-934 as the principal polymers. The formulation that involved a prudent combination of polymers—specifically, HPMC and Carbopol-934—emerged as the ideal or optimized formulation, guaranteeing a sustained release for up to 24 hours, according to a thorough study of the findings obtained. The specifications for sustained-release dose forms were not only met, but also surpassed by this particular formulation.

The novel formulation technique used to create these floating pills offers longer half-life in the stomach, allowing ranitidine to be released gradually over a 12-hour period. As a result, there may be a considerable reduction in the frequency of ranitidine doses required, improving patient compliance and convenience.

Moreover, the application of low-density polymers—like HPMC, which has a molecular weight of 15000—not only shows to be economical but also enhances the quality of floating tablet creation. This is a significant breakthrough in the creation of ranitidine hydrochloride sustained-release formulations.

In summary, the unique approach of using floating tablets has great potential to advance the field of sustained-release formulations, especially for the medication ranitidine hydrochloride. The improved formulation's effectiveness highlights the potential of this strategy to improve patient adherence, optimize drug release profiles, and enhance therapeutic outcomes.

ADHERENCE TO ETHICAL STANDARDS

Acknowledgments

I am very thankful to the department of pharmaceutics, Mewar University, my guide and Assistant Professor Mr.Pankaj Chasta, and all the faculties involved for providing facilities to carry out research work.

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