https://doi.org/ 10.33472/AFJBS.6.9.2024.543-555

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Optimizing Gastroretentive Floating Tablets with HPMC and Sodium Bicarbonate for Controlled Drug Release of Bisoprolol

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Article History

Volume 6,Issue 9, 2024

Received:21 Mar 2024

Accepted : 18 Apr 2024

doi: 10.33472/AFJBS.6.9.2024.543-555

ABSTRACT

This study explores the development and evaluation of a floating gastroretentive drug delivery system (GRDDS) utilizing a hydroxypropyl methylcellulose (HPMC) matrix and sodium bicarbonate as a gas-generating agent to sustain the release of bisoprolol over a 24-hour period. The objective was to formulate a floating tablet that initiates floating within 15 minutes and maintains a consistent drug release through hydrodynamic balance. The drug release profile was segmented into various phases: an initial burst in the first hour, followed by a steady release phase extending up to 8 hours, and concluding with a tailing off phase up to 12 hours, eventually leading to complete dissolution by 24 hours. The release kinetics were analysed, assuming near zero-order kinetics, indicative of a controlled release mechanism. The influence of polymer concentration on the release rate was significant, as increased HPMC content slowed the release, providing a denser gel barrier, while higher levels of sodium bicarbonate enhanced the buoyancy and modified release dynamics by increasing the surface area exposed to gastric fluids. This research underscores the potential of floating GRDDS of bisoprolol in improving the bioavailability and efficacy of drugs requiring prolonged gastric retention. The study provides a foundational understanding for optimizing drug release profiles of bisoprolol in floating tablet formulations.

Keywords: Gastroretentive Drug Delivery System, Floating Tablets, Controlled Release, Hydroxypropyl Methylcellulose, Sodium Bicarbonate, Gas-generating agent

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) represent a significant advancement in the field of pharmaceutical technology, specifically designed to enhance the delivery of drugs within the gastrointestinal tract. Among various GRDDS, floating drug delivery systems (FDDS) are particularly notable. These systems are designed to remain buoyant in the stomach for an extended period, thereby maximizing the drug's residence time at the site of absorption and enhancing bioavailability. This introduction explores the concept, mechanisms, benefits, and clinical significance of gastroretentive floating drug delivery systems (Namdev and Jain, 2019, Schneider et al., 2019, Tripathi et al., 2019). The primary goal of FDDS is to achieve prolonged gastric retention, thus ensuring that the drug remains in the gastric region for an extended period and is released slowly at the desired rate. This is particularly useful for drugs that are specifically absorbed from the stomach or the upper part of the small intestine. Floating drug delivery systems work on the principle of buoyancy. These systems are

formulated to be less dense than gastric fluids, which allows them to float in the stomach for an extended period without affecting the gastric emptying rate (Hua, 2020, Jacob et al., 2020, Das et al., 2021).

The buoyancy of these systems is typically achieved through one of two mechanisms: gas-forming systems and non-gas forming systems. Gas-forming systems incorporate ingredients that generate gas upon contact with gastric fluid, thus lowering the density of the formulation and causing it to float. Non-gas forming systems, on the other hand, are made from swellable polymers that absorb gastric fluid and swell to a size that prevents their exit through the pylorus, while remaining light enough to float on the gastric contents. The importance of gastroretentive systems lies in their ability to improve drug efficacy and patient compliance (de Souza et al., 2021, Rathor et al., 2021). Many drugs are absorbed more efficiently in the stomach or upper parts of the intestine. By retaining the drug in the stomach, FDDS can increase the concentration gradient of the drug between the formulation and the absorption site, leading to enhanced bioavailability. Floating systems can provide a prolonged release of the drug, which is beneficial for drugs with a short half-life and those required to act over a sustained period. This reduces the frequency of dosing and can improve patient compliance. For drugs that act locally in the stomach, such as antacids or antibiotics for Helicobacter pylori, FDDS ensures that the drug is released directly at the site of action, increasing its effectiveness. By providing a more controlled and sustained drug release, FDDS minimize the fluctuations in plasma drug concentration, thereby maintaining drug levels within the therapeutic window and reducing side effects. The clinical applications of gastroretentive floating drug delivery systems are vast and varied. They are particularly useful for drugs that are soluble only at acidic pH, such as certain antifungal and antibiotic medications. Additionally, drugs used in the treatment of peptic ulcer disease, such as proton pump inhibitors and H2 receptor antagonists, benefit greatly from increased retention time in the stomach (Vrettos et al., 2021, Almutairi et al., 2022, Blynskaya et al., 2022, Grosso and de-Paz, 2022, Rafiee and Abdul Rasool, 2022).

Moreover, FDDS can be crucial for the treatment of diseases that require a localized action in the upper part of the small intestine, such as duodenal ulcers. The ability of these systems to release drugs at a controlled and predictable rate also makes them suitable for chronic therapies, such as those required for cardiovascular and neurodegenerative diseases, where consistent drug levels can be crucial for effective management. Despite the benefits, the development of effective FDDS faces several challenges (Rajora and Nagpal, 2022, Uboldi et al., 2022). The variability in gastric physiology such as pH and motility, the presence of food, and differences in the gastric emptying rate can affect the performance of floating systems. Advances in polymer science, formulation techniques, and a better understanding of gastric motility are driving the development of more robust and adaptable FDDS. In assumption, gastroretentive floating drug delivery systems represent a promising approach in the field of pharmaceutical sciences, offering significant benefits in terms of improving the efficacy and convenience of drug therapies. As research continues to evolve, these systems are likely to

become increasingly sophisticated, with the potential to target a wider range of diseases and conditions more effectively (Rajora and Nagpal, 2022, Uboldi et al., 2022, Mahmoud and Schulz-Siegmund, 2023, Yoshida and Kojima, 2023).

Bisoprolol is a highly selective β_1-adrenergic receptor blocker commonly prescribed in the treatment of cardiovascular diseases such as hypertension, angina pectoris, and heart failure. As a member of the beta-blocker class, bisoprolol works primarily by reducing the heart rate and cardiac output, which lowers blood pressure and decreases the heart's demand for oxygen. This pharmacologic profile makes bisoprolol an effective agent in managing long-term cardiovascular conditions. However, the pharmacokinetics and therapeutic efficacy of bisoprolol present certain challenges that can be effectively addressed through gastroretentive drug delivery systems (GRDDS). Bisoprolol has a relatively low oral bioavailability of about 30-40%, primarily due to its partial absorption in the gastrointestinal tract and first-pass metabolism in the liver. The drug is characterized by a relatively short half-life, typically around 10-12 hours, necessitating twice-daily dosing to maintain therapeutic plasma concentrations. Moreover, bisoprolol is predominantly absorbed in the upper gastrointestinal tract. These properties make maintaining consistent drug levels challenging, impacting patient compliance and overall therapeutic outcomes (Chaturvedi et al., 2014, Jankovic, 2014, Hulkower et al., 2015, Kiel and Deedwania, 2015, Ågesen et al., 2019, Aoun and Tabbah, 2019).

The characteristics of bisoprolol make it an ideal candidate for formulation into a gastroretentive floating drug delivery system for several reasons. By retaining the dosage form in the stomach and upper gastrointestinal tract, GRDDS can enhance the absorption window of bisoprolol. This could potentially increase its bioavailability by providing a more prolonged exposure to its primary absorption sites. Bisoprolol’s absorption in the upper part of the gastrointestinal tract aligns well with the design of GRDDS, which are engineered to remain buoyant in gastric fluids. By floating in the stomach, the drug can be released slowly at a controlled rate, improving the efficiency of drug delivery and reducing the variability in plasma levels. Incorporating bisoprolol into a floating drug delivery system can extend its release, allowing for once-daily dosing. This not only improves patient adherence by simplifying the dosing regimen but also helps maintain more consistent blood levels of the drug, which is crucial for managing cardiovascular conditions effectively (Digne-Malcolm et al., 2016, Eguchi, 2016, Wong et al., 2016, Meattini et al., 2017, Sinnott et al., 2017, Tataru and Barry, 2017). Controlled release of bisoprolol through GRDDS can help mitigate the peaks and troughs in drug levels associated with conventional dosing, potentially reducing the risk of side effects commonly linked to higher plasma concentrations, such as bradycardia and fatigue. Environmental pH changes along the GI tract can affect the solubility and stability of many drugs. The use of GRDDS ensures that bisoprolol is released in a more controlled environment, potentially stabilizing its release profile against the variable pH conditions of the gastrointestinal tract. Given these considerations, the development of a gastroretentive delivery system for bisoprolol offers a promising approach to enhance its therapeutic efficacy

and patient compliance. By addressing the limitations associated with the conventional oral delivery of bisoprolol, GRDDS can significantly improve the management of chronic cardiovascular diseases, aligning with the goals of modern pharmaceutical care which emphasize both efficacy and patient-centeredness. This approach underscores the potential of advanced drug delivery technologies in transforming the treatment landscape for widespread health conditions (Gach et al., 2017, Tataru and Barry, 2017, Widimský, 2017, Pham et al., 2018, Aoun and Tabbah, 2019, Kishi and Fujii, 2019, Marti et al., 2024, Maslov et al., 2024).

EXPERIMENTAL

Materials:

Bisoprolol was provided as a complimentary sample by Ranchet Pharma, India. The other materials used included Hydroxy Propyl Methyl Cellulose K4M obtained from Research Lab Fine Chemicals in Mumbai, sodium bicarbonate from Loba Chemicals, Carbopol 934P from S.D. Fine Chemicals in Mumbai, along with talc and magnesium stearate. The equipment utilized comprised a tablet compression machine from Rotary Tablet Press F.P. Machinery in Ahmedabad, a UV visible spectrophotometer by Shimadzu Corporation, as well as a dissolution test apparatus, electronic balance, hardness tester, and friability test apparatus.

Methods:

Manufacturing of Floating Tablets:

Bisoprolol, HPMC (Hydroxy Propyl Methyl Cellulose), Carbopol, and sodium bicarbonate were each sieved through a number 80 mesh. Subsequently, the drug was blended with these polymers and additional components according to specified weight ratios. The mixture was then compressed using a flat-faced punch (5 mm diameter) on an eight-station tableting machine. The specific formulations are detailed in Table 1 (Shaikh et al., 2011).

Table 1. Formulation table for the gastroretentive formulation

Components and Ingredients	**Bisoprolol (mg)**	**HPMC K4M (mg)**	**Carbopol 934P**	**Sodium bicarbonate**	**Magnesium stearate**	**Talc**
GRF1	10	50	10	60	2	1
GRF2	10	70	5	45	2	1
GRF3	10	90	2	30	2	1
GRF4	10	110	1	15	2	1

Evaluation of Floating Tablets:

Hardness Test:

The hardness of the tablets was evaluated using a Pfizer hardness tester, which quantifies the force needed to crush the tablets, expressed in kilograms per square centimeter (Kg/cm^2).

Friability Test:

To assess the friability, we began by removing any loose dust from 10 tablets. These tablets were then placed in a friabilator and subjected to rotation at 25 revolutions per minute for four

minutes. After this process, any additional dust was removed, and the weight of the remaining tablets was recorded. The percentage of friability was calculated using the following formula:

$$\text{Percent Friability} = \frac{\text{Weight}_{\text{final}} - \text{Weight}_{\text{original}}}{\text{Weight}_{\text{original}}} \times 100$$

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Uniformity of Weight:

Each of the 20 tablets was carefully cleaned and subsequently weighed using an electronic balance to verify uniform weight throughout the batch.

In Vitro Floating Studies:

The floating time of the tablets was observed using a USP dissolution apparatus-II, which was set to stir at 50 rpm in 900 ml of 0.1N HCl. The solution was maintained at a temperature of 37±0.5°C. This test measured the duration for which the tablets remained buoyant, including any initial delay before the tablets started to float. The observation was made visually.

Swelling Index:

Tablets were accurately weighed and immersed in 50 ml of water. After remaining in the water for 60 minutes, they were removed and carefully dried using filter paper to remove any surface moisture, then weighed again. The swelling index was determined using the following formula:

$$\text{Swelling Index} = \frac{\text{Wet Weight} - \text{Dry Weight}}{\text{Dry Weight}} \times 100$$

In Vitro Dissolution Studies:

Dissolution testing of the floating tablets was conducted using a USP paddle apparatus, set to operate at 50 rpm in 900ml of 0.1N HCl, while maintaining a constant temperature of 37±0.5°C. Periodically, 5ml samples were withdrawn from the dissolution medium and immediately replaced with fresh medium to maintain a consistent volume. The rate of drug release was analyzed by measuring the absorbance at 238 nm using a UV-Visible spectrophotometer.

Data Analysis Models:

The drug release data from the studies were analyzed using various kinetic models to understand the release mechanics and efficiency of the floating tablet formulations. These models included:

Zero-order kinetic model, which plots cumulative percent of drug released versus time, indicating a constant release rate.

First-order kinetic model, which uses the log of the percent drug remaining versus time to show a release rate dependent on the drug concentration.

Higuchi's model, which correlates cumulative percent drug released with the square root of time, suggesting a diffusion-based release.

Korsmeyer-Peppas equation, which plots the log of the cumulative percent drug released versus log time, useful for understanding the mechanism of drug release when the release behavior does not follow conventional patterns.

Each model provides distinct insights into the release characteristics of the floating tablet formulations.

RESULTS

In this study, we developed hydrodynamically balanced systems (HBS) of Bisoprolol using hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate as a gas-generating agent in various ratios, aiming to achieve controlled drug release through floating tablets. The evaluation of these HBS tablets focused on several critical quality metrics:

Hardness: The tablets exhibited a consistent hardness, with values ranging from 4.28 to 5.21 Kg/cm².

Friability: The tablets demonstrated excellent durability, with friability percentages between 0.81% and 0.88%.

Weight Uniformity: All batches-maintained uniformity within acceptable limits, reflecting consistent manufacturing quality.

Swelling Index: The swelling index increased with higher concentrations of polymer and sodium bicarbonate, indicating effective tablet expansion under gastric conditions.

The floating characteristics of the tablets were also visually assessed:

Floating Lag Time: Varied from 4.3 to 8.9 minutes, indicating the time taken for the tablets to start floating.

Floating Time: The tablets-maintained buoyancy for durations ranging from 19 to 22 hours, ensuring prolonged gastric retention.

The composition of the tablets influenced the drug release dynamics:

Drug Release: Increased polymer content resulted in a slower release rate over 10 hours, whereas higher sodium bicarbonate levels accelerated the release.

To elucidate the release mechanism, we applied various kinetic models:

Drug Release Kinetics: Linear regression analysis supported first-order release kinetics, with R^2 values ranging from 0.8364 to 0.9965, indicative of a consistent drug release rate. The release patterns also conformed to the Korsmeyer-Peppas model, suggesting a predominantly diffusion-based release mechanism.

Table 2. Evaluation of the formulations

Code of formulations	**GRF1**	**GRF2**	**GRF3**	**GRF4**
Hardness (Kg/cm^2)	4.28	4.77	5.21	4.87
Friability (% w/w)	0.82	0.81	0.88	0.87
Average weight (mg)	130.4	130.3	129.7	133.2
Floating lag time (min)	8.9	6.7	4.3	5.7
Floating time (hrs)	19	20	22	21
Swelling index (%)	170.34	156.7	140.5	139.5

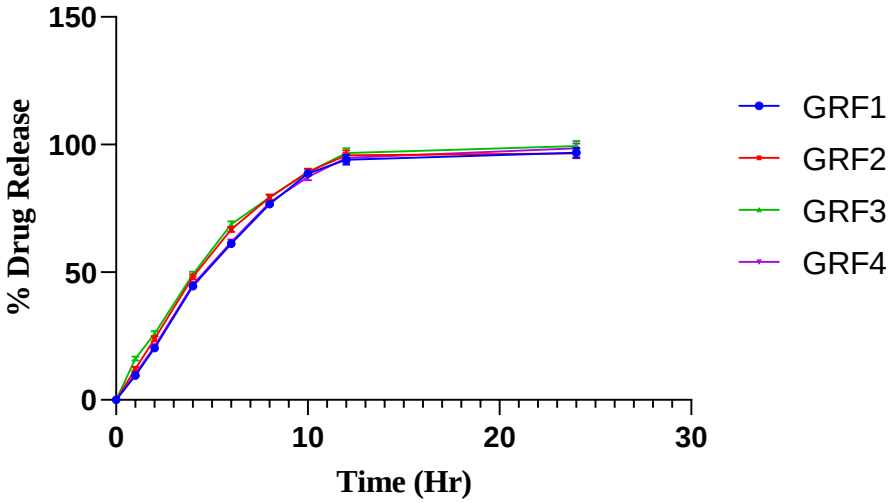

Figure 1. *In vitro* drug release study

Table 3. Pharmacokinetic and mathematical modelling of the *in vitro* release profile

Code of formulations		Zero order	First order	Higuchi	Peppas	Hixson Crowell
GRF1	R^2	0.926	0.9819	0.8364	0.9945	0.9698
	Slope	0.2874	-0.0019	9.0904	2.0663	0.0022
	Intercept	-38.36	1.5556	-101.23	-4.0456	0.6383
GRF2	R^2	0.9285	0.9861	0.8396	0.995	0.9628
	Slope	0.2797	-0.0019	8.8526	2.0922	0.0021
	Intercept	-37.303	1.7332	-98.586	-4.1241	0.628
GRF3	R^2	0.9291	0.9866	0.8404	0.9961	0.9596
	Slope	0.2677	-0.0019	8.4794	2.129	0.0021
	Intercept	-35.781	1.552	-94.498	-4.238	0.6009
GRF4	R^2	0.9306	0.9863	0.8467	0.9965	0.9955
	Slope	0.2671	-0.002	9.4894	2.3071	0.003
	Intercept	-35.803	1.602	-93.499	-4.238	0.6009

DISCUSSION

The evaluation of hydrodynamically balanced floating tablet formulations (GRF1 to GRF4) indicates distinct characteristics and performance across the different formulations, as detailed in the provided data. Discussion centers on the hardness, friability, average weight, floating characteristics, swelling index, and the kinetic models applied to understand the drug release mechanisms.The hardness of the tablets varied slightly across the formulations, with GRF3 exhibiting the highest hardness (5.21 Kg/cm²), suggesting a more robust tablet structure. This correlates with its marginally higher friability (0.88%), although all formulations remained below 1% friability, indicating excellent tablet integrity. The variation in hardness may be attributed to differences in compression force during manufacturing or the ratio of ingredients,

affecting the compactness and mechanical strength of the tablets. The average weight of the tablets showed minor discrepancies, all within an acceptable range for uniform dosage. The highest weight was observed in GRF4 (133.2 mg), which could influence both drug release and floating behavior. The swelling index, which indicates the tablet's ability to absorb water and expand, was highest in GRF1 (170.34%) and decreased progressively through the series. This reduction might be due to varying polymer concentrations, affecting the gel-forming ability and, consequently, the tablet's buoyancy and drug release. Floating lag time decreased from GRF1 to GRF3, improving the promptness of buoyancy, which is crucial for maintaining the tablet in the gastric region. This quicker onset of floating could be due to modifications in the formulation, such as the balance between hydrocolloid and gas-forming agents. The floating time was excellent across all formulations, with tablets maintaining buoyancy for 19 to 22 hours, ensuring prolonged gastric retention for sustained drug release. The kinetic analysis shows a strong correlation in the first-order model across all formulations ($R^2 > 0.98$), indicating that the drug release rate is concentration dependent. This model was confirmed as the most fitting, supported by high R^2 values in the Peppas model as well, which further suggests that the drug release mechanism is predominantly diffusion-controlled, particularly for GRF3 and GRF4, where the Peppas R^2 values were highest. The consistent slopes and intercepts across the kinetic models further reinforce the uniform behavior of these formulations under test conditions.

CONCLUSION

The formulation variations, as represented by GRF1 through GRF4, demonstrate the impact of minor compositional changes on the physical and release characteristics of floating tablets. The data suggest a careful balance between polymer content for swelling, hardness for mechanical strength, and the correct proportion of gas-forming agents to optimize both immediate and sustained release properties in a gastric setting. The kinetic analysis not only assists in confirming the release dynamics but also aligns with the practical outcomes seen in floating lag and duration, corroborating the formulation strategy's effectiveness for sustained drug delivery via floating tablets. Determining the "best" formulation among GRF1, GRF2, GRF3, and GRF4 depends on specific criteria related to the intended therapeutic use and desired characteristics of the floating tablets. GRF3 has the highest hardness (5.21 Kg/cm^2), which suggests it may be the most robust and potentially the most resistant to physical stress during handling and administration. All formulations demonstrate excellent friability (all below 1%), indicating good durability. GRF2 and GRF1 have slightly lower friability (0.81% and 0.82% respectively), which might be marginally preferable. Weight consistency is crucial for dose accuracy. All formulations are relatively consistent, with GRF2 and GRF3 showing the least deviation in average weight. GRF1 exhibits the highest swelling index (170.34%), which could indicate better performance in gastric fluid, potentially enhancing gastric retention. Floating Lag Time: GRF3 begins to float the quickest (4.3 minutes). GRF3 also maintains buoyancy the longest (22 hours), which is beneficial for sustained drug release and prolonged gastric retention. The Peppas model, which describes the drug release mechanism,

shows the highest R^2 value for GRF4 (0.9965), suggesting a highly predictable diffusion-based release mechanism. However, GRF3 is also strong in this area (R^2 = 0.9961). GRF3 appears to be the optimal formulation overall, balancing quick onset of floating, prolonged floating time, robust hardness, consistent weight, and strong performance in drug release kinetics. This formulation would likely provide the most reliable and sustained drug delivery in a gastric environment. However, the choice of the best formulation can also depend on additional factors not covered in the data, such as the cost of ingredients, ease of manufacturing, patient compliance, and specific clinical outcomes related to the drug being delivered.

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