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Optimization of non-effervescent riboflavin gastroretentive floating tablets using mixture design

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Abstract. Gastroretentive Floating Drug Delivery Systems (GRFDDS) are long-acting oral dosage forms that float on gastric juice and remain in the stomach for an elongated period gradually delivering drug substances to the upper part of the gastrointestinal system. This study aims to develop and enhance the bioavailability and stomach retention of non-effervescent riboflavin floating tablets by using a variety of polymers. In this investigation, both pre-compression evaluation and post-compression of all the tablet materials were performed according to USP specifications. In vitro, buoyancy analyses were carried out to achieve minimum floating lag time and maximum floating duration. The tablet employed direct compression methods using HPMC K17, Carbopol 940p, and polypropylene foam powder. In vitro, buoyancy studies were performed to achieve minimum floating lag time and maximum floating duration. Tablets were evaluated for physicochemical properties according to USP specifications. An optimized tablet with a floating lag time of 0.77 minutes and a floating time of 48.74 minutes was developed using Design of Experiments (DoE). The results indicated that the optimized formulation, designated as Y, performed the best. It consists of 0.45% polypropylene foam powder, 0.15% HPMC K17, and 0% Carbopol 940p. The developed non-effervescent riboflavin floating tablets have the potential to improve the bioavailability and therapeutic efficacy of riboflavin by enhancing its gastric residence time.

Keywords: floating tablets, functional polymers, gastroretentive, mixture design, riboflavin

INTRODUCTION

Vitamins can be naturally obtained through regular dietary intake from plant and animal-based foods (Comerford *et al.*, 2021). There are two types of vitamins: fat-soluble (Vitamins A, D, E, and K) and water-soluble (Vitamins B and C). Water-soluble vitamins are not easily stored by the body; therefore, any excess is excreted in the urine (Hrubša *et al.*, 2022). For the body to continue growing, developing, and maintaining health, it must obtain these vitamins in sufficient proportions. One of the water-soluble vitamins is vitamin B2 or riboflavin, which is involved in several oxidative-reduction activities within cells (Lee *et al.*, 2023). Consequently, it could play a major role in energy metabolism, cell signalling, protein folding, and so forth (Tang *et al.*, 2022). A lack of riboflavin can result in metabolic disorders, impeded growth in children, skin and mucous lesions, cancer, ariboflavinosis, inflammatory disorders such as angulus infections, anemia, glossitis, cheilitis, sepsis, hair loss, cataracts, and migraine (Lee *et al.*, 2016; Lee *et al.*, 2023; Murakami *et al.*, 2010; Olfat *et al.*, 2022).

When it comes to oral medication delivery systems, sustained release (SR) dosage forms have been essential for increasing medication bioavailability, preventing adverse effects, and improving patient compliance (Vrettos *et al.*, 2021). However, due to the brief and irregular gastric emptying time, SR systems may not be able to fully release the drug to its absorption site, particularly for medications with a limited upper gastrointestinal (GI) tract absorption window.

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Gastroretentive (GR) methods have been developed to address this limitation. GR systems maximize drug absorption in the proximal GI tract by remaining in the stomach longer than typical (Ahmad *et al.*, 2023; Nguyen *et al.*, 2020; Streubel *et al.*, 2006). It was demonstrated that the floating system was particularly successful in extending the duration of gastric residence time for small-to-medium-sized tablets and considerably lowering fluctuations in the duration of gastric emptying time for large-sized tablets. Floating GRDDS can greatly lessen the risk of early gastric emptying of swellable systems by floating over gastric juice separated from the pylorus (Seongkyu *et al.*, 2018; Tripathi *et al.*, 2019).

It is reported that there is limited absorption of riboflavin from the gastrointestinal tract (Ibrahim, *et al.*, 2019). Typically, patients must take their prescriptions two or three times a day (Jaeger & Bosch, 2016). About half of American patients do not take their medications as prescribed by their doctors, resulting in a substantial annual loss of $100 billion. This issue may be more severe in underdeveloped nations. One crucial strategy for resolving the aforementioned issues is the use of controlled or sustained release oral formulations, which can improve patient compliance and therapeutic outcomes (Fu *et al.*, 2018). This study investigated the formulation and optimization of non-effervescent riboflavin floating tablets, using different functional polymers as excipients to achieve buoyancy properties.

MATERIALS AND METHODS

Riboflavin is used as an active pharmaceutical ingredient (API) and was purchased from Takeitglobal. Hydroxypropyl methylcellulose (HPMC) K17 and PFP (polypropylene foam powder) are used for tablet binders. Carbopol 940p and Magnesium Stearate were bought from Sigma-Aldrich. They were used as suspending agents and lubricants, respectively. Polypropylene foam powder acts as a floating agent. Besides that, talc and lactose were used as anti-clumping agents and diluent agents, individually.

Pre-compression studies

The pre-compression test comprises multiple tests: angle of repose, which measures the cohesive behavior of powder, tap, and bulk density, compressibility and flowability of the powder, and the Hausner ratio to calculate powder flow characteristics.

Angle of repose

The angle of repose was established using the funnel method. To get the maximum cone height (h), the mixture was poured via a vertically adjustable funnel (Kalman, 2021). The heap's radius (r) was measured, and the angle of repose was computed using equation (1).

$$\tan\theta = \frac{h}{r} \qquad (1)$$

Where,
θ = angle of repose
h= height of cone
r= radius of powder cone

Tap density

Tapped density is the bulk density of a powder that has been crushed through tapping or vibration (Amidon *et al.*, 2009). Bulk density measures the volume occupied by the particles, while tapped density is calculated by placing a graduated cylinder containing a specified powder mass on a mechanical tapping instrument functioned for a predetermined tap number (100). The bulk density is calculated by equation (2) while the tapped density is calculated by multiplying the weight of the drug in the cylinder by the final volume using equation (3).

$$\text{Bulk density} = \frac{Weight\ of\ samples}{Volume\ occupied\ by\ the\ sample} \qquad (2)$$

$$\text{Tapped density} = \frac{Weight\ of\ samples}{The\ tapped\ volume} \qquad (3)$$

Hausner ratio

The Hausner's ratio was determined using the following equation (4):

$$\text{Hausner ratio} = \frac{Untapped\ apparent\ volume}{Tapped\ apparent\ volume} \qquad (4)$$

Carr's Index

The Carr's Index test is a method for determining the compressibility of a powder. It is a measure of the proclivity of a powder to form arches or bridges when compacted. A high Carr's Index powder is hard to compress, whereas a low Carr's Index powder is simple to compress. (Singh *et al*., 2018). Equation (5) displays the compressibility index formula.

$$\text{Carr's Index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} x100 \quad (5)$$

Preparation of riboflavin tablets

The drug, diluent, and other excipients were screened through a mesh and pre-blended using a ziplock bag. Just before compression, the lubricant was added, and the mixture was once again combined. A single punching tablet machine was used to compress the tablet mixtures directly. The formulation is generated using Design of Expert (DoE) version 13. An 11-run was used to study the different functional polymers which are PFP, HPMC, and carbopol (X1, X2, X3) on floating lag time (Y1) and floating time (Y2). The formulations prepared are shown in Table 1 together with their compositions.

Riboflavin tablet compression

Floating tablets containing 50 mg of riboflavin were prepared through direct compression. All the constituents were weighed and mixed using a ziplock bag. After all the weighed formulations underwent pre-compression testing, the riboflavin and excipient were pounded in a mortar and pestle to obtain a uniform powder blend. After being well mixed, the powder mixture was put through 800 µm and 425 µm mesh. On a single punch tableting machine, tablets were compressed directly.

In-vitro study and optimization

Floating lag time and floating time are measured using an in-vitro test. The experiment was carried out with 300 mL of 0.1 N HCl as the dissolution media. It is prepared by mixing approximately 297.9 mL of deionized water, 2.1 mL of hydrochloric acid, and 0.6 g of sodium chloride. The temperature was maintained at 37.5°C with pH ranging from 1.2 to 1.5. Floating time and lag time are obtained and inserted in the response number column in the Design Expert software. Floating lag time was defined as the amount of time needed for the tablets to reach the surface and float. The total floating time was calculated as the amount of time the dose form remained on the surface continuously (Louis *et al*., 2020). To measure the floating lag time, each tablet was gently placed in the dissolution medium, and the time taken for the tablet to rise to the surface was recorded as the floating lag time. Floating duration was measured as the total time the tablet remained buoyant on the surface of the medium. Then, the software generated and gave the most optimized formulation that theoretically produced the highest number of floating times and the lowest number of lag times. The graph of contour 3D shows the highest point (red area), which illustrates the most optimized formulation of Carbopol 940p, HPMC K17, and PFP. After that, post-compression investigations were conducted to assess the improved formulation.

Table 1. Riboflavin tablet composition using Design of Expert (DoE)

Ingredient (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Riboflavin	20	20	20	20	20	20	20	20	20	20	20
Polypropylene foam powder (X1)	28.47	41.41	3	28.47	16.53	20	42.40	31.50	13.03	28.8	53.42
HPMC K17M (X2)	17.73	18.58	30	17.73	30	9.97	0	0	20.92	30	6.57
Carbopol 940p (X3)	13.79	0	27	13.79	13.46	30	17.60	28.50	26.04	1.2	0
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3
Lactose	14	14	14	14	14	14	14	14	14	14	14
Talc	3	3	3	3	3	3	3	3	3	3	3

Post-compression evaluation

Evaluation of tablet characteristics on weight variation, friability, content uniformity, hardness, and tablet dimensions.

Weight variation

Twenty tablets were chosen at random and weighed. The mean weight value was calculated and used to compare the weights of the individual tablets to assess for uniformity.

Hardness test

A hardness tester was used to measure the hardness. The acquired result was the mean of the ten pills resistance, which was stated in Newton's (N) unit. The diameter and thickness were measured and characterized using the features of this equipment. Three pills were measured, and the average value was taken.

Friability test

Friability is ascertained by using a friability. Twenty tablets were inserted in the machine with a 25-rpm rotation speed for 4 minutes where the chamber was allowed to rotate about 100 times. A 1% weight-loss maximum is acceptable (Kim *et al.*, 2018a; Kim *et al.*, 2018b).

RESULTS AND DISCUSSION

The floating tablets of riboflavin were made by a direct compression technique using PFP, Sodium Alginate, HPMC, Carbopol 940p, and several types of excipients. The study intends to determine the appropriate mix of biopolymers to use as an excipient in riboflavin tablets. Three functional polymers; Carbopol, PFP, and HPMC K17 were assessed. The response variable measurements were Y1: floating lag time and Y2: floating time. The three polymers were utilized as constituents in a mixture, with the amount of each component varying from 0 to 1. The Design of Expert program suggested 11 formulations in total. The composition of the functional polymers includes 60% of the component, 20% riboflavin as an active ingredient, 14% lactose as a filler, 3% talc as a glidant, and 3% magnesium stearate as a lubricant. The design and outcome of the experiment, which included one replication and model points, are shown in Table 2.

Formulations 1 and 4 are regarded as replication models in this experiment. A lack-of-fit test can be used to assess the suitability and efficiency of the provided models. Table 3 provides an overview of the sequential model comparison and the lack-of-fit test. The software indicates a highly significant p-value (< 0.005) for Y1 in both the linear and cubic models.

However, the quadratic and special cubic models were unsuitable for data fitting due to the significant p-value (> 0.05). Similar results are shown for Y2's linear and cubic compared to Quadratic models, which fit the data with low p-values (< 0.05) of 0.0157 and 0.0280, respectively. Table 3 shows that the lack-of-fit test yields low p-values (0.0091 and 0.0738 for YI and Y2, respectively), suggesting that the linear model is appropriate. A lack-of-fit test determines if a pattern adequately matches the data.

The adjusted coefficients of determination (adjusted R2) for the linear model equations Y1 and Y2 are 0.5623 and 0.5574, respectively. This means the model can explain 56.23% and 55.74% of the outcomes.

The model accounts for approximately 56% of the variability in the outcome, leaving around 44% unaccounted for. This is a moderately suitable match, and additional elements could impact the result that has not been accounted for. A high coefficient of determination does not guarantee a reliable indicator of match quality. Similarly, as this statistic is mostly acted upon by the variability in the independent variable, a moderate R2 does not always imply a negative association. (Hamilton *et al.*, n.d.). Linear regression analysis was conducted using two indicators to establish the regression model. The resulting linear regression equations are as follows:

$$Y1 = -135.540A + 429.965B + 203.477C \quad (6)$$

$$Y2 = -16.5759A + 387.717B + 255.033C \quad (7)$$

Analysis of variance (ANOVA) in Table 4 shows that the linear mixture model is significant with p-values of 0.0150 and 0.0157 for Y1 and Y2, accordingly. Based on the equation above,

Table 2. The optimal design formulations and results

Formulation	X1	X2	X3	Y1	Y2
1	28.47	17.73	13.79	10	65
2	41.41	18.58	0	5	85
3	3	30	27	170	170
4	28.47	17.73	13.79	9	71
5	16.53	30	13.46	210	210
6	20	9.97	30	21	79
7	42.40	0	17.60	7	54
8	31.50	0	28.50	19	61
9	13.03	20.92	26.04	198	198
10	28.80	30	1.20	62	62
11	53.42	6.57	0	2	35

Table 3. Model comparison based on the lack-of-fit of the design model

Type of Model	Sequential p-value		Lack-of-Fit p-value		Adjusted R^2		Predicted R^2	
	Y1	Y2	Y1	Y2	Y1	Y2	Y1	Y2
Linear	0.0150	0.0157	0.0091	0.0738	0.5623	0.5574	0.3988	0.3595
Quadratic	0.5806	0.8029	0.0081	0.0596	0.5114	0.4097	-0.4654	-0.6673
Special Cubic	0.3873	0.6555	0.0076	0.0520	0.5054	0.3025	-2.3528	-4.6416
Cubic	0.0076	0.0520	-	-	0.9999	0.9953	-	-

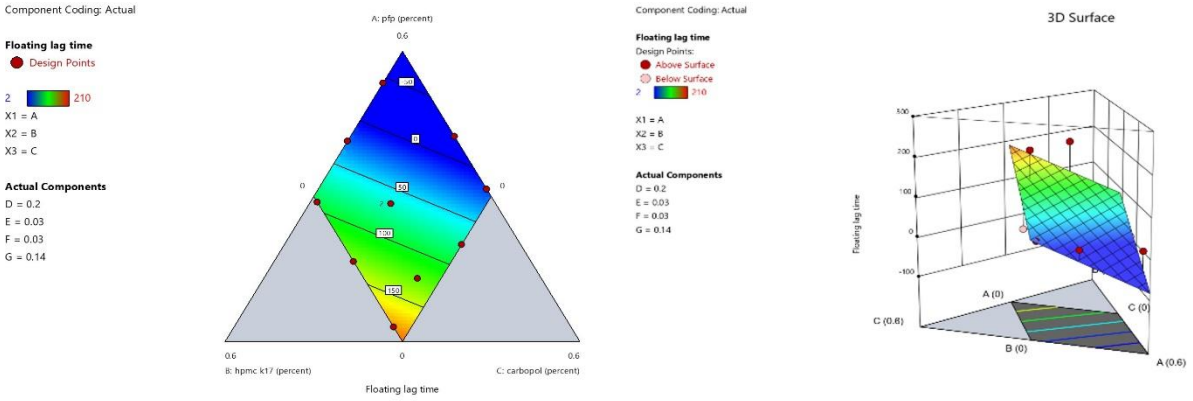
component A is polypropylene foam powder, B is HPMC K17M and component C is carbopol 940p. There is no correlation or interaction shown between the materials. This is due to the usage of a linear model. A linear model only shows an equation or significant change for individual materials. All three materials significantly impact lag floating time and floating time as shown by the p-value of the linear mixture model in Table 4 (p = 0.0157), which is less than 0.05.

Table 4. ANOVA (Analysis of variance) for the response of Y1 and Y2 linear models

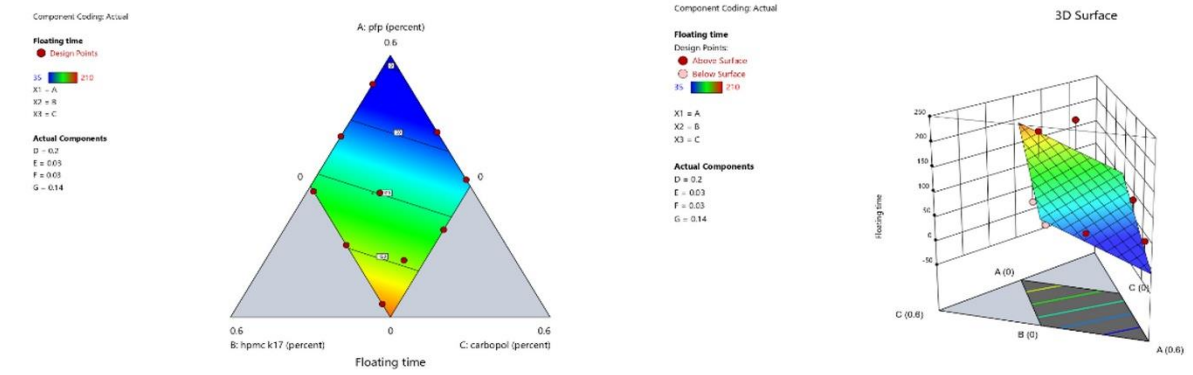
Source	Y1	Y2
	p-value	p-value
Model	0.0150	0.0157
Linear Mixture	0.0150	0.0157
Lack of Fit	0.0091	0.0738

Effects of mixture constituents and formulation optimization

The alterations in the mixing design component of the riboflavin tablet formulation are shown by the contour map and three-dimensional response surface models (Figure 1). The contour map's base is restricted to a maximum value of 0.3 for points B and C, because of the constraint applied during the initial stages of optimization. Only component A completely covers the entire base, which measures 0.6. The floating lag time decreases as the amount of polypropylene foam powder increases. The ability of the tablet to float for a longer period is greatly improved by the low density of PFP, which is 0.8 g/cm^3, indicating that it is lower than the density of simulated stomach fluid, which is 1.004 g/cm^3. The trapped air within the closed-cell structure of the foam acts as a cushion, resulting in the displacement of a larger volume of liquid relative to its weight. The tablet floats because it has an inherent ability to oppose the force of gravity pulling it downwards. Our study found PFP to be highly effective in reducing the floating lag time of riboflavin gastroretentive floating tablets. Specifically, our optimized formulation achieved a floating lag time of just around 1 minute. This finding aligns with Kandukoori *et al.* (2018), who investigated the influence of PFP on the gastroretentive properties of cefditoren pivoxil floating tablets and reported that increasing PFP concentration decreased the floating lag time of the tablets. They observed that



a) Floating Lag Time



b) Floating Time

Figure 1. Mixture analysis surface and contour plots for a) floating lag time and b) floating time

formulations containing PFP showed superior floating properties compared to those using sodium bicarbonate as the floating agent.

The HPMC K17 and Carbopol 940p significantly contribute to extending the duration of floating time. According to Newton *et al.* (2014), the integration of a hydroxypropyl methylcellulose (HPMC), gas-generating agent with microcrystalline cellulose resulted in improved drug content as well as optimal floating (floating lag time, 30 s; floating duration, >8 h), which is almost near to our results. The phenomenon can be attributed to the shaping of a bioadhesive gel layer by HPMC K17 and Carbopol 940p, which effectively traps air within the tablet. Despite its porous nature and low density, the presence of HPMC K17 and Carbopol 940p in PFP aids in the confinement of air bubbles (Patil *et al.*, 2006). The gel layer acts as a diffusion barrier, impeding the penetration of stomach acids and slowing down the dissolution of the drug. This regulated release mechanism ensures a steady and continuous delivery of the drug throughout the lengthy time of buoyancy. DoE- software recommended triple of recommendations and anticipated outcomes are given in Table 5.

The desirable criteria of the projected optimization function determine the polymer ratio. The evaluation of this study to obtain an effective riboflavin tablet relies on the criterion of shorter floating lag time and longer maximum floating time. Subsequently, the anticipated value of the response is established. The floating lag time response values were configured as "in a range from 0 to 1," for effervescent and "in a range from 0 to 10," for non-effervescent while the floating time was "maximum up to 12h." The top three highest desirabilities were used as a reference for selecting components for the optimization process.

Pre-compression screening of optimized tablet

Compatibility, flowability, and powder properties including angle of repose, bulk density, Hausner ratio, tapped density, and Carr's index are assessed on the pre-compressed tablet (Table 6). Before the tablet punching procedure, all tests must meet the official USP standards to ensure compliance. The floating tablets of riboflavin were prepared by direct compression method for evaluating HPMC K17, polypropylene foam powder, and Carbopol 940p. The results indicated that the angle of repose was measured at 29.76° to 30.10°, however, the previous study concluded, the standard ideal value for the angle of repose is 30° or below considered an excellent flowability (Moravkar *et al*., 2022). The compressibility study was also performed to determine the Carr's index, the result indicated the Carr's index (CI) was calculated between 16.87% and 23.57%, whereas according to the standard specifications, the CI value below 25% is considered a fair to possible flowability (Kalal *et al*., 2018; Singh & Krishnaswamy, 2023). The Hausner ratio (HR) was measured to evaluate the compressibility properties of riboflavin powder. The HR values were found to be 1.21 and 1.30. According to Katal *et al*., these values fall within the range indicative of possible flowability (Kalal *et al*., 2018).

Evaluation of the tablet

The manufactured floating riboflavin tablets were tested for general appearance, median weight, thickness, hardness, friability, and drug content, among other post-compression parameters. The outcomes are displayed in Table 7.

Validation of the model

The software optimization yielded an ideal formula of 43% polypropylene foam powder, 10.8% HPMC K17, and 6.2% Carbopol 940p. The formulation contained 60% excipient. The other fixed components comprised 20.0% riboflavin, 14.0% lactose, 3.0% talc, and 3.0% magnesium. The estimated response values under this formulation were predicted to have a floating lag time of 1.011 minutes and a floating time of 50.729 minutes. Three corroborative trials were conducted, resulting in a floating lag time of 3 minutes and a floating time of 46 minutes for the tablets. A t-test was conducted to verify the agreement between the observational and anticipated values which are provided in Table 8.

Table 5. Three suggested combinations recommended by DoE and predicted results

Number	A: Polypropylene Foam Powder	B: HPMC K17	C: Carbopol 940p	Y1: Floating Lag Time(min)	Y2: Floating Time (min)	Desirability
X	0.43	0.11	0.06	1.01	50.73	1
Y	0.45	0.15	0	0.77	48.74	1
Z	0.42	0.10	0.08	3.22	52.70	1

Table 6. Pre-compression characterisation of the powder

Formulation	X	Y	Z
Angle of Repose	29.76	28.60	30.10
Tapped Density	0.63	0.71	0.72
Bulk Density	0.53	0.55	0.55
Carr's Index	16.87	23.05	23.57
Hausner Ratio	1.21	1.29	1.30

Table 7. Physicochemical evaluation of riboflavin tablets

Formulation	Non-effervescent matrices with HPMC K17, polypropylene foam powder, and Carbopol 940p		
	X	Y	Z
Weight variation(mg)	1350	1379	1329
Thickness (mm)	3.81	3.84	3.72
Diameter (mm)	16.53	16.57	16.51
Hardness (N)	64	53	81
Friability (%)	0.74	0.6	0.5

Table 8. T-test of optimized tablet

Formulation	Floating lag time			Floating time		
	X	Y	Z	X	Y	Z
Obtained	3	5	10	46	57	63
Predicted	1.01	3.22	7.77	50.73	52.70	55.13
p-value	0.57			0.35		

The results showed no statistically significant deviation from the expected values ($p > 0.05$), suggesting that the i-optimal mixture design may effectively predict the best formulation of riboflavin tablets. During the buoyancy test, the tablets were immersed in stomach fluids, floated in the liquid, and increased in size due to hydration aided by gel-forming polymers. Table 9 displays the floating lag time and floating time of the optimized tablet.

Table 9. Floating lag time & Floating time of the optimised tablet

Formulation	Floating lag time(minute)	Floating time(minute)
X	3	46
Y	5	57
Z	10	63

CONCLUSION

The development of non-effervescent riboflavin floating tablets in this study demonstrates a promising approach to enhancing the gastric residence time and sustained release of riboflavin, thereby potentially improving its bioavailability and therapeutic efficacy. This gastroretentive delivery system addresses the challenges posed by riboflavin's limited absorption window and low bioavailability. Utilizing the direct compression method, we formulated gastroretentive floating tablets incorporating PFP, HPMC K17, and Carbopol 940p, optimizing for maximum floating time and minimal floating lag time. The low porosity and foam density of PFP contribute to tablet buoyancy, while the gel layer formed by HPMC K17 extends the floating duration. These findings underscore the significant potential of riboflavin sustained-release tablets in advancing contemporary pharmaceutical research and improving health outcomes. While this study primarily focused on the formulation and optimization aspects, future research should aim to rigorously evaluate the in vitro drug release profiles, stability, and in vivo performance of the optimized formulation. Furthermore, exploring alternative polymers or combination approaches may enhance the floating properties and drug release characteristics, thereby contributing to the development of even more effective gastroretentive delivery systems.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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