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Review Article

Mixture design for screening polymers in riboflavin effervescent gastroretentive floating tablets

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ABSTRACT

Oral sustained-release formulations improve therapeutic efficacy and patient compliance. Floating drug delivery systems (FDDS) prolong gastric residence by floating over gastric contents, enhancing upper intestinal absorption. Riboflavin, a water-soluble vitamin with low intestinal uptake, was selected as the model drug to produce direct-compression floating tablets. A mixture design (DOE) approach optimized five polymers, carrageenan, chitosan, Carbopol 940, HPMC K4M, and HPMC K75, combined with effervescent agents. Eighteen formulations were prepared and evaluated for floating lag time and cumulative drug release. Numerical optimization using the desirability function in Design Expert software identified polymer compositions achieving desirability = 1.000, with predicted release of 71–79%: Carrageenan 12–15%, Carbopol 940 4–17%, and HPMC K75 0.6–12%. Based on DOE contour plots and predicted responses, formulations F6, F10, and F12 were selected as optimal screening candidates, exhibiting low release at 6 h and acceptable floating lag times (≤300 s). Contour and 3D surface analysis revealed polymer-specific effects: carrageenan strongly retarded release via gel formation, Carbopol 940 provided intermediate modulation through swelling and diffusion, HPMC K75 offered moderate control, HPMC K4M weak retardation, and chitosan accelerated release. The best formulations balanced buoyancy and sustained release, highlighting carrageenan and Carbopol 940 as key excipients for FDDS. These findings demonstrate the utility of experimental design for excipient screening and the potential to tailor polymer combinations to improve riboflavin bioavailability.

Keywords:
Gastroretentive drug delivery system; Floating tablets; Mixture design (DOE); Riboflavin; Polymer

1. INTRODUCTION

The oral route is a widely accepted and preferred approach for delivering medication into the systemic circulation. The pharmaceutical industry has increasingly emphasized oral controlled-release drug delivery because it provides multiple advantages, such as improved therapeutic performance, higher patient compliance, and greater convenience in dosage design and administration. Medications that are eliminated quickly and absorbed efficiently from the gastrointestinal tract tend to leave the body in a short period of time. To achieve the aimed therapeutic effect, these drugs need to be dosed often. Controlled oral sustained-release formulations have been designed to overcome this limitation. By releasing the drug gradually into the GI tract, these formulations help maintain adequate systemic concentrations over an expanded time frame [1]. The goal of gastroretentive drug delivery is to target the upper gastrointestinal tract for site-dependent drug release that can have local or systemic therapeutic effects. Extending this residence period leads to a marked improvement in gastric retention time. In recent decades, numerous technological approaches have emerged

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to achieve this goal, including: sinking systems with increased density, buoyant floating systems, magnetically controlled devices, super-porous hydrogels, formulations that adhere to gastric mucosa, and expandable or unfoldable platforms that limit their passage through the pylorus[2].In recent years, floating drug delivery systems (FDDS) have emerged as one of the principal strategies investigated within pharmaceutical research. FDDS significantly enhances the bioavailability and controlled delivery of drugs with short half-lives or localized stomach targets by extending gastric residence time. They are useful in treating gastrointestinal tract conditions, including gastroesophageal reflux disease (GERD), increasing patient compliance, and decreasing the frequency of doses. Floating gastric systems rely on reduced density to stay buoyant in the stomach, which helps maintain the formulation in the gastric region longer [3]. Traditional floating systems frequently struggle with delayed buoyancy due to their formulation structure, which may allow the dosage form to exit the stomach before the floating mechanism becomes effective [4,5]. Furthermore, to float, function properly, and prevent gastrointestinal irritation, a low-density system needs a lot of fluid in the stomach. Riboflavin (vitamin B2) is a crucial supplement for the human body, which has multiple functions to regulate a healthy body. Riboflavin is commonly prescribed in dietary supplements for the treatment of inflammatory conditions like angular infections, glossitis, cheilitis, sepsis, cataracts, and migraine [6]. A lack of riboflavin may lead to symptoms such as fissured or inflamed lips, desquamating skin, oedematous mucous membranes, anaemia related to iron deficiency, ulcerations in the mouth, cracking at the lip corners, throat discomfort, and the oral–ocular–genital complex. Thus, there is constant attention paid to riboflavin's extended-release delivery methods. Due to the limited intestinal absorption window for oral riboflavin absorption, gastric floating formulations inherently provide benefits such as lower required doses and extended therapeutic duration compared to alternative sustained-release systems[7].

During pre-formulation studies, optimising the composition of the excipient combination to produce a product with the necessary properties is a frequent challenge. When evaluating one or more blending qualities is the goal, the investigator can employ a collection of instruments and methods referred to as experimental research methodology. Previous studies indicate that, under dynamic physiological settings, the gastric floating system can keep the dosage form in the stomach long enough for full drug release at the predetermined rate[8]. This study presents a novel combination of polymers and the effervescent technique, utilising a DOE (Design of Experiment) mixture design study to enhance bioavailability, reduce floating lag time, and improve sustained release. Therefore, the primary objective is to determine which polymer plays the dominant role in delaying release and the most influential polymer formulation that provides the best effect in the formulation for moving forward with the optimisation process to achieve gastric retention, with a focus on buoyant properties of the gastroretentive dosage form.

2. MATERIALS AND METHODS

2.1. Material

The active pharmaceutical ingredient, riboflavin (purity ≥ 98%), was obtained from Take It Global Sdn Bhd, Malaysia. The functional polymers Carrageenan, Chitosan, Carbopol 940 (MW ~1,250,000 Da), Hydroxypropyl Methylcellulose K4M (viscosity ~4,000 mPa·s), and Hydroxypropyl Methylcellulose K75 (viscosity ~75,000 mPa·s) were obtained from Sigma-Aldrich, USA along with magnesium stearate, talc, and microcrystalline cellulose (MCC). Lactose, citric acid, and sodium bicarbonate were obtained from HmbG. All materials were of pharmaceutical grade.

2.2. Formulation of tablets using mixture design approach

Tablets were fabricated through direct compression using a manual single-punch tablet press (Shakti, India). The riboflavin floating formulations were developed using this technique in combination with the excipients such as lactose, sodium bicarbonate, microcrystalline cellulose, citric acid, talc, and magnesium stearate. The objective of this study was to establish which mixture of biopolymers provides the best excipient functionality in riboflavin tablet formulations. Five functional polymers, chitosan, carrageenan, Carbopol 940, HPMC K75, and HPMC K4M were evaluated. The measured response variables included floating lag time and cumulative drug release (%) at 6 h. In this study, the five polymers served as independent mixture variables and the two responses served as dependent variables. Each polymer proportion ranged between 0 and 1, with the total concentration of all five functional polymers combined fixed at 30% w/w of the tablet weight. A simplex-lattice mixture design was generated using Design Expert® software (version 13.0, Stat-Ease Inc., Minneapolis, MN, USA), which proposed 18 formulations in total. Riboflavin was incorporated at 10% w/w, with sodium bicarbonate (20% w/w) and citric acid (3% w/w) forming the effervescent system. Lactose (29% w/w) served as the diluent, microcrystalline cellulose (6% w/w) acted as the disintegrant, while talc (1% w/w) and magnesium stearate (1% w/w) were incorporated to improve powder flow and provide lubrication, respectively. Details of the

Table 1. Polymer ratios (%) of each component as recommended by the mixture design (DOE).

Formulation	Polymer Ratio				
	Carrageenan	Chitosan	Carbopol940	HPMCK4M	HPMCK75
	(%)	(%)	(%)	(%)	(%)
1	7.5	7.5	7.5	0	7.5
2	7.5	7.5	0	7.5	7.5
3	3	3	3	18	3
4	0	7.5	7.5	7.5	7.5
5	0	30	0	0	0
6	6	6	6	6	6
7	7.5	7.5	7.5	7.5	0
8	3	3	3	3	18
9	0	0	0	0	30
10	7.5	0	7.5	7.5	7.5
11	3	3	18	3	3
12	6	6	6	6	6
13	18	3	3	3	3
14	30	0	0	0	0
15	6	6	6	6	6
16	0	0	0	30	0
17	3	18	3	3	3
18	0	0	30	0	0

experimental design and corresponding results, including replications and model points, are summarized in Table 1.

Furthermore, physical parameters such as tablet hardness and thickness act as latent factors that may have contributed to the variability observed in the cumulative drug release profiles. While all formulations remained within pharmacopeial limits, the observed range in hardness (81–110 N) and thickness (9.84–10.09 mm) likely influenced the internal porosity and matrix density of the tablets. For formulations F5, F9, F14, F16, and F17, these physical variations could have subtly altered the surface area available for dissolution or the rate of polymer relaxation and matrix erosion. Such minor differences in tablet integrity, while not controlled as independent variables in the mixture design, represent inherent process variations that can influence cumulative release percentages. A summary of all independent variables, fixed components, response variables, and latent factors used in this experimental design is presented in Table 2.

2.3. Pre-compression studies

Precompression studies involve essential assessments performed on powder blends or granules before tablet compression. These evaluations focus on determining flow behaviour, compressibility, and bulk density to ensure consistency and quality during formulation. Their purpose is to confirm that the powder blend performs reliably throughout the manufacturing process, thereby reducing problems such as capping and lamination that could compromise tablet integrity.

Table 2. Summary of independent variables, fixed components, response variables, and latent factors in the mixture design experimental framework.

Variable category	Variable	Role in study	Measurement or level
Independent mixture factors	Carrageenan (H), Chitosan (J), Carbopol 940 (K), HPMC K4M (L), HPMC K75 (M)	Polymer components varied by DOE	0–30% within total polymer fraction
Fixed formulation components	Riboflavin (A), Lactose (B), Microcrystalline cellulose (C), Citric acid (D), Sodium bicarbonate (E), Talc (F), Magnesium stearate (G)	Kept constant across formulations	Riboflavin 10%, sodium bicarbonate 20%, citric acid 3%, lactose 29%, MCC 6%, talc 1%, magnesium stearate 1%
Response variables	Cumulative drug release at 6 h, floating lag time	Main DOE responses	%, seconds
Latent/process variables	Hardness, thickness, friability, powder flow, compressibility	Not independent DOE factors but may influence release and buoyancy	Measured during pre- and post-compression evaluation

2.3.1. Angle of repose

The angle of repose was determined using the conventional funnel approach. A powder blend that had been precisely weighed was positioned in the funnel with its outlet just touching the powder surface. After the powder formed a freely flowing cone, its diameter was measured and used in the designated equation to compute the angle of repose.

$$\text{Angle of repose, } \theta = \tan^{-1} \frac{H}{R} \quad (1)$$

Where θ indicates the angle of repose, H is the height of the powder cone (cm) and R is the radius of the powder cone base (cm).

2.3.2. Bulk density

The bulk density test expresses the relationship between powder mass and its uncompressed volume. A 10 g sample, sieved through a 45 µm screen, was poured into a 100 mL measuring cylinder. The uncompressed volume of powder was measured after the top surface was lightly polished to prevent compaction. The apparent bulk density (g/mL) was calculated using the following formula:[9].

$$\text{Bulk Density}\left(\frac{g}{mL}\right) = \frac{\text{Weight of Powder (g)}}{\text{Bulk Volume (mL)}} \quad (2)$$

2.3.3. Carr's index

Carr's index is typically calculated via the bulk and the tapped density measurements. Substitution of a given formula will yield the Carr's index [10]:

$$\text{Carr's index} = \left(\frac{\text{Tapped Density-Bulk Density}}{\text{Tapped Density}}\right) \text{x } 100 \quad (3)$$

2.4. *In vitro* dissolution study

The drug release behavior was assayed through an *in vitro* dissolution analysis, and the outcomes are inserted into the Design Expert software as a response. The floating matrix tablets were subjected to dissolution testing using the USP XXIII paddle apparatus Type II (Delta, China). Dissolution was accomplished in 900 mL of 0.1 N HCl at 100 rpm, with 5 mL samples taken at set intervals and immediately substituted with fresh medium. After filtration through Whatman No. 1 paper, the sample's absorbance was recorded at 444 nm utilizing a UV spectrophotometer (Shimadzu SPD-10A VP, Japan). The continuous floating duration and floating lag time of each tablet were recorded to investigate the correlation between the buoyancy mechanism and the resulting cumulative drug release profile [10]. The percentage of cumulative drug release was calculated using the equation derived from the Beer-Lambert calibration:

$$\% \text{ Cumulative drug release} = \frac{C \text{ x } V}{W} \text{ x } 100 \quad (4)$$

Where C is the concentration of riboflavin (mg/mL) determined from the regression equation (y = 9.9638x), V is the volume of the dissolution medium (900 mL), and W is the theoretical drug content in the tablet (mg).

2.4.1. UV spectrophotometric determination of riboflavin content

UV-visible spectrophotometric techniques are commonly employed for the quantitative determination of Vitamin B2 in pharmaceutical and research-based analyses. In the present investigation, Riboflavin content was determined using a UV-visible spectrophotometric technique by recording the absorbance at 444 nm with 0.1 N HCl as the solvent medium. The analytical wavelength of 444 nm was selected based on the established visible absorption maximum of riboflavin in acidic aqueous media consistent with published dissolution methodology for riboflavin-based floating formulations[10].

2.4.2. Reagents

Preparation of 0.1N HCl: A volume of 100 mL of 1 M HCl was transferred into a volumetric flask and diluted with distilled water to obtain a final volume of 1000 mL.

Preparation of Standard Solution: An accurately weighed 30 mg quantity of riboflavin was transferred into a 100 mL volumetric flask and dissolved using 0.1 N HCl to obtain a primary stock concentration of 0.30 mg/mL. Subsequently, 5 mL of the prepared stock solution was pipetted into another volumetric flask and diluted to 10 mL with 0.1 N HCl, resulting in a final concentration of 0.15 mg/mL.

2.4.3. Procedure

The prepared stock solution was further diluted using 0.1 N HCl to obtain riboflavin concentrations of 0.0047, 0.0094, 0.01875, 0.0375, 0.075, and 0.15 mg/mL. The absorbance of each dilution was recorded at 444 nm using a UV spectrophotometer (Shimadzu SPD-10A VP, Japan), with 0.1 N HCl employed as the blank solution.

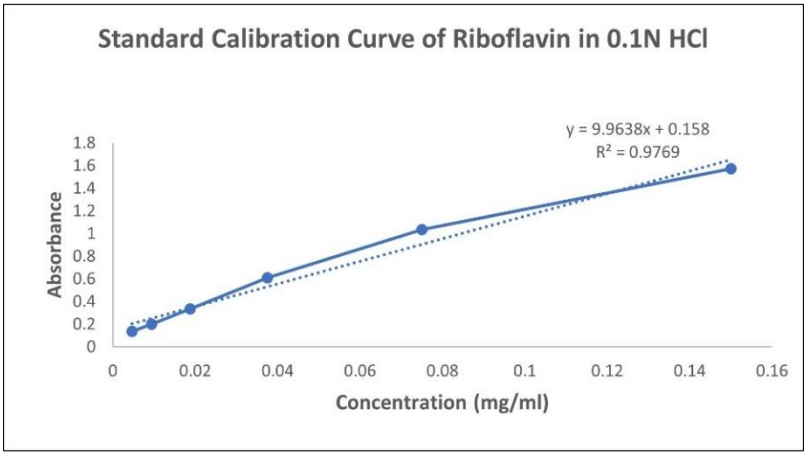

Figure 1. Standard calibration curve of riboflavin in 0.1N HCl determined by UV-visible spectrophotometry at 444 nm. The solid line represents the Beer-Lambert regression through the origin (y = 9.9638x, used for concentration calculations), and the dotted line represents the full linear regression with intercept (y = 9.9638x + 0.158, R^2 = 0.9769).

2.5. Post-compression studies

Post-compression studies were then carried out to evaluate the enhanced formulation. Tests were conducted on the physical evaluation characteristics.

2.5.1. Hardness and tablet dimensions

Tablet hardness was measured using a hardness tester (Sotax, Switzerland) and reported in Newtons (N). For each batch, five tablets were randomly selected, tested, and the mean ± standard deviation calculated. Tablet thickness was measured using the hardness tester's built-in features; three tablets per batch were measured, and the average values recorded. All formulations exhibited hardness and thickness within pharmacopeial specifications [11,12].

2.5.2. Friability

Friability was determined using a friabilator (Roche, Switzerland). Twenty tablets were placed in the friabilator, rotated at 25 rpm for four minutes (approximately 100 rotations). Weight loss was calculated, with a maximum permissible limit of 1%. All tested tablets met the pharmacopeial friability criteria.[10,11].

3. RESULTS AND DISCUSSION

3.1. Method validation

Linear regression analysis of the calibration data produced the equation y = 9.9638x with a correlation coefficient (R^2) of 0.9769, confirming linearity across the concentration range of 0.0047–0.15 mg/mL and compliance with Beer–Lambert's law. The regression equation without the intercept (y = mx) was applied for all subsequent riboflavin concentration calculations during dissolution studies. The calibration curve is presented in Figure 1.

3.2. Physicochemical evaluation of riboflavin tablets

Evaluation of the fine powder blend before compression demonstrated that its flowability and compressibility characteristics, reflected by the angle of repose, bulk and tapped density, and Carr's index, met the criteria for direct compression. Table 3 presents the pre-compression study results for all 18 formulations. Angle of repose values ranged from 33.69° (F16) to 39.12° (F10). An angle of repose below 40° indicates good to fair flowability, sufficient to enable uniform die filling during direct compression. Most formulations fell within the 34–38° range, suggesting minimal interparticle friction and good powder flow. Only F10 (39.12°) and F11 (38.66°) approached the upper boundary, indicating slightly increased cohesiveness, though both remained within the acceptable limit. Bulk density values ranged from 0.445 g/mL (F16) to 0.619 g/mL (F13, F15), while tapped density ranged from 0.531 g/mL (F6) to 0.747 g/mL (F15), reflecting moderate variability in particle packing across the batches. Regarding compressibility, a Carr's index below 25% is generally accepted as indicative of good compressibility. Most formulations met this criterion (F1–F9, F11, F13–F18), with F11 recording the lowest value of 5.99%, indicating excellent powder flow and efficient packing. Formulations F10 (26.8%) and F12 (25.5%) exhibited borderline values marginally above the 25% threshold, indicating passable but slightly reduced compressibility; however, both remained within acceptable limits for direct compression processing. Overall, the combined assessment of angle of repose, density measurements, and Carr's index confirms that all 18 formulations possessed suitable flow and compressibility properties for direct compression, ensuring consistent tablet quality.

Table 3. Results of pre-compression studies.

Formulation	Angle of Repose (θ)	Tapped Density(g/ml)	Bulk Density(g/ml)	Carr's Index (%)
F1	34.73	0.619	0.488	21.20
F2	36.75	0.635	0.508	20.00
F3	36.25	0.667	0.552	17.25
F4	38.19	0.584	0.479	18.00
F5	36.25	0.635	0.488	23.14
F6	38.19	0.532	0.478	10.15
F7	36.75	0.577	0.478	17.15
F8	35.72	0.611	0.498	18.52
F9	36.75	0.591	0.488	17.44
F10	39.12	0.619	0.453	26.80
F11	38.66	0.651	0.612	5.99
F12	36.25	0.619	0.461	25.50
F13	34.73	0.726	0.619	14.74
F14	37.72	0.591	0.470	20.47
F15	34.73	0.747	0.619	17.14
F16	33.69	0.591	0.445	24.70
F17	36.62	0.668	0.508	23.95
F18	36.75	0.597	0.498	16.60

3.3. Dissolution study

The *in vitro* dissolution study demonstrated a clear influence of the polymeric composition on the release behaviour of riboflavin from the effervescent floating tablets (Table 4). Among all formulations, F6, F10, and F12 exhibited significantly ($P<0.0169$) slower release (<40% drug release at 6 hours), indicating a stronger polymeric gel barrier and extended retention of the drug within the matrix. This prolonged release behaviour can be attributed to the higher proportion of high-viscosity polymers (carrageenan and Carbopol 940), which enhanced gel layer formation, reduced water penetration, and consequently delayed diffusion of the drug.

Formulations F5, F9, F14, F16, and F17 exhibited cumulative drug release exceeding 100% at 6 hours. This observation can be attributed to several factors. First, sampling variability during dissolution testing, including incomplete volume replacement or localized concentration gradients in the dissolution vessel, may introduce measurement error at extended time points. Second, swelling-driven matrix erosion in formulations with high proportions of hydrophilic polymers such as chitosan and HPMC K4M can cause rapid structural breakdown, releasing drug at a rate that transiently exceeds the theoretical 100% threshold when calculated against the nominal drug content. Third, minor non-uniformity in drug distribution within the tablet matrix during direct compression cannot be entirely excluded as a contributing factor. These values do not indicate actual drug content above the labelled amount but reflect the cumulative nature of the calculation and inherent variability in dissolution testing of swellable matrix systems. Formulations F6, F12, and F15 were additionally included as replicates to estimate experimental variability (pure error) and to enable the lack-of-fit test within the DOE model.

The controlled release observed in F6, F10, and F12 suggests that these formulations successfully maintained the drug within the swollen polymeric network, which is ideal for prolonged gastric retention and sustained therapeutic effect, aligning with the design objective of a gastroretentive floating delivery system.

A clear correlation between floating behaviour and cumulative drug release profile was observed across formulations (Table 4). The floating lag time ranged widely from 3 s (F9, F16) to 490 s (F3), reflecting the strong influence of polymer composition on the rate of gas entrapment and matrix hydration. Formulations dominated by carrageenan, a strong gel-forming polysaccharide, produced a rapid, cohesive gel layer upon contact with 0.1N HCl, trapping carbon dioxide generated by the sodium bicarbonate and citric acid effervescent system and achieving buoyancy within seconds to minutes. In contrast, formulations with higher proportions of chitosan or HPMC K4M, which form weaker and more porous gel networks, allowed faster CO_2 escape and delayed or inconsistent buoyancy, resulting in longer floating lag time values. Formulations F6, F10, and F12, which contained dominant carrageenan and Carbopol 940 proportions, demonstrated moderate and consistent floating lag time values (300 s, 145 s, and 295 s respectively), indicating controlled hydration that favoured simultaneous buoyancy

Table 4. Obtained response from dissolution test.

Formulation	Response	
	R1 (Cumulative release at 6 hours) (%)	R2 Floating Lag Time (s)
1	73.82	394
2	89.15	356
3	82.53	490
4	96.41	200
5	101.21	55
6	33.38	300
7	82.62	294
8	66.58	475
9	109.30	6
10	24.15	145
11	50.02	64
12	32.79	295
13	46.07	76
14	102.09	5
15	57.19	298
16	109.70	3
17	111.30	301
18	82.88	60

and sustained drug release. This mechanistic link between polymer gel strength, effervescent response, and drug release confirms that polymer selection directly governs both the buoyancy behaviour and release kinetics of these floating matrix tablets. Ultra-fast floating behaviour was noted in F16 (3 s), F14 (5 s), and F9 (6 s), which can be attributed to rapid hydration and immediate CO_2 entrapment within the matrix. However, such formulations also exhibited faster drug release (>100% within 6 hours), suggesting weaker gel strength and premature erosion of the polymer barrier [13].

Statistical analysis of the quadratic model for cumulative drug release at 6 hours is presented in Table 5. The model confirmed that the polymer composition had a significant collective influence on the response (F-value = 4.98, p = 0.0169). Among the binary interaction terms, the combination of Carrageenan and HPMC K75 (HM) was the most significant contributor

Table 5. ANOVA for the quadratic model.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remarks
Model	11796.63	9	1310.74	4.98	0.0169	significant
[(1)]Linear Mixture	2011.78	4	502.94	1.91	0.2024	
HJ	1387.85	1	1387.85	5.27	0.0508	
HK	705.86	1	705.86	2.68	0.1403	
HL	874.00	1	874.00	3.32	0.1060	
HM	1932.76	1	1932.76	7.34	0.0267	
JK	196.86	1	196.86	0.7473	0.4125	
JL	0.0000	0				
JM	0.0000	0				
KL	0.0000	0				
KM	0.0000	0				
LM	0.0000	0				
Residual	2107.51	8	263.44			
Lack of Fit	1720.10	6	286.68	1.48	0.4563	not significant
Pure Error	387.41	2	193.71			
Cor Total	13904.14	17				

Note: H = carrageenan, J = chitosan, K = Carbopol 940, L = HPMC K4M, and M = HPMC K75.

to release retardation (p = 0.0267), followed by a borderline significant interaction between Carrageenan and Chitosan (HJ, p = 0.0508), while other interaction terms showed no substantial contribution to the response. The non-significant lack-of-fit (p = 0.4563) confirmed that the model adequately represents the experimental data without systematic deviation. The model demonstrated acceptable fit, with an R^2 of 0.8484, indicating that 84.84% of the variance in drug release was explained by the polynomial model. The Adjusted R^2 of 0.6779 and Adequate Precision value of 8.2137, exceeding the recommended minimum threshold of 4, confirm a sufficient signal-to-noise ratio and validate the reliability of the model for identifying optimal polymer compositions within the design space.

The trace plot analysis of cumulative drug release at 6 hours (R1) revealed how various polymers affect the drug release kinetics. The principal goal of this experiment was to identify which polymers could be used to achieve a slower cumulative drug release during the first 6 hours, which is essential for the development of extended-release tablets. The variables labelled A–M in the figures 2-4 represent the fixed formulation components used in the experimental design. Specifically, H, J, and K correspond to the independent polymer variables, namely carrageenan, chitosan, and Carbopol 940, respectively, while the remaining variables (A–G, L, and M) denote other formulation excipients maintained at constant concentrations throughout the optimization study. The numerical values shown under "Actual Components" indicate the percentage composition of each fixed component in the formulation. From Figure 2, a strong downward trend is evident in K. Carbopol940 (K) is one of the most promising options for delayed release, as indicated by the plot data. Carrageenan (H) and HPMC K75 (M) display stable, moderate curves, reflecting their ability to maintain a consistent, slower release profile, indicating that this polymer can sustain a steady, slower cumulative drug release over time. Chitosan (J) exhibits an upward trend in the trace plot, indicating a concentration-dependent increase in cumulative drug release. This behaviour can be explained by the distinct hydration and erosion characteristics of chitosan in acidic dissolution medium (0.1 N HCl). At lower concentrations, chitosan may not exert a dominant effect on drug release, as the polymer content is insufficient to significantly alter the overall matrix structure or gel integrity. However, as the chitosan concentration increases, greater water uptake and penetration into the

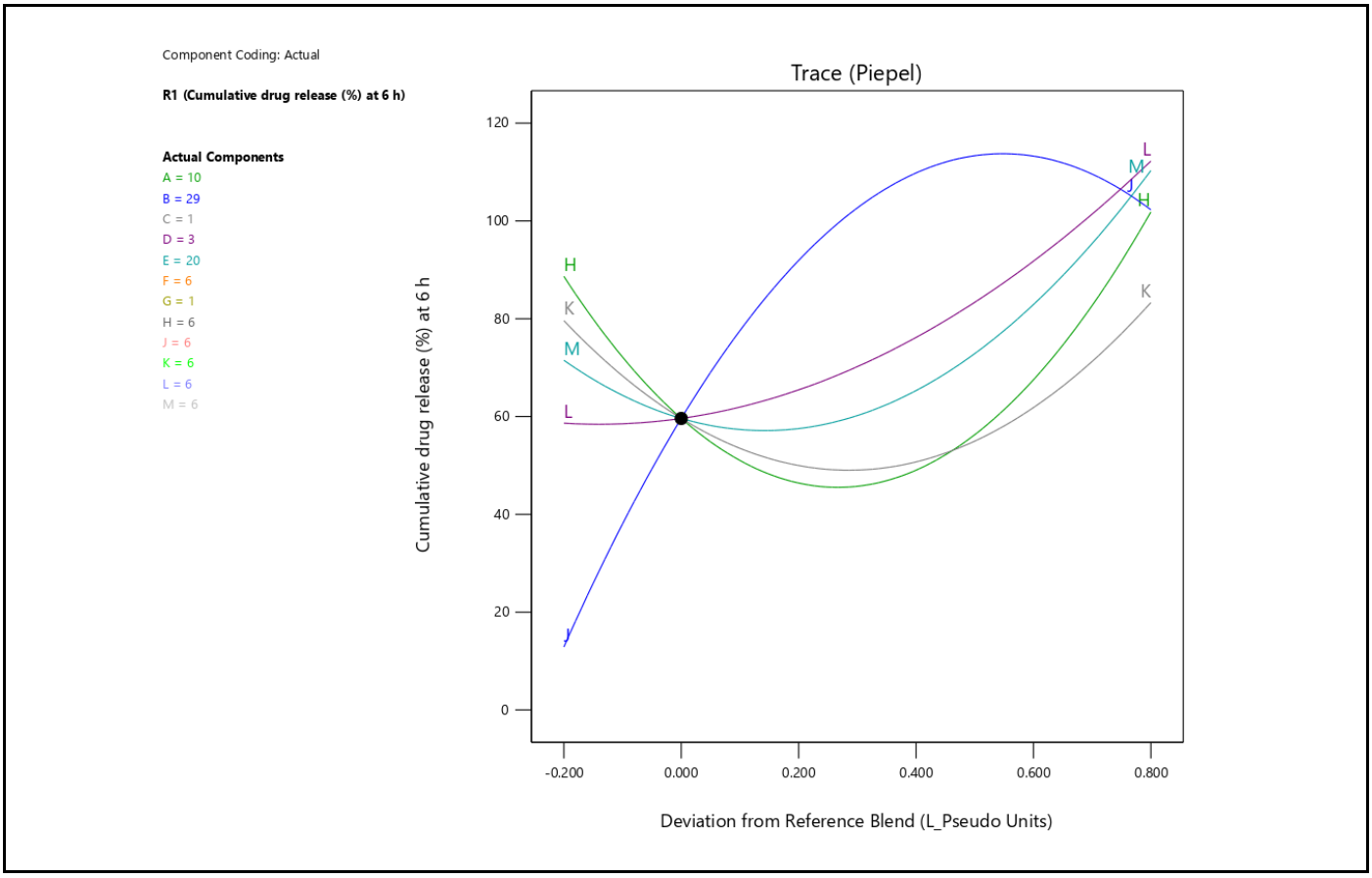

Figure 2. Trace (Piepel) plot showing the effect of formulation components on cumulative riboflavin release at 6 h. A = riboflavin, B = lactose, C = microcrystalline cellulose, D = citric acid, E = sodium bicarbonate, F = talc, G = magnesium stearate, H = carrageenan, J = chitosan, K = Carbopol 940, L = HPMC K4M, and M = HPMC K75.

tablet matrix is expected, resulting in pronounced swelling followed by subsequent erosion of the polymeric network. This progressive loss of matrix integrity leads to accelerated drug diffusion and higher cumulative release values at 6 h. The dissolution medium (0.1 N HCl) further amplifies this effect, as chitosan undergoes hydration, swelling, and eventual dissolution in acidic conditions, unlike carrageenan and Carbopol 940, which maintain their gel structure and integrity under the same conditions. Previous studies have reported that drug release from chitosan-based systems is influenced by polymer swelling, diffusion, and erosion mechanisms [14]. This polymer's gelling and viscosity properties enable it to slow down the drug's diffusion, making it a suitable candidate for extended-release formulations, especially when gradual, sustained release is desired within the first 6 hours.

Therefore, in the present formulation, lower concentrations of chitosan provided a more balanced gel structure and improved matrix integrity, resulting in a slower and more controlled drug release profile. In contrast, at higher concentrations, increased water uptake and penetration into the tablet led to higher swelling, followed by progressive erosion of the entire matrix. The resulting loss of matrix integrity compromised the gel barrier, facilitating faster drug diffusion into the dissolution medium and ultimately yielding higher cumulative drug release at 6 h. This concentration-dependent erosion behaviour of chitosan in acidic media confirms that while chitosan can function as a matrix-forming polymer in controlled-release systems, its proportion must be carefully minimised when formulating in acidic dissolution environments to preserve tablet integrity and achieve the desired sustained-release profile.[14]. This indicates that chitosan can still be effectively used in controlled-release systems when incorporated at optimized concentrations and in suitable polymer combinations. Similar findings have been reported in recent studies demonstrating that the swelling behaviour, porosity, and erosion characteristics of chitosan significantly influence release kinetics in gastroretentive and controlled drug delivery systems [15]. The alignment between the contour plots and trace plot analysis strengthens the conclusion. These findings suggest that Carbopol940, Carrageenan, HPMC K75, and Chitosan serve as key polymers for achieving extended-release characteristics, whereas component (J) Chitosan should be minimised to prevent rapid drug diffusion during the initial hours for developing riboflavin tablet formulations with enhanced time.

3.4. Effects of mixture constituents on drug release

The contour map and three-dimensional response surface of each element visually illustrate the relationship between the components of the riboflavin tablet formulation's mixing design. This experiment's goal is to achieve a lower cumulative drug release (%) at 6 h. The contour map and three-dimensional response surface plots illustrate the effects of Carrageenan (H), Chitosan (J), and Carbopol 940 (K) concentrations on the cumulative drug release of the riboflavin tablet formulation. As shown in Figure 3, the blue region indicates a lower cumulative drug release (%), while the red zone represents the highest cumulative drug release (%). Increasing the concentration of Carrageenan markedly reduced the cumulative drug release (%) at 6 h, suggesting stronger gelation and matrix integrity. This behaviour is consistent with its known release-retardant properties due to its high molecular weight, strong gel-forming ability, and high viscosity, which limits diffusion of the drug through the hydrated matrix. Similar findings were reported[16] where it described Carrageenan as an effective sustained-release polymer in hydrophilic matrix systems, and high viscosity makes it appropriate for use in the preparation of extended-release formulations[17].

For the purpose of this discussion, polymers are classified based on their gel-forming capacity and viscosity grade. Carrageenan and Carbopol 940 are classified as high-viscosity or strong gel-forming polymers due to their capacity to form dense, viscous gel layers upon hydration, which effectively retard drug diffusion and enhance matrix integrity. HPMC K75 is classified as a moderate gel-forming polymer, providing intermediate release control. In contrast, chitosan and HPMC K4M are classified as low-viscosity or weak gel-forming polymers at the concentrations tested, as they produce less structured gel networks that offer comparatively lower resistance to drug diffusion and matrix erosion. These viscosity characteristics directly governed both the floating behaviour and release kinetics observed across the 18 formulations.

Conversely, formulations with a higher proportion of chitosan exhibited a faster drug release profile, as indicated by the red zones on the contour plot (Figure 4). This can be attributed to the behaviour of chitosan in acidic medium (0.1 N HCl): at higher concentrations, increased water uptake and penetration into the tablet matrix promotes pronounced swelling and subsequent erosion of the matrix. The higher the chitosan level, the greater the extent of swelling and erosion, which progressively erodes the matrix structure and compromises the gel barrier, facilitating rapid diffusion of riboflavin into the dissolution medium. This erosion-driven release mechanism, characteristic of chitosan in acidic environments, distinguishes it from the diffusion-controlled release profile observed with carrageenan and Carbopol 940. These observations align with previous studies by Mehmood *et al.*[14], which reported enhanced drug diffusion and erosion-controlled release in chitosan-based matrices.

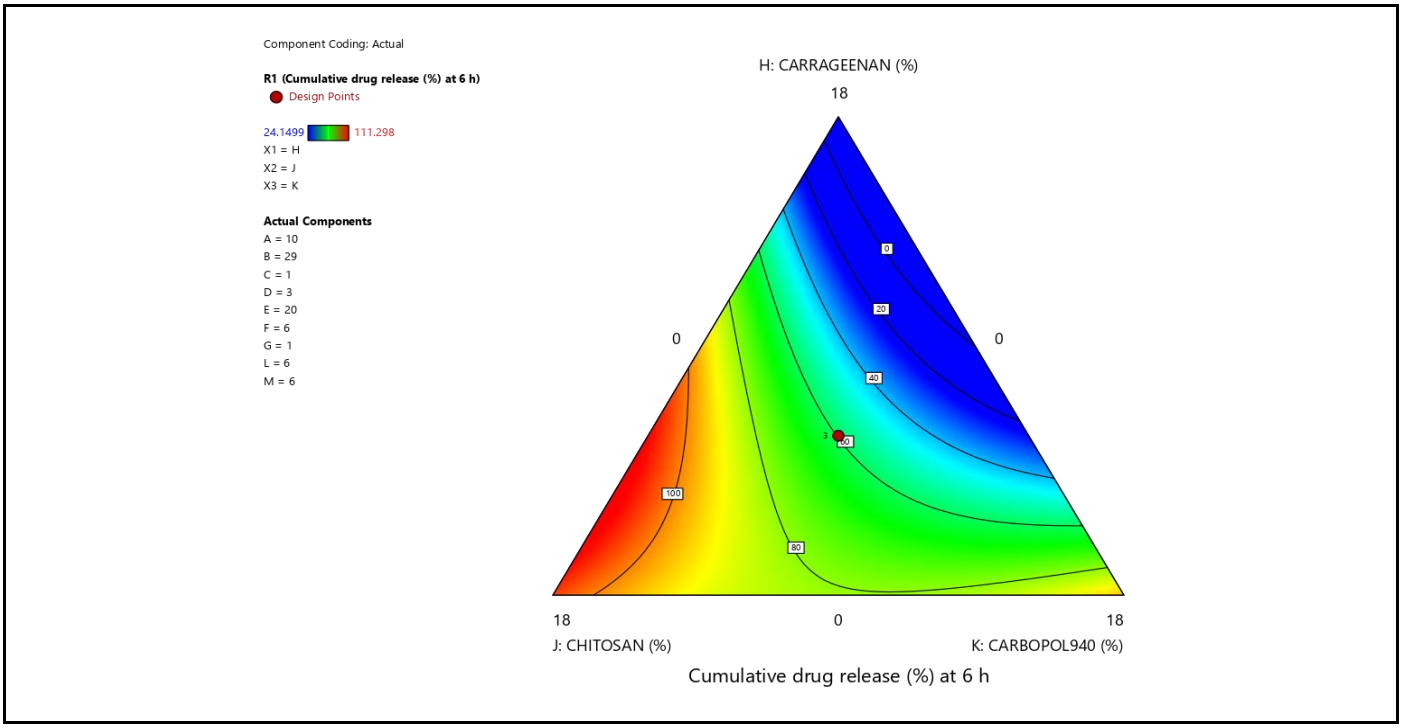

Figure 3. Contour plot showing the influence of carrageenan (H), chitosan (J), and Carbopol 940 (K) on cumulative riboflavin release at 6 h. Blue regions indicate lower cumulative release, while red regions indicate higher cumulative release.

In Figure 3, Formulations containing higher levels of Carbopol 940 demonstrated intermediate release behaviour. Carbopol's cross-linked polyacrylic acid structure provides moderate swelling and mucoadhesive properties, allowing a balance between diffusion and matrix integrity. This supports earlier findings by George *et al.* [18], who noted that Carbopol contributes to controlled swelling and moderate retardation of drug release in combination polymer systems.

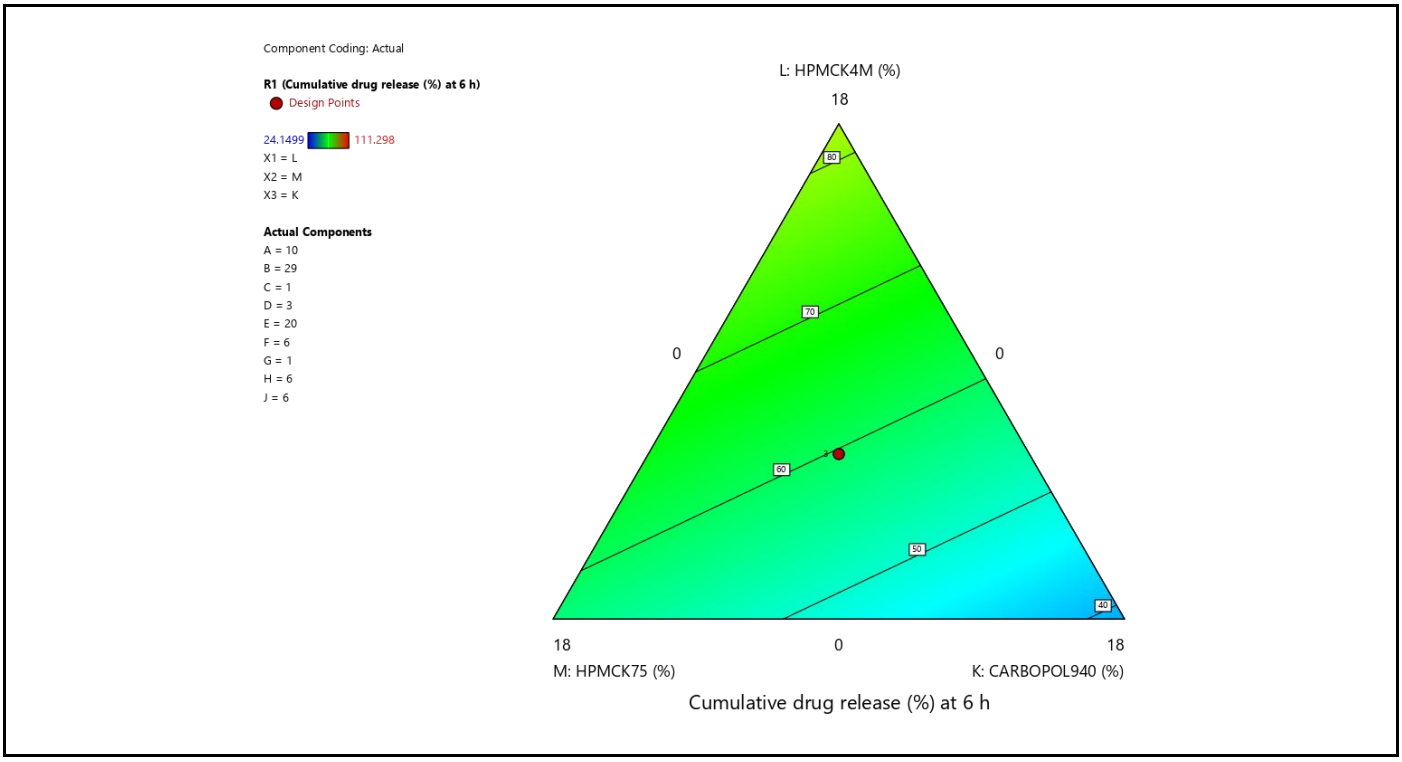

Figure 4. Contour plot showing the influence of HPMC K4M (L), HPMC K75 (M), and Carbopol 940 (K) on cumulative riboflavin release at 6 h. Blue-green regions indicate lower cumulative release, while yellow-green regions indicate higher cumulative release.

Moreover, Figures 3 and 4 were selected because they represent the most influential polymer combinations affecting the release behaviour of riboflavin floating tablets. Figure 3 illustrates the interaction of carrageenan, chitosan, and Carbopol 940, while Figure 4 shows the effect of HPMC K4M, HPMC K75, and Carbopol 940. Although other polymer combinations were evaluated during formulation optimization, only the most significant and representative ternary plots were included to improve clarity and avoid redundancy.

Overall, the central design point on the contour plot, representing balanced proportions of the three polymers, exhibited a drug release of approximately 60–70%, suggesting an optimal combination for sustained release. These findings confirm that carrageenan exerts the strongest release-retardant effect through its dense gel-forming ability, Carbopol 940 provides intermediate modulation via swelling and diffusion control, and chitosan promotes faster release at higher concentrations. The model highlights the synergistic potential of these polymers in achieving controlled release characteristics in hydrophilic matrix tablets. The model thus highlights the synergistic potential of these polymers in achieving controlled release characteristics in hydrophilic matrix tablets.

To support the formulation selection with statistical rigour, a numerical optimization was performed using the desirability function in Design Expert software (Table 6). Target constraints were defined as follows: Chitosan and HPMC K4M were set to minimize, as both were associated with faster drug release or weaker gel integrity; Carrageenan, Carbopol 940, and HPMC K75 were set within their full experimental range; and the response variable (cumulative drug release at 6 h) was set to minimize. The resulting coefficient estimates revealed that the interaction between Carrageenan and HPMC K75 (HM = −899.13) and the interaction between Carrageenan and Carbopol 940 (HK = −605.96) exerted the strongest release-retardant effects among all polymer combinations. The numerical optimization generated multiple solutions with a desirability score of 1.000, all converging on a similar polymer composition: Carrageenan (12–15%), Carbopol 940 (4–17%), and HPMC K75 (0.6–12%), while Chitosan and HPMC K4M approached zero. The predicted drug release for these optimal solutions ranged from 71–79%, consistent with the extended-release target. Based on these statistically derived criteria and cross-referencing with the experimental dissolution data (Table 4), formulations F6, F10, and F12 were confirmed as optimal screening candidates, demonstrating cumulative drug release below 40% at 6 h and floating lag times of 300 s, 145 s, and 295 s respectively — fully consistent with the desirability-optimised polymer profiles. These formulations provide a foundation for formal optimisation and *in vivo* evaluation in a subsequent study.

3.5. Post-compression studies

Post-compression studies were then carried out to evaluate the enhanced formulation. Tests were conducted on the physical evaluation characteristics (Table 7). All the formulated riboflavin floating tablets (F1–F18) exhibited acceptable physicochemical properties, confirming their suitability for oral gastro-retentive delivery. The hardness values ranged between 81 and 110 N, indicating sufficient mechanical strength to withstand handling and compression forces. Notably, F3 and F9 showed the highest hardness (110 N), which may be attributed to higher polymer binding and strong interparticulate bonding. The friability for all formulations was below 1%, confirming excellent mechanical resistance. This complies with pharmacopoeial limits (<1%), indicating that the tablets can resist abrasion during packaging and shipping. Every formulation passed the friability test with sufficient resistance to abrasion and mechanical shock. The range was between 0.50% to 0.76%, which is consistent with the typical range. The thickness of the tablets remained consistent (9.84–10.09 mm) across all formulations, suggesting uniform die fill and no significant variation in compression force during tabletting.

5. CONCLUSIONS

This study successfully formulated effervescent riboflavin floating tablets, implementing a mixture-design approach to systematically evaluate the functional roles of five polymers in controlling buoyancy and drug release behaviour. Targeting riboflavin's restricted intestinal absorption and low systemic availability, the gastroretentive system developed in this study has the

Table 6. Selected optimal solutions (Desirability = 1.000).

Carrageenan (%)	Chitosan (%)	Carbopol 940 (%)	HPMC K4M (%)	HPMC K75 (%)	Predicted R1 (%)	Desirability
14.4	0	8.4	0	7.2	79.1	1.000
12.9	0	4.4	0	12.7	75.9	1.000
12.8	0	17.2	0	0	71.1	1.000
13.8	0	12.4	0	3.8	75.8	1.000

Table 7. Result of physicochemical evaluation of formulated riboflavin tablets.

Formulation	Hardness (N)	Friability (% weight loss)	Thickness (mm)
F1	82 ± 4	0.76 ± 0.14	10.09 ± 0.05
F2	90 ± 5	0.68 ± 0.10	10.04 ± 0.02
F3	110 ± 7	0.50 ± 0.13	9.840 ± 0.06
F4	96 ± 5	0.57 ± 0.20	10.03 ± 0.05
F5	81 ± 4	0.75 ± 0.08	10.07 ± 0.07
F6	84 ± 5	0.73 ± 0.07	10.08 ± 0.06
F7	92 ± 3	0.69 ± 0.14	10.01 ± 0.04
F8	98 ± 5	0.62 ± 0.14	10.04 ± 0.06
F9	110 ± 5	0.51 ± 0.06	9.84 ± 0.05
F10	85 ± 2	0.69 ± 0.07	10.06 ± 0.12
F11	93 ± 7	0.61 ± 0.06	10.02 ± 0.11
F12	87 ± 4	0.71 ± 0.12	10.06 ± 0.10
F13	84 ± 7	0.66 ± 0.08	10.09 ± 0.09
F14	83 ± 3	0.68 ± 0.05	10.08 ± 0.01
F15	85 ± 3	0.66 ± 0.13	10.07 ± 0.06
F16	83 ± 5	0.68 ± 0.11	10.08 ± 0.01
F17	91 ± 5	0.63 ± 0.14	10.02 ± 0.02
F18	93 ± 4	0.61 ± 0.12	10.02 ± 0.11

Note: Data are presented as mean ± SD

The tablets were fabricated by direct compression and incorporated a combination of polymers, including HPMC K4M, HPMC K75, chitosan, carrageenan, and Carbopol 940. This study demonstrated that polymer composition strongly influences riboflavin tablet release profiles. Carrageenan and Carbopol 940 were efficacious in release-retardant excipients, while HPMC K75 provided moderate control, and HPMC K4M showed weaker performance. Chitosan, in contrast, promoted faster release and was less suitable for sustained delivery. The formulation can be optimised to ensure prolonged floating duration. The screening study identified formulations F6, F10, and F12 as promising candidates, based on DOE analysis of drug release at 6 h and floating lag time. These formulations provide a foundation for further optimization and *in vivo* studies.

Overall, this work highlights the value of mixture design as an efficient tool for polymer screening in gastroretentive systems and demonstrates a clear foundation for future optimization of riboflavin floating tablets. Further work should include prolonged stability studies and *in vivo* evaluation to confirm gastric retention behavior and improve translational relevance.

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Author contribution

U.T.A.K: literature review; experimental procedures; data analysis; and preparation of the manuscript.
K.L.W.P: Responsible for manuscript revision.
N.A.M.A.K: Visualization, Conceptualisations, and evaluating its academic quality.
M.A.S.M.A.: Manuscript refinement and detailed review.
M.A.A.: Conceptualizations; study design; visualization; Editing and reviewing the manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

None to declare.

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