RESEARCH PAPER

Formulation and In-vitro Evaluation of Hydrodynamically Balanced System by Quality by Design Approach

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Received: 25-7-2026; Revised: 10-8-2026; Accepted: 01-09-2026; Available Online: 4-9-2026

ABSTRACT

This study focuses on the development and biopharmaceutical evaluation of a gastric floating drug delivery system (GFDDS) for Rabeprazole, utilizing the semi-synthetic polymer carboxymethyl ethyl cellulose (CMEC) and the synthetic polymer polyethylene oxide (PEO). A central composite design approach was employed to optimize the quantities of CMEC or PEO and the concentration of sodium bicarbonate, which served as the independent variables. The dependent variables assessed included: percentage of drug released at 1 hour (D1hr), at 3 hours (D3hr), and the time required for 95% of the drug to be released (t95). Both numerical and graphical optimization techniques were used to refine the formulation parameters. The experimental results of the optimized formulations closely aligned with the predicted outcomes. Stability studies performed under accelerated conditions (40±2°C/75±5% RH) confirmed the stability of the optimized formulations. Additionally, the optimized floating tablets demonstrated significantly higher relative bioavailability compared to a marketed formulation, suggesting enhanced drug absorption and efficacy.

Keywords: Rabeprazole, Quality by Design, Hydrodynamically Balance System, Carboxymethyl ethyl cellulose, Polyethylene oxide, etc..

How to cite this article: Mandar Prakash Kor1* Dr. Abhijeet D. Kulkarni2. Formulation and In-vitro Evaluation of Hydrodynamically Balanced System by Quality by Design Approach. Int J Drug Deliv Technol. 2026;16(78s):441-455. DOI: 10.25258/ijddt.16.78s.53.

INTRODUCTION

The oral route remains the most widely used method for administering medications, with controlled oral drug delivery systems offering several distinct advantages. The success of such systems is influenced by various physiological factors, including the transit time through the gastrointestinal (GI) tract, duration of gastric retention, variability in stomach emptying, pH differences across GI segments, the drug's release profile, and its primary absorption site. These variables can lead to challenges such as inconsistent absorption, incomplete drug release, and a shorter period of drug retention in the stomach. Such limitations are particularly problematic for drugs that are best absorbed in the upper portion of the small intestine. To address this, gastric floating drug delivery systems (GFDDS) have been developed. These systems are designed to remain buoyant in the stomach for extended periods, thereby increasing gastric residence time and potentially improving the bioavailability of drugs with a narrow absorption window [1-3].

Gastro-retentive floating drug delivery systems (GFDDS) are among the most commonly employed approaches to prolong the residence time of dosage forms in the stomach. Achieving buoyancy requires a precise equilibrium between the system's mass and volume. For the formulation to float, its density must be lower than that of gastric fluids—typically less than 1 g/cm³. A key advantage of floating systems is their ability to extend gastric retention time (GRT) without affecting the natural rate of gastric emptying. GFDDS are categorized into several types, including hydrodynamically balanced systems, low-density systems, hot-melt extrusion systems, and effervescent systems. These systems are especially beneficial for drugs that are either poorly soluble or unstable in the higher pH environment of the intestines [4-7].

Rabeprazole belongs to the class of proton pump inhibitors and shares similar therapeutic effects and mechanisms with omeprazole. It is quickly absorbed following oral administration, with peak levels in the blood occurring approximately 3.5 hours post-dose. When taken as an enteric-coated tablet, its oral bioavailability is around 52%,

primarily due to first-pass metabolism. This bioavailability remains consistent whether taken as a single dose or over repeated administrations. Additionally, around 97% of Rabeprazole binds to plasma proteins [8].

Polyethylene Oxide (PEO) is a non-ionic, hydrophilic polymer known for its high molecular weight and distinctive physicochemical characteristics, making it a widely used retarding agent in controlled drug delivery applications. On the other hand, Carboxymethyl Ethyl Cellulose (CMEC), a semi-synthetic polymer with excellent water dispersibility, serves effectively as an enteric coating material and also plays a role in forming matrices for sustained drug release. To date, there is limited or no documented pharmacokinetic evaluation of drug delivery systems utilizing CMEC [9].

Initial investigations conducted in our laboratory identified CMEC and PEO WSR 301 as particularly promising polymers for the formulation of floating tablets. In a related study, Srikanth et al. developed gastro-retentive floating tablets containing Rabeprazole, utilizing CMEC and employing a three-factor statistical model with an extensive set of experimental runs. Their research involved evaluating the in vivo buoyancy characteristics of the tablets in healthy human subjects, revealing that gastric retention was notably prolonged in the fed state compared to the fasted state [10].

In contrast, the present study adopts a two-factor central composite design to optimize the formulation process using a reduced number of experimental trials. Compared to earlier approaches, this work emphasizes a more efficient optimization strategy through the selection and analysis of both dependent and independent variables.

Traditional optimization methods typically involve changing one variable at a time while keeping all other factors constant under controlled conditions. However, this approach limits the ability to evaluate interactions between variables and often results in less reliable outcomes, potentially leading to misleading conclusions. Additionally, it can be resource-intensive, requiring numerous experimental runs and excessive use of excipients. To address these limitations, statistical optimization techniques offer a more efficient alternative. By using structured experimental designs, statistical methods allow for simultaneous evaluation of multiple factors, leading to a better understanding of formulation behavior and enhancing product robustness and efficiency in development [11, 12].

The current research focused on formulating a gastroretentive drug delivery system (GFDDS) for Rabeprazole utilizing a novel semi-synthetic polymer, carboxymethyl ethyl cellulose (CMEC), along with a synthetic polymer, polyethylene oxide (PEO WSR 301). To optimize the formulation, a central composite design under the framework of response surface methodology (RSM) was employed. The formulation variables—specifically, the quantities of polymer and sodium bicarbonate—were treated as independent variables. The measured outcomes included drug release after 1 hour (D1hr), drug release after 3 hours (D3hr), and the time required to achieve 95% drug release (t95). A statistical approach was adopted to determine the optimal formulation, and the model's reliability was assessed by comparing predicted values with actual experimental data. The range and levels of the formulation variables were determined based on preliminary studies carried out in-house. The core hypothesis driving this study was that Rabeprazole, when delivered through floating tablets, could remain longer in the stomach, potentially improving its bioavailability [13-15].

Material and Method

Rabeprazole sodium, ethyl cellulose, HPMC K100M was purchased from Balaji drug supplier surat, Gujarat, India

Rabeprazole sodium was obtained from a local pharmaceutical supplier in Surat, Gujarat, India. Carboxymethyl ethyl cellulose and polyethylene oxide (PEO WSR 301) were sourced from Unichem Laboratories Ltd, Goa. Povidone K30, sodium bicarbonate ($NaHCO_3$), and magnesium stearate were kindly provided by Hetero Drugs Ltd, Hyderabad. All other reagents and chemicals used were of analytical grade.

Experimental design

The formulation experiments and their optimization were carried out using Design Expert software (Version 7.1.6, Stat-Ease Inc., Minneapolis, MN). A central composite design with two factors and three levels was employed to structure and refine the experimental runs. Based on this design, a total of 11 experimental trials were executed for each polymer. The design incorporated two independent formulation variables: X1, representing the amount of polymer used (either CMEC or PEO), and X2, indicating the concentration of sodium bicarbonate. The dependent responses evaluated were Y1 (D1hr), Y2 (D3hr), and Y3 (t95). Tables 1 and 2 provide a summary of the variables and their respective ranges [16].

Table 1: Level of formulation variables (Central composite design)

Variables	**Range and levels**		
	-1	**0**	**1**
CMEC based formulations			
CMEC (mg) X1	200	240	280
% w/w Sodium bicarbonate concentration (to the total tablet weight) X2	5	10	15
PEO WSR 301 based formulations			
PEO WSR 301 (mg) X1	160	200	240
% w/w Sodium bicarbonate concentration (to the total tablet weight) X2	5	100	15

Table 2: Variable levels and formulae of floating tablets by central composite design

Formulation code	**Variables**		**Ingredient (mg/tablet)**						**Total tablet weight (mg)**
	X1	**X2**	**Rabeprazole**	**CMEC**	**PEO WSR 301**	**Sodium bicarbonate**	**Povidone**	**Magnesium stearate**	
RC1	-1	-1	80	200	-	16	16	3	315
RC2	+1	-1	80	280	-	20	20	4	404
RC3	-1	+1	80	200	-	53	16	4	353
RC4	+1	+1	80	280	-	68	22	5	455
RC5	-1.415	0	80	183.43	-	31.57	16	3	314
RC6	-1.415	0	80	296.57	-	45.43	22	4	448
RC7	0	-1.414	80	240	-	10	18	4	352
RC8	0	+1.415	80	240	-	71	21	4	416
RC9	0	0	80	240	-	38	19	4	381
RC10	0	0	80	240	-	38	19	4	381
RC11	9	0	80	240	-	38	19	4	381
RP1	-1	-1	80	-	160	13	-	3	256
RP2	+1	-1	80	-	240	17	-	4	341
RP3	-1	+1	80	-	160	43	-	3	286
RP4	+1	+1	80	-	240	57	-	4	381

RP5	-1.415	0	80	-	143.43	25.57	-	3	252
RP6	+1.415	0	80	-	256.57	37.43	-	4	378
RP7	0	-1.415	80	-	200	8.5	-	2.5	291
RP8	0	+1.415	80	-	200	58.5	-	3.5	342
RP9	0	0	80	-	200	31.5	-	3.5	315
RP10	0	0	80	-	200	31.5	-	3.5	315
RP11	0	0	80	-	200	31.5	-	3.5	315

Preparation of gastric floating tablets (GFT)

Each gastric floating formulation was prepared to contain 80 mg of Rabeprazole. As outlined in Table 2, all components were precisely weighed and passed through a #40 mesh sieve (420 µm). Rabeprazole was thoroughly blended with the chosen polymer (either CMEC or PEO) to achieve uniformity. When required, sodium bicarbonate and povidone K30 were incorporated into this mixture. The resulting blend was then lubricated using pre-sifted magnesium stearate (sieved through #60 mesh, 250 µm). Finally, the lubricated powder was compressed into tablets using a 16-station rotary tablet press (manufactured by Cadmach Machinery Co. Pvt. Ltd., India) fitted with 9 mm flat-faced round punches [17].

Tablet assay and physical evaluation

The assay of GFT was conducted using 0.1 N hydrochloric acid as the extraction medium. The resulting samples were then analyzed using a UV-Visible spectrophotometer (Shimadzu UV-1601, Shimadzu Corp.) at a wavelength of 290 nm, as described by Srikanth (2011b). Additionally, tablet formulations were assessed for various physical parameters, including weight variation (n=20), hardness (n=5) using a Monsanto hardness tester, and friability (n=20) utilizing a Roche Friabilator operated at 100 rpm [18].

In vitro buoyancy studies

The in vitro buoyancy of the GFT was evaluated by determining its floating lag time. Tablets were introduced into a beaker filled with 0.1 N hydrochloric acid, and the duration taken for each tablet to rise and remain buoyant on the surface was recorded as the floating lag time [19].

In vitro dissolution studies

The dissolution profile of Rabeprazole from the gastroretentive formulation (n = 3) was evaluated using an in vitro method. Testing was performed with a USP Type II dissolution apparatus (Lab India, Disso 2000) containing 900 mL of 0.1N hydrochloric acid as the dissolution medium, maintained at 37 ± 0.5°C and stirred at 50 rpm, in accordance with USP 36-NF31 (2013) guidelines. At predetermined time points, 5 mL samples were withdrawn and immediately replaced with an equal volume of fresh medium to maintain sink conditions. Each collected sample was filtered through a 0.45 µm membrane filter and suitably diluted with 0.1N HCl prior to analysis. The absorbance was then measured at 290 nm using a UV-Visible double-beam spectrophotometer (Shimadzu UV1601, Shimadzu Corporation, Kyoto, Japan) [20].

Data analysis and validation

Design Expert software was utilized to statistically validate the polynomial models through ANOVA-based analysis. Each formulation, based on different polymers, underwent 11 experimental runs, which included replicates of factorial and axial points, along with triplicate center points. Model adequacy was assessed by analyzing key statistical parameters such as significant coefficients, coefficient of variation (CV), coefficient of determination (R^2), and adjusted R^2 values. Both numerical and graphical optimization techniques were applied to identify the optimal formulation composition. Three-dimensional response surface plots were generated to illustrate the influence of independent variables on the measured formulation responses. Formulations proposed by the software as statistically optimal were subsequently prepared and evaluated. The experimentally obtained results were then compared with the software-predicted outcomes to validate the model accuracy [21-23].

Result and Discussion

Physical evaluation

The drug content in the formulations was determined using UV spectrophotometry at 290 nm. The percentage of drug present in all the formulations ranged from 99.96% to 102.05%, as shown in Table 3. All floating tablet formulations met the official pharmacopeial requirements for weight uniformity. The measured hardness of the tablets was between 4 and 6 kg/cm², while the friability for all formulations remained below 0.5%.

Table 3: Tableting characteristics and observed responses of Rabeprazole floating tablets

Formulation	Tableting characteristics		Observed responses (n=3)		
	Assay [y] (%)	FLT* (S)	D_{1hr} (%)	D_{3hr} (%)	t_{95} (h)
RC1	100.58 ± 0.43	405	33.13	61.99	10
RC2	100.85 ± 0.24	260	24.46	50.99	12
RC3	100.02 ± 0.05	200	24.13	46.08	13
RC4	100.99 ± 0.98	98	14.85	38.99	15
RC5	100.46 ± 0.46	342	28.24	49.99	11
RC6	100.64 ± 0.24	149	19.13	42.13	13.5
RC7	100.25 ± 0.75	105	29.16	50.44	11
RC8	101.02 ± 0.06	242	19.98	41.06	14
RC9	101.57 ± 0.05	228	18.68	43.24	12.5
RC10	100.87 ± 0.27	220	18.8	42.16	12.8
RC11	102.02 ± 0.08	396	17.02	41.63	12.5
RP1	101.09 ± 0.09	248	26.78	54.87	6
RP2	100.98 ± 0.4	194	18.90	37.33	13
RP3	100.69 ± 0.46	74	21.53	41.13	10
RP4	100.46 ± 0.57	315	14.25	28.13	15
RP5	99.96 ± 0.18	125	24.99	46.06	9
RP6	102.05 ± 0.05	350	17.32	41.74	13
RP7	101.07 ± 0.08	92	23.96	45.82	8
RP8	100.79 ± 0.26	212	18.02	39.73	13
RP9	100.57 ± 0.55	226	18.50	40.13	12.5
RP10	100.19 ± 0.98	219	18.02	38.13	12.2

RP11	101.05 ± 0.46	127	19.44	41.73	14

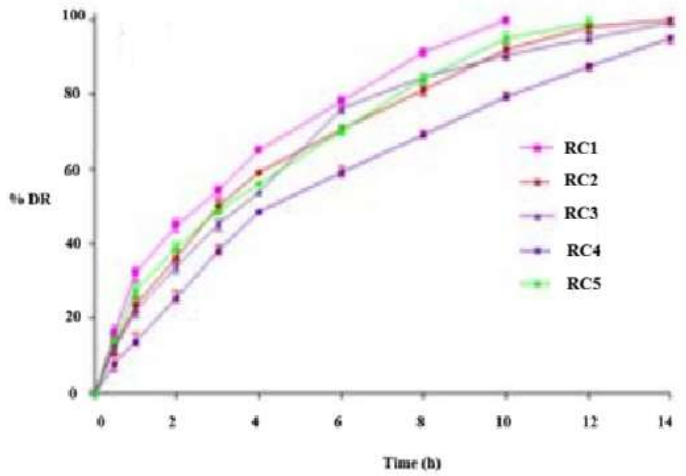
In-vitro buoyancy studies

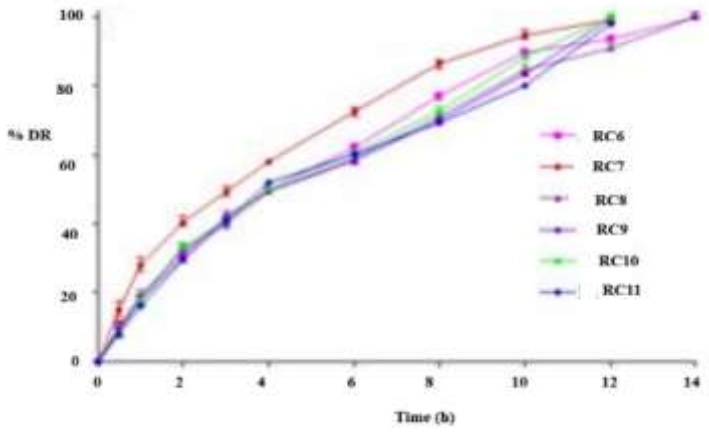
All tablet formulations exhibited floating lag times of less than 7 minutes (Table 3), indicating efficient buoyancy in 0.1 N HCl and confirming their suitability for gastro-retentive drug delivery.

In-vitro dissolution studies

Figure 1 illustrates the in vitro dissolution profiles of Rabeprazole floating tablets formulated using CMEC and PEO. Initial studies indicated that CMEC-based formulations released the drug more rapidly during the first 1-2 hours, exceeding the USP 36-NF31 standard, which requires that no more than 20% of the drug be released within the first hour. To address this, 5% w/w povidone K30 was incorporated into all CMEC-based tablets to slow down the initial release. Table 3 summarizes the dissolution parameters (D1hr, D3hr, and t95) for all the formulations tested. Analysis of the dissolution profiles and parameters revealed that among the CMEC formulations, RC 4, 8, 9, 10, and 11 complied with USP guidelines, which specify a maximum of 20% drug release in the first hour and between 20-45% releases within 3 hours. For the PEO formulations, only PP 2, 4, 6, 8, 9, 10, and 11 met these USP criteria.

a) **b)**





c) **d)**

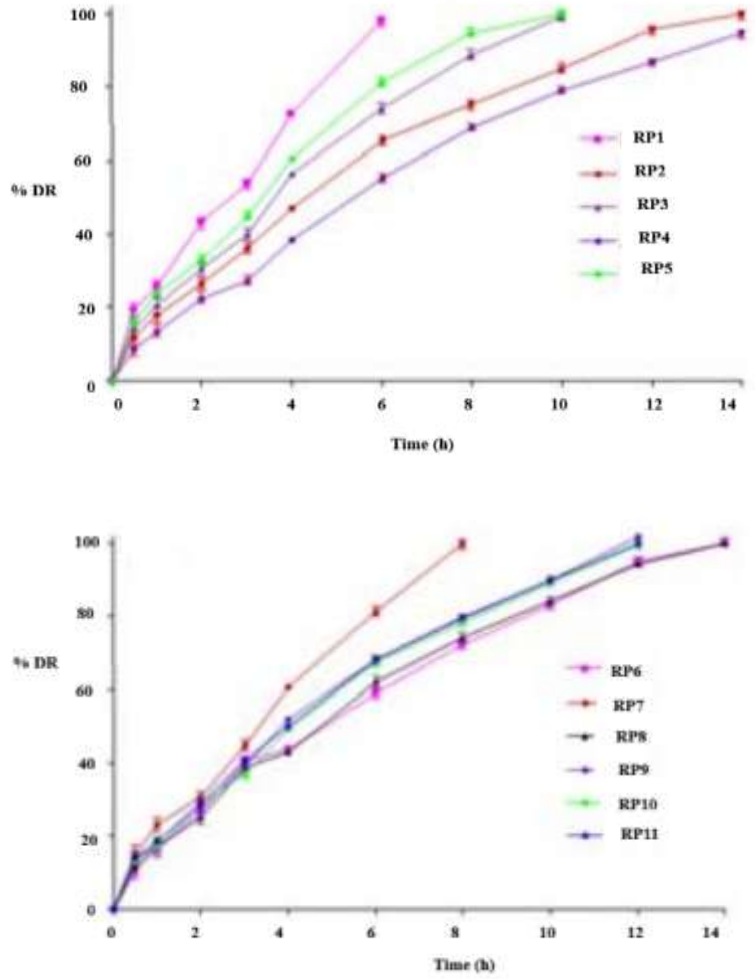


Fig. 1: Dissolution profile of Rabeprazole floating tablets: (a-b): CMEC based floating tablets, (c-d): PEO based floating tablets

Data analysis and validation

The responses observed for the floating tablets formulated with CMEC and PEO are presented in Table 3. To analyze these responses, an appropriate polynomial equation was chosen based on various statistical criteria, including standard deviation, R^2, adjusted R^2, predicted R^2, and the predicted residual sum of squares (PRESS), as evaluated by the Design-Expert software. According to the model summary statistics, a linear model was found to best fit the data for all responses in both CMEC- and PEO-based formulations, except for the D1hr response in CMEC formulations, which was better described by a quadratic model. The PRESS value serves as an indicator of model fit, with smaller values suggesting a better fit to the experimental data. Table 4 summarizes the comparative values of R^2, adjusted R^2, predicted R^2, standard deviation, and PRESS, along with the regression equations derived for each response. In the regression analysis, a positive coefficient indicates a direct relationship with the response, while a negative coefficient implies an inverse relationship. The results indicate that both CMEC and PEO polymers, as well as sodium bicarbonate, negatively impact the D1hr and D3hr responses but have a positive effect on the t95 response.

Table 4: Model summary statistics for responses D1hr, D3hr and t95

Source	Standard deviation	R2	Adjusted R2	Predicted R2	PRESS	
CMEC based formulations						
D1hr						
Linear	4.26	0.7531	0.6889	0.6039	134.30	
2FI	4.48	0.7533	0.6432	0.4655	179.69	Suggested
Quadratic	2.41	0.9800	0.9500	0.8282	60.69	
D3hr						
Linear	4.08	0.7929	0.7386	0.6015	145.34	
2FI	4.32	0.7929	0.6999	0.2427	272.08	Suggested
Quadratic	4.04	0.8799	0.7498	0.1836	292.97	
t95						
Linear	0.29	0.9800	0.9726	0.9465	2.34	
2FI	0.31	0.9800	0.9673	0.9098	3.08	Suggested
Quadratic	0.33	0.9859	0.9617	0.8520	4.30	
Regression equationsa						
D1hr = +18.20 -4.74 *A- 5.08 *B +0.098 *A*B+3.69 *A2 +4.14*B2						
D3hr = +41.39 -4.05 *A- 6.04*B						
t95 = +12.61 +0.95*A +2.29*B +0.000*A*B- 0.15*A2 -0.020*B2						
PEO based formulations						
D1hr						
Linear	2.34	0.9095	0.8844	0.8395	24.96	Suggested
2FI	2.43	0.9102	0.8673	0.8022	30.20	
Quadratic	0.98	0.9768	0.9435	0.8094	29.19	
D3hr						
Linear	5.17	0.6888	0.6085	0.3009	306.47	Suggested
2FI	5.37	0.7008	0.5683	-0.1521	492.88	
Quadratic	5.98	0.7212	0.4322	-0.9913	854.32	
t95						
Linear	2.48	0.7867	0.7308	0.6134	31.82	Suggested
2FI	2.54	0.7996	0.7093	0.4862	41.71	
Quadratic	2.21	0.9180	0.8258	0.4713	42.87	
Regression equationsa						
D1hr = +20.16 -4.26*A- 3.29*B						
D3hr= +41.35- 5.59*A- 4.95*B						
t95 = +11.44 +3.22*A+2.64*B						

The model was assessed for lack of fit (LOF) using Design Expert software, and it was found to be adequate. Table 5 provides a summary of the ANOVA results. When the p-value is less than 0.05, it suggests that the LOF is statistically significant. A significant LOF implies that the model chosen to represent the response does not sufficiently capture the variability observed. This may require using a more complex model or applying a transformation. In some cases, it might indicate that a polynomial model is insufficient to describe the system accurately. For all responses related to both CMEC and PEO formulations, the LOF was not found to be significant.

Table 5: Summary of ANOVA results in analyzing lack of fit and pure error

Source	**Sum of squares**	**df**	**Mean square**	**F value**	**p-value prob>F**	
CMEC based formulations						
D1hr						
Model	319.29	5	64.67	33.33	0.0009	Significant
Residual	10.86	5	2.98			
Lack of fit	8.73	3	3.58	3.43	0.3159	Not significant
Pure error	2.13	2	2.07			
Core total	328.12	10				
D3hr						
Model	27.57	2	139.29	15.43	0.0023	Significant
Residual	77.72	8	10.60			
Lack of fit	70.52	6	12.60	4.23	0.2670	not significant
Pure error	8.21	2	3.61			
Core total	353.28	10				
t95						
Model	21.34	5	4.07	40.32	0.0005	Significant
Residual	0.51	5	0.10			
Lack of fit	0.45	3	0.15	4.94	0.1731	Not significant
Pure error	0.060	2	0.031			
Core total	20.84	10				
PEO based formulations						

D1hr						
Model	127.29	2	64.15	36.78	0.0001	Significant
Residual	15.13	8	2.77			
Lack of fit	14.09	6	3.19	5.19	0.2158	Not significant
Pure error	2.05	2	0.53			
Core total	141.41	10				
D3hr						
Model	293.35	2	147.18	9.46	0.0108	Significant
Residual	139.38	8	18.31			
Lack of fit	132.87	6	22.99	7.77	0.1346	Not significant
Pure error	6.51	2	3.26			
Core total	430.71	10				
t95						
Model	61.34	2	31.17	14.91	0.0026	Significant
Residual	18.36	8	3.18			
Lack of fit	16.50	6	3.59	2.79	0.2984	Not significant
Pure error	1.87	2	0.94			
Core total	78.69	10				

The importance of the model is determined by the p-value, which must be less than 0.05. Any term that is not statistically significant may be excluded from the model unless its inclusion is necessary to maintain the model's structure. In this study, all response variables had p-values below 0.05, demonstrating the significance of the models.

Table 6: Comparison of observed and predicted responses

Dependent variables	**Observed**	**Predicted**	**Relative error (%)**
RCso (statistical optimized CMEC based formulation)			
D1hr	17.88	18.577	5.02
D3hr	43.88	41.866	-5.91
t95	12.50	12.51	0.09
RPso (statistical optimized PEO based formulation)			
D1hr	18.99	18.606	-3.14
D3hr	40.59	38.95	-5.33

t95	12.53	12.500	-0.19

Figures 2 and 3 present two-dimensional contour plots and three-dimensional response surfaces, respectively. These visualizations illustrate how two variables influence the response over a given time period.

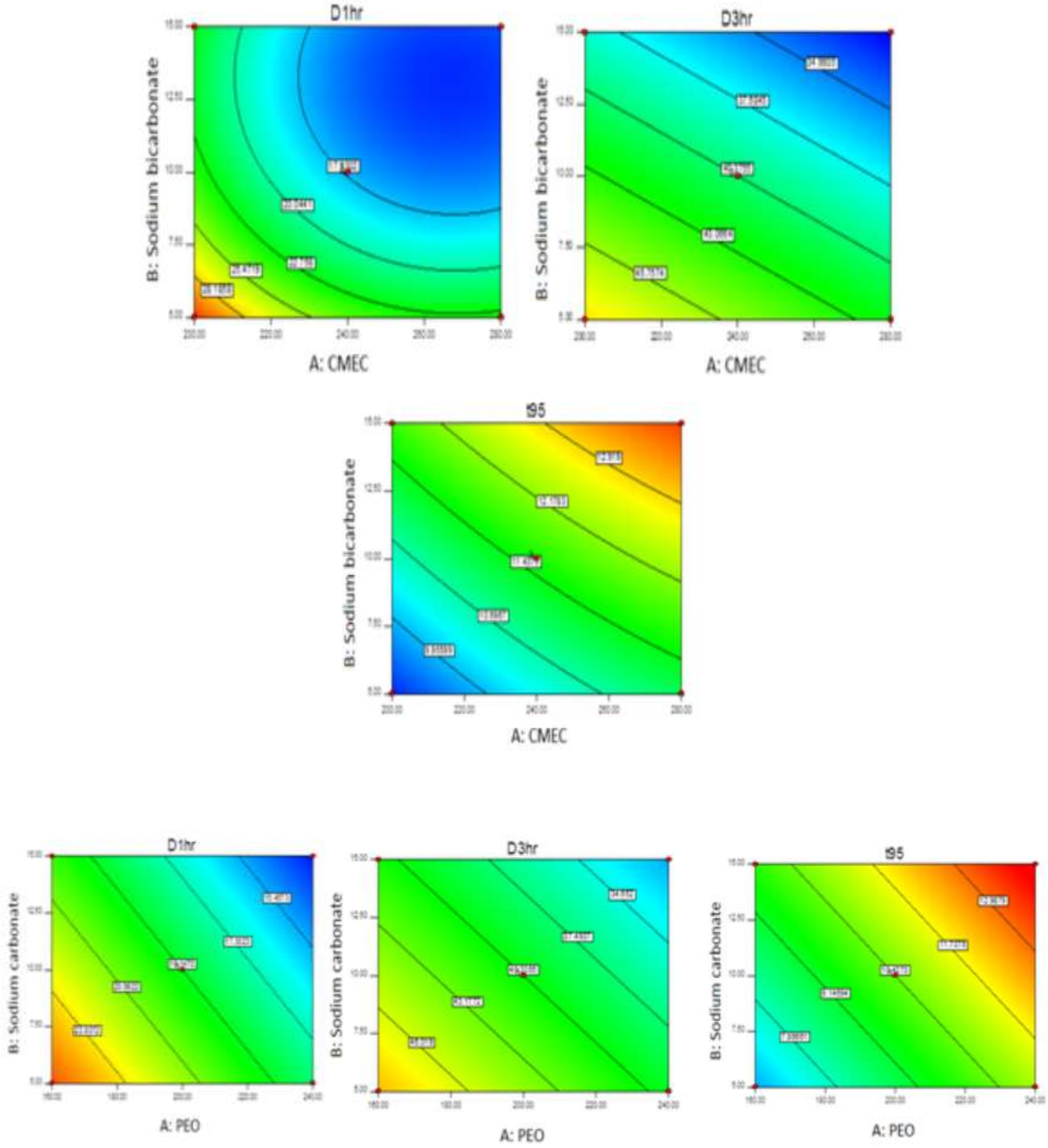


Fig.2: Contour plot for the effect of independent variables on observed responses

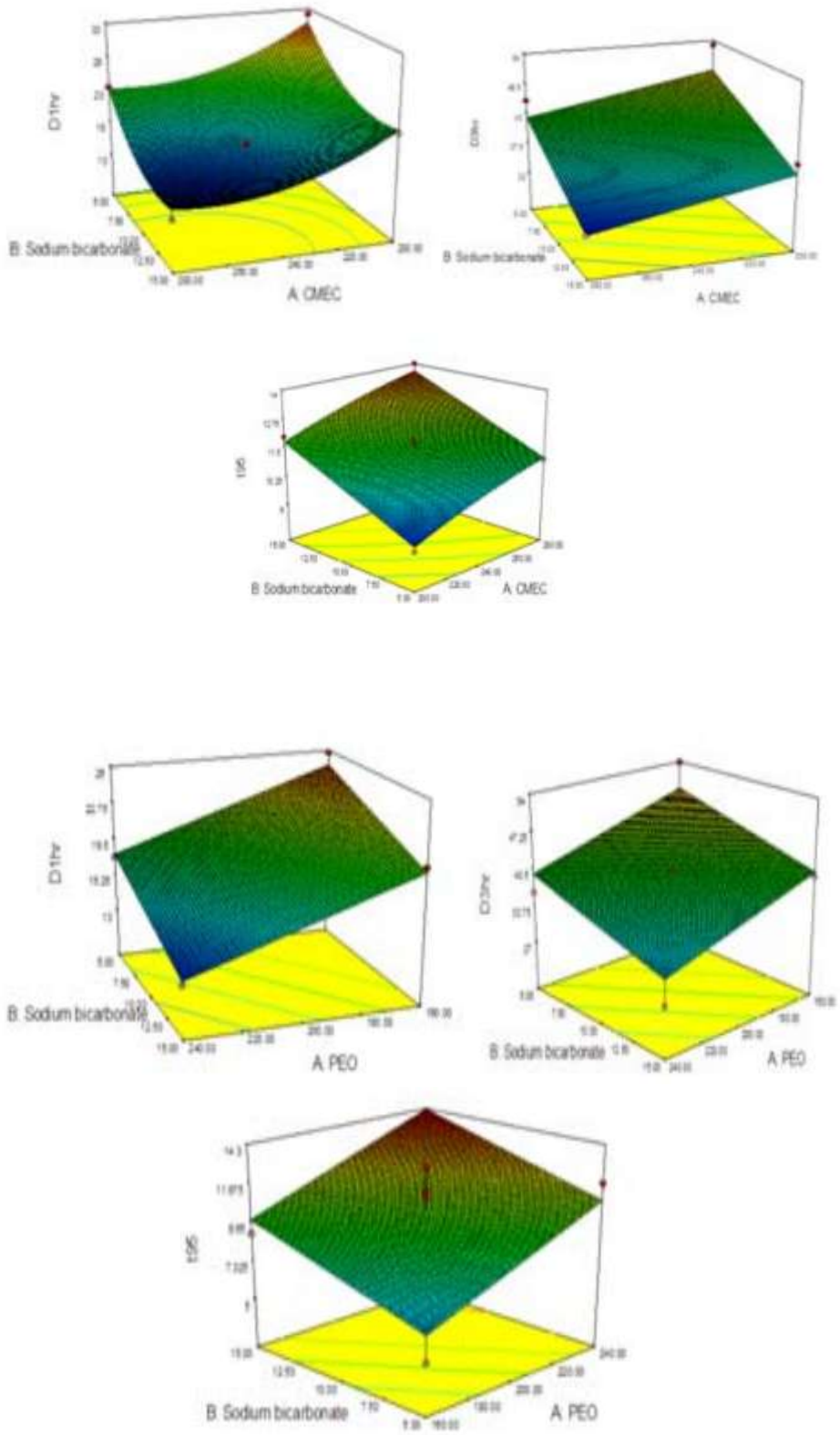


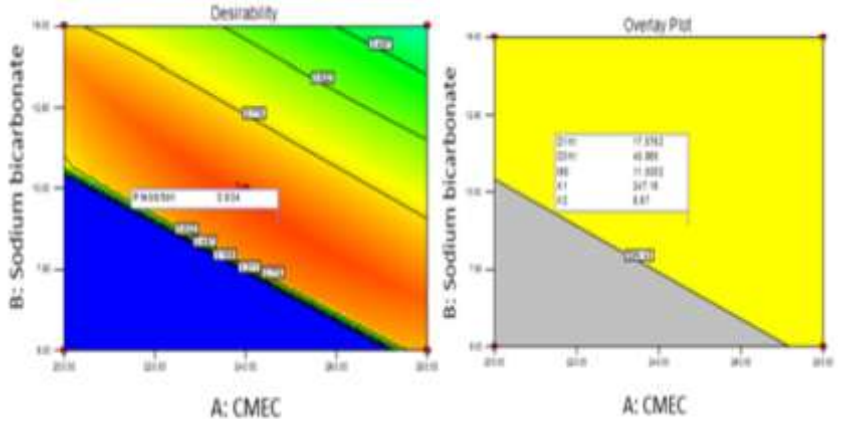
Fig. 3: Response surface plot for the effect of independent variables on observed responses

Both numerical and graphical optimization methods were applied to determine the best levels of the independent variables (X1 and X2). The optimization focused on achieving specific responses, including 20% drug release, D3hr values within the range of 20 to 45%, as dictated by USP dissolution standards (USP 36-NF31), and a t95 value of 11.5 hours. According to USP criteria for propranolol HCl extended-release formulations, the drug release limits

are set as follows: no more than 20% at 1 hour, between 20% and 45% at 3 hours, 45% to 80% at 6 hours, and at least 80% by 12 hours. While most formulations met the dissolution criteria at 6 and 12 hours, they fell short at the 1- and 3-hour marks. Since drug release at these early time points is critical, the optimization incorporated D1hr and D3hr alongside t95 as key constraints. These criteria were consistently applied across all formulations.

An extensive grid and feasibility analysis was conducted to identify the optimal formulations. The desirability and overlay plots, illustrated in Figure 4, reveal a single solution with the highest desirability score. After systematically varying all the variables and reassessing the grid and feasibility outcomes, the Design Expert software recommended 248.17 mg of CMEC with 9.98% sodium bicarbonate for formulations based on CMEC. For formulations utilizing PEO, the suggested amounts were 211.40 mg of PEO WSR 302 and 12.54% sodium bicarbonate.

A)



B)

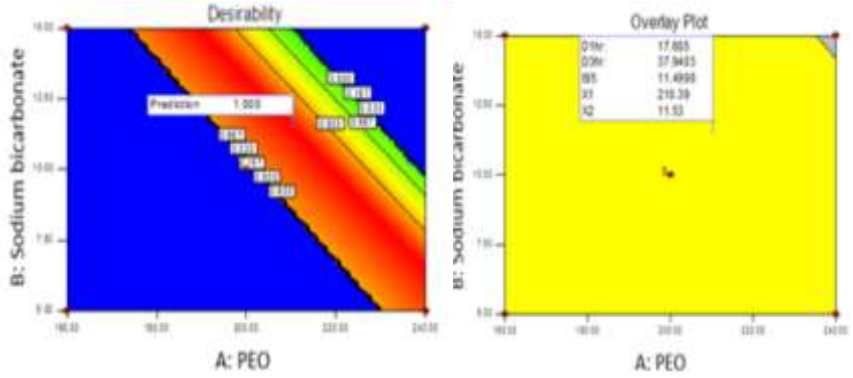


Fig. 4: Desirability and overlay plot for optimization of floating tablets: A) CMEC based formulations; B) PEO based formulations

Conclusion

Statistical optimization serves as an effective approach, especially when multiple variables need to be assessed simultaneously. This study employed a central composite design to statistically optimize the formulation of a gastroretentive drug delivery system (GFDDS). Various formulations were developed and optimized, and the observed responses of the final formulation closely aligned with the predicted outcomes. The optimized gastroretentive floating tablet (GRFT) demonstrated a notable enhancement in the bioavailability of Rabeprazole, as evidenced by increased area under the curve (AUC) and mean residence time (MRT) compared to the commercially available product. The findings also indicated that administering the dosage after a high-calorie, high-fat breakfast can extend the gastric retention time (GRT) of the GRFT, subsequently improving the oral bioavailability of the drug. Overall, the study concludes that the combination of a novel semi-synthetic polymer, carboxymethyl ethyl cellulose (CMEC), and the synthetic

polymer polyethylene oxide (PEO), can effectively serve as carriers in the formulation of GFDDS for highly soluble drugs like Rabeprazole.

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