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Original Article

OPTIMIZATION, DEVELOPMENT AND EVALUATION OF REPAGLINIDE CONTROLLED RELEASE GASTRO-RETENTIVE FLOATING TABLET USING CENTRAL COMPOSITE DESIGN

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ABSTRACT

Objective: The recent study's objective was to optimize and formulate a controlled-release gastro-retentive floating tablet of RG using a central composite design, which provides continuous release of Repaglinide for up to 24 h.

Methods: Repaglinide gastro-retentive floating tablet (RG-GRF Tablet) was prepared by direct compression method. The optimization was carried out using a three-factor and three-level Central Composite design. The amount of Eudragit RSPO (A), HPMC K-100M (B) and Sodium bicarbonate (C) were selected as independent variables and the Cumulative % drug release in 1.5 h (DR1.5), Cumulative % drug release in 8 h (DR8), Cumulative % drug release in 24 h (DR24) and Floating lag time (FLT) were used as dependent variables.

Results: CCD analysis results shows that predicted and experimental values for optimized formulation were found to be almost similar. Optimized amounts of Eudragit RSPO, HPMC K-100M, and $NaHCO_3$ were 14.351 mg, 44.438 mg, and 10 mg, respectively, with the highest possible desirability value of 0.898. The experimental values at optimized preparation conditions were found to be DR1.5 is 30.68%, DR8 is 64.90%, DR24 is 96.54%, and FLT is 4.41 min. The release data from the optimized formulation were closely matched with the Korsmeyer-Peppas model and *in vitro* drug release studies indicated that the RG-GRF Tablet continuously releases the drug for 24 h in a controlled manner.

Conclusion: Current research concludes that RG-GRF Tablets provide drug release for up to 24 h, and the derived central composite design can be used for forecasting the DR1.5, DR8 and DR24 as well. RG can also be made more bioavailable by extending the gastric residence time.

Keywords: Gastro-retentive, Floating tablet, Central composite design, Repaglinide, Controlled release

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INTRODUCTION

Fast gastric emptying caused by conventional oral dosage forms reduces the bioavailability of many pharmacological compounds for which the stomach is the primary site of absorption [1] or proximal portions of the small intestine or points out a problem with absorption in the distal part of the intestine [2]. Controlled drug delivery systems with an extended residence time in the stomach can be used to improve the absorption as well as bioavailability of the drug. To extend the stomach retention duration [3] of a dosage form, many pharmaceutical strategies have been used. The Gastro-retentive Floating Drug Delivery System [4, 5] is an alternative approach to drug delivery that can improve the drug's continuous release over a longer period, in a controlled manner at the required absorption site, until the entire amount of the drug has been released from the dosage form [6].

Repaglinide (RG) is a new oral anti-diabetic drug of BCS-II in the Biopharmaceutical Classification System [7], used to treat type 2 diabetes. It has low oral bioavailability (56%), low aqueous solubility, and a short terminal elimination half-life (1 h) but is quickly and totally absorbed from the digestive tract [8, 9]. Because of its short plasma half-life and high dosing frequency, the immediate-release tablet is taken before each meal to maintain its therapeutic plasma levels. RG is a good candidate [10] for the development of a gastro-retentive dosage form because of its short duration of action, quick clearance, stability against enzymes, and most of its absorption takes place in the upper GIT (stomach). Repaglinide Gastro-retentive Floating tablet (RG-GRF Tablet) was used to improve the residence duration in the stomach [11] so that we can reduce the dosing frequency of the drug since this medication must be taken for an extended period to improve patient compliance [12, 13].

Central Composite Design [14] is an effective statistical and mathematical technique for investigating both the critical values at which the desired response would be achieved and the possible interactions between the independent and dependent variables were analyzed. In this study, we used the CCD to systematically examine the effects of various formulation factors on the drug release and buoyant characteristics of an RG-GRF Tablet. To achieve the desired result, the quantity of different excipients (HPMC-K 100M and Eudragit RSPO) and gas generating agent ($NaHCO_3$) were chosen as independent variables, while the Cumulative % Drug Release in 1.5 H (DR1.5), Cumulative % Drug Release in 8 H (DR8), Cumulative % Drug Release in 24 H (DR24), and Floating Lag Time (FLT) were chosen as dependent variables and based on the findings of initial research carried out in our lab, these formulation variables ranges were selected.

Our research's objective was to formulate an RG-GRF Tablet with a controlled drug release pattern of up to 24 h and Total Floating Time (TFL) of 24 h using different concentrations of Eudragit RSPO, HPMC K-100M and Sodium bicarbonate.

MATERIALS AND METHODS

Repaglinide was purchased from Yarrow Chem Products Mumbai. Hydroxypropyl methylcellulose (HPMC K-100M), polyvinylpyrrolidone (PVP K30) and eudragit RSPO were obtained from Colorcon Co., Ltd India. Anhydrous Lactose, Sodium bicarbonate, Microcrystalline Cellulose (MCC-101), Citric acid, Talc and Magnesium stearate were procured from SD Fine Ltd., Mumbai, and all other chemicals used were of analytical grade.

Preparation of repaglinide solid dispersion (RG-SD)

The solvent evaporation technique [13] was used to prepare RG-SD. RG and PVP K30 were precisely weighed in a 1:10 ratio. The mixture of RG and PVP K30 were added to the anhydrous ethanol. Using a water bath at 60 °C with vigorous stirring, the solvent was evaporated and formed a product. Then it was dried in a vacuum oven. The prepared solid dispersion was milled and dried out in a vacuum for 24 h, which is then subjected to pulverization and sieving.

Preparation of repaglinide gastro-retentive floating tablet (RG-GRF tablet)

Direct compression technology [15] was used for the preparation of RG-GRF Tablets. 22 mg RG-SD and matrix forming agent (Eudragit

RSPO, HPMC K-100M and Xantham Gum), and excipients (Anhydrous Lactose, Sodium bicarbonate, Microcrystalline cellulose and Citric acid) (except glidants and lubricants) separately processed through mesh #16 and then mixed for 15 min. The blend was stirred for a further five minutes after the addition of lubricants and glidants. The bulk was then compressed directly into tablets using Rimek Minipress-II MT Rotary tablet 12 station machine, Karnavati engineering ltd.

Characterization of repaglinide solid dispersion and repaglinide gastro-retentive floating tablets

Solubility studies

A solubility study [16] was performed to determine the saturation solubility of pure RG as well as for RG-SD. The conical flask containing 25 ml of distilled water and an excess amount of RG-SD was shaken for 24 h at 37±0.5 °C. The dispersion was then filtered using a 0.45 m membrane filter. Following the proper dilution with distilled water, the drug concentration was then determined by UV Spectrophotometer (Shimadzu-1800, India) at 241 nm, and the drug solubility was measured.

DSC studies

A differential scanning calorimeter was used to conduct the DSC measurements (Mettler Toledo). The 2-5 mg sample was put in aluminium pans, scanned between 30 °C to 200 °C at the rate of 10 °C/min, and then analyzed under an inert nitrogen atmosphere.

XRD measurement

The XRD studies of RG and RG-SD were conducted using an X-ray diffractometer (D8 Advance XRD) with a 2.2 kw sealed X-Ray tube (Cu-Kα). A scanning rate of 10°/min over a 2θ angular range of 5–80° with an increment of 0.05° was used for obtaining X-ray powder diffraction patterns.

Determination of drug content

RG drug content was determined by weighing 20 tablets [17], and their mean weight was calculated before being finely powdered. 30 ml of methanol was added to a 100 ml volumetric flask and powder equivalent to 10 mg was dissolved in it. After sonication, make up the volume up to the mark of the volumetric flask with methanol and filtered it. By using methanol an aliquots of obtained filtrate diluted up to 10 ml the samples were then spectrophotometrically analyzed at 241 nm.

Evaluation of RG-gastro-retentive floating tablet

The prepared tablets were evaluated for various physical characteristics such as hardness, weight variation; total floating time, *in vitro* drug release and *in vitro* floating lag time.

***In vitro* floating studies**

In vitro floating study of RG-GRF Tablets was carried out by immersing them in the USP type II (Electrolab India) apparatus; containing 1000 ml of 0.1 M HCl (37±0.5 °C, 50 rpm). For each tablet formulation (n = 6), the total floating time and the floating lag time (FLT), the time required for RG-GRF tablets to reach the medium's surface, was measured [18].

***In vitro* release study**

In vitro drug release test was performed for RG-GRF Tablets using USP Type II dissolution apparatus (Electrolab, India), containing 900 ml of 0.1N HCl. The apparatus temperature and speed of the paddle were maintained at 37±0.5 °C and 50 rpm, respectively. At 0, 1.5, and 24 h, 5 ml of the sample was drawn out from the apparatus and replaced with 5 ml of 0.1 N HCI. The amount of RG was then measured with a UV spectrophotometer at 241 nm.

Study of drug release kinetics

To identify the best mathematical model for the determination of the kinetics of drug release [19] and mechanism of drug release from RG-GRF Tablets, several models can be investigated like Zero-order, first order, Higuchi and Korsmeyer–Peppas equation. In the current investigation, the drug release data obtained from the optimized RG-GRF tablet was fitted into the different models as shown in fig. 4.

Experimental design

The central composite design was used to create an experimental design that determines the relative relevance of two or more factors with each other's and also provides the information of interaction with each other. It also can be used to determine the intensity of the responses. Total three-factor and three-level were used for optimizing the RG-GRF tablet [20]. A three-factor (A, B, C), three-level (-1, 0+1) design can be established by including a central point (table 1). The effect of independent variables, including Eudragit RSPO (A), HPMC K-100M (B) and $NaHCO_3$ (C), on DR1.5, DR8, DR24 and FLT, respectively, were investigated using CCD [21]. The CCD model along with coded level and un-coded levels, were shown in table 1.

Table 1: Dependent and Independent variables with their corresponding levels for RG-GRF tablet

Coded	Independent variables	Range and label					
		-α	-1	0	+1	+α	Constrains
A	Eudragit RSPO	3.18	10	20	30	36.82	Range
B	HPMC K-100M	19.55	40	55	70	120.45	Range
C	$NaHCO_3$	3.18	10	20	30	36.82	Range
	Dependent variables						
DR1.5	Cumulative % Drug release at 1.5 h (%)						20-40
DR8	Cumulative % Drug release at 8 h (%)						40-65
DR24	Cumulative % Drug release at 24 h (%)						90-100
FLT	Floating Lag Time (min.)						Minimize

To create this experiment, a CCD with a quadratic model was used. According to the CCD, seventeen experiments were performed randomly, summarized in table 3. We coded Real levels of independent variables according to the following equation;

$$Z = Z0 - -ZC/\Delta Z \ldots. (1)$$

Where Z indicated the coded level, Z0 (real level), ΔZ (Step change) and ZC (Actual value at the central point). As a result of this equation, specific equations were derived for each independent variable in order to code their actual values based on the above equation. Specific equations for independent variables A, B and C are mentioned in below Equations.

$$Z_1 = (A-20)/10 \ldots. (2)$$

$$Z_2 = (B-55)/15 \ldots. (3)$$

$$Z_3 = (C-20)/10 \ldots. (4)$$

Statistical analysis

Design Expert Software version 11 was used to do statistical analysis on the experimental data. To choose the best fitting polynomial model, several statistical parameters like lack-of-fit, p-value, and predicted and adjusted R^2 value of different polynomial models was compared. The Design Expert software generated 3-D response surface graphs was plotted, to examine the influence of independent variables on formulation responses. Software-generated formulas that have been suggested were created and evaluated. The predicted and experimental values were compared.

RESULTS AND DISCUSSION

Characterization of RG-SD and RG-GRF tablets

Solubility studies

Solubility studies of RG and RG-SD were performed and indicated that the solubility of solid dispersion was increased many folds. The solubility of solid dispersions was found to be 0.3503 g/ml, compared with the solubility of pure RG of 0.034 g/ml.

DSC studies

DSC thermograms of pure RG with Eudragit RSPO, HPMC K-100M and solid dispersion are shown in fig. 1. With Eudragit RSPO and HPMC K-100M, pure RP showed a similar peak at about 137 °C that was comparable with the melting point of RG. Conversely, the RG peak showed a considerable drop and no similar peaks were seen in the solid dispersion, indicating that the drug had changed from its crystalline state to an amorphous state.

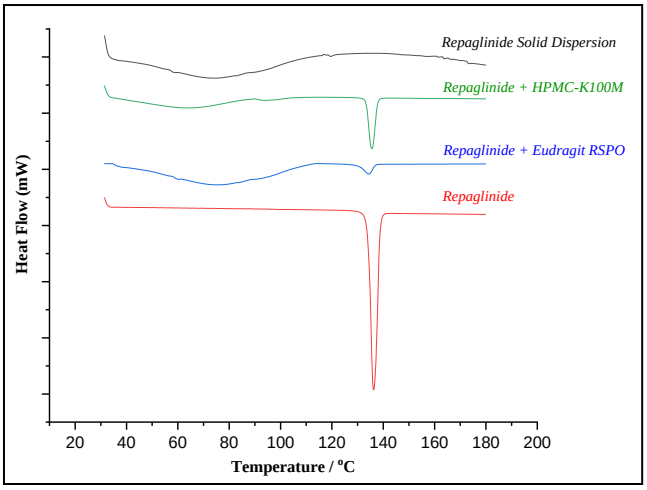

Fig. 1: DSC graph of Pure RG, RG-SD, RG with Eudragit RSPO and RG with HPMC K-100M

XRD studies

The XRD diffractograms of pure RG with Eudragit RSPO, HPMC K-100M, and RG-SD (fig. 2) were studied. The diffraction pattern of pure RG shows the different peaks at 2 Theta = 7.60 20.26, 22.90, 23.96, 30 and 33. The crystal character of the pure RG was amply demonstrated by these peaks. Furthermore, a significant decrease in characteristic peaks suggests the presence of amorphous forms.

Evaluation of RG-gastro-retentive floating tablets

RG-GRF tablets were evaluated for physical characteristics and results of drug content, hardness, weight variation and total floating time were shown in table 2. The total floating time for all the formulations was more than 24 h and the result of all other parameters came within the range.

In vitro floating studies

All formulations had floating lag times between 3 to 5 min illustrated in table 3. Total floating time (n=6) was measured in the 0.1 N HCl for all formulations and it was found to be more than 24 h as shown in table 2. All formulations showed good intact of tablets during this extended period. According to the data, floating lag time decreased as the concentration of sodium bicarbonate increased. Sodium bicarbonate created pores on the surface of the tablet, which helps in allowing the liquid to penetrate the tablet surface, resulting in rapid swelling of the tablet. Rapid swelling increased the total floating time, which kept it intact for a longer duration of time.

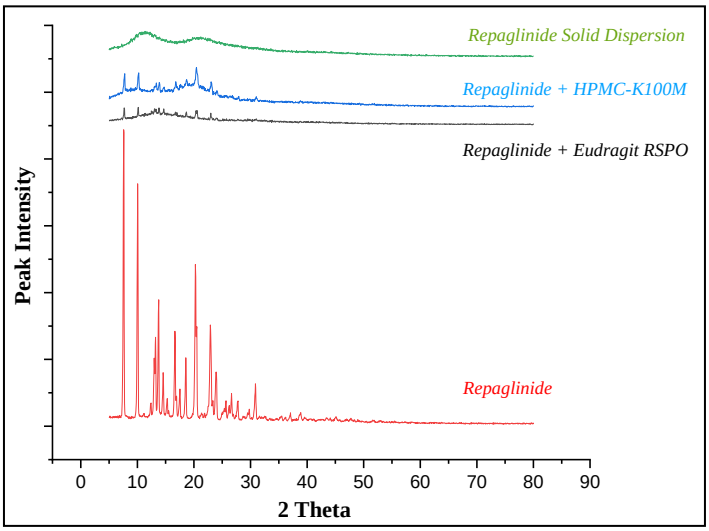

Fig. 2: Diffractogram of pure RG, RG-SD, RG with eudragit RSPO and RG with HPMC K-100M

Table 2: Physical characteristics of RG-GRF tablets

Formulation	Weight variation (%) mean±SD (n=6)	Hardness (kg/cm2) mean±SD (n=6)	Drug content (%) mean±SD (n=6)	Total floating time
F-1	392±3.45	7±0.23	98.11±0.62	>24
F-2	384±5.41	6±0.34	96.08±1.63	>24
F-3	390±2.14	6±0.24	97.54±3.61	>24
F-4	391±6.25	7±0.43	97.75±3.25	>24
F-5	382±4.58	5±0.27	95.52±2.52	>24
F-6	393±4.15	6±0.41	98.25±3.36	>24
F-7	394±3.55	7±0.26	98.58±3.61	>24
F-8	403±4.98	7±0.34	100.73±0.92	>24
F-9	396±6.55	7±0.28	99.10±1.17	>24
F-10	390±5.11	6±0.33	97.5±2.36	>24
F-11	384±4.61	6±0.40	96.18±2.43	>24
F-12	387±2.65	6±0.38	96.78±3.50	>24
F-13	392±5.61	7±0.45	98.08±4.01	>24
F-14	389±4.22	6±0.31	97.25±0.76	>24
F-15	392±2.45	6±0.22	98.11±2.01	>24
F-16	388±4.31	6±0.29	97.14±0.91	>24
F-17	390±4.55	6±0.34	97.55±0.64	>24

In vitro release study

The RG release was significantly affected by the types of controlled release material. The release of optimized RG-GRF tablet was found to be 30.68%, 64.90% and 96.54 % at 1.5h, 8h and 24h, respectively. All formulations of RG showed drug release up to 24 h ranging between 73.55% to 100.35%, but an insufficient drug release was observed at higher concentrations of HPMC K-100M and Eudragit RSPO.

The controlled release of RG-GRF tablets were shown in fig. 3. The combination of Eudragit RSPO and HPMC K-100M controlled the dissolution pattern of RG. The dissolution graph also illustrated that the combination of both polymers provides continuous drug release for up to 24h, the hydrophilic polymer (HPMC K-100M) retarded the drug release more significantly than that of the hydrophobic polymer (Eudragit RSPO). It was attributed to the difference in the mechanism of drug release [22]. In further detail, the former (hydrophilic polymers) controlled the release of the RG by diffusion, whereas the latter (hydrophobic polymers) released the drug through erosion as well as diffusion process [23], confirmed by the n value of Korsmeyer–Peppas model (n=0.45). Additionally, it was claimed that when exposed to water, the hydrophobic polymer matrix would quickly disintegrate, facilitating a quicker release of the medication. As also previously reported [24], higher levels of HPMC viscosity were directly linked to faster swelling, which produced a highly thick gel barrier and hindered the release of the medication. Different combination of matrix-forming agents shown in table 3 is responsible for the difference in the drug release profiles. A single HPMC-K 100M matrix cannot be able to sustain the drug release of RG for up to 24 h, which was not suitable, but the combination of HPMC-K 100M and Eudragit RSPO showed the desired release profile over the test period. A higher concentration of HPMC K-100M was responsible for the formation of a thick gel layer, which may be the main reason for the reduction in drug release.

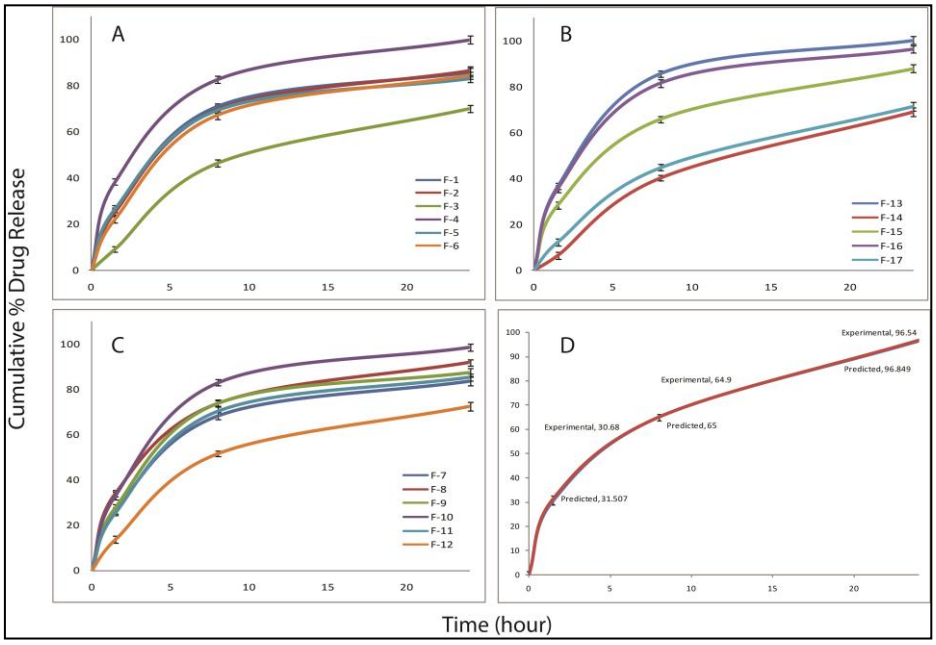

Fig. 3: Dissolution profile of RP-GRF tablets (A, B and C) and predicted and the experimental response of optimized RG-GRF tablet (D)

Study of release kinetics

To study the release kinetics of optimal RG-GRF tablet several kinetic models were estimated, like zero order, 1st order, Higuchi and Korsmeyer–Peppas model, as shown in fig. 4. The release data from the optimized formulation most significantly matched with the Peppas model, as shown by the correlation coefficient. The calculated correlation coefficients for the zero-order were found to

be 0.854, for first order (0.966), for Higuchi (0.988), and for Korsmeyer-Peppas models (0.997). Furthermore, the finding suggested that tablet erosion as well as diffusion both contributed to controlling drug release, also revealed by the value of release exponent n (n=0.452). Peppas model employed the n-value to characterize various release mechanisms [25]. When the release mechanism involved an unknown or more than one type, the Peppas model is typically used to analyze it.

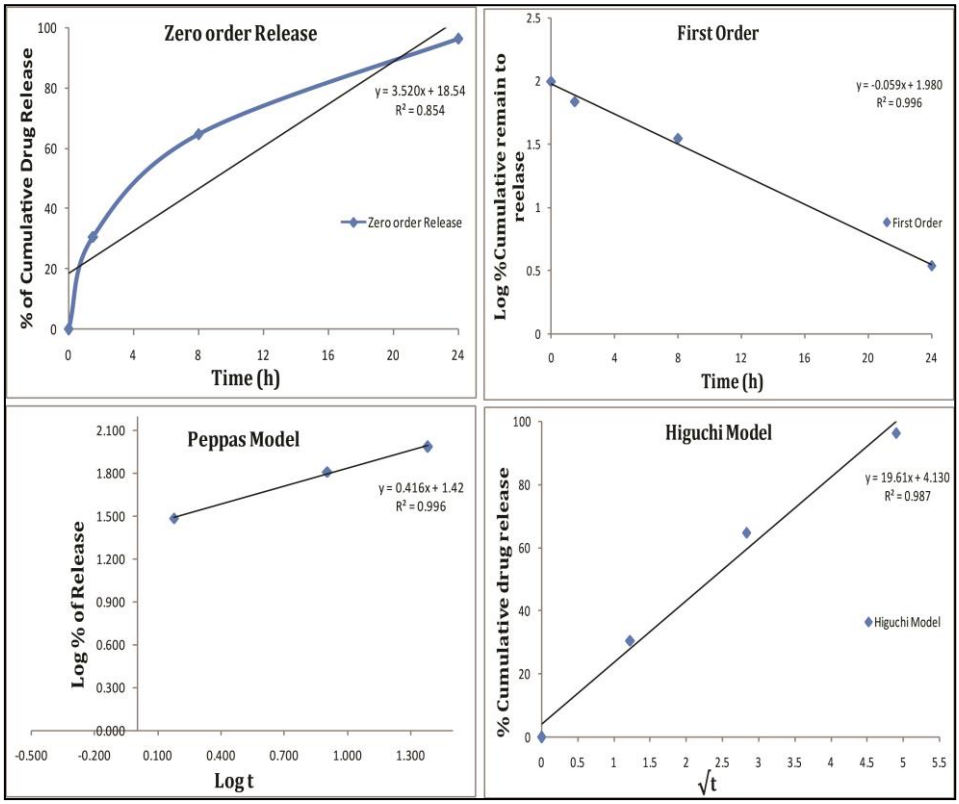

Fig. 4: Kinetic models of optimized RG-GRF tablet

Table 3: Experimental design for RG-GRF tablet with independent variables and values of responses

Runs	Space type	Independent variables			Response values			
		Eudragit RSPO (mg)	HPMC K-100M (mg)	$NaHCO_3$ (mg)	DR1.5 (h) mean±SD (n=6)	DR8 (h) mean±SD (n=6)	DR24 (h) mean±SD (n=6)	FLT (min) mean±SD (n=6)
1	Center	20	70	20	25.55±2.48	55.6±0.87	90.61±1.25	4.83±1.66
2	Center	20	70	20	25.11±1.85	55.33±1.45	91.44±2.14	4.86±2.45
3	Factorial	30	100	30	9.07±0.98	31.55±1.55	75.08±2.81	4.2±2.74
4	Axial	3.18207	70	20	38.32±2.44	67.68±2.15	99.89±1.25	3.58±.24
5	Factorial	10	100	10	26.55±1.68	54.49±1.65	87.98±2.15	4.0±0.81
6	Axial	20	70	3.18207	22.11±1.98	52.12±1.21	89.4±1.11	4.51±1.34
7	Factorial	30	40	30	26.43±2.54	53.67±2.14	87.92±2.47	3.91±1.57
8	Factorial	10	100	30	34.21±2.78	58.98±1.01	96.85±1.45	3.48±2.01
9	Axial	20	70	36.8179	27.85±1.73	58.85±2.14	92.65±1.68	3.53±1.03
10	Factorial	10	40	10	33.09±2.45	68.11±0.57	98.3±2.84	4.0±2.05
11	Center	20	70	20	25.74±2.13	55.43±1.42	90.45±1.14	4.9±1.66
12	Axial	20	120.454	20	13.78±1.98	36.66±2.45	77.59±2.01	4.45±2.14
13	Factorial	10	40	30	36.71±2.11	70.77±1.74	100.35±1.4	3.61±2.55
14	Factorial	30	100	10	6.38±1.87	26.11±1.91	73.55±1.84	5.0±1.24
15	Factorial	30	40	10	28.41±2.45	50.1±2.11	93.01±2.54	4.51±2.46
16	Axial	20	19.5462	20	35.55±2.31	66.64±0.75	96.54±0.87	4.2±1.41
17	Axial	36.8179	70	20	12.21±2.05	29.72±2.14	77.24±1.22	4.63±1.82

Experimental design and statistical analysis

CCD is a mathematical tool for model development that aims to optimize the number of independent variables that are taken into consideration [26]. The effect of independent variables on DR1.5, DR8, DR24 and FLT are shown in table 3. In order to predict the values of the response variable, polynomial equation coefficients were calculated using experimental data. The following coded equation was derived for each response variable from the CCD.

Coded equation

Drug Release in 1.5 H =+25.1218-7.62852* A-6.2271* B+1.58481* C-3.79375* AB-1.32125* AC+1.08875* BC ……. (5)

Drug Release in 8 H = 55.454-11.3321* A-8.92886* B+2.01206* C-2.5875* AB+0.2325* AC+0.4625* BC-2.38981* A^2-1.34683* B^2+0.00904598* C^2 ……. (6)

Drug Release in 24 H = 90.8099-6.73747* A-5.71068* B+0.939149* C-2.31* AB-1.81* AC+1.68* BC-0.721348* A^2-1.25168* B^2+0.148394* C^2 …… (7)

Floating Lag Time = 4.86449+0.314559* A+0.0783818* B-0.289829* C+0.11375* AB-0.06125* AC-0.04125* BC-0.272103* A^2-0.194321* B^2-0.302155* C^2 …… (8)

By using design expert software, 17 formulations were prepared based on various polymer concentrations in accordance with the CCD. The results of the analysis suggested that the data obtained from the experiment corresponded well with a 2FI (Two Factor Interaction) model for DR1.5 and a quadratic polynomial model for DR8, DR24 and FLT.

The model's significance was determined by the p-value, which should be<0.05. In our research, the P values for DR1.5, DR8, DR24 and FLT were found to be<0.0001 (table 4), suggesting that the models are significant. The experimental and predicted values have a significant link, as indicated by the R^2 value of 0.9987 for DR1.5, 1.000 for DR8, 0.9991 for DR24 and 0.9990 for FLT. The model's ability to predict the response was supported by the Predicted R^2 (0.9960 for DR1.5, 0.9999 for DR8, 0.9958 for DR24 and 0.9951 for FLT) and the Adjusted R^2 (0.9979 for DR1.5, 1.0000 for DR8, 0.9980 for DR24 and 0.9977 for FLT).

Table 4: Fit summary of results of regression analysis for responses

Response	Model	Sequential p-value	Lack of fit p-value	Adjusted R^2	Predicted R^2	Remarks
DR1.5	Linear	<0.0001	0.0081	0.8846	0.8202	
	2FI	<0.0001	0.3548	0.9979	0.9960	Suggested
	Quadratic	0.3095	0.3685	0.9981	0.9944	
DR8	Linear	<0.0001	0.0015	0.9453	0.9226	
	2FI	0.1345	0.0019	0.9582	0.9487	
	Quadratic	<0.0001	0.8978	1.0000	0.9999	Suggested
DR24	Linear	<0.0001	0.0264	0.8800	0.8184	
	2FI	0.0011	0.0877	0.9666	0.9635	
	Quadratic	<0.0001	0.8531	0.9980	0.9958	Suggested
FLT	Linear	0.0054	0.0082	0.5209	0.4685	
	2FI	0.8058	0.0066	0.4329	0.2305	
	Quadratic	<0.0001	0.8770	0.9977	0.9951	Suggested

For all variables, lack of fit was non-significant (p≤0.05), also indicating that our model is statistically correct (table 5). Positive and negative values shown in the coded equation (Equation 5-8) represent a relationship between the variable (Independent and dependent), An increase in value (+value) means that it favors the optimization, while a decrease in value (-value) indicates the opposite.

Table 5: Regression coefficient values and p-value for RG-GRF tablet

Regression coefficient	DR1.5	P-Value	DR8	P-Value	DR24	P-Value	FLT	P-Value
Intercept	25.12	0.0000	55.45	<0.0001	90.81	<0.0001	4.86	<0.0001
A	-7.63	<0.0001	-11.33	<0.0001	-6.74	<0.0001	0.3146	<0.0001
B	-6.23	<0.0001	-8.93	<0.0001	-5.71	<0.0001	0.0784	<0.0001
C-	1.58	<0.0001	2.01	<0.0001	0.9391	<0.0001	-0.2898	<0.0001
AB	-3.79	<0.0001	-2.59	<0.0001	-2.31	<0.0001	0.1137	<0.0001
AC	-1.32	<0.0001	0.2325	0.0002	-1.81	<0.0001	-0.0613	0.0002
BC	1.09	<0.0001	0.4625	<0.0001	1.68	<0.0001	-0.0413	0.0023
A^2	-	-	-2.39	<0.0001	-0.7213	0.0004	-0.2721	<0.0001
B^2	-	-	-1.35	<0.0001	-1.25	<0.0001	-0.1943	<0.0001
C^2	-	-	0.0090	0.7569	0.1484	0.2401	-0.3022	<0.0001
R^2	0.9987		1.000		0.9991		0.9990	

*P-values less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

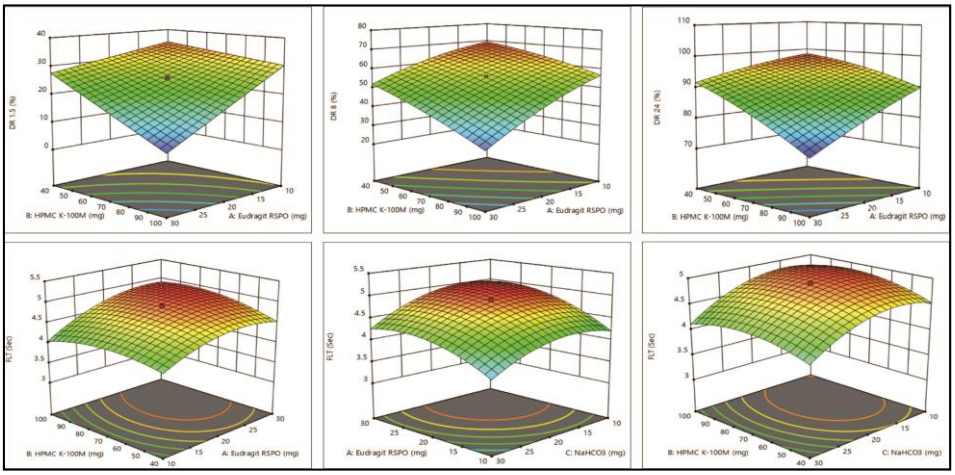

Fig. 5: Response surface plots for the effect of independent variables on observed responses

The amount of (A) and (B) have negative effects on DR1.5, DR8, and DR24 while positive effects on FLT. The amount of (C) has a positive effect on DR1.5, DR8, and DR24 and a negative effect on FLT. The effect of (A) on DR1.5, DR8 and DR24 were 1.2, 1.3 and 1.17 times more than the effect of (B), respectively. The interaction effect of (A) and (B) on all responses was found to be significant ($p \leq 0.0500$). Interaction of (A) and (B) was found negative for DR1.5, DR8 and DR24 while positive for FLT. Interaction of (A) and (C) was found negative for DR1.5, DR24 and FLT and positive for DR8. The effect of (A), (B) and (C) on DR1.5, DR8, DR24 and FLT were clearly understood by contour plot and 3D surface response plot as shown in fig. 5 and fig. 6. These graphs illustrated the amount of Eudragit RSPO and HPMC K-100M significantly affect the drug release in 1.5h, 8h and 24 h while the amount of $NaHCO_3$ significantly affect the FLT.

To visualize the impact of independent variables on dependent variables, a contour plot (fig. 6) was used. In such plots, we can examine how two independent variables can influence a dependent variable at the same time. A constant level of the third independent variable was maintained throughout all the figures. The plot demonstrated that as the concentration of Eudragit RSPO and HPMC K-100M increased, the DR1.5, DR8, and DR24 decreased. The graph also showed that Eudragit RSPO had a significant impact on FLT, whereas HPMC K-100M had a very small impact. The contour plot demonstrated that increasing the concentration of Eudragit RSPO at fixed concentration of sodium bicarbonate decreased the DR1.5, DR8, and DR24. The drug release is being slowed down as evidenced by an increase in the concentration of Eudragit RSPO. The drug release was also slowed down by a higher HPMC K-100M concentration because it forms a substantial gel layer around the tablets. This would lead to a slower rate of drug release due to the lengthening of the diffusion path. The FLT increases with an increase in Eudragit RSPO concentration.

The value of Regression coefficients for independent variables was summarized in table 4. A higher R^2 value (Nearer to one) indicates a better model fitting to actual data; however, lower R^2 values show that response factors were insufficient to explain the variation in behavior [27]. The composition of the optimized formulation as shown in table 6 was selected based on the criteria for getting the minimum FLT and applying DR1.5 (20–40%), DR8 (40–65%) and DR24 (90–100%) constraints. The range of independent variables was predicted by an overall desirability function which is dependent on all studied formulation variables. A new batch was prepared and analyzed using an optimized formula for DR1.5, DR8 and DR24 as well as FLT in triplicate, in order to validate the accuracy of the computed optimum factors and projected responses.

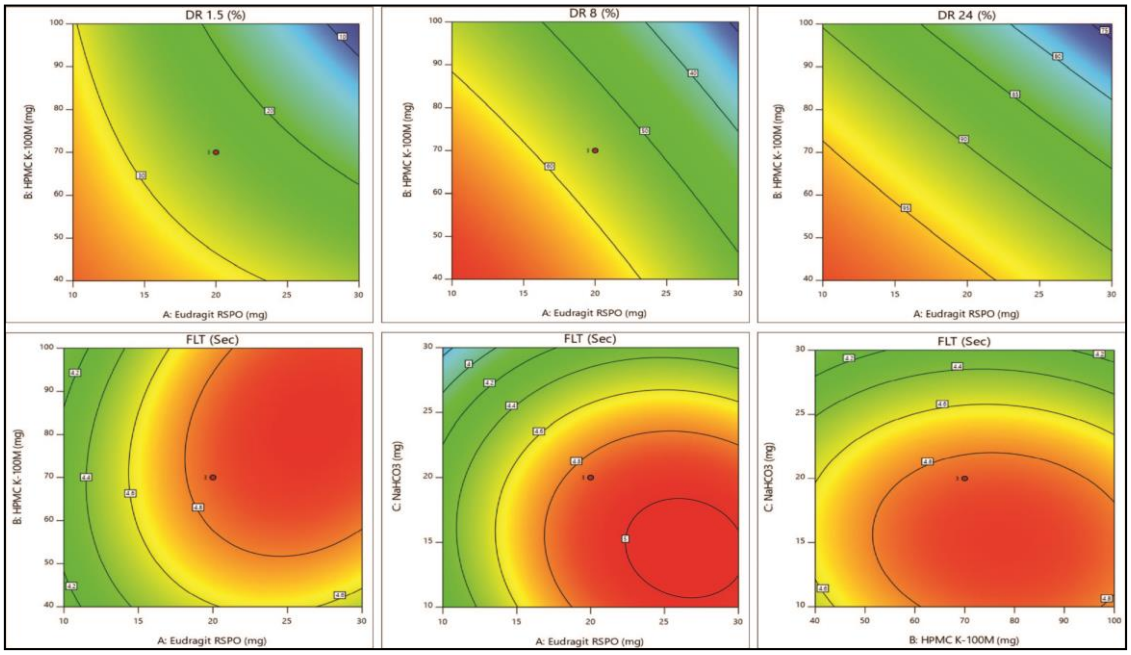

Fig. 6: Contour plots for the effect of independent variables on response variables

Table 7 summarizes the observed and predicted responses for the optimized RG-GRF tablet.

Predicted and experimental values were found to be quite similar.

Table 6: Optimized formulation for RG-GRF tablets

Ingredients	Quantities (mg)
RG-SD	22
Eudragit RSPO	14.35
HPMC-K 100M	44.44
NaHCO3	10
Citric Acid	5
Xantham Gum	30
MCC-101	166.22
Lactose	100
Mg-stearate	4
Talc	4

Verification of CCD model

The model's usefulness for predicting response values was examined using the optimized concentration of independent variables. The optimized levels of Eudragit RSPO (A), HPMC K-100M (B), and $NaHCO_3$ (C) contents were found to be 14.351 mg, 44.438 mg, and 10 mg, respectively, with a maximum value of desirability of 0.898.

The optimized formulation as shown in table 6 was prepared and validated using the optimized concentration of independent variables. Table 7 and fig. 3 (D) illustrated that Predicted response values and experimental response values were in close conformity. Predicted response values provided by the software were DR1.5 (31.50%), DR8 (65.00%), DR24 (96.85%), and FLT (4.365 min). conversely, the experimental values at optimal preparation conditions were found to be DR1.5 (30.68%), DR8 (64.90%), DR24 (96.54%), and FLT (4.41 min.). All responses showed a relative error of less than 3% between predicted and observed values. The results demonstrate that the model used in our experimental design is valid and predictable, especially concerning the quality characteristics, which are in good agreement with theoretical predictions.

Table 7: Optimum level, experimental and predicted value of response at optimized condition

Optimum level	Coded levels	Actual levels
A-Eudragit RSPO	-0.57	14.351
B-HPMC K-100M	-0.70	44.438
C-$NaHCO_3$	-1.0	10
Response	Predicted value	Experimental value mean±SD(n=6)
DR1.5	31.507	30.68±1.46
DR8	65.00	64.90±1.73
DR24	96.849	96.54±1.18
FLT	4.365	4.41±0.46

CONCLUSION

According to the findings of the current study, gastro-retentive floating repaglinide tablets represent a novel and revolutionary tactic for the delivery of repaglinide in the management of diabetes. This study examined the use of a central composite design for statistical optimization in the development of formulation using eudragit RSPO, HPMC K-100M and $NaHCO_3$. Our research shows the importance of response surface methods to investigate the relationship amongst the dependent and independent variables and to optimize the concentration of polymers. The Predicted response values and experimental response values were in close agreement. It is possible to draw the conclusion from the current experiment that the combination of these independent variables can be used to formulate gastro-retentive repaglinide floating tablets. The target set's requirements were all met by the optimized formulation, which also produced satisfactory results for DR1.5, DR8, DR24, and FLT.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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