

Optimized gastroretentive floating carvedilol tablets: an approach for prolonged gastric residence time and enhanced absorption

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ABSTRACT

Carvedilol (CVD) is an antihypertensive agent with short elimination half-life, pH-dependent solubility, and narrow absorption window. So, the present study aimed to prolong its gastric residence time that entailed a development of an optimized gastro retentive floating tablets (GRFTs) using 3² full factorial design. The tablets were fabricated by direct compression using hydroxypropyl methylcellulose and carbopol 940 as release retarding polymers. The quality attributes of the tablets were evaluated. The buoyancy lag time, total floating time, swelling ability and in vitro release studies were also carried out in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Statistical data analysis revealed that the optimized formulation containing 21.91% HPMC and 15% carbopol 940 had acceptable hardness, optimum floating behavior and 24h controlled-release pattern. The design succeeded to develop CVD-GRFTs with floating ability and controlled release behavior that could improve its solubility, and improve its availability at the best absorptive site.

INTRODUCTION

Carvedilol (CVD) is clinically prescribed in the management of hypertension, myocardial infarction and congestive heart failure (Wen *et al.*, 2010). It exhibits low bioavailability (about 25%) after oral administration due to extensive first-pass metabolism in liver. It has a short plasma half-life of about 6 hours with an elimination half-life of 2 hours (Neugebauer *et al.*, 1990; Tanwar *et al.*, 2007; Ubaidulla *et al.*, 2007). Its solubility in water is less than 1µg/ml above pH 9.0, 23µg/ml at pH 7, and about 100µg/ml at pH 5 at room temperature indicating to pH-dependent solubility (Brook *et al.*, 2010). It's extremely lower solubility at alkaline pH levels may affect its availability at the absorptive site (Chakraborty *et al.*, 2009). So, the development of CVD in a gastro retentive floating dosage form making it excellent candidate for improving solubility, enhancing absorption and controlling its release.

Limited bioavailability of orally administered drugs due to their narrow absorption window can be considered as a challenge in the development of controlled release formulations. To prolong the residence of a formulation at the preferred absorptive site, several approaches were reported (Garg and Gupta 2008). These approaches include floating systems (Hosny and El-Say 2013), expandable systems (Klausner *et al.*, 2003; Matharu *et al.*, 2011), bioadhesive systems (Chavanpatil *et al.*, 2006; Attia *et al.*, 2008) and high density systems (Davis *et al.*, 1986). The floating systems may be effervescent type which generate carbon dioxide gas upon contact with gastric fluid or non-effervescent one. The latter type can be further divided into hydro-dynamically balanced systems (Sheth and Tossounian 1984), alginate beads (Shishu *et al.*, 2007); hollow microspheres (Gangadharappa *et al.*, 2011); raft systems incorporating alginate gels (Hampson *et al.*, 2010), superporous hydrogels (Mayur *et al.*, 2013) and magnetic systems (Ito *et al.*, 1990). Drugs which are poorly soluble at an alkaline pH; are absorbed in the stomach; act locally in the stomach; have a narrow absorption window; and/or unstable in the alkaline pH are favorable to be formulated in floating drug delivery system as suggested by Singh and Kim (Singh and Kim 2000).

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There are several factors control gastric residence time (GRT) of dosage form (Davis *et al.*, 1990). One particular factor is the fed state of the stomach which is considered the preferred timing for administration of the dosage form to avoid the migrating myoelectric complex (MMC) (Wilding *et al.*, 1982). This strong motor activity clears undigested material from the stomach throughout the relaxed and open pylorus into the intestine. This MMC, which is known as the house-keeper wave, occurs every 1.5 to 2 hours under fasting conditions but are inhibited by food. Hence, decreasing the gastric emptying rate and prolonging drug release (Davis *et al.*, 1986; Fix *et al.*, 1993). Also, it was expected that administration of a dosage form larger than 15 mm with food prevent its passage through the pyloric valve into the small intestine and increase GRT. In addition, swellable objects which might also have floating characteristics will retain in the stomach. Moreover, density of the dosage form should be less than 1.004g/ml to be floated on the gastric contents (Clarke *et al.*, 1995). Tetrahedron and ring-shaped devices compared with other shapes were reported to have better gastric residence time (GRT) 90 to 100% retention at 24 hours (Dixit 2011). The present study includes development and optimization of gastro retentive floating tablets (GRFTs) of carvedilol using response surface methodology to prolong its gastric residence time and enhance absorption. The developed formulations was evaluated for floating and swelling properties as well as the release behavior. Therefore, an attempt was made to develop CVD-GRFTs which would increase its solubility and bioavailability.

MATERIALS AND METHODS

Materials

Carvedilol (CVD) was kindly provided as a gift from Riyadh Pharma, Riyadh (Saudi Arabia), Carbopol940 (CRP) was purchased from BF Goodrich Chemical Company, Ohio (USA). Hydroxypropyl methylcellulose (HPMC), was purchased from Aqualon (UK). Sodium bicarbonate was procured from Prolabo (France). Citric acid was obtained from Sigma-Aldrich Company, St. Louis, MO (USA). All other chemicals were of analytical purity.

Methods

Experimental Design

A three level factorial design was utilized to study the effect of two variables namely, HPMC percentage (X_1) and CRP percentage (X_2) in 9 runs. The optimization was carried out to develop CVD-GRFTs with short buoyancy lag time (BLT), long total floating time (TFT) and controlled release behavior. Statgraphics® Centurion XV, Software, Version 15.2.05 (StatPoint, Inc., Warrenton, VA) was used to generate and evaluate the statistical experimental design. The response variables were, buoyancy lag time (BLT) as Y_1 ; total floating time (TFT) as Y_2 ; the initial CVD release after 2 h as Y_3 , and the cumulative CVD release after 12 h as Y_4 . Table 1 displays the factors and the observed results for the investigated responses according to the 3-level full factorial design.

Preparation of CVD-GRFTs

Nine formulations containing 25mg CVD as active pharmaceutical ingredient were prepared by direct compression technique. All the ingredients were separately passed through a 60 mesh sieve, accurately weighed and mixed in geometrical order. In addition to the specified amounts of HPMC and CRP, each tablet contains 50 mg sodium bicarbonate, 20 mg citric acid as gas generating agents, and 1% of purified talc and magnesium stearate as glidant and lubricant, respectively. The tablet weight was completed to 200mg with microcrystalline cellulose. Powder blend equivalent to 50 tablets from each formula was mixed for 10 minutes.

The weight of the tablets were designed to be 200 mg by feeding manually to the die and compressed under a constant compression force, using 9 mm flat round punches using a tablet machine (Erweka, GmbH, Heusenstamm, Germany).

Evaluation of the prepared CVD-GRFTs

The prepared CVD-GRFTs were evaluated for visual appearance, uniformity of weight and content, thickness, hardness, and friability according to USP standard procedures for tablets (The United States Pharmacopeia, 2005).

Table 1: Quality attributes of the prepared CVD-GRFTs.

Run	Tablet weight (mg)	Tablet thickness (mm)	Drug content (%)	Friability (%)	Hardness (kg/cm ²)
R1	203 ± 0.24	3.09 ± 0.01	99.63 ± 0.35	0.01 ± 0.02	7.06 ± 0.18
R2	196 ± 1.04	3.11 ± 0.05	102.61 ± 1.42	0.24 ± 0.08	5.13 ± 0.23
R3	202 ± 0.39	3.12 ± 0.02	96.43 ± 1.55	0.12 ± 0.05	5.64 ± 0.13
R4	199 ± 1.11	3.10 ± 0.03	95.25 ± 0.59	0.26 ± 0.07	5.08 ± 0.12
R5	198 ± 0.13	2.98 ± 0.05	103.0 ± 1.19	0.53 ± 0.08	4.79 ± 0.28
R6	209 ± 0.24	3.15 ± 0.02	97.98 ± 1.39	0.61 ± 0.10	4.16 ± 0.53
R7	207 ± 1.02	3.11 ± 0.05	103.7 ± 2.03	0.03 ± 0.01	6.34 ± 0.71
R8	205 ± 0.33	3.07 ± 0.05	98.55 ± 1.33	0.09 ± 0.03	6.01 ± 0.32
R9	206 ± 0.21	3.21 ± 0.04	104.13 ± 0.74	0.09 ± 0.02	6.22 ± 0.17

Swelling ability

The swelling ability (water uptake) of the developed tablets was evaluated as the adopted method by Dorozynski *et al.*, (Dorożyński *et al.*, 2011) and the swelling index percentage (SI) was calculated using the equation (1);

$$\text{Swelling Index (\%)(SI)} = \frac{(\text{The weight of swollen tablet at time } t - \text{The initial weight of the dry tablet})}{\text{The initial weight of the dry tablet}} \times 100 \quad (1)$$

Floating behavior

The floating behavior of the tablets was visually determined according to the method described by several researchers (Rosa *et al.*, 1994; Jagdale *et al.*, 2009; Yin *et al.*, 2013; El-Zahaby *et al.*, 2014). Briefly, a tablet was placed in a glass beaker containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 °C. The time between tablet introduction and its buoyancy was considered the buoyancy lag time (BLT) and the time during which the tablet remains buoyant was considered the total floating time (TFT). Both times were recorded for each formulation. All experiments were done in triplicate.

In Vitro release study

The *in vitro* release of CVD from the prepared formulations was carried out using the USP dissolution Apparatus, type-II (paddle apparatus) Erweka, DT 700 LH, (Germany) at a rotational speed of 100 rpm. The study was carried out in 900 mL 0.1N HCl which was selected as a dissolution medium and the temperature was maintained at 37 ± 0.5 °C for 24 h. Aliquots of 5 mL were withdrawn and replenished with fresh medium to maintain constant volume. Samples were filtered and analyzed spectrophotometrically at a wavelength of 241 nm. All experiments were done in triplicate.

Kinetic treatment of the release data

The release data of CVD from the prepared batches were fitted to different kinetic orders or models; zero order (Wagner 1969), first order (Desai *et al.*, 1966), diffusion (Higuchi 1963), and Korsmeyer model (Korsmeyer *et al.*, 1983; Ritger and Peppas 1987) to explore the best fit order/model and the exact mechanism of drug release from the tablets.

Statistical analysis and optimization

Data obtained from the prepared CVD-GRFTs were analyzed using Statgraphics software. Polynomial models,

including linear, interaction and quadratic terms were generated for all the response variables using the software. In addition, analysis of variance (ANOVA) was used to recognize the significant effect of factors on the investigated responses. The factor estimate and P- values were also calculated. The relationship between the studied factors and responses was further revealed using contoured response surface plots. These plots are useful not only in the study the effects of various factors on the response at a given time but also in the prediction of the responses at intermediate levels of independent variables. Consequently, a new formulation with the desired responses will be generated based on the numerical optimization technique.

RESULTS AND DISCUSSION

Quality attributes of the prepared CVD-GRFTs

CVD-GRFTs were developed using release controlling polymers such as HPMC and CRP, and gas generating agent like NaHCO_3 and citric acid. The incorporation of microcrystalline cellulose “Avicel PH101” in the formulations was recommended to improve the flow ability and compressibility of powder blend in direct compression process (El-Say *et al.*, 2015). Avicel was also added to the formulations due to its swelling ability on contact with aqueous fluids which increase the water uptake and porosity of the matrix that would enhance floating behavior (Garg and Gupta 2009). All the developed tablets showed an acceptable quality attributes (Table 2) and met the pharmacopoeial requirements for weight, drug content and friability. All the prepared tablets were compressed with a diameter of about 9 mm which was reported to be enough for an increased GRT (Dixit 2011). The tablets weight ranged from 196 to 209 mg with standard deviation less than 2% (The British pharmacopoeia, 1998). The values of tablets thickness ranged from 3.07 ± 0.05 to 3.21 ± 0.04 mm, whereas, the percentage of drug content ranged from 95.25 ± 0.59 % to 104.13 ± 0.74 % of the labeled potency which confirm drug uniformity among different batches (The United States Pharmacopoeia 2005). In addition, the hardness of the tablets ranged from 4.16 ± 0.53 kg/cm² to 7.06 ± 0.18 kg/cm² and the friability percentage for all formulations was less than 1%, indicating good mechanical strength of the prepared batches. On the contrary, the increase in the hardness ($>5-6$ kg/cm²) would affect the penetration of the dissolution medium to the tablet matrix which may lead to prolongation of the floating lag time (Gambhire *et al.*, 2007; Singh *et al.*, 2013; Qi *et al.*, 2015).

Table 2: Design matrix including investigated variables with the observed values of responses (Y_1 - Y_4) for 9 formulations of CVD-GRFTs.

Run	Factors		Responses			
	HPMC (%), X_1	Carbopol (%), X_2	Buoyancy lag time (s), Y_1	Total floating time (h), Y_2	Initial release after 2 hours (%), Y_3	Release after 12 hours (%), Y_4
R1	10	5	173.2 ±4.15	12.1 ±0.23	52.92 ±0.15	89.25 ±1.13
R2	20	15	62.2 ±2.53	20.3 ±1.55	41.37 ±0.09	75.34 ±1.52
R3	20	10	49.4 ±1.15	22.4 ±1.34	29.81 ±0.65	68.61 ±2.11
R4	30	5	37.9 ±0.56	20.5 ±0.65	25.66 ±1.12	57.10 ±0.94
R5	30	10	35.7 ±0.75	23.1 ±0.77	35.47 ±0.34	67.70 ±1.34
R6	30	15	11.5 ±0.25	24.9 ±1.58	27.02 ±0.74	60.17 ±2.23
R7	10	10	133.3 ±3.24	13.3 ±0.15	43.30 ±0.84	76.75 ±0.85
R8	10	15	192.4 ±5.12	10.7 ±0.84	62.14 ±2.09	86.37 ±2.15
R9	20	5	91.8 ±1.67	18.7 ±1.95	36.13 ±0.34	79.85 ±1.12

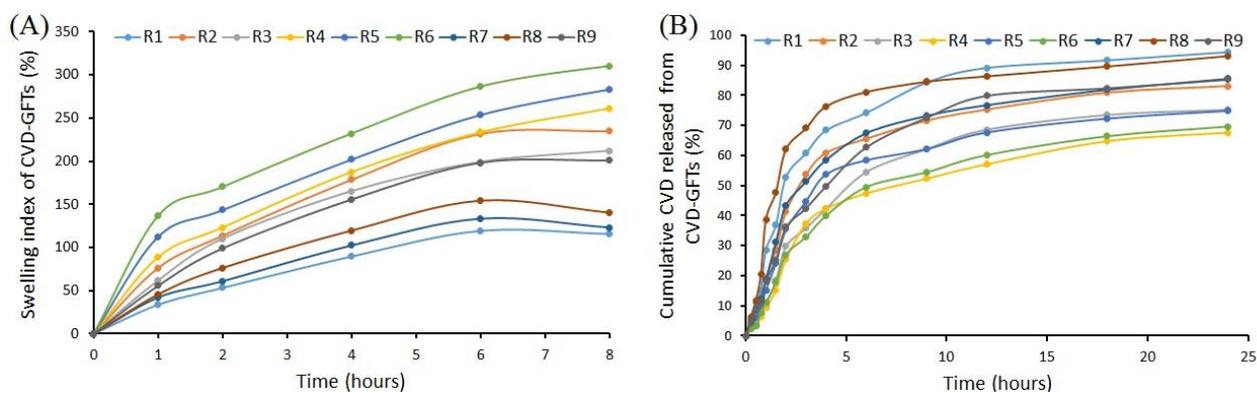


Fig. 1: Swelling indices (A) Release profiles (B) of different CVD-GRFTs in 0.1 N HCl at 37°C (n=3).

Swelling indices

The ability of the matrix tablets to uptake dissolution medium is an important factor that affect its buoyancy and drug release behavior (Figure 1). It was noticed that the type of polymer affected on the dissolution medium uptake by the prepared matrices. Tablets with more percentage of HPMC exhibited more swelling compared to those with CRP owing to the resistance of the network structure of CRP to the movement of water molecules (Prasanth *et al.*, 2011). Formula R6 showed the highest swelling index ($310.54\% \pm 1.43$) throughout the study period due to the high affinity of HPMC-containing matrices to the aqueous medium. In contrast, the maximum swelling indices of formulae R8, R7, and R1 containing lower HPMC percentage were 154.44 ± 0.75 , 133.45 ± 0.51 and 119.23 ± 0.93 were achieved after 6 hours, respectively.

Floating behavior

The *in vitro* floating study revealed the ability of most formulations to float in short lag time and maintain buoyant more than 12 h (Table 2). The presence of NaHCO_3 and citric acid in an optimized ratio (2.5:1) as gas generating mixture provide the desired floating behavior by induction of effervescence that increase the porosity of the tablet matrix leading to rapid hydration and enhancing their floating ability (Pare *et al.*, 2008; Tadros 2010). In addition, the generated CO_2 that entrapped in the gel layers formed by the hydrophilic polymers may increase the tablet porosity making it float for long period of time. The prolonged residence time of drug in stomach could improve the solubility of CVD and increase its availability owing to prolonged drug residence at the favorable site of absorption. As shown in Table 2, the HPMC/CRP ratio has a marked effect on the floating lag time of the formulations R4–R6. The lag time of these formulations, containing HPMC in high percentage, were 14.5–37.9s only. This time was statistically shorter than that obtained with other formulations containing low percentage of HPMC (R1, R7, & R8).

In vitro release studies

Release profiles of all formulations of three-level full factorial design are shown in Figure 1B. It is clear that CVD %

released after 24 hours ranged from 67.64 in run R4 to 94.42% in run R1. Indeed, as the HPMC percentage was increased, the amount of CVD released was decreased. This postulation was confirmed after study the release behavior of the formulations that have the same percentage of CRP (5%) namely R4, R9 and R1.

The release was increased from 67.64 to 85.22 until reaching 94.42% as the HPMC percentage decreased from 30 to 20 to 10%, respectively. In general, tablets formulated employing CRP exhibited rapid release when compared to those formulated with HPMC.

Tablets formulated with HPMC gave slow and complete drug release in 24 hours and were found to be the best floating formulations based on *in vitro* buoyancy and drug release characteristics and these tablets were found suitable for 24 hours administration i.e., once-a-day administration (Chowdary and Hussainy, 2012).

It was noticed that, most formulations displayed an initial burst effect which may be due to the time needed to form the gel layer that control the drug release or could be due to the rapid drug dissolution from the surface of the tablets. Interestingly, this effect was less predominant with those formulations containing higher percentage of HPMC; R4-R6; owing to the formation of strong surface barriers that reduce the initial burst drug release (Kulkarni and Bhatia 2009).

Kinetic treatment of the release data

Kinetic treatment of the results revealed that all formulations release profile was fitting to Higuchi diffusion model except formulations R1, and R8 which fitted to first order kinetics. Based on the developed floating formulations containing swellable polymers, as HPMC and CRP, the release behavior showed (n) values lies between 0.5 and 1 that follow anomalous; non-Fickian release which controlled by a combination of diffusion and polymer relaxation. This finding is in a good agreement with the previous works with similar complexity of the formulations indicating the coupling of diffusion and erosion for controlling the drug release (Chavanpatil *et al.*, 2006; Hosny and El-Say 2013).

Table 3: Statistical analysis of variance (ANOVA) of the responses (Y_1 - Y_4) results.

Factors	Buoyancy lag time (Y_1), s		Total floating time (Y_2), h		Release after 2h (Y_3), %		Release after 12h (Y_4), %	
	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value
X_1	-137.93	0.0047*	10.8	0.0006*	-23.47	0.0383*	-22.467	0.0355*
X_2	-12.267	0.5468	1.533	0.1113	5.273	0.4842	-1.44	0.8301
X_1X_1	59.067	0.1563	-6.067	0.0145*	10.697	0.4200	-3.42	0.7694
X_1X_2	-22.8	0.3797	2.9	0.0408*	-3.93	0.6613	2.975	0.7194
X_2X_2	44.067	0.2548	-3.467	0.0615	9.227	0.4802	7.32	0.5416
R^2	95.589		99.009		83.271		82.469	
Adj. R^2	88.239		97.358		55.390		53.251	
SEE	22.184		0.8395		8.1141		7.537	
MAE	11.301		0.3951		4.0721		3.770	

Note: *Significant effect of factors on individual responses.

Abbreviations: X_1 , HPMC percentage; X_2 , Carbopol percentage; X_1X_2 , the interaction term between the factors; X_1X_1 , and X_2X_2 are the quadratic terms between the factors; R^2 , R-squared; Adj- R^2 , Adjusted R-squared; SEE, standard error of estimate; and MAE, Mean absolute error.

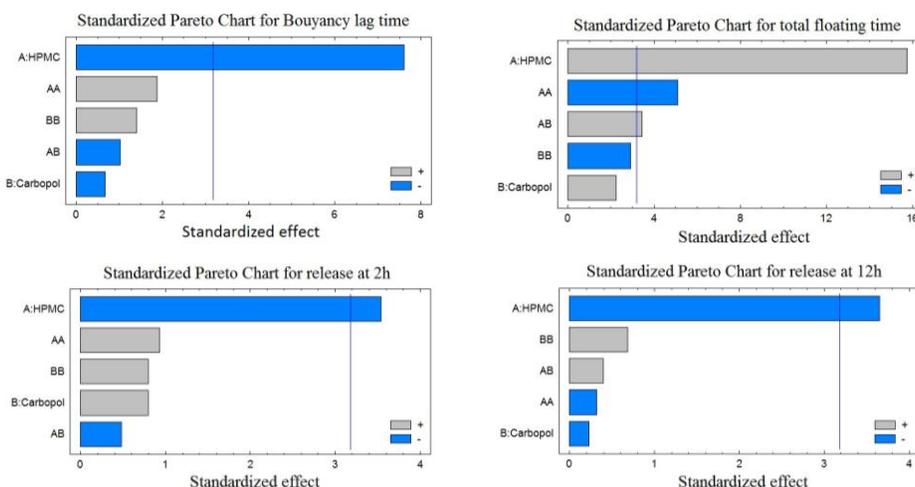


Fig. 2: Standardized Pareto Charts showing the significant factors on the responses (Y_1 - Y_4)

Statistical data analysis and model validation

Fitting of data to the model

Based on the three-level full factorial design, the experimental runs, their factor levels as well as the observed values of the responses (Y_1 - Y_4) for 9 formulations of CVD-GRFTs are summarized in Table 1. In order to determine the levels of factors which yielded optimal BLT, TFT and the percentage of drug release after 2 and 12 hours, mathematical relationships were generated between the factors and responses. The results obtained from the experiment were statistically analyzed for response variables (Y_1 - Y_4) by the Statgraphics software. The values of estimate, probability (P-value), R^2 , adjusted R^2 , standard error of estimate, and the mean absolute error values for each response were shown in Table 3 along with their ANOVA results. The regression coefficients for each term in the regression model are presented in Equations 2-5.

$$\text{Buoyancy lag time } (Y_1) = 363.978 - 16.43 X_1 - 14.293 X_2 + 0.295 X_1^2 - 0.228 X_1 X_2 + 0.881 X_2^2 \quad (2)$$

$$\text{Total floating time } (Y_2) = -3.978 + 1.463 X_1 + 0.96 X_2 - 0.03 X_1^2 + 0.029 X_1 X_2 - 0.069 X_2^2 \quad (3)$$

$$\text{Initial release after 2 hours } (Y_3) = 82.878 - 2.919 X_1 - 2.377 X_2 + 0.053 X_1^2 - 0.039 X_1 X_2 + 0.185 X_2^2 \quad (4)$$

$$\text{Cumulative release after 12 hours } (Y_4) = 109.817 - 0.737 X_1 - 3.667 X_2 - 0.017 X_1^2 + 0.029 X_1 X_2 + 0.146 X_2^2 \quad (5)$$

Three-dimensional contoured response surface plots

Statgraphics software generated the three-dimensional contoured response surface plots which displayed the effects of the investigated variables on the response variables (buoyancy lag time (Y_1), total floating time (Y_2), initial release after 2 hours (Y_3), and cumulative release after 12 hours (Y_4)). Buoyancy lag time (Y_1) was decreased with increasing level of X_1 , and in contrary the total floating time (Y_2) was increased at higher levels of X_1 as evidenced in the Pareto chart (Figure 2) and contoured response surface plots (Figure 3). Also, both the initial (Y_3) and cumulative (Y_4) drug release were significantly affected by X_1 as depicted in Figures 3 and 4. Upon decreasing levels of X_1 from 30 to 10%, the initial and the cumulative drug release were increased from 25.66 to 52.92 and from 57.10 to 89.25%, respectively.

The response surface optimization was performed to get the optimum levels of the formulation variables; HPMC percentage (X_1) and CRP percentage (X_2) to develop CVD-GRFTs with short buoyancy lag time, long total floating time, and sustained release pattern. Upon "trading off" a variety of response variables, the following criteria were accepted: buoyancy lag time < 1 minute, total floating time more than 24 hours, initial drug release $\geq 30\%$ and cumulative release after 12 hours $\geq 75\%$. Accordingly, formulation R2 was ranked as best formulation that achieved the maximum desirability.

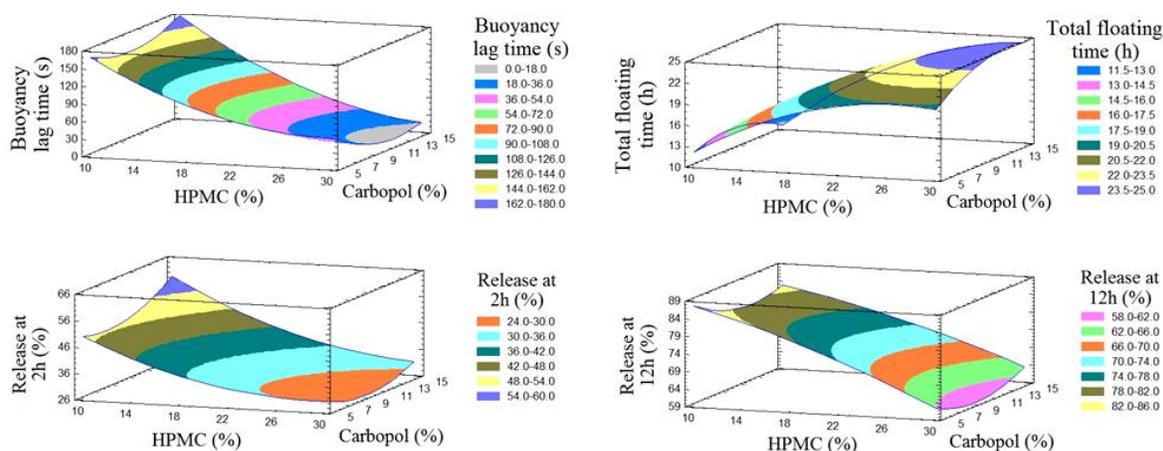


Fig. 3: Response surface plots (3D) showing the effect of X_1 and X_2 on all responses (Y_1 - Y_4)

Table 4: Optimum combination of factors, predicted, observed values, the residuals and the prediction error percentage for the optimized formulations of CVD-GRFTs.

Factors	Optimum			
HPMC percentage, (X_1)	21.11			
Carbopol percentage, (X_2)	9.6			
Responses	Predicted	Observed	Residual	Prediction error (%)
Buoyancy lag time, (Y_1)	54.73	53.92	0.81	1.48
Total floating time, (Y_2)	21.85	22.25	-0.4	1.83
Initial release after 2h, (Y_3)	37.52	36.43	1.09	2.91
Cumulative release after 12h, (Y_4)	73.17	75.10	-1.93	2.64

Residual = predicted value – observed value

Prediction error (%) = (observed value – predicted value)/predicted value \times 100%

Validation of optimized CVD-GFT formulation

Considering the aim of the study of attaining a compromise between excellent floating behavior and sustained drug release pattern, a new optimized formulation was suggested. This optimized formulation was proposed to contain 21.11% HPMC and 9.6% CRP beside the other excipients. The optimized CVD-GRFT was prepared and estimated for the responses as depicted in Table 4. The observed values of the responses were compared with that of the predicted values that confirmed no considerable residuals and the predicted error percentage of the responses were below 6% (Mujtaba *et al.*, 2014). This finding endorsed the reliability of the 3-level full factorial design for optimizing CVD-GRFTs.

CONCLUSION

Based on the present findings it can be concluded that, the combination of HPMC and CRP in a floating matrix is promising for gastroretention of the incorporated drug for more than 24 hours. The use of 3-level full factorial design proved to be an effective tool to develop CVD-GRFTs with short buoyancy lag time, long floating duration and desired sustained release behavior. The swelling ability of the matrix tablets was considered as an important contribution in gastroretention and drug release behavior. The release of CVD from the optimized formulation followed Higuchi kinetics with anomalous mechanism that controlled by diffusion through the swollen matrix and erosion. The developed CVD-GRFTs combines excellent buoyant ability

and suitable drug release pattern; thereby increases gastric residence time and enhances the absorption leading to increased bioavailability of carvedilol.

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