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ORIGINAL ARTICLE

Formulation Optimization for Gastroretentive Drug Delivery System of Carvedilol Cocrystals Using Design of Experiment

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Abstract

Objectives The objective of this study was to develop a gastroretentive dosage form (GRDF) of carvedilol cocrystals that were prepared utilizing hot-melt extrusion (HME) in order to prolong its gastric residence time. GRDF was optimized using Box-Behnken Design.

Methods The carvedilol nicotinamide cocrystals prepared in the ratio of 1:2 (drug:coformer) utilizing hot-melt extrusion (Omega10). The tablets were prepared by direct compression using cocrystals along with remaining excipients that include HPMC K4M, HPMC E50, Carbopol 934P, sodium bicarbonate, microcrystalline cellulose, talc, and magnesium stearate. Concentrations of HPMC E50, HPMC K4M, and Carbopol 934P were selected as independent factors while the gastroretentive parameters such as floating lag time (FLT), percentage of drug release in 2 h, and percentage of cumulative drug release in 12 h were selected as dependent variables in optimizing GRDF of carvedilol cocrystals. Test such as total floating time (TFT), floating lag time (FLT), swelling studies, dissolution studies, and precompression parameters such as bulk density (BD), tapped density (TD), compressibility index (CI), Hausner's ratio (HR), and angle of repose were carried out on the optimized formulation.

Results The optimized tablets (F2) prepared by direct compression showed FLT of 11 s after placing the tablets in 0.1 N HCl (pH 1.2) with controlled drug release for 12 h where the mechanism of drug release was found to be Non-Fickian type of diffusion (swelling, erosion, and diffusion). The in vitro drug release profile of the optimized formulation (F2) was found to be 81.4% at 12 h in comparison with a formulation containing only carvedilol (65.55% drug release at 12 h).

Conclusion The study concluded that the cocrystals of carvedilol that were successfully prepared by HME could be used to prepare and optimize the floating tablets to achieve desired gastroretentive performance with good drug release profile for carvedilol. The results of the comparison of drug release profile between optimized formulation and formulation containing pure drug stressed the importance of preparing cocrystals. The formulation scientist in the future may adopt these strategies in developing GRDF for cocrystals of any drug.

Keywords Co-crystals · Carvedilol · Hot melt extrusion · Gastro retentive drug delivery · Design of experiment

Introduction

Carvedilol is a third-generation non-cardioselective β-blocker used in the treatment of hypertension and demonstrated potential in the treatment of cardiovascular diseases such as myocardial infarction and arrhythmias [1–3]. Carvedilol belongs to BCS class II thus it behaves as a low soluble and a high permeable drug so once it is available in the form of a solution, it rapidly gets absorbed. Due to hepatic first-pass metabolism, the oral bioavailability of carvedilol is low, i.e., around 25% [4, 5]. Cocrystals are convenient in improving the bioavailability, solubility, stability, and dissolution rate of a drug. Different methods to prepare cocrystals include solvent evaporation, solvent crystallization, solid state grinding, solvent drop grinding, hot-melt extrusion (HME), and sonocrystallization. However, HME technology can be used to produce cocrystals feasible on manufacturing scale by controlled heat and shear deformation [1–3, 6]. Carvedilol exhibits pH-dependent solubility profile with high solubility in

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acidic pH (545.1–2591.4 μg/mL within the pH range 1.2–5.0) and low solubility in alkaline pH (5.8–51.9 μg/mL within the pH range 6.5–7.8) [7]; hence, the development of carvedilol cocrystals into GRDF will make it an excellent candidate for enhancing absorption, improving the solubility, and controlling the release [8].

Since carvedilol exhibits higher solubility in acidic pH with narrow absorption window, therefore to improve its oral bioavailability, it is necessary to prolong the residence time of the dosage form at the site of absorption [9]. Several approaches have been undertaken to increase the gastric residence time such as expandable systems, bioadhesive systems, high-density system, and floating systems that include effervescent (volatile liquid containing system and gas generating system) and non-effervescent systems (hydrodynamically balanced system, raft forming system, microballons, super porous systems, alginate beads, magnetic systems) [10–13] as shown in Fig 1.

Only those drugs that have low solubility in alkaline pH, act locally at the stomach, have narrow absorption window, or are unstable at alkaline pH are favored to be formulated into GRDF [9]. Ichikawa et al. developed a floating pill containing effervescent layer and swellable layer coated on the sustained release pill. The effervescent layers, i.e., sodium bicarbonate and tartaric acid, were separated by the swellable polymer to avoid contact between the two agents. As the system was immersed in a buffer, CO_2 was generated that got entrapped in the swollen polymer forming swollen pills with a density of less than 1 g/mL. They drug released in a sustained manner and the pill remained buoyant for a duration greater than 12 h [14] while Ozdemir et al. formulated floating bilayer tablets of furosemide. One layer contained solid dispersion of low aqueous soluble furosemide that was prepared by kneading method along with polymers such as HPMC and CMC. The second layer contained $NaHCO_3$ and citric acid. The in vitro release studies showed that the tablets remained buoyant for more than 6 h with a sustained release activity. Radiographic studies proved that the tablet remained buoyant for more than 6 h and increased the bioavailability of the drug 1.8 times than that of conventional tablet [15].

As per Table 1, several excipients can be used in a GRDDS. In experiment excipients such as HPMC K4M, HPMC E50, HPMC K15M (hydrocolloidal nature helps in achieving gel-like matrix), Carbopol 934P, Carbopol 971P (swellable polymers used for entrapment of gas molecules helping the system stay buoyant for longer duration), sodium bicarbonate, citric acid (gas generating agents), microcrystalline cellulose (release rate enhancers), magnesium stearate, and talc (improve flow property of blend) were used to develop floating tablets with desired gastroretentive properties such as FLT, TFT, and drug release. In the actual study, the combination of HPMC E50 and K4M along with Carbopol 934P was used to achieve the desired gastroretentive properties of the floating tablet.

The aim of this current study was to develop and systematically optimize gastroretentive floating tablets of carvedilol cocrystals using response surface methodology (Box-Behnken Design) so that the tablet remains buoyant in the gastric fluids of the stomach and upper part of gastro intestinal tract (GIT) with lower FLT and controlled drug release. The optimized formulation was evaluated for floating, release behavior, and swelling properties. Hence, utilizing the concepts of design of experiment (DOE), an attempt was made to develop floating tablets of carvedilol cocrystals to improve its solubility.

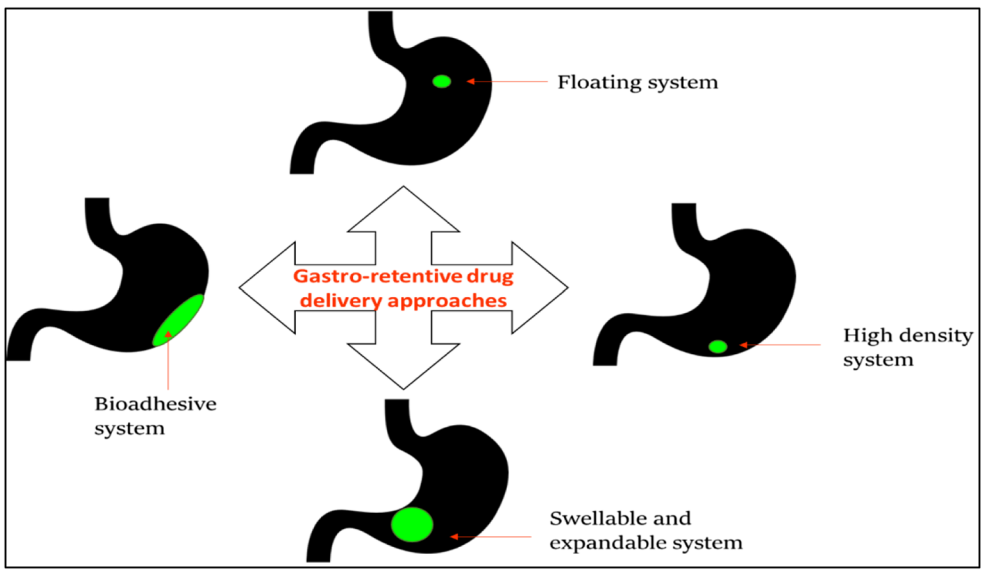

Fig. 1 Different approaches to gastroretentive drug delivery

Table 1 Structural components of effervescent GRDDS

Sr. no.	Structural components	Examples
1	Polymers(hydrocolloids)	Hydroxy propyl methyl cellulose (HPMC) (K4M, K15M, K100M, E50), sodium CMC, HPC, acaia, pectin, casein, chitosan, agar, gellan gum.
2	Inert fatty constituents	Beeswax, fatty acids long-chain fatty alcohols
3	Effervescent materials	Citric acid, tartaric acid, sodium bicarbonate
4	Release rate enhancer	Lactose, mannitol
5	Buoyancy enhancers	Carbopol (934P, 971P), ethyl cellulose

Materials and Methods

Materials

Carvedilol USP was gifted by Mylan laboratories Ltd., Hyderabad, India. Nicotinamide was purchased from Suvidhinath Laboratories, Gujarat. HPMC K4M and HPMC E50 were procured from Rolex Chemical Industries, Bangalore. Carbopol 934P was obtained from HIMEDIA Lab Pvt. Ltd., Mumbai. Microcrystalline cellulose was obtained from SD Fine Chem Ltd., Mumbai. Sodium bicarbonate was obtained from KEM light Laboratories Pvt. Ltd., Mumbai. Hydrochloric acid was purchased from Qualigens, Mumbai. All other reagents used in the research work were of analytical grade.

Preparation of Carvedilol Cocrystals by Hot-Melt Extruder

Carvedilol (10 g) and nicotinamide (20 g) were taken in a 1:2 ratio and blended for 15 min using a mortar and pestle. Cocrystallization was carried out using a co-rotating Twin Screw Hot Melt Extruder (Omicron 10P, STEER, India) having a diameter ratio (Do/Di) of 1.71. The powdered blend was fed into the extruder at a rate of 20 rpm using a gravimetric screw feeder. The four heating zones in the barrel were set at 32 °C (B1), 85 °C (B2), 92 °C (B3), and 90 °C (B4) at a screw speed of 175 rpm. The screw configurations and barrel heating zones are shown in Fig. 2. The product obtained was dried in the oven at 40 °C for 10 min to remove any residual moisture (if present). The results for successful preparation and characterization of cocrystals can be found in article *Mechanochemical synthesis of carvedilol cocrystals utilizing hot melt extrusion technology.*

Preparation of CRV GRDF

Carvedilol nicotinamide cocrystals in the ratio 1:2 were initially prepared utilizing HME by varying parameters such as barrel temperature and screw speed. The cocrystals and all excipients (except magnesium stearate and talc) were weighed accurately and mixed geometrically in a mortar and pestle for 10 min and later passed through 40# sieve to achieve a homogenous blend. After adding magnesium stearate and talc, the powder mixture was again mixed in a mortar and pestle for 10 min and compressed using an automatic tablet punching machine (Rimek Rotary Tablet Press, Karnavati Eng. Pvt. Ltd.). The final weight of the tablet was adjusted to 200 mg and hardness was set to 6–8 kg/cm^3.

Preliminary Trials

Preliminary trials were conducted in order to screen several excipients and find their best combination to obtain desired gastroretentive properties such as FLT, TFT, and controlled drug release. Based upon the trials conducted as shown in Table 2 and results in a particular ratio of HPMC E50, HPMC K4M and Carbopol 934P were selected for further optimization using DOE.

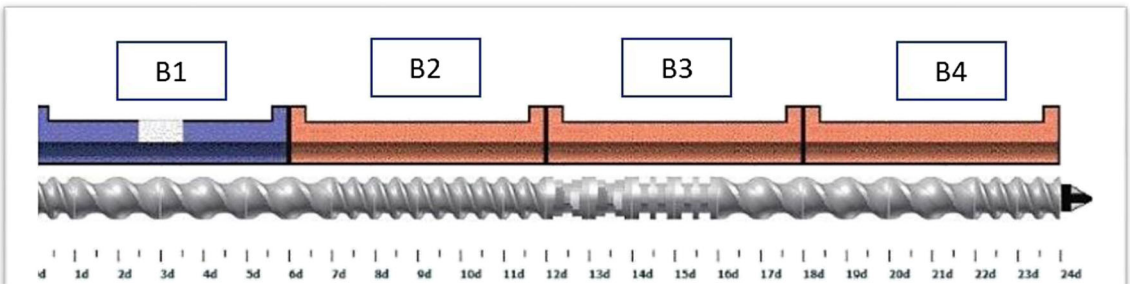

Fig. 2 Screw configuration of Omicron 10P (Do/Di 1.71)

Table 2 Preliminary trial batches

Ingredients (mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11
Cocrystals	200	200	200	242.42	242.42	200	200	151.51	151.51	76	76
HPMC K4M	50	40	–	12	10	–	15	13.3	20	13.3	20
HPMC K15M	50	–	–	48	–	15	–	–	–	–	–
HPMC E50	–	40	–	–	40	45	45	26.6	20	26.6	20
Carbopol 934P	–	40	100	30	20	–	–	10	10	10	10
Carbopol 971P	–	–	–	–	–	30	30	–	–	–	–
Sodium bicarbonate	50	50	50	45	45	45	45	35	35	35	35
Citric acid	20	20	20	15	15	15	15	–	–	–	–
Microcrystalline cellulose	30	10	30	7.58	27.58	50	50	13.49	13.49	39	39
Total weight of tablet (mg)	400	400	400	400	400	400	400	250	250	200	200

Experimental Design, Statistical Analysis, and Data Optimization

Box-Behnken Design was utilized to study the effect of three variables namely the concentration of HMPC E50 (A), HPMC K4M (B), and Carbopol 934P (C) in 17 runs. The optimization was carried out to develop carvedilol floating tablets that remain buoyant for a longer period with lower FLT and controlled release. Design Expert v. 9 was used to optimize and generate the statistical experimental design. The response variables were TFT, percentage drug release at 2 h, and cumulative percentage drug release at 12 h. The TFT was not considered as a response variable since all tablets remained buoyant above 12 h. The final formulation of the tablet is shown in Table 3.

Data obtained of all the formulation were analyzed using Design Expert v. 9. Polynomial, Quadratic, and linear models were generated for all the responses. A numerical optimization technique was used to generate formulations with desired responses; the goals are combined into an overall desirability function. A list of solutions which meet the criteria was reported. Analysis of variance (ANOVA) was used to identify a significant effect of factors on response regression coefficients. The factor estimates and p value were also

Table 3 Tablet formulation generated from software

Batch	Cocrystals (mg)	HPMC E50 (mg)	HPMC K4M (mg)	Carbopol 934P (mg)	Sodium bicarbonate (mg)	MCC (mg)	Talc (0.5%)	Mg. stearate (0.5%)
B1	76	20	10	10	35	49	1	1
B2	76	30	10	10	35	39	1	1
B3	76	20	20	10	35	39	1	1
B4	76	30	20	10	35	29	1	1
B5	76	20	15	8	35	46	1	1
B6	76	30	15	8	35	36	1	1
B7	76	20	15	12	35	42	1	1
B8	76	30	15	12	35	32	1	1
B9	76	25	10	8	35	46	1	1
B10	76	25	20	8	35	36	1	1
B11	76	25	10	12	35	42	1	1
B12	76	25	20	12	35	32	1	1
B13	76	25	15	10	35	39	1	1
B14	76	25	15	10	35	39	1	1
B15	76	25	15	10	35	39	1	1
B16	76	25	15	10	35	39	1	1
B17	76	25	15	10	35	39	1	1

Table 4 Precompression parameters along with their formulas

Precompression parameters	Formula
Bulk density	$\frac{\text{Mass of powder blend}}{\text{Volume of powder blend before tapping}}$
Tapped density	$\frac{\text{Mass of powder blend}}{\text{Volume of powder blend after tapping}}$
Hausner's ratio	$\frac{\text{Tapped density}}{\text{Bulk density}}$
Percent compressibility index	$\frac{(\text{Tapped density})-(\text{Bulk density})\times 100}{\text{Tapped density}}$
Angle of repose	$\theta = tan^{-1}h/r$ where, h is height in cm, r is radius in cm

calculated. The relationship between the factors and its responses was portrayed on contoured plots and 3D response surface plots that give information on studying effects of several factors on a single response. A design space was generated with a list of predicted results, so to validate the experimental design, three trials were carried out where the observed results were compared with the predicted results.

Evaluation of Optimized Floating Tablet

Precompression Studies of Powder Blend for Optimized Product [16]

The optimized formulation was characterized for their micromeritic properties that include tapped density, bulk density, Carr's index, Hausner's ratio, and angle of repose. Tapping method was used to determine the tapped density and percent compressibility index of powder blend. Angle of repose measures the resistance to particle flow that was determined using the fixed funnel method. All the parameters were calculated using the formula given in Table 4.

Table 6 Results of experimental batches

Batch	Response		
	FLT (sec)	% CDR after 2 h	% CDR after 24 h
B1	15	37.38	79.65
B2	13	45.7	84.67
B3	12	31.34	81.93
B4	9	37.37	74.66
B5	11.16	32.55	76.38
B6	11.2	48.42	78.33
B7	10.8	34.79	77.04
B8	10.2	22.83	63.57
B9	13	57.5	83.33
B10	12.1	47.15	82.17
B11	10.5	40.7	77.9
B12	10.23	27.08	74.35
B13	12.6	57.05	86.61
B14	12.5	55.4	87.27
B15	12	55.26	85.91
B16	12.2	54.15	87
B17	12.3	53.75	87.6

Post Compression Studies [17]

The floating tablets of carvedilol cocrystals were evaluated for thickness, friability, hardness, and uniformity of weight according to the USP standard procedure.

Table 5 Formulation composition and its effect on gastroretentive properties

Evaluation parameters				
Batch	Floating lag time (min)	Total floating time (h)	Percentage drug release at the end of 12 h	Results
B1	–	–	–	Tablet did not float
B2	1.57	8	30.31	Shape was intact
B3	0.57	–	–	Tablet broke
B4	0.22	24	57.62	Tablet was initially disintegrating
B5	0.21	24	–	Shape of tablet was not intact
B6	3	24	49.85	The FLT was too high
B7	3	24	35.7	The FLT was too high
B8	0.3	14	77.04	Tablet was intact
B9	0.32	16	76.38	Tablet was intact
B10	0.2	16	82.7	Tablet was intact
B11	0.2	16	78.33	Tablet was intact

Table 7 Results of p values, regression coefficient, and F values for various responses

Responses	p values			R^2	F	Model p value
	A (HPMC E50)	B (HPMC K4M)	C (Carbopol 934P)			
FLT	0.08838	0.01795	0.08006	0.524	4.77	0.01861
% CDR after 2 h	0.0541	0.00185	0.00012	0.973	28.31	0.00010
% CDR after 12 h	0.0102	0.0162	0.00022	0.978	35.35	5.14E−0.5

Table 8 Polynomial equation for various responses

Response	Polynomial equation
FLT	21.87235 − 0.139*A − 0.20425*B − 0.35813*C
% CDR after 2 h	− 650.141 + 33.392*A + 5.6602*B + 53.142*C − 0.0229*AB − 0.69575*AC − 0.08175*BC − 0.51269*A^2 − 0.17429*B^2 − 1.91431*C^2
% CDR after 12 h	86.878 − 1.72125*A − 1.555*B − 3.41875*C − 3.0725*AB − 3.855*AC − 0.5975*BC − 6.129*A^2 − 0.5215*B^2 − 6.919*C^2

In vitro buoyancy determination [18] Floating behavior of tablet was determined by placing the tablet in a beaker containing 200 mL of 0.1 N HCl (pH 1.2 at 37.5°C). The FLT and TFT were determined by visual observation.

Water uptake studies or swelling studies [18] The swelling behavior of the tablet was determined by initially weighing the tablet (Wo) and then placing it in a beaker containing 200 mL of 0.1 N HCl. At regular intervals of 1, 2, 3, 4, 6, 8, and 12 h, the tablet was withdrawn, and excess of water was wiped using tissue paper and weighed. The percentage of swelling was determined by the formula given below

$$\%\mathrm{WU} = \frac{(\mathrm{Wt}-\mathrm{Wo}) \times 100}{\mathrm{Wo}}$$

where Wt is the weight of tablet swollen at time t and Wo is the initial weight of the tablet.

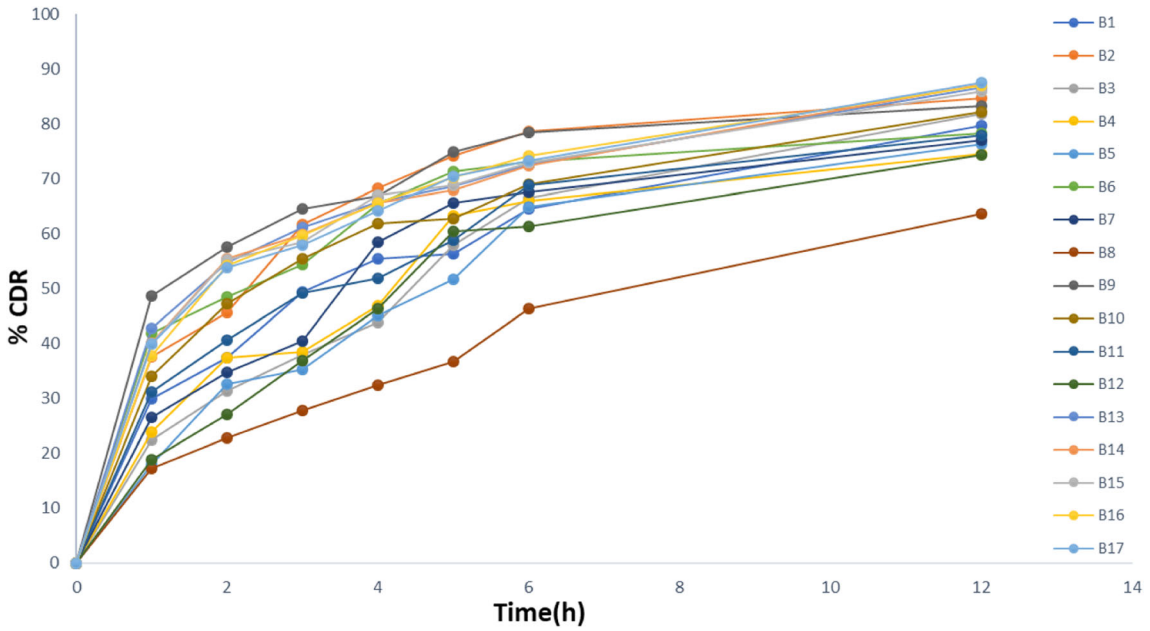

Fig. 3 In vitro drug release of carvedilol floating tablets in 0.1 N HCl

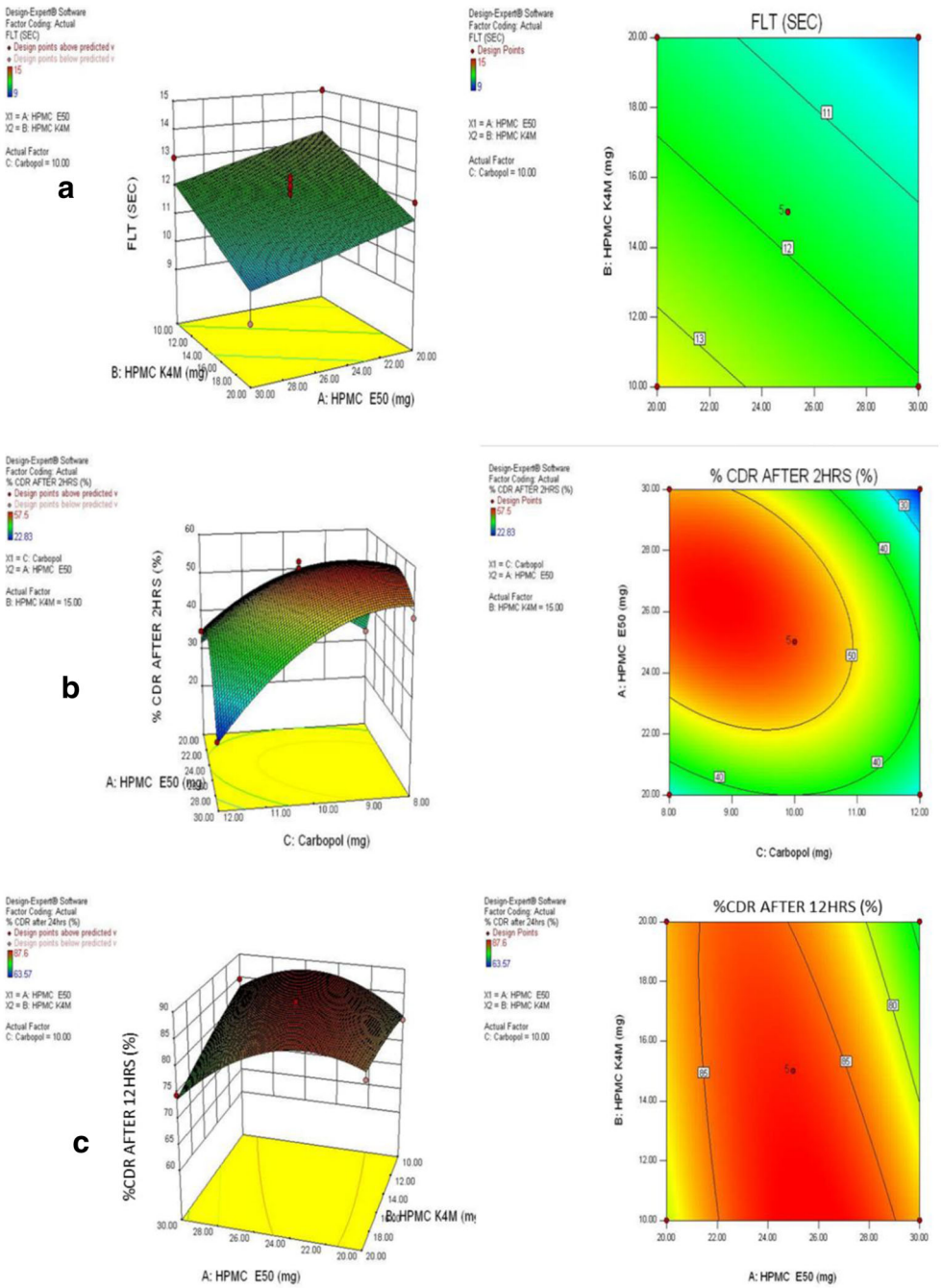

Fig. 4 Response surface plots showing effect of concentration of HPMC E50, HPMC K4M, and Carbopol on FLT (**a**), %CDR after 2 h (**b**), and %CDR after 12 h (**c**)

In vitro dissolution studies [19] The in vitro dissolution studies were carried out using USP apparatus II (Paddle) at 50 rpm in 900 mL of 0.1 N HCl maintained at 37.5°°C ± 0.5°°C for 12 h. Five milliliters of samples was withdrawn at intervals of 1, 2,

Table 9 Solutions generated by software that meet the criteria required for formulation (predicted)

Batch	HPMC E50 (mg)	HPMC K4M (mg)	Carbopol 934P (mg)	FLT (s)	%CDR after 2 h	%CDR after 12 h
F1	21.26	19.75	8.5	11.82	36.2	82
F2	20	20	10	11.42	31.44	83.46
F3	20.083	18.03	9.7	11.89	36.34	83.25

3, 4, 5, 6, and 12 h and replenished with the same amount of dissolution medium. Test samples were then filtered using Whatman filter paper and diluted if necessary. These samples were analyzed using a UV-Visible Spectrophotometer at 284 nm. Similar procedures were used in the comparison of drug release studies between optimized formulation (F2) and formulation containing pure carvedilol.

Drug Release Kinetic Studies [20]

The drug release kinetics of optimized formulation were studied by plotting the in vitro dissolution data in various kinetic models like zero-order, first-order, Higuchi's, and Korsemeyer peppas model. The first-order and zero-order model predict whether the drug release is dependent on the concentration of the drug or not. The Higuchi's model and Korsemeyer peppas model describe the drug release mechanism. The kinetic modelling of drug release was performed on optimized cocrystals and formulation.

Results and Discussion

Preliminary Trials

Preliminary trials were performed on 11 batches to study the effect of polymer concentrations alone and in combination on the gastroretentive properties. The results for each batch is shown in Table 5

Experimental Design, Statistical Analysis, and Data Optimization

The results of the experimental batches generated from software (B1 to B17) in order to optimize the combination of HPMC E50, HPMC K4m, and Carbopol 934P to obtain desired properties of GRDF are shown in Table 6. The response surface plots are shown in Fig. 4.

Effect of Formulation Variables on FLT

The FLT varied from 9 to 15 s among all the formulations from B1 to B17. The magnitude of coefficients of A, B, and C shows negative and significant effects on TFT as p values are lesser than 0.05 and greater than F values as shown in Table 7 that indicate that the model terms are significant. The polynomial equation for all responses is shown in Table 8. The negative effect indicates that low concentrations of polymer causes an increase in FLT.

Table 11 Percentage residual error

Percentage residual error	FLT (sec)	%CDR after 2 h	%CDR after 12 h
F1	2.7	0.16	0.73
F2	3.67	11.31	4.27
F3	5.04	13.66	1.07

Effect of Formulation Variables on %CDR after 2 and 12 h

The in vitro drug release is shown in Fig. 3. According to the polynomial equation shown in Table 8, the concentration of A, B, and C positively affects the initial drug release from the tablet after 2 h while after 12 h, the factors A, B, and C and their interaction have a negative and significant effect on drug release. The F values are greater than p values that are lesser than 0.05 hence, indicating the model terms to be significant. The relationship of each variable on the response is shown in response surface plots, i.e., Fig. 4.

Validation of Box-Behnken Design

From numerical optimization, the set criteria were maximum %CDR after 2 and 12 h and minimum FLT. The software generated a list of solutions with the highest desirability values that met the criteria and were compared with the actual results as shown in Tables 9 and 10. The percentage residual error is shown in Table 11 and meets the criteria of below 15% thus showing insignificant differences between the predicted results and actual results. The batch F2 was selected as the optimized batch as it depicts B3 of the experimental batch.

Precompression Studies

The precompression studies were performed on the powder blend, and it was found that the optimized drug excipient blend had excellent to good flow properties. The incorporation of microcrystalline cellulose improved the flow property and

Table 10 Results of optimized batch (actual)

Batch	HPMC E50 (mg)	HPMC K4M (mg)	Carbopol 934P (mg)	FLT (s)	%CDR after 2 h	%CDR after 12 h
F1	21.26	19.75	8.5	11.5	34.26	81.40
F2	20	20	10	11	30.45	79.89
F3	20.083	18.03	9.7	11.29	42.09	84.66

Table 12 Precompression studies on optimized drug excipient blend F2

Precompression parameters	Results of optimized batch	Results
Bulk density	0.46	–
Tapped density	0.52	–
Hausner's ratio	11.53	Good
Percent compressibility index	1.13	Good
Angle of repose	23.74	Excellent

compressibility of powder blend. The results are shown in Table 12.

Postcompression Studies

The results for the postcompression studies are shown in Table 13. The weight of the tablet ranged from 0.197 to 0.204 mg and complied with limits of British Pharmacopoeia. The thickness of tablet ranged from 5.42 to 5.50 mm while the drug content ranged from 97.5 to 104.35% hence depicting uniformity among batches. The hardness of tablet ranged from 6.48 to 7.3 kg/cm^2; however, an increase in hardness would have increased the FLT due to poor penetration of dissolution medium in the tablet. The friability was less than 1% thus indicating good mechanical strength of tablet.

In Vitro Buoyancy Determination

The optimized batch F2 showed floating lag time of 11 s, and the tablet remained buyout and retained its shape for a duration of 14 h.

Swelling Studies

The swelling studies were performed for three optimized batches, i.e., F1, F2, and F3, and its swelling percentage is shown in Table 14. From the graph of swelling studies as shown in Fig. 5, it was observed that tablets with a higher percentage of HPMC showed higher swelling index as compared to tablets containing carbopol because carbopol network structure restricts the movement of water molecules.

Table 14 Swelling percentage of F1, F2, and F3

Time (h)	Swelling percentage (%)		
	F1	F2	F3
0	0	0	0
1	30.65	28.25	22.5
2	39.19	37.2	30.15
3	42.71	39.86	38.65
4	46.23	41.75	40.22
6	50.25	49.35	44.75
8	50.75	50.02	48.3
12	52.26	52.15	51.35

In Vitro Dissolution Studies of Optimized Batch F2

The in vitro dissolution studies were carried out in 0.1 N HCl where the dissolution data of optimized formulation F2 was compared with dissolution of formulation containing pure drug as shown in Fig. 6. The optimized formulation showed 81.4% drug release at 12 h while pure drug showed drug release of 60.55% at 12 h. The optimized formulation showed a higher percentage of drug release at the end of 12 h as compared to drug; however, further optimization in formulation may be required.

Kinetic Modeling of Drug Release

The regression coefficient (R^2) values for release data of optimized formulations of F1, F2, and F3 obtained by curve fitting method for zero-order, first-order, Higuchi model, and Korsemeyer peppas model are shown in Table 15. The Higuchi model is dominant as compared to the other models which indicated that drug release depends on the square root of time. The mechanism of drug release was projected using Korsemeyer peppas model where "n" value was found to be between 0.45 and 0.85 indicating that drug release occurred by Non-Fickian or anomalous type of diffusion (swelling, erosion, and diffusion).

Table 13 Post compression studies of optimized formulation F2

Postcompression studies	Values of optimized product	Result
Weight variation	200.02 mg	All the tablets were within limits
Thickness	5.45mm^2	–
Hardness	6.48–7.3 kg/cm^2	–
Drug content	102.5	Within limits
Friability	0.082	In limit

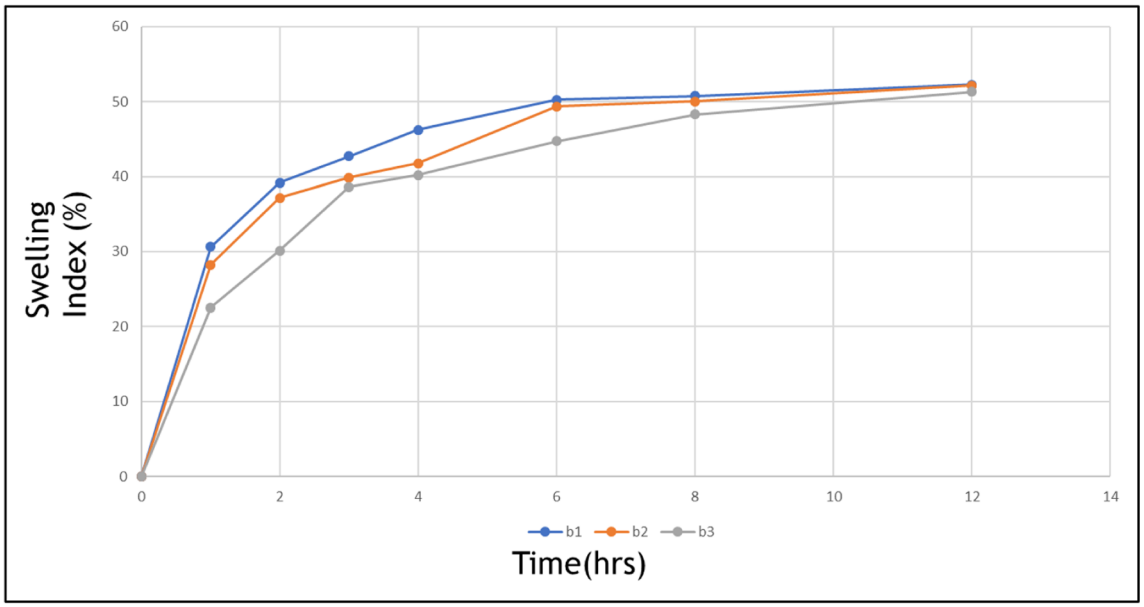

Fig. 5 Swelling percentage index of batch F1, F2, and F3

Discussions

Preliminary Trials

The formulation B1 tablet did not float which may be due to the absence of a swelling agent which made it necessary to include a rapid swelling agent, e.g., carbopol. In formulation B4, carbopol 934p was incorporated which caused the tablet to float in 0.21 s hence indicating that faster swelling may allow the gastric fluid to penetrate the tablet much quickly and hence causing a faster reaction between sodium bicarbonate and citric acid thus generating the gas quickly required for buoyancy. However, the combination of HPMC K4M and HPMC K15M caused a reduction in drug release which may be due to the higher viscosity of these polymers inhibiting the drug to release by forming viscous layers around the tablet. Efforts were also made to formulate the tablet without the use of HPMC as in B3, but the tablet broke which makes it necessary to incorporate HPMC as they act as release retarding agents along with swelling properties. In formulation B2, the HPMC K15M was replaced by a polymer of lower viscous grade, i.e., HPMC E50; this allowed an initial good release but at the end of 12 h, the release was just 57.62% which required further modification in the ratio of the polymers. Similarly, the combination of HPMC E50 with HPMC K15M was performed which did not maintain the shape of the tablet. In

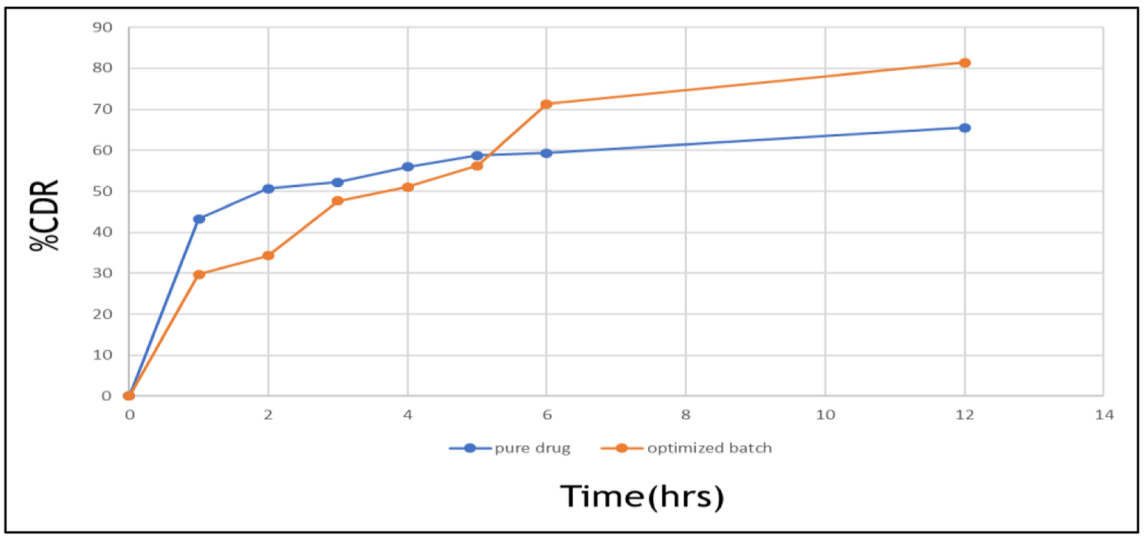

Fig. 6 In vitro dissolution of optimized batch F2 and formulation containing pure drug

Table 15 Regression coefficient (R^2) values of drug release data obtained from various kinetic models

Batch	Zero-order R^2	First-order R^2	Higuchi model R^2	Korsemeyer peppas model	
				R^2	n
F1	0.87	0.90	0.913	0.953	0.45
F2	0.80	0.90	0.913	0.947	0.55
F3	0.82	0.90	0.91	0.95	0.48

formulations B6 and B7, carbopol 934P was replaced with carbopol 971P which resulted in tablets having higher FLT. Hence, the polymers HPMC K4M, HPMC E50, Carbopol 934P, sodium bicarbonate, and microcrystalline cellulose were selected in further batches by only changing the ratios of HPMC and Carbopol 934P to meet the requirements for GRDF. By reducing the weight of tablet from 400 to 200 mg, it was observed that the drug release at the end of 12 h was high without affecting the shape of the tablet as seen in formulation B8 to B11 shown in Tables 1 and 4. It was also observed that eliminating the use of citric acid in the formulation had no impact on the gastroretentive properties of the tablet which may be due to the acid requirement being met by H^+ ions of the gastric fluids thus causing gas generation by the reaction of H^+ ions with sodium bicarbonate.

Experimental Design

Effect of Formulation Variables on FLT

From the polynomial equation, as shown in Table 7 and response surface plot (A) shown in Fig. 3, it shows that an increase in the concentration of polymer decreases the FLT which is ideal. Formulation B1 has maximum FLT of 15 s where conc. of polymers (HPMC E50, HPMC K4M, and carbopol 934P) is lower while formulation B4 has least FLT of 9 s where conc. of polymers is higher. This may be due to rapid swelling of polymers in contact with gastric fluid causing a faster generation of CO_2 that entraps between the swollen polymers forming a swollen tablet with a density less than 1 g/mL.

Effect of Formulation Variables on %CDR after 2 h

Results as shown in Fig. 3 clearly indicated that initially, drug release was majorly affected by concentration of HPMC E50; however, the concentration of HPMC K4M and carbopol 934P also affected the initial drug release. As the concentration of HPMC E50 was increased, the drug release at initial phase was higher which may be due to a less viscous polymer or may be due to the time required to form the gel layer that controls the drug release was higher or even due to the rapid dissolution of the drug from the surface of the tablet.

Effect of Formulation Variables on %CDR after 12 h

Although HPMC K4M may form slow and less complex matrix at an initial time point, during the later phase, the interaction of all three polymers significantly retarded the drug release with a matrix formed for a longer duration. Hence, according to the results depicted in Fig. 3, it is evident that decreasing the concentration of polymers leads to a higher percentage of drug release at the end of 12 h.

Conclusion

The gastroretentive floating tablets of carvedilol cocrystals were successfully developed to achieve gastroretention with desired properties. According to studies conducted in preliminary trials, HPMC or carbopol alone could not provide the desired properties; hence, it was necessary to use them in combination which was studied by applying the concepts of design of experiment (Box-Behnken Design). The optimized formulation met all the criteria's necessary for gastroretention, i.e., TFT of 12 h, FLT of 11 s, and continuous drug release (by swelling, erosion, and diffusion), i.e., %CDR at 2 h and 12 h at 34.26% and 81.4% respectively. However, conducting pharmacokinetic studies would provide a better insight into the improvement in bioavailability of the drug. Hence, it could be concluded that carvedilol cocrystals could be developed into a floating tablet on the appropriate selection of excipients with suitable combinations at particular ratios in order to achieve the gastroretentive properties, and utilizing the design of experiment approach could be useful to optimize a floating tablet with least FLT and maximum TFT and drug release.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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