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Original Article

BOX-BEHNKEN DESIGN FOR OPTIMIZATION OF FORMULATION VARIABLES FOR CONTROLLED RELEASE GASTRORETENTIVE TABLET OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT

Objective: To develop a Verapamil hydrochloride controlled release gastro-retentive (CRGR) tablet for once-daily dosing using the response surface Box-Behnken Design (BBD) approach for the improvement of bioavailability and reduction in dosing frequency to overcome the issues related to the conventional tablet formulation.

Methods: For the optimization, 3^3Box-Behnken design was used. The independent variables were selected, the amount of Compritol 888 ATO (A), HPMC K15M (B), and Sodium bicarbonate (C). The dependent variables were Cumulative % drug release in 1.5 h (Q1.5), 8 h (Q8), 24 H (Q24) and floating lag time (FLT). Flow properties of pre-compressed powder, physical characteristics, drug content, floating lag time, total floating time and *in vitro* dissolution study of all formulation were assessed. *In vitro* dissolution study of optimized formulation that was prepared experimentally was performed and compared with predicted data obtained from the software. Drug release kinetics of the optimized formulation was also assessed to know the mechanism of drug release from the CRGR tablets.

Results: Responses of experimental runs were found as Q1.5: 12.78-33.62 (%), Q8: 43.03-64 (%), Q24: 78.77 to 103.57 (%) and floating lag time as 3.01 min to 5.08 min. The predicted optimized formula with the highest desirability value of 0.963 containing amount 126.030 mg, 160.00 mg and 80.955 mg of Compritol 888 ATO, HPMC K15M and Sodium biarbonate respectively was prepared and evaluated. The experimental values from optimized formulation were obtained as Q1.5: 23.397%, Q8; 57.744%, Q24: 97.150% and FLT: 3.12 min. Predicted and experimental results were found comparable for all the responses. The release data from the optimized formulation were best fitted in the Higuchi (r^2 = 0.999) and the Korsmeyer-Peppas ((r^2 = 0.998, n=0.54) model. The *in vitro* drug release studies indicated that the Verapamil hydrochloride gastroretentive tablet releases the drug in controlled manner for 24 h.

Conclusion: This study found that using Box-Behnken Design with the response and variable relation, it is possible to achieve an optimum formulation with desirable characteristics. This study also established the suitability of Compritol 888 ATO-HPMC K15M combination with Sodium bicarbonate to increase the gastric residence time tablet formulation had once-daily dosing of the Verapamil Hcl with improved bioavailability for effective management of hypertension.

Keywords: Box Behnken Design, Verapamil Hcl, Controlled release gastroretentive tablet

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INTRODUCTION

Verapamil Hydrochloride is an L-type voltage-gated calcium channel blocker antihypertensive of BCS-I drug having low absolute bioavailability (20%) due to short biological half-life (4.0±1.5 h), pH-dependent solubility (pKa 8.6), lower solubility in intestines with higher pH (0.44 mg/ml at pH=7.32), and first-pass metabolism by the intestinal wall too [1, 2]. The bioavailability of verapamil hydrochloride can be increased by gastric retention [3, 4]. The use of an oral controlled release gastro retentive drug delivery system (GRDDS) for the treatment of hypertension is an effective approach [5, 6]. Among the various gastroretentive drug delivery methods, the floating drug delivery system (FDDS) is a known effective method for delivering drugs specifically to the stomach [4, 7, 8].

Design of experiments (DoE) has been an exceptionally valuable method for building design spaces [9, 10]. The response surface methods Central Composite Design (CCD) and Box-Behnken designs (BBD) are strong, effective, and systematic response surface methodology (RSM) that speed up the process of developing pharmaceutical dosage forms and enhance research productivity [11]. Box-Behnken designs (BBD) use fewer experimental runs, which makes the application more practical and effectively estimates first-order and second-order coefficients than CCD [12].

The goal of this study was to develop once-daily dosing of controlled release gastro-retentive (CRGR) floating formulation of Verapamil hydrochloride with desirable characteristics using BBD with the response and variable relation. This study might be used in the numerous experiments with different variables and outcomes.

MATERIALS AND METHODS

Verapamil HCl (VH) was made available as a gift sample by Matrix Laboratories Ltd. Hyderabad, India. Compritol 888 ATO was provided as gift samples by Gattefose Ltd., HPMC K15Mwas supplied by Colorcon Asia Pvt. Ltd. India, sodium bicarbonate, citric acid, xantham gum, microcrystalline cellulose, talc, and magnesium stearate were procured from the department were of analytical grade. All other substances including solvents were of analytical grade.

Selection of excipients

In the selection of excipients, preliminary batches were prepared using Compritol 888 ATO (lipid-based excipient) and various HPMC (HPMC K4M, HPMC K15M, and HPMC K100M), effervescent generating agents (in different concentration) with half the concentration of citric acid as pH modifier along with other excipients like magnesium stearate, talc and xantham gum.

Drug excipient compatibility study

To check for any potential interactions, the Differential Scanning Calorimeter (DSC) of Mettler-Toledo (RJC) was used to conduct DSC analyses of both pure drugs and drug-polymer mixtures. Triturating drugs, polymers, and their mixtures reduced their size such that they could be heated at a rate of 10 °C/min from 30 °C to 180 °C in sealed aluminum pans and 40 ml/min nitrogen flow was present [13].

Methods

Preparation of verapamil HCl CRGR tablet formulations

Verapamil HCl CRGR Tablets were prepared using the direct compression method [14]. The following ingredients were processed

through sieve number #30. VH was blended with the excipients (diluents, polymers, binders, effervescent generating agent) except the lubricant and glidant for 10 min afterward the lubricant and glidant were added to the blend and mixed for 10 min. Then, the mixture was compressed using flat-faced punches equipped with Rimek Mini Press-II MT Rotary Tabletting 12 station Machine (Karnavati Engineering Ltd.) to the desired weight of 760 mg/tablet.

Experimental design; optimization by (Box-behnken design)

CRGR tablet of VH was optimized utilizing the response surface 3 factors 3 levels Box-Behnken Design using Design Expert® Software (Version 11) [15]. The three selected independent variables (factor) were the amount of compritol 888 ATO (A) and amount of HPMC k15M (B) and the amount of sodium bicarbonate (C) mg per tablet. Each factor was checked at three levels (-1, 0,+1). The dependent variables were taken as cumulative drug release (%) in 1.5 h (Q1.5 h), 8 h (Q8 h), 24 h (Q24 h) and floating lag time (FLT) [16]. The batches were formulated in different compositions as per the design.

The constraints were defined as Q1.5 (15-25%), Q8 (50-60%), and Q24 (95-100%) and minimal floating lag time (FLT) as required for the controlled drug delivery system are shown in table 1.

Table 1: Variables and constraints in box-behnken experimental design

Independent variable	Level			Constraints
	-1	0	+1	
A: Compritol 888 ATO (mg/tab)	120	140	160	In the range
B: HPMC K15M (mg/tab)	160	180	200	In the range
C: $NaHCO_3$ (mg/tab)	70	80	90	In the range
Dependent Variable				
$Q_{1.5}$: % Cumulative drug release in 1.5 h (%)				15-25
Q_8: % Cumulative drug release in 8 h (%)				50-60
Q_{24}: % Cumulative drug release in 24 h (%)				95-100
FLT: Floating lag time (min)				Minimum

Flow properties of pre-compressed powder

The flow properties of pre-compressed powder of verapamil Hcl floating tablets were evaluated using Carr's index and Hausner's ratio.

Evaluation of CRGR tablets

The produced tablets were tested for weight variation (n=20), hardness (n=6), *in vitro* buoyancy studies (floating lag time (n=6) and total floating time (n=6)) and *in vitro* drug dissolution testing (n=6). *In vitro* dissolution study data of optimized formulation was fitted into mathematical models to know the drug release kinetics. Drug content (n=6) samples of tablets were prepared and diluted with 0.1 N HCl and examined using a UV spectrophotometer (Shimadzu 1800, India) at 278 nm [17].

***In vitro* buoyancy studies**

The tablets were put into a 100 ml beaker that already had 100 ml of 0.1 N HCl in it. The floating lag time was determined to be the length of time it took for the tablet to surface and float. The total floating time or buoyancy time of the tablets which was established for the formulations (F1-F15) was the period during which they continued to float [3].

***In vitro* dissolution study**

USP Dissolution Apparatus II(Electrolab, USP Type-2 India) was used to examine the release of Verapamil Hcl from CRGR [18]. The dissolution medium was kept at 900 ml, 0.1N HCl at 37±0.5 °C with a 50 rpm rotating speed [19]. 5 ml aliquots were collected and given an equivalent volume of fresh medium at intervals. The samples were analyzed using a UV-VIS double-beam spectrophotometer (Shimadzu 1800, India) at 278 nm.

Statistical analysis

Data obtained from an experiment were statistically analyzed using Design Expert Software (version11. Ink). By contrasting various polynomial models' coefficients of variation, predicted and adjusted multiple correlation coefficients, and lack-of-fit statistics, the best-fitting polynomial models were determined [20]. A significant difference was found using analysis of variance. Design Expert Software (version 11. Ink) was used to create 2D contour and 3D response surface plots to better understand how the concentration of the polymer affected the response variables.

Drug Release kinetic modeling of the optimized formulation

The dissolution profile data of the experimentally developed optimized formulation were fitted into Zero order, First order, Higuchi and Korsmeyer Peppas models to identify the kinetic modeling or release mechanism [21] of drug form CRGR, the ideal model is the one with the greatest correlation coefficient.

RESULTS AND DISCUSSION

Drug excipient compatibility study

DSC was used to examine the physiochemical compatibilities and the interactions between the drug and the excipient that was being employed. The melting point of VH in its pure form was 144.53 °C, whereas the drug-polymer mixture showed just a very minor variation from 144.37 °C to 145.189 °C, indicating that there is no apparent alteration in the drug's melting point (USP monograph). The DSC of the pure drug and drug-polymer combination is shown in fig. 1 indicating that the drug is compatible with both the polymers.

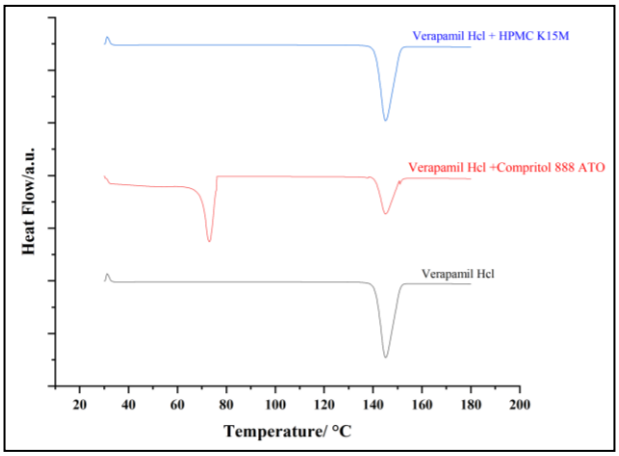

Fig. 1: DSC graph of VH, VH-Compritol 888 ATO and VH-HPMC K15M

Flow properties of pre-compressed powder

Pre-compression characteristics of powder like flow properties were determined by calculating Carr's index and Hausner's ratio. Carr's index ranges from 11.18% to 16.87% and Hausners's ratio ranges from 1.12 to 1.21 as reported in table 2 showing good flow characteristics of all batches.

Evaluation of VH-CRGR tablets

All post-compressed VH-CRGR tablet parameters, such as weight variation, hardness and drug content were found within the acceptable range as shown in table 2.

For formulations F1 to F15, *in vitro* total floating time (TFT) was determined on 6 tablets of each batch and found more than 24 h as shown in table 2 and floating lag time ranges from 3.01 min to 5.08 min as shown in table 3.

Table 2: Physical characteristics of verapamil hydrochloride pre-compressed powder and CRGR tablets

Formulation	Hausner's ratio (mean±SD) (n=6)	Carr's index (CI) (%) (mean±SD) (n=6)	Weight variation (%)	Hardness (kg/cm2) (mean±SD) (n=6)	% Drug content (mean±SD) (n=6)	Total floating time (H)
F1	1.15±0.02	11.18±0.02	760±4.54	7±0.49	99.58±1.28	>24
F2	1.15±0.04	13.08±3.52	764±2.36	7±0.71	97.38±2.18	>24
F3	1.21±0.08	17.12±5.60	764±1.41	7±0.85	96.06±1.28	>24
F4	1.12±0.01	16.87±1.14	768±2.14	6±1.06	99.58±1.28	>24
F5	1.14±0.02	12.87±1.71	765±2.83	5±0.55	100.12±1.28	>24
F6	1.15±0.02	13.05±1.99	768±4.24	7±0.21	102.43±1.28	>24
F7	1.16±0.04	14.35±4.26	762±3.48	6±0.45	99.58±1.28	>24
F8	1.13±0.01	11.79±1.01	760±1.61	7±0.26	101.58±1.28	>24
F9	1.16±0.01	14.36±1.08	769±2.67	5±0.87	96.38±1.28	>24
F10	1.15±0.03	13.23±2.97	762±4.32	7±0.35	99.58±1.28	>24
F11	1.18±0.01	15.62±1.06	765±3.51	5±0.87	99.58±1.28	>24
F12	1.19±0.06	16.08±4.11	764±4.76	5±0.91	98.35±1.28	>24
F13	1.20±0.05	16.73±3.46	763±4.86	6±0.66	99.58±1.28	>24
F14	1.20±0.02	16.66±1.85	764±3.67	6±0.78	102.46±1.28	>24
F15	1.18±0.02	15.43±2.13	769±1.21	6±0.29	100.18±1.28	>24

In vitro dissolution studies

Table 2 and fig. 2 depict an analysis of the *in vitro* drug release of VH from CRGR tablet formulations (F1-F15). They demonstrate that the release rate from the CRGR tablets which included Compritol at a greater concentration of 160 mg and HPMC at a lower concentration of 160 mg was extremely slow, releasing 78.77% after 24 h. Additionally, they demonstrate that, even when the compritol 888ATO concentration was held constant, an increase in HPMC content has a major impact on the matrix tablet release behavior since the release rate increases with HPMC concentration.

In general, hydrophilic polymers that depend on absorbing water to cause gel swelling and matrix relaxation, which subsequently facilitates drug dissolution and diffusion from the matrix, may be the cause of the faster VH release with the increased HPMC concentration [22] or HPMCK15M dissolves more quickly and produces holes or either of channels in the matrix, which positively impacted drug release [16, 23]. The presence of the lipid-based excipient compritol 888 ATO in the same matrix may lead the system to form an endless matrix network, delaying the release of the drug and preventing the entrance of the dissolving media. Media that dissolves takes longer to enter the tablet. As a result, there is less drug dissolution and diffusion from the tablet matrix, resulting in a controlled or sustained release pattern for a longer duration. Even with a significant quantity of drug present in the tablet matrix, this formulation technique produced satisfactory results for water-soluble drugs like nifedipine Hcl [16], pseudoephedrine [22], chlorpheniramine maleate [24], etc.

Data and Statistical analysis of Box-Behnken experimental design

Three factors three levels (3^3) Box-Behnken statistical experimental design of RSM generated 15 experiments. Table 3 lists the dependent and independent variables (responses) for each of the 15 experimental runs. According to the findings FLT results ranged from 3.01 min to 5.08 min and cumulative drug release (%) results ranged from Q1.5: 12.78 to 33.62, Q8: 43.03 to 64, and Q24: 78.77 to 103.57. Using Design Expert all the responses were fitted and observed for linear, 2FI, and quadratic models.

Table 3: Experimental design for verapamil Hcl controlled release gastro retentive tablet with Independent variables and response values (dependent variables)

Run	Independent variables			Responses (Dependent variables)			
	A: Compritol 888 (mg/tab)	B: HPMC K15M (mg/tab)	C: Sodium bicarbonate (mg/tab)	Q1.5 H (%) (mean±SD) (n=6)	Q8H (%) (mean±SD) (n=6)	Q24H (%) (mean±SD) (n=6)	FLT (min) (mean±SD) (n=6)
1	140	160	70	19.66±1.78	55.6±1.93	91.16±1.95	4.59±0.05
2	140	180	80	21.44±1.14	54.13±0.25	92.57±1.19	3.48±0.08
3	160	180	70	12.78±1.62	45.02±0.25	81.79±1.21	4.56±0.01
4	140	200	90	23.10±1.57	55.56±1.55	89.92±0.57	3.06±0.04
5	140	180	80	21.84±1.12	52.56±0.57	94.3±1.35	3.29±0.05
6	120	200	80	33.08±1.01	64±1.16	99.78±1.72	3.42±0.12
7	140	160	90	19.93±1.22	55.85±1.65	93.07±1.10	3.10±0.21
8	120	160	80	27.77±1.72	62.95±1.33	97.74±1.25	3.34±0.34
9	160	200	80	15.69±1.08	46.34±1.89	82.27±1.92	3.57±0.26
10	160	180	90	15.89±1.22	49.74±1.92	79.49±1.17	3.11±0.35
11	140	180	80	20.32±1.10	55.32±1.27	95.02±1.05	3.18±0.36
12	160	160	80	13.96±1.10	43.03±1.27	78.77±1.05	3.36±.09
13	140	200	70	23.83±1.04	57.33±1.45	91.78±1.37	5.17±0.03
14	120	180	90	27.55±1.65	63.56±1.44	100.24±1.56	3.01±0.12
15	120	180	70	33.62±1.35	67.79±1.11	103.57±0.87	5.08±0.16

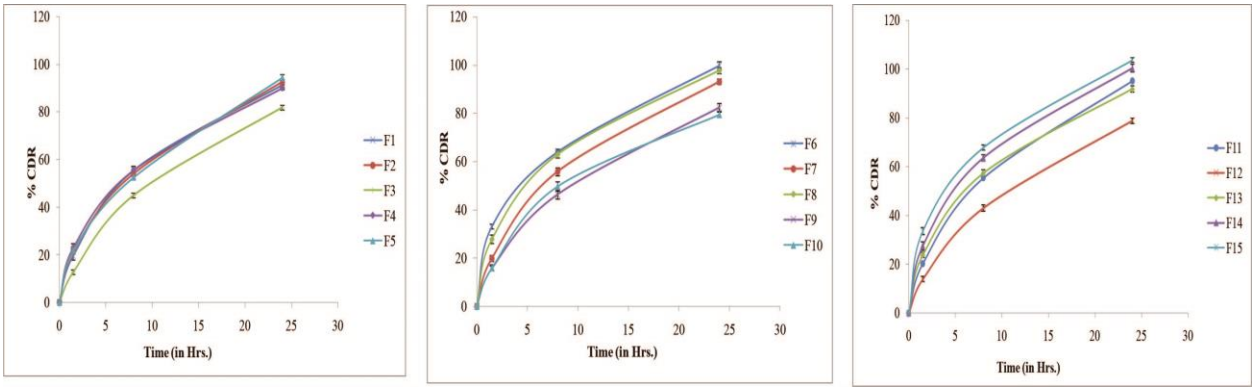

Fig. 2: Drug dissolution graph of (a) F1-F5 (b) F6-F10 (C) F11-F15

Table 4: Fit summary of the result of regression analysis for responses

Response	Model	Sequential p-value	Lack of fit p-value	R^2	Adjusted R^2	Predicted R^2	
Q1.5 H	Linear	<0.0001	0.1649	0.9441	0.9289	0.8862	
	2FI	0.0057	0.4378	0.9874	0.9780	0.9576	Suggested
	Quadratic	0.1005	0.7011	0.9960	0.9889	0.9667	
Q8 H	Linear	<0.0001	0.3163	0.9360	0.9186	0.8744	
	2FI	0.1451	0.3933	0.9662	0.9409	0.8681	
	Quadratic	0.0430	0.8304	0.9925	0.9791	0.9517	Suggested
Q24 H	Linear	<0.0001	0.2291	0.9329	0.9147	0.8828	Suggested
	2FI	0.8780	0.1717	0.9381	0.8917	0.7816	
	Quadratic	0.1568	0.2290	0.9763	0.9337	0.6732	
FLT	Linear	0.0003	0.1243	0.8022	0.7483	0.6334	
	2FI	0.7722	0.0962	0.8267	0.6968	0.3169	
	Quadratic	0.0026	0.6132	0.9878	0.9657	0.8830	Suggested

Based on the results obtained for Sequential p-value, Lack of fit p-value, R^2, Adjusted R^2, and Predicted R^2, the best fit model for dependent variables Q1.5, Q8, Q24, and FLT were 2FI (p-value<0.0001), quadratic (p-value<0.0001), linear (p-value<0.0001), and quadratic (p-value =0.0026) respectively. The model's ability to predict the response was supported by the Predicted R^2 (0.9576 for Q1.5, 0.9517 for Q8, 0.8828 for Q24 and 0.8830 for FLT) and the Adjusted R^2 (0.9780 for Q1.5, 0.9791 for Q8, 0.9147 for Q24 and 0.9657 for FLT) as shown in table 4.

To ascertain the model's significance further ANOVA (Analysis of variance) was used. The results of the ANOVA showed that the polynomial model could adequately represent the experimental data, with coefficient of determination (R^2) values for the % CDR at the Q1.5, Q8, Q24 and FLT found 0.9874, 0.9925, 0.9329, and 0.9878, respectively as shown in table 4. The models' reliability for various responses were further increased by the fact that lack of fit p-values was larger than 0.05 [15] as shown in table 4. Regression equations 1, 2, 3, and 4 were also produced using Design Expert for analyzing the effect of various independent variables on different dependent variables.

Regression coefficient values of independent variables (factor) for various responses are presented in terms of estimated coefficient and p-value in table 5 and if a factor has effects that significantly deviate from zero and P<0.05, it is assumed that it has an impact on the response. While a negative sign denotes an antagonistic influence of the factor on the chosen response and a positive sign denotes a synergistic effect.

Table 5: Regression coefficient values for VH-CRGR tablet prepared using BBD

Factors	%CDR (Q1.5H)		%CDR (Q8H)		%CDR(Q24H)		FLT(Min)	
	Estimated coefficient	p-Value	Estimated coefficient	p-Value	Estimated coefficient	p-Value	Estimated coefficient	p-Value
A	-7.96	<0.0001	-9.27	<0.0001	-9.88	<0.0001	-0.0312	0.5559
B	1.80	0.0007	0.7250	0.1086	0.3762	0.6477	0.1038	0.0904
C	-0.4275	0.2355	-0.1288	0.7432	-0.6975	0.4024	-0.8900	<0.0001
AB	-0.8950	0.0941	0.5650	0.3315	-	-	0.0325	0.6623
AC	2.29	0.0012	2.24	0.0080	-	-	0.1550	0.0779
BC	-0.2500	0.6102	-0.5050	0.3808	-	-	-0.1550	0.0779
A^2	-	-	0.2596	0.6552	-	-	0.0329	0.6706
B^2	-	-	-0.1829	0.7517	-	-	0.0729	0.3633
C^2	-	-	2.26	0.0090	-	-	0.5904	0.0005

*p-values less than 0.0500 indicate model terms are significant. In this case A, AC and C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

From table 5, it is observed that A has an antagonistic effect on Q1.5 hr, Q 8hr and Q24 hr with a p-value of<0.0001 for all the responses. Factor B has a positive effect on Q 1.5 hr with a p-value of 0.0007 and Q 24h (p=0.0904), but showed no significant effect on Q 8hr (p=0.1086). Factor A and B both are insignificant for response FLT but Factor C has a negative effect on FLT with a p-value<0.0001. The

interactive effect of AB and BC are insignificant but AC is a somewhat significant model term. It can also be observed that the quadratic term C^2 with p-value =0.0005 also has a significant effect on response FLT.

The regression equation (in coded terms) 1, 2, 3 and 4 were also generated as mentioned below;

%CDR (Q1.5) = 22.0307-7.9625A+1.7975B-0.4275C-0.895AB+2.295AC-0.25BC.... (1)

%CDR (Q8) = 54.0033-9.27125A+0.725B-0.12875C+0.565AB+2.2375 AC-0.505BC+0.259583A^2-0.182917B^2+2.26458C^2..... (2)

%CDR (Q24) = 91.4313-9.87625 A+0.37625B-0.6975C ..... (3)

FLT= 3.31667-0.03125A+0.10375B-0.89C+0.0325AB+0.155AC-0.155BC+0.0329167 A^2+0.0729167B^2+0.590417 C^2..... (4)

The positive terms in equations (1, 2, 3 and 4) denote a favorable effect on the responses (dependent variables), whereas the negative terms denote an inverse link between the independent and dependent variables. Compritol 888 ATO (A) concentration has a detrimental impact on Q1.5, Q8, Q24, and FLT. The quantity of HPMCK15M (B) has a favorable impact on Q1.5, Q8, and Q24 and a detrimental impact on FLT. A: Compritol 888 ATO (mg/tablet) is the most influencing factor that negatively affects the total drug release from the CRGR tablets, according to the impacts and Sodium bicarbonate has a negative impact on FLT and a negligible impact on Q1.5, Q8, and Q24 with (P value=>0.05) as shown in table 4, (fig. 4 d-f). The CDR (%) Q1.5, Q8 and Q24 major effect plots can be used to prove this (fig. 4 a-c).

2D and 3D response surface plots are shown in fig. 3 and fig. 4 respectively, which are both highly helpful for examining the interactions between the chosen independent factors and the dependent variables. Both 2D and 3D plots are helpful for examining the simultaneous effects of two independent variables on the dependent variable. The third independent variable was kept constant in all the depicted figures.

It is evident from the polynomial equations (1, 2, 3 and 4), 2D (two-dimensional) contour graphs (fig. 3), and 3D (three-dimensional) response surface graphs (fig. 4) that Compritol 888 ATO and HPMC K15M play a significant role in the drug release and sodium bicarbonate on floating lag time. So, this combination of lipophilic and hydrophilic polymers with effervescence-producing agents can be used in particular to control the release of verapamil hydrochloride in the stomach environment for the development of floating drug delivery tablets with a minimum FLT.

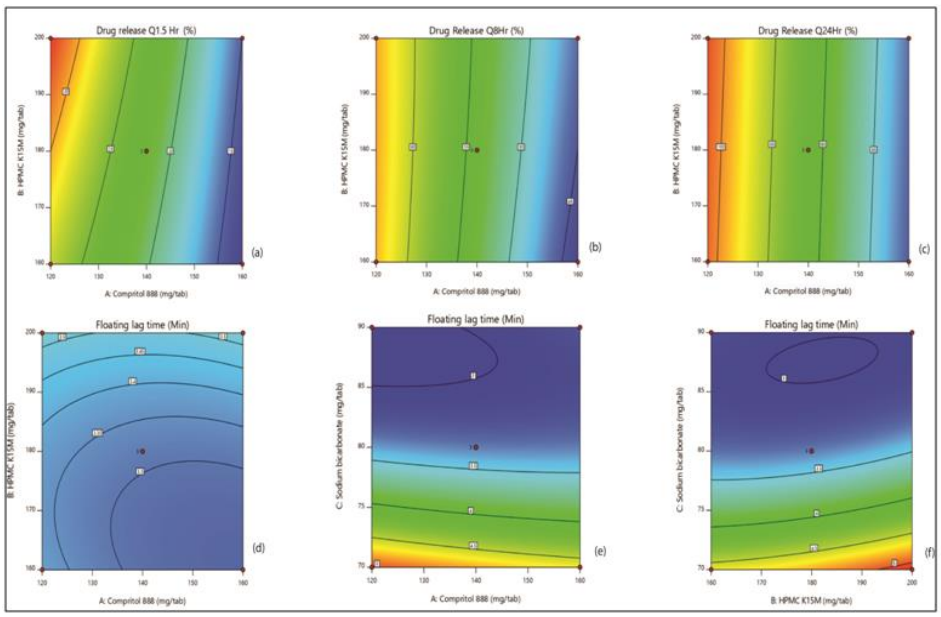

Fig. 3: 2D contour plots between the independent variables and dependent variables

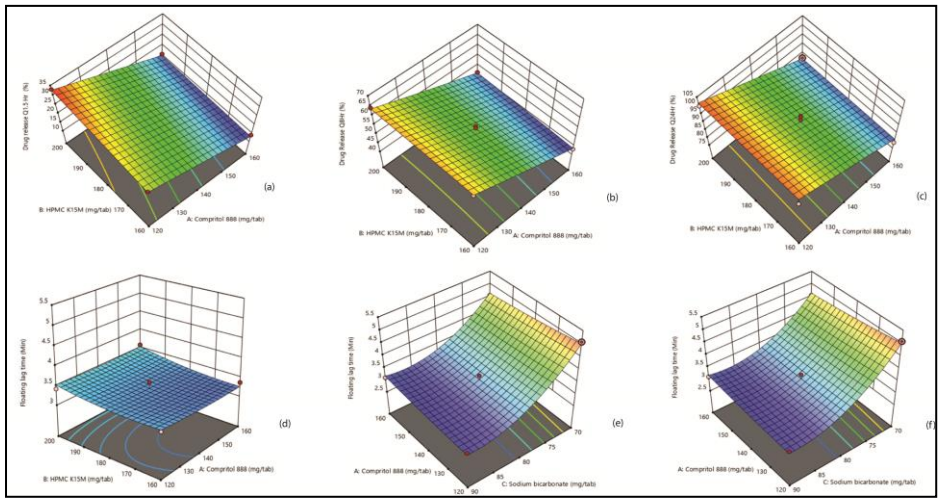

Fig. 4: 3Dresponse surface plots showing the effect of independent variables on dependent variables

Optimization of formulation

The optimum formula for the development of VH-CRGR was selected based on the criteria of achieving the least floating lag time (FLT) and applying constraints to Q1.5-15-25%, Q8-50-60%, and Q24 (95-100%). About 41 solutions were given by the software, and out of them, the solution with the maximum desirability (0.963) was selected for the CRGR tablets preparation. CRGR tablets were compressed according to the optimized level of polymers and sodium bicarbonate (table 6) and assessed for FLT, Q1.5, Q8, and Q24 to ensure the accuracy of the estimated optimal factors and expected responses. The predicted and experimental values showed a strong agreement with similar values for various responses as shown in table 6 and fig. 5. The derived mathematical equations and model are therefore believed to be reliable and validated for projecting the FLT, Q1.5, Q8, and Q24.

Table 6: Level, experimental and predicted value of responses at optimized condition

Variables	Coded level	Optimum level
A-Compritol 888	-0.698	126.030
B-HPMC K15M	-0.9	160.00
C-Sodium bicarbonate	0.095	80.955
Response	Predicted value	Experimental value (mean±SD) (n=6)
%CDR (Q1.5 H)	25	23.397±1.05
%CDR (Q8 H)	60	57.744±1.51
%CDR (Q24 H)	97.887	97.150±1.70
FLT (Min)	3.271	3.12±0.615

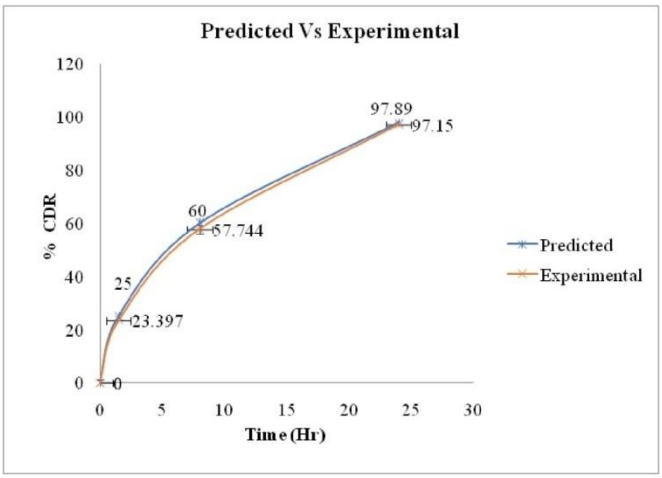

Fig. 5: Comparison of drug release profile of predicted and experimental response of optimized VH-CRGR tablet

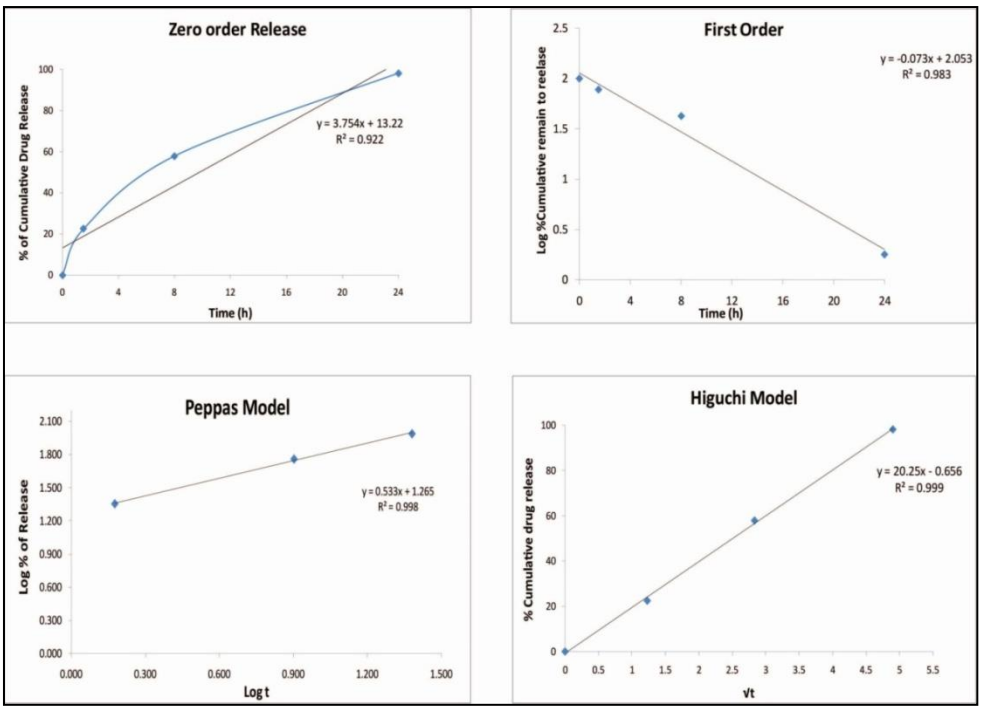

Fig. 6: Drug release kinetics of optimized VH-CRGR tablet formulation

Kinetics modeling of drug release for optimized formulation

Model dependent approaches

The drug dissolution profile data of optimized formulation were fitted to different drug release mathematical kinetic models of zero order, first order, Higuchi, and Korsmeyer-Peppas. Drug release data was the best fitted in Higuchi with r^2 = 0.999 and Krosmayer Peppas with r^2 = 0.998, the critical value of n= 0.54 as compared to Zero order r^2 = 0.918 and first order r^2 =0.989 as shown in fig. 6 suggesting diffusion and non-fickian anomalous transport i.e. drug release by diffusion from hydrated matrix simultaneously and by rearrangement of polymeric chains occurring slowly cause time-dependent anomalous effects.

CONCLUSION

It can be concluded from the present research that the Box-Behnken experimental design can effectively optimize controlled release gastro retentive formulation with minimum run as it offers the advantages of minimum cost and time. This research also investigated the impact of independent variable Compritol 888 ATO, HPMC K15M and sodium bicarbonate on dependent variable. Dependent variables compritol 888 ATO (mg/tab) and HPMC (mg/tab) has mainly influenced the release of drug from tablet on other hand floating lag time (min) has mainly impacted by Sodium bicarbonate (mg/tab). The predicted response values and experimental results were in good aggrement which confirms design validity and optimization. Compritol 888 ATO, HPMC K15M in combination with sodium bicarbonate is effective for development of gastro retentive floating formulation which releases the verapamil hydrochloride in controlled manner for 24 h. So, the bioavailability of the drug may also be improved because of the maximum absorption expected with increasing solubility in the acidic environment of the stomach.

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ABBREVIATION

CRGR; Controlled Release Gastro-Retentive, VH; Verapamil Hydrochloride, RSM; Response surface methodology, BBD; Box-Behnken Design, CCD; Central Composite Design, DSC; Differential Scanning Calorimeter, FLT: Floating lag time, TFT; Total floating time.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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