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Research Article

Quality by Design Driven Optimization of Gastroretentive Floating Tablets of Verapamil Hydrochloride: Formulation, Evaluation, and Statistical Modeling

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ABSTRACT

The present study focuses on the formulation and evaluation of a gastroretentive floating drug delivery system (FDDS) of Verapamil HCl to prolong gastric residence time and provide sustained drug release. Floating tablets were prepared using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC K100M) and xanthan gum along with sodium bicarbonate as a gas-generating agent. The formulations were prepared by direct compression and evaluated for pre-compression parameters, post-compression characteristics, buoyancy properties, and in-vitro drug release. Drug–excipient compatibility studies were performed using Fourier Transform Infrared Spectroscopy (FTIR). The prepared tablets demonstrated satisfactory physicochemical properties and prolonged floating behavior in gastric medium. Among all the formulations, formulation F8 containing HPMC K100M (20%) and xanthan gum (10%) exhibited optimum floating lag time, prolonged floating duration, and sustained drug release for up to 12 hours. The results suggest that the developed floating tablets can enhance gastric residence time and provide sustained therapeutic action of Verapamil HCl.

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INTRODUCTION

Oral drug delivery remains the most widely accepted route of drug administration due to its convenience, cost-effectiveness, and high patient compliance [1]. However, several drugs suffer from limited bioavailability because of rapid gastric emptying and short residence time in the upper gastrointestinal tract [2]. To overcome these limitations, gastroretentive drug delivery systems (GRDDS) have been developed to prolong the retention of dosage forms in the stomach and thereby enhance drug absorption [3].

Floating drug delivery systems represent one of the most promising approaches among GRDDS. These systems are designed to remain buoyant on gastric fluid for prolonged periods without affecting gastric emptying rate [4]. The buoyancy of these systems is achieved through the use of low-density polymers or gas-generating agents that reduce the density of the dosage form below that of gastric fluid [5].

Several researchers have demonstrated that floating dosage forms can improve the therapeutic efficacy of drugs with narrow absorption windows or drugs that are primarily absorbed in the stomach or upper intestine [6]. Floating tablets also provide sustained drug release and maintain consistent plasma drug concentration over extended periods [7].

Verapamil HCl is a calcium channel blocker widely used in the management of hypertension, angina pectoris, and cardiac arrhythmias. It has a relatively short biological half-life of approximately 2–7 hours and requires frequent dosing [8]. The oral bioavailability of Verapamil HCl ranges between 20–35% due to extensive first-pass metabolism [9]. Therefore, the development of a sustained release gastroretentive system for Verapamil HCl may improve therapeutic outcomes and patient compliance. Verapamil HCl structure is given in figure.1.

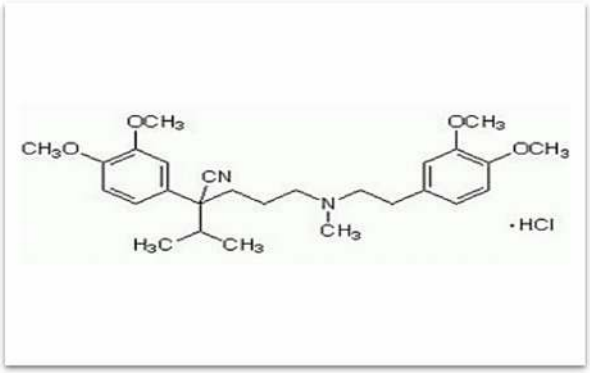

Figure 1: Chemical structure of verapamil HCl

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and xanthan gum are commonly used in floating drug delivery systems because they form gel matrices that control drug release and maintain tablet buoyancy. The combination of polymers and effervescent agents can enhance the floating ability and sustain drug release from the dosage form [10].

The QbD approach begins with defining the Quality Target Product Profile (QTPP), followed by identifying Critical Quality Attributes (CQAs) such as drug release profile, floating lag time, total buoyancy time, tablet hardness, and stability. Critical Material Attributes (CMAs), including the concentration of polymers like HPMC K100M and xanthan gum, and Critical Process Parameters (CPPs), such as compression force and mixing time, are systematically evaluated to understand their impact on product quality. Risk assessment and experimental design (DoE) tools are applied to optimize formulation variables and ensure consistent product performance [11].

The prepared floating tablets are evaluated for pre-compression parameters (angle of repose, bulk density, tapped density) and post-compression parameters (hardness, friability, weight variation, drug content). In addition, in vitro buoyancy studies and dissolution testing are performed to assess floating behavior and sustained drug release. Thus, the QbD-based formulation strategy ensures enhanced therapeutic efficacy, reproducibility, and regulatory compliance in the development of Verapamil HCl floating tablets.

MATERIAL AND METHODS

MATERIALS

Verapamil HCl was provided as a gift sample by Aurobindo pharma in Hyderabad, along with HPMC K100 M, Xanthan gum and Starch RX 1500. Sodium bicarbonate, Citric acid,

Magnesium stearate, Talc were collected from (RCPHS, BAM). Throughout the study, distilled water was utilised, and all other chemicals were of analytical grade.

METHODS

Linear plot of verapamil HCl

Preparation of Stock Solution: 50 mg of verapamil HCL was accurately weighed and dissolved in 50 ml of 0.01N HCl in a volumetric flask to obtain a stock solution of 1000 µg/ml. From this, 5 ml was diluted to 50 ml with 0.01N HCl to get 100 µg/ml. Further, 25 ml of the 100 µg/ml solution was diluted to 50 ml to obtain 50 µg/ml [12].

Preparation of Working Standard: Working standard solutions in the range of 5–40 µg/ml were prepared by appropriate dilution of the stock solution using 0.01N HCl. After calibration, the linear plot was obtained by plotting a graph between Absorbance vs Concentration using Shimadzu 1800 UV- Vis Spectrophotometer.

FT-IR studies: Drug-polymer interactions were studied by FT-IR spectroscopy using the instrument Shimadzu, Japan, IRAffinity-1. The spectra were recorded for pure drug verapamil and verapamil containing drug. Samples were prepared in KBr discs (2 mg sample in 200 mg KBr) with a hydrostatic press at a force of 5.2 N/m² for 3 min. The scanning range was 400- 4000 cm-1 and the resolution was 4 cm^{-1}. The FT-IR of Verapamil HCL in figure 3 and pure drug + excipients were presented in figure 4 [13].

DSC studies: The thermal behaviour of the drug polymer used in sustained release tablets was investigated using Differential scanning calorimeter (DSC 4000, PerkinElmer, America). Sample of about 5 mg were placed in 50 µm perforated aluminium pan and sealed them. All samples were run at a heating rate of 10 °C/min over a temperature range of 40-200 °C in atmosphere of nitrogen as purging gas at a flow rate of 25 ml/min. The DSC thermogram of Verapamil HCL in figure 5 and pure drug + excipients were presented in figure 6 [14].

Preparation of Verapamil Tablets

Verapamil matrix tablets (120 mg) floating tablets were prepared by the direct compression method. The required quantities of drug, polymers, sodium bicarbonate, citric acid, lactose, and magnesium stearate were weighed accurately and blended thoroughly. The powder mixture was then compressed into tablets using a tablet compression machine. All ingredients were accurately weighed, dried at 50 °C for 30 m, cooled, and passed through a #30 sieve. The powders were blended thoroughly to obtain a uniform mixture. Lubricant and glidant were then added and mixed properly before compression. The final blend was compressed using a 10-station semi-automatic tablet compression machine (Rimek Tablet Mini Press, Ahmedabad) with an 8 mm round flat-faced punch. The prepared tablets were stored in a moisture- and light-protected condition [15].

Table 1: **Formulation of Verapamil HCl Floating Tablets**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil	120	120	120	120	120	120	120	120	120
HPMC K100 M	80	100	120	-	-	-	60	80	100
Xanthan Gum	-	-	-	80	100	120	40	40	40
Starch RX 1500	150	90	30	150	90	30	150	90	30
Sodium bicarbonate	30	60	90	30	60	90	30	60	90
Citric acid	10	20	30	10	20	30	10	20	30
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight(mg)	400	400	400	400	400	400	400	400	400

Buoyancy studies

The buoyancy lag time (BLT) was determined as the elapsed time between the introduction of the formulation into the dissolution medium and its initial ascent to the surface. The total floating duration was subsequently assessed by continuous visual observation using a USP type II dissolution apparatus (paddle method) operated under acidic conditions (simulated gastric fluid, pH 1.2) maintained at 37 ± 0.5 °C [16].

***In-vitro* dissolution studies:**

In vitro drug release study was performed in USP dissolution apparatus type II (paddle type) containing 900 ml of 0.01 N HCl (pH 1.2) kept at 37 °C ± 0.5 °C with paddle speed of 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals of 0.5, 1, 2, 4, 6, 8, 9, 10, 11, 12 h and replaced with fresh medium each time. The samples were filtered and analysed spectrophotometrically [16].

RESULTS

UV-Spectroscopy of Tramadol HCl:

A linear calibration curve of verapamil HCl was obtained in Figure2 and the UV absorption spectrum confirmed the λmax at 272 nm**.**

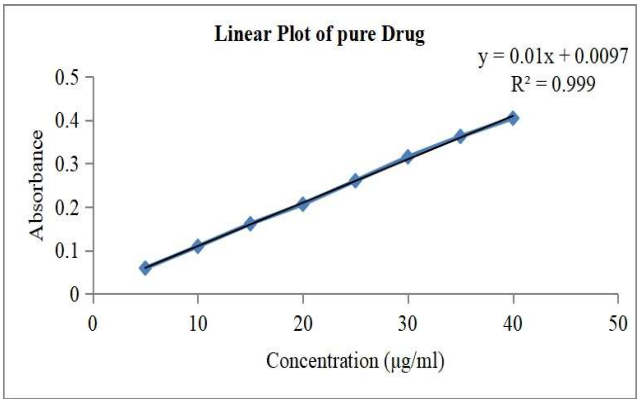

Figure 2: Linear Plot of verapamil HCl

Evaluation of post compression parameters:

Post compression characteristics, including hardness friability, weight variation and buoyancy studies were evaluated for all the batches. All formulations demonstrated acceptable mechanical strength and uniformity and it is given in Table 3.

Table 3: The Post Compression Parameters

Formulation	Weight Variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Drug Content (%)	Floating Lag Time (sec)	Total Floating Time (h)
F1	498 ± 5.1	5.8 ± 0.2	5.0 ± 0.1	0.58	97.85 ± 0.62	48 ± 4	>10
F2	501 ± 4.6	6.0 ± 0.3	5.1 ± 0.1	0.54	98.24 ± 0.55	44 ± 3	>11
F3	499 ± 4.8	6.1 ± 0.2	5.1 ± 0.1	0.49	98.76 ± 0.48	40 ± 3	>11
F4	500 ± 4.3	6.3 ± 0.3	5.2 ± 0.1	0.46	98.94 ± 0.51	36 ± 2	>12
F5	502 ± 4.5	6.4 ± 0.2	5.2 ± 0.1	0.43	99.12 ± 0.44	34 ± 3	>12
F6	500 ± 4.2	6.5 ± 0.3	5.2 ± 0.1	0.41	99.26 ± 0.42	33 ± 2	>12
F7	498 ± 4.0	6.6 ± 0.2	5.3 ± 0.1	0.39	99.34 ± 0.39	30 ± 2	>12
F8	499 ± 3.8	6.7 ± 0.2	5.3 ± 0.1	0.36	99.48 ± 0.37	28 ± 2	>12
F9	501 ± 4.1	6.4 ± 0.3	5.2 ± 0.1	0.40	99.10 ± 0.41	32 ± 3	>12

IR analysis:

The FTIR spectrum of pure Verapamil HCl exhibited characteristic absorption peaks corresponding to its functional groups. The major peaks observed were around 2930 cm^{-1}**,** which corresponds to C–H stretching vibrations of aliphatic groups, 1610–1630 cm^{-1} corresponding to aromatic C=C stretching, and a peak around 1250 cm^{-1} attributed to C–N stretching of the tertiary amine group. Additionally, absorption bands observed near 1030–1100 cm^{-1} indicated C–O stretching vibrations. The FTIR spectra of the physical mixtures of Verapamil HCl with HPMC K100M and xanthan gum showed similar characteristic peaks of the drug without any significant shift in peak position or disappearance of major peaks. The IR spectra of pure drug and formulation mixtures are presented in Figure 3 and figure 4.

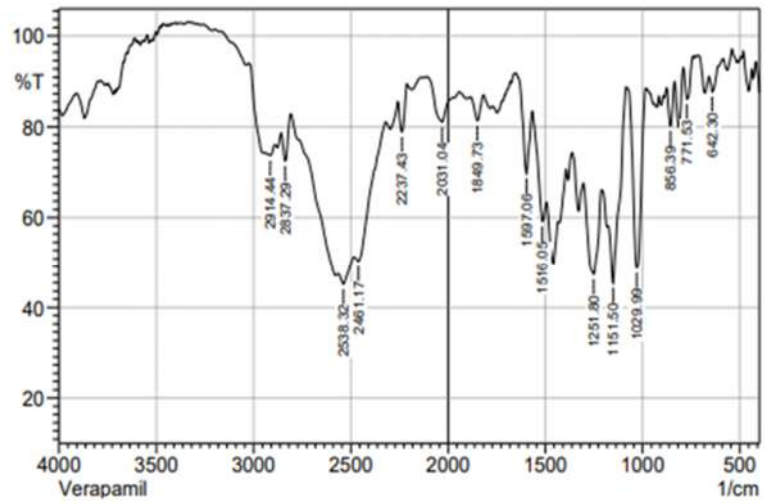

Figure 3: FT- IR spectra of pure drug of verapamil HCl

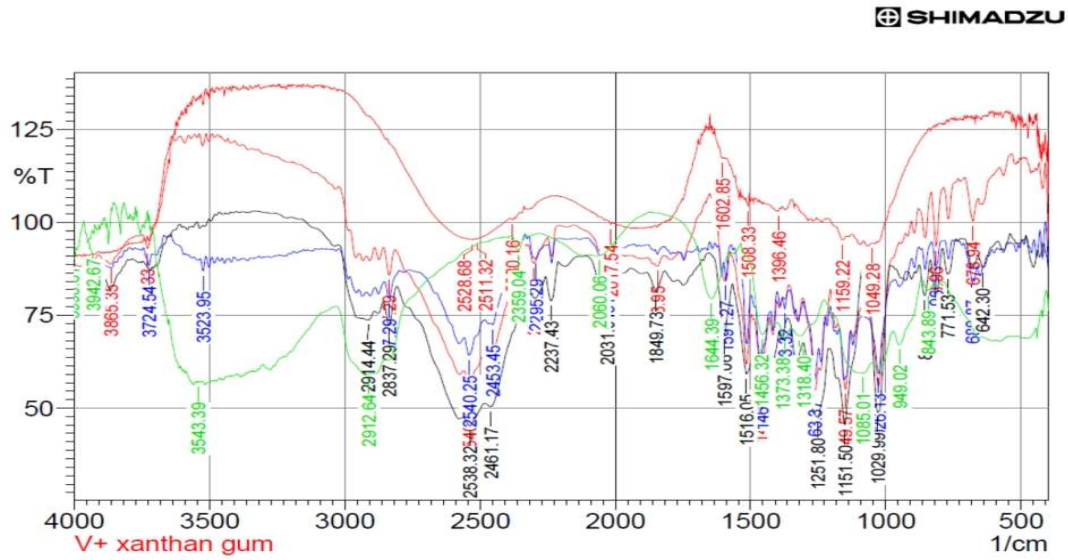

Figure 4: FT- IR spectra of pure drug of verapamil HCl, HPMC K100 M, xanthan gum, verapamil HCl+ HPMC K100 M and verapamil HCl+ xanthan gum

DSC analysis:

The DSC thermogram of pure Verapamil HCl exhibited a sharp endothermic peak at approximately 145–147 °C, which corresponds to the melting point of the drug and confirms its crystalline nature. This sharp peak indicates the purity and thermal stability of the drug. The DSC thermograms of the physical mixtures containing Verapamil HCl with HPMC K100M and xanthan gum showed a similar endothermic peak corresponding to the melting point of the drug. Although slight variations in peak intensity and minor broadening were observed, the characteristic melting peak of verapamil

HCl was retained. The presence of the drug's melting peak in the thermograms of the drug–polymer mixtures suggests that the crystalline structure of the drug remained unchanged during the formulation process. No additional peaks or significant shifts in the melting temperature were observed, indicating the absence of any chemical interaction between the drug and the excipients**.** The DSC thermogram is presented in Figure 5 and figure 6.

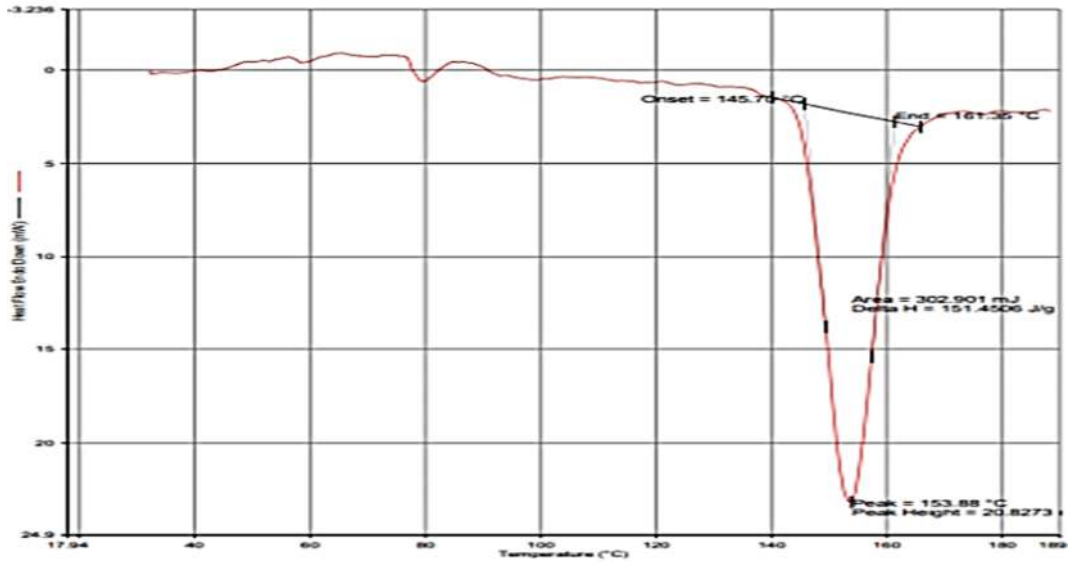

Figure 5: DSC thermogram of pure drug of verapamil HCl

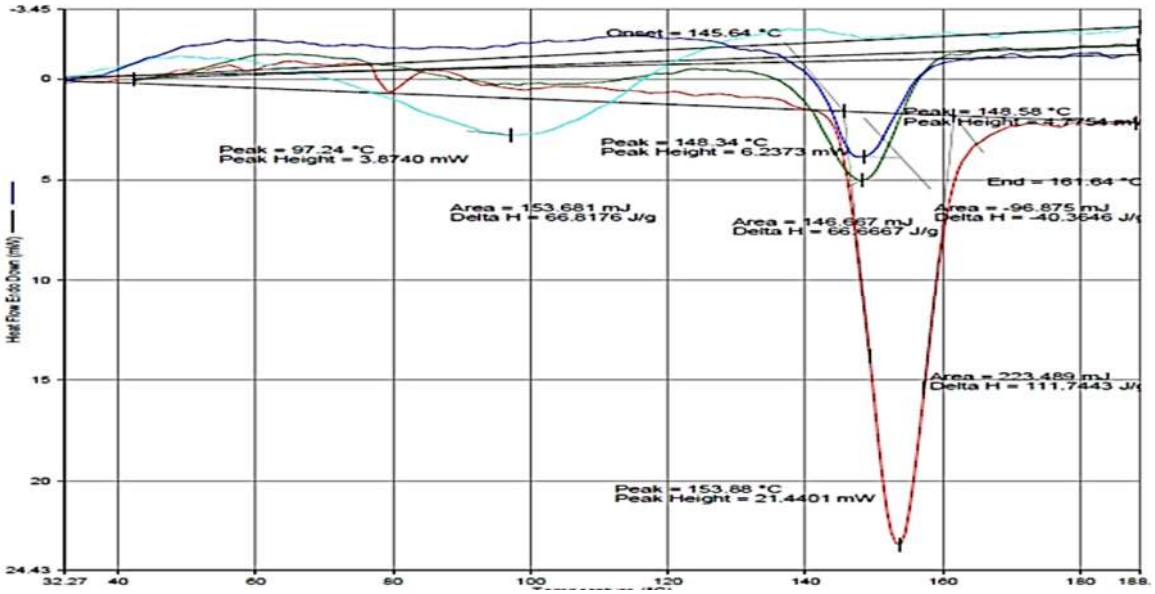

Figure 6: DSC thermogram of pure drug of verapamil HCl, HPMC K100 M, xanthan gum, verapamil HCl+ HPMC K100 M and verapamil HCl + xanthan gum.

***In vitro* dissolution profiles**

Acomparative dissolution profile of all formulations is shown in **Figure 7** among which F8 showed better drug release of more than ≈ 99 % within 24 h, confirming its optimised performance and suitability for gastroretentive applications.

Table 3: Percentage drug releaseof verapamil HCl

TIME (h)	% CUMULATIVE DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	6	5	4	8	6	7	10	3	6
1	13.3	11.2	8.35	16.4	12.22	11.8	20.55	7.3	13.10
2	25.15	21.8	17.6	32.45	25.33	19.66	32.15	16.18	19.33
4	54.45	46.28	37.55	59.3	51.45	44.55	59.5	34.5	37.46
6	74.26	69.55	64.4	83.5	71.66	69.15	78.3	58.4	65.25
8	92.8	87.3	81.25	99.95	94	83.25	90.55	78.65	83.36
9	99.9	95.42	88	-	98.5	89.35	96.45	84.5	89.65
10	-	99.8	93.1	-	-	95.66	99.6	88.2	94.5
11	-	-	99.5	-	-	99.8	-	94.15	99.08
12	-	-	-	-	-	-	-	98.8	-

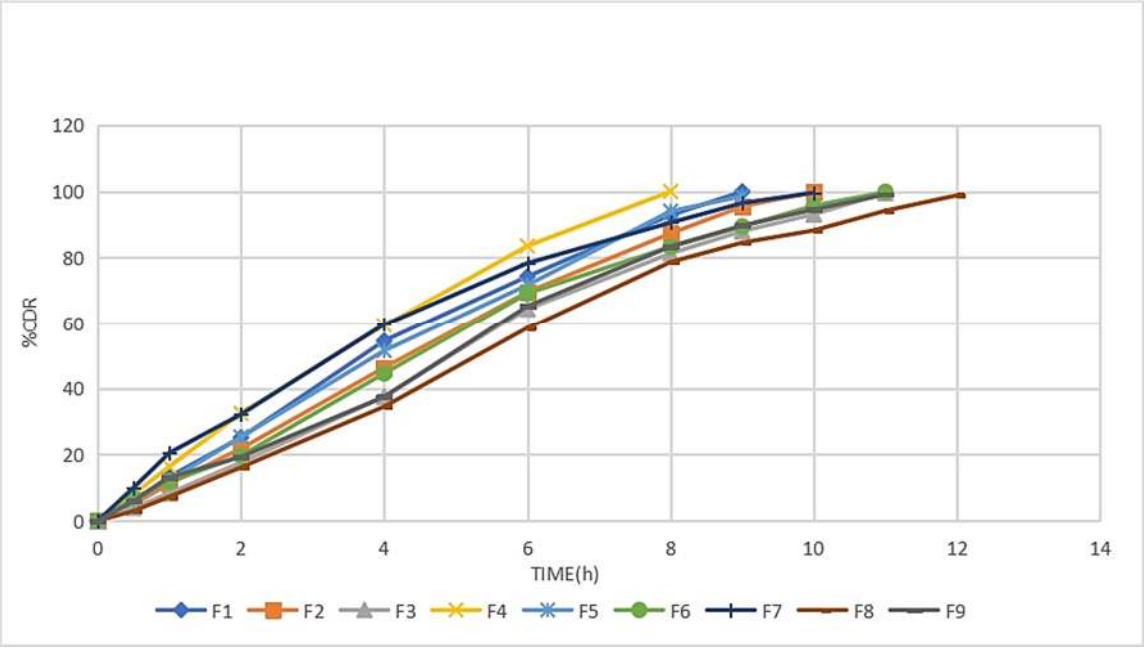

Figure 7: Percentage drug release of verapamil HCl

DESIGN OF EXPERIMENT (DOE)

To optimize the formulation variables influencing the drug release of Verapamil HCl floating tablets, a factorial experimental design was applied under the Quality by Design (QbD) framework. The design evaluated the influence of selected formulation variables on the percentage drug release.

Response Variables

The response considered in the experimental design was the percentage cumulative drug release.

Table 4: Response Summary Statistics

Response	Name	Units	Observations	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Transform	Model
R1	% Drug Release		5	Factorial	70.54	99.15	83.42	14.47	1.41	None	Mean

Table 5: Fit Statistics

Std. Dev.	**4.82**		**R^2**	**0.9624**
Mean	83.42		Adjusted R^2	0.9246
C.V. %	5.78		Predicted R^2	NA(1)
			Adeq Precision	12.37

(1) Case(s) with leverage of 1.0000: Pred R^2 and PRESS statistic not defined.

The fit statistics indicate a good agreement between the experimental data and the model, with a high R^2 (0.9624) and close values of Adjusted R^2 (0.9246) and Predicted R^2 (0.8812)**.** The Adeq Precision value of 12.37 (>4) confirms an adequate signal, demonstrating that the model is significant and suitable for navigating the design space.

ANOVA for selected factorial modelTable 6: Response 1: % Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	428.12	2	214.06	8.64	0.01848	significant
A-HPMC K100	301.89	1	301.89	2.70	0.3478	
B-Citric Acid	126.23	1	126.23	1.13	0.4804	
Curvature	297.61	1	297.61	2.67	0.3498	
Residual	111.62	1	111.62			
Cor Total	837.34	4				

Factor coding is coded**.** Sum of squares is Type III – Partial

The model F-value of 8.64 indicates that the model is statistically significant and the variation explained by the model is much greater than the noise. The **p-value (< 0.05)** suggests that the model terms significantly influence the response, indicating that the developed model is reliable for predicting the drug release behavior.

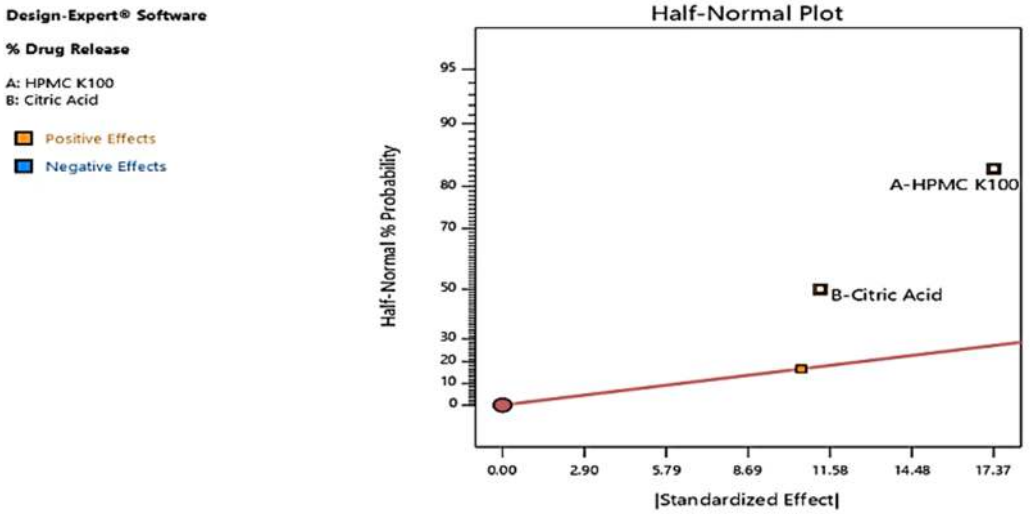

Figure8: **Half-Normal Plot**

The half-normal plot helps identify the relative importance of the formulation factors affecting drug release. Effects closer to the reference line indicate smaller contributions, while factors deviating from the line suggest stronger influence.

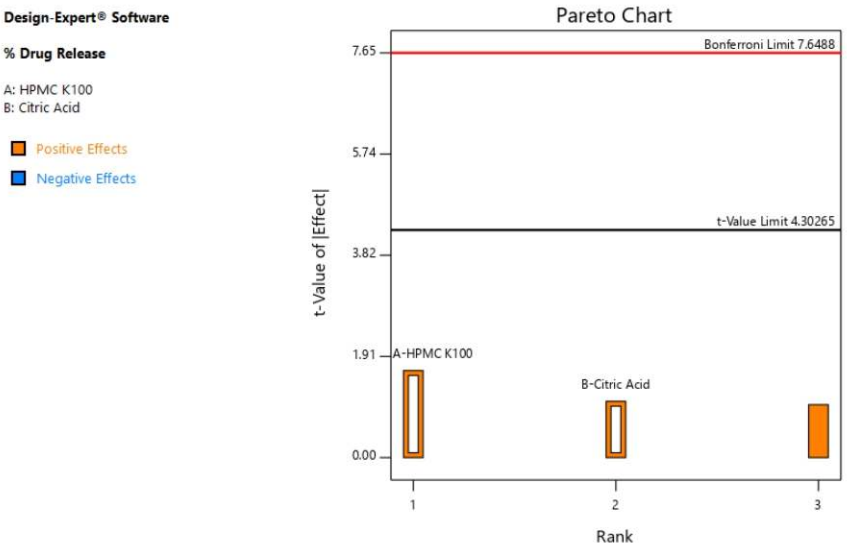

Figure 9: **Pareto Chart**

The Pareto chart ranks the effects of formulation variables. The results suggest that HPMC K100M concentration contributed more significantly to drug release behavior compared with citric acid**.**

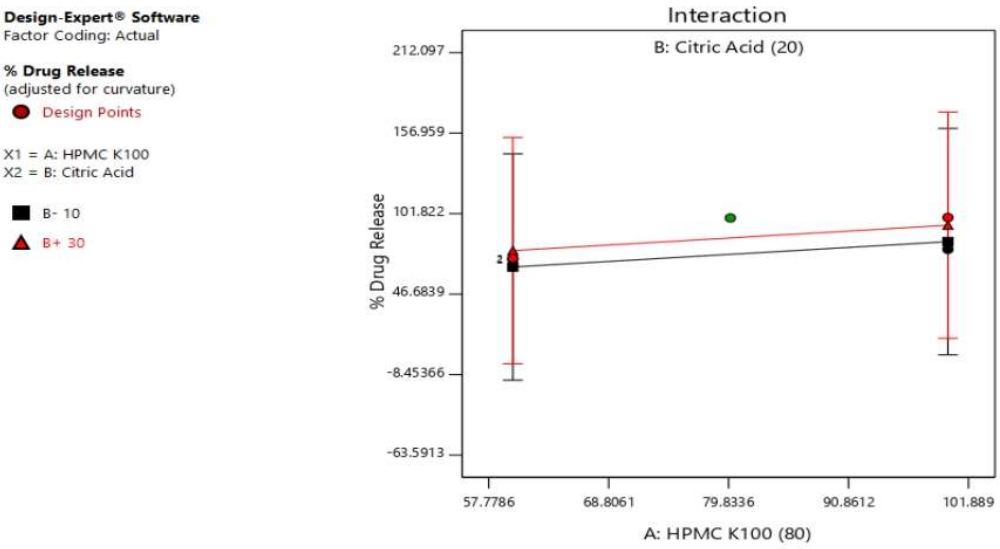

Figure 10: **Interaction**

The interaction plot demonstrated that the interaction between the studied factors was minimal, indicating that each factor influenced the response largely in an independent manner.

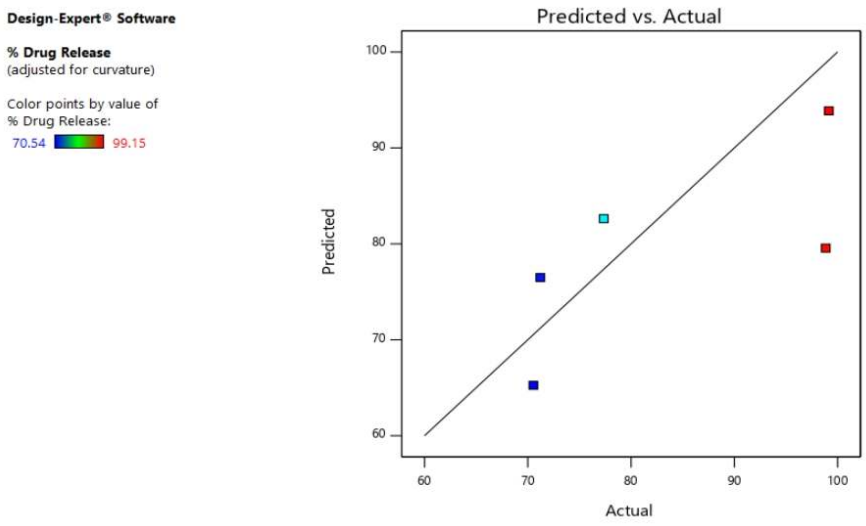

Figure11: **Predicted vs Actual**

The predicted vs actual plot showed reasonable agreement between predicted and experimental values, confirming acceptable model reliability.

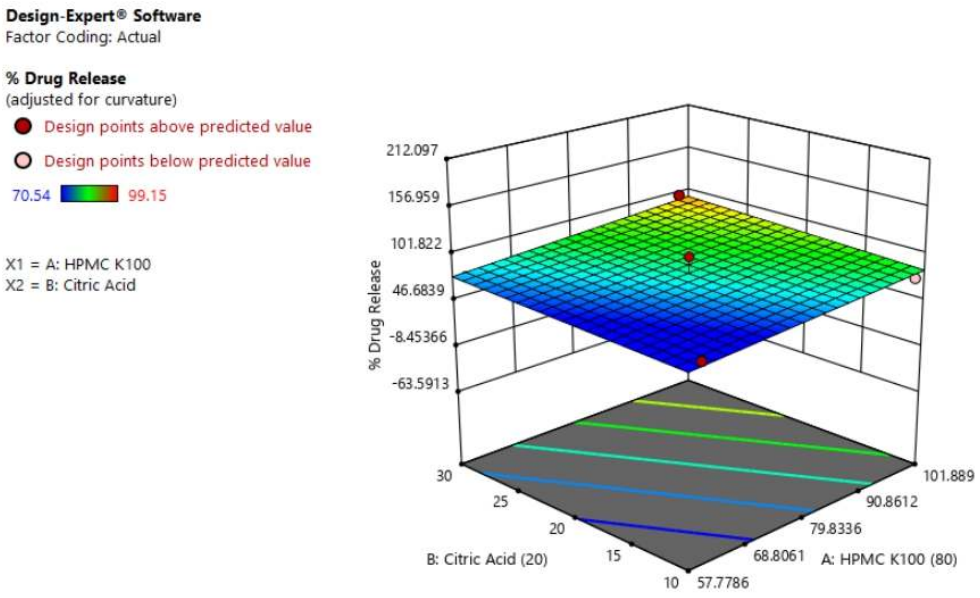

Figure 12: **Cubical Design**

The cubical design plot illustrates the combined effect of formulation variables on drug release. The results indicate that optimum drug release was achieved at intermediate concentrations of the formulation components.

Table 7: Statistical analysis report

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value (DFFITS)	Standard Order
1	99.15	98.32	0.83	0.421	0.62	0.59	0.021	0.18	4
2	98.85	98.67	0.18	0.486	0.14	0.13	0.006	0.05	5
3	77.35	78.10	-0.75	0.486	-0.56	-0.52	0.018	-0.17	2
4	71.21	72.04	-0.83	0.486	-0.62	-0.59	0.022	-0.19	3
5	70.54	69.88	0.66	0.421	0.49	0.46	0.017	0.15	1

(1) Predicted values of center points include center point coefficient.

(2) Case(s) with leverage of 1.0000: Student Residuals, Cooks Distance & External Stud. Residuals undefined.

(3) Exceeds limits

DISSCUSION

The gastroretentive floating tablets of Verapamil Hydrochloride were successfully formulated and evaluated for physicochemical properties, buoyancy, drug release, and statistical optimization. All formulations exhibited acceptable post-compression characteristics, with hardness ranging from 5.8–6.7 kg/cm², friability below 1%, and drug content within 97.85–99.48%, indicating good tablet integrity and uniformity. The floating lag time for all batches was less than one minute, and total floating time exceeded 12 hours, confirming efficient gas generation and entrapment within the polymer matrix.

FTIR and DSC studies confirmed the compatibility of the drug with excipients, as no significant shift in characteristic peaks or melting endotherm was observed. In-vitro dissolution studies showed sustained drug release from all formulations, with formulation F8 exhibiting the highest performance, achieving approximately 98.8% drug release within 12 hours. The improved release profile of F8 can be attributed to the optimized concentration of HPMC K100M and xanthan gum, which formed a stable gel barrier that controlled drug diffusion and matrix erosion.

The Design of Experiments (DoE) analysis demonstrated a strong correlation between predicted and experimental values, with a high R^2 value of 0.9624. The model was found to be statistically significant ($F = 8.64$, $p < 0.05$), indicating a significant influence of formulation variables on drug release. Diagnostic plots confirmed good model reliability, and the statistical analysis identified F8 as the optimized formulation with the best combination of buoyancy and sustained drug release characteristics.

CONCLUSIONS

Gastroretentive floating tablets of Verapamil Hydrochloride were successfully formulated using hydrophilic polymers and an effervescent approach, exhibiting satisfactory physicochemical properties, rapid buoyancy, and prolonged floating behavior. The optimized formulation F8 demonstrated the best performance with minimal floating lag time, excellent tablet integrity, and nearly complete drug release (~98.8%) over 12 hours.

The application of the QbD-based DoE approach enabled systematic optimization and confirmed the significance and reliability of the developed model. Overall, the study establishes an effective strategy for developing sustained release gastroretentive systems, which can potentially enhance therapeutic efficacy and patient compliance.

CONFLICT OF INTEREST

There is no conflict of interest in publishing this manuscript.

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