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Original Article

Quality by Design-Based Formulation and Evaluation of Gastroretentive Floating Tablets of Tramadol Hydrochloride

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ABSTRACT

Objectives: The current research is aimed to design and development of a Floating Drug Delivery System (FDDS) for tramadol HCl by enhancing the gastric residence time and by releasing the drug at the targeted site. **Materials and Methods:** The formulations were developed by using xanthan gum, HPMC K100M CR, and a combination of both the drug and excipient compatibility study was determined by IR and DSC studies. Quality by Design (QbD) approach was implemented to optimize floating formulations, which were evaluated for the pattern of drug release, floating properties, and dissolution data. **Results:** The formulation F8, which consists of HPMC K100M CR and xanthan gum (15% + 10% of tablet weight), was identified as the optimal formulation based on improved sustained release of over 90%, buoyancy lag time of 10 sec and a total buoyancy time of 24 hr. Accelerated stability studies were conducted at 40 ± 2℃ for 30 days on the optimized formulations, and it was observed that there were no significant changes during or after the period. **Conclusion:** Optimized floating tablets of tramadol HCl showed a buoyancy time of over 24 hr, and a rapid floating action was observed. The drug release followed non-Fickian diffusion (n = 0.605).

Key words: Quality by Design (QbD), Floating system, Compatibility, Drug release kinetics and stability.

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INTRODUCTION

Among all the routes for drug delivery, oral delivery is considered the most preferred and convenient route due to its safety and effectiveness in varied conditions of gastrointestinal tract throughout its entire length (Priyadarshan *et al*., 2024 and Robinson & Lee, 1978). Gastroretentive Drug Delivery Systems (GRDDS) are dosage forms that can achieve sustained drug delivery in the stomach. Gastro-retention is important for drugs that are not stable in intestinal pH also for those drugs that are likely to have an absorption window into the stomach region (Sharma *et al*., 2024).

Some of the problems related to conventional dosage forms can be overcome by floating drug delivery systems, especially for those drugs that are primarily absorbed in the stomach (Prakash *et al*., 2025). The floating enables the targeted drug delivery with the ability to release the drug at the desired site (Blynskaya *et al*., 2022). Floating drug delivery systems are broadly grouped as effervescent or non-effervescent types, where an effervescent tablet generally contains a blend of hydrophilic polymers or release rate retarding polymers and gas-generating excipients (Thapa & Jeong, 2018).

Tramadol HCl, a synthetic opioid analgesic, is classified as a BCS Class I drug due to both high solubility and permeability. It targets opioid receptors and inhibits the re-absorption of serotonin and norepinephrine to maintain moderate to severe pain, among other uses. Its half-life for elimination ranges from 4 to 6 hr, with absorption occurring primarily in the stomach. In order to maintain a significant plasma concentration tramadol HCl needs to be administered multiple times which makes it an ideal drug for developing gastro retentive floating dosage form (Bouni *et al*., 2024).

In this study, it is aimed to develop and optimize floating gastro retentive formulations for tramadol HCl by using hydrophilic polymers like HPMC K100 M CR, xanthan gum and a mixture of both. A QbD approach was applied to ensure robust formulation development and to identify critical formulation variables impacting drug release and buoyancy.

MATERIALS AND METHODS

Materials

Tramadol HCl was received from VerGo Pharma Research Laboratories Pvt. Ltd., (Goa, India) as a gift sample. HPMC (Methocel) K100M CR, Sta-Rx 1500 was supplied by Colorcon

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Asia Pvt. Ltd., (Mumbai, India) as gift samples. Xanthan gum, MCC, Sodium bicarbonate, Citric acid, Magnesium stearate, and Talc were purchased from Loba Chemie Pvt. Ltd., (Mumbai, India). All chemicals of analytical grade were used in the work.

Methods

Dissolution studies

The dissolution study for tramadol HCl floating tablets were carried out using USP dissolution apparatus type I (basket type) containing 900 mL of 0.1N HCl (pH ≈ 1.2) at 75 rpm at 37°C ± 0.5°C. At regular intervals, an aliquot (5 mL) was withdrawn and was replaced with the same amount of fresh dissolution media maintained at 37°C ± 0.5°C. The aliquots were withdrawn and analyzed for the absorbance using UV-visible spectrophotometer at 272 nm (Bouni *et al*., 2024).

IR studies

The IR study was carried out using a Shimadzu, Japan IR instrument. A mixture of the sample and KBr was prepared by triturating at a 1:100 ratio. After compression, KBr discs were prepared for scanning. Parameters included a scanning at from 4000 to 400 cm^{-1} (Murthy *et al*., 2014).

DSC studies

DSC 400 from PerkinElmer, USA was employed for the thermal analysis. Samples weighing approximately 2-4 mg of tramadol HCl or its equivalent were sealed and incubated at temperatures ranging from 30°C to 300°C with 25 mL min^{-1} nitrogen flow at a scan rate of 20°C min^{-1} (Murthy *et al*., 2014).

Stability studies

The stability study was carried out as per the ICH guidelines using a stability chamber (Thermolab), maintained at a temperature of 40 ± 2°C and at a relative humidity of 75 ± 5%.

Manufacturing of floating tablets of Tramadol HCl

Each ingredient of the formulation batch weighed accurately using an electronic balance (Sartorius) and passed through a 40 # sieve and mixed homogeneously. The lubrication method was followed before the formulation of tablets by direct compression using a Rimek Tablet mini press (Ahmedabad), which is a multi-station automatic tablet press with a round flat-faced 10 mm punch. The formulation of different batches is given in Table 1.

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 (Sameeraja *et al*., 2015).

Drug release kinetics studies

The rate of drug absorption is a cumulative result of a process like dissolution of the drug, blood flow, GI motility etc., (Fatema *et al*., 2019). A thorough grasp of the drug's release mechanism and kinetics is essential for the design of pharmaceutical floating dosage forms, as determined by kinetic studies (Shargel *et al*., 2005). It is crucial to have a solid grasp of the mechanisms underlying drug release kinetics since changes in a formulation's design, both qualitative and quantitative, can be detected as variations in drug release. These changes may also affect a dosage form's performance *in vivo* (Mahapatra *et al*., 2014). The techniques applied in kinetic models illustrate the entire drug release from the formulation and dissociation curves. Several models are frequently used to characterize drug release, including Zero order, First order, Higuchi model, Korsmeyer-Peppas (K-P), Hixson Crowell (H-C) and regression models (Mahapatra *et al*., 2013).

RESULTS

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 which are shown in Table 2.

The result of the accelerated stability study conducted on F8 is given in Table 3. After 30 days at 40 ± 2℃/75 ± 5% RH, no significant changes were noted, especially in drug content, buoyancy, or swelling index, confirming formulation's physical and chemical stability.

Dissolution data

A comparative dissolution profile of optimized formulations i.e., F3, F7, F8 and F9 is shown in Figure 1 among which F8 showed better drug release of more than 96% within 24 hr, confirming its optimized performance and suitability for gastroretentive applications.

IR analysis

The drug-excipient interaction causes a notable shift in the drug-excipient mixture's IR spectrum. Tramadol HCl exhibits a notable peak at 3306.13 cm^{-1}, which suggests N-H stretching. Absorption for the aromatic C-H (sp2) stretch is found at 3018.73 cm^{-1}. Peaks at 2483.46 cm^{-1} and 2608.84 cm^{-1} show the C-H (sp3) bond's stretch. Peaks caused by N-H bending are at 1578.8 cm^{-1}. Peak C-C stretching was recorded at 1481.39 cm^{-1}. 1176.63 cm^{-1} absorption band indicates C-N stretching. A peak at 1046.43 cm^{-1} describes the stretching of C-O bond. These spectral features are consistent with previously reported FTIR data for tramadol HCl, confirming its structural integrity (Gupta *et al*., 2019). The FTIR spectra of Tramadol HCl and physical mixtures revealed no significant shifts in characteristic peaks, confirming no chemical interaction between the drug and polymers. The IR spectra of pure drug and formulation mixtures are presented in Figure 2.

DSC analysis

Tramadol HCl formulations were evaluated for their compatibility with the other excipients through DSC thermogram analysis. The thermogram was run in a range of 40 to 300℃ at a thermal rate of 20℃/min. From the results it was observed that tramadol HCl shows a sharp peak, indicating a melting point at temperature of 183℃, corresponding to its melting point, ensuring the crystalline nature and purity of drug (Devi *et al*., 2024). DSC studies did not reveal any notable interactions between the drug and polymers utilized in the floating formulations. The DSC thermogram is presented in Figure 3.

Kinetic release studies

For each prepared formulation, the coefficient of determination (r^2) was calculated using a variety of kinetic model equations, such as zero order, first order, Higuchi model, K-P model, and H-C cubic root model. This allowed the identification of the drug release mechanism. The drug release mechanism was found to be leaning more toward the Higuchi equation, suggesting a diffusion-type of drug release. The data was examined using the K-P equation to validate the diffusion mechanism. For all formulations, the 'n' values for the K-P model varied from 0.5 to 0.685, indicating non-Fickian or anomalous diffusion is most likely the mechanism underlying the pattern of drug release. This divergence may be explained by the drug's enhanced diffusivity from the polymer matrix as a result of solvent-induced relaxation. The correlation coefficient values for the optimized formulations are shown in Table 4.

ANOVA for selected factorial model

2^3 factorial fractional design table used for analyzing the effect of three factors HPMC K-100 CR, Sodium bicarbonate and Citric acid at different concentrations have a significant impact on drug release given in Table 5. The highest drug release (96.68) was observed when all factors were at moderate levels (60 mg each), suggesting an optimal balance for sustained drug release.

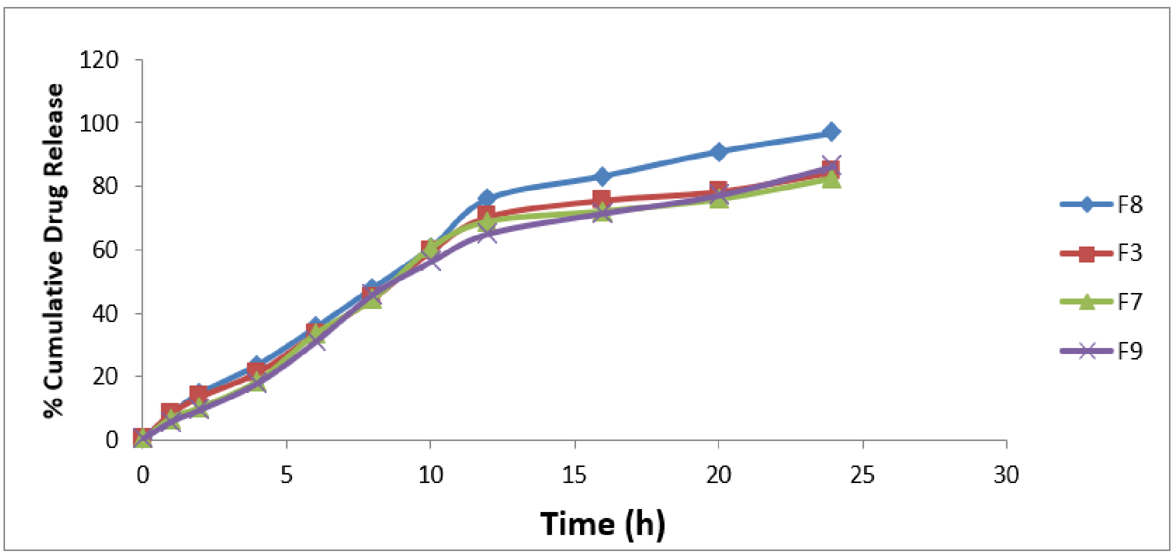

Figure 1: Drug release profile of F3, F7, F8 and F9.

Table 1: Formula for different batch.

Sl. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Tramadol HCl	100	100	100	100	100	100	100	100	100
2	HPMC K-100 CR	60	80	100	-	-	-	40	60	80
3	Xanthan gum	-	-	-	60	80	100	40	40	40
4	Sodium bicarbonate	30	60	90	30	60	90	30	60	90
5	Citric acid	10	20	30	10	20	30	10	20	30
6	Talc	5	5	5	5	5	5	5	5	5
7	Magnesium stearate	5	5	5	5	5	5	5	5	5
8	Sta-Rx1500	40	40	40	40	40	40	40	40	40
9	Microcrystalline cellulose	150	90	30	150	90	30	130	70	10
10	Total (mg)	400	400	400	400	400	400	400	400	400

Table 2: The Post Compression Parameters.

Formulation batch	Hardness (kg/ cm²)	% Friability	WV (mg)	DC (%)	BLT (s)	TFT (h)	SI (%)
F1	5.43±0.31	0.51	400±1.62	77.20±0.11	28 s	>10h	89.42±0.22
F2	5.52±0.24	0.53	400±1.78	69.12±0.13	24 s	>15h	91.70±0.38
F3	5.39±0.19	0.47	400±1.63	84.45±0.12	12 s	>24h	93.45±0.42
F4	5.35±0.13	0.50	400±1.64	87.65±0.14	65 s	>24h	91.37±0.29
F5	5.29±0.17	0.41	400±1.87	75.48±0.17	83 s	>18h	92.70±0.41
F6	5.12±0.14	0.47	400±1.63	78.45±0.12	90 s	>12h	93.45±0.42
F7	5.38±0.22	0.42	400±0.76	82.41±0.10	11 s	>24h	93.46±0.51
F8	5.41±0.16	0.41	400±1.59	97.68±0.11	10 s	>24h	96.48±0.45
F9	5.37±0.15	0.43	400±1.65	86.38±0.12	5 s	>24h	96.28±0.56

Table 3: Table showing results of stability studies for optimized tablet formulation (F8).

Formulation batch	Hardness (kg/ cm²)	% Friability	WV (mg)	DC (%)	BLT (s)	TFT (h)	SI (%)
F8	5.47±0.13	0.44	400±1.23	96.60±0.19	10 s	>24 h	96.57±0.39

Table 4: Correlation coefficient values of different mathematical models from F3, F7, F8, and F9.

Sl. No.	Formulations	Zero order Plot		First order plot		Higuchi Model		K-P plot			H-C plot	
		r^2	K_0	r^2	K_1	r^2	K_H	r^2	N	K	r^2	K
1	F3	0.908	3.699	0.963	-0.084	0.953	19.92	0.833	0.601	1.081	0.980	-3.071
2	F7	0.897	3.645	0.966	-0.032	0.944	19.66	0.864	0.539	1.123	0.972	-3.033
3	F8	0.939	4.241	0.969	-0.058	0.960	22.56	0.841	0.605	1.114	0.990	-3.481
4	F9	0.931	3.776	0.988	-0.035	0.954	20.10	0.890	0.495	1.159	0.984	-3.103

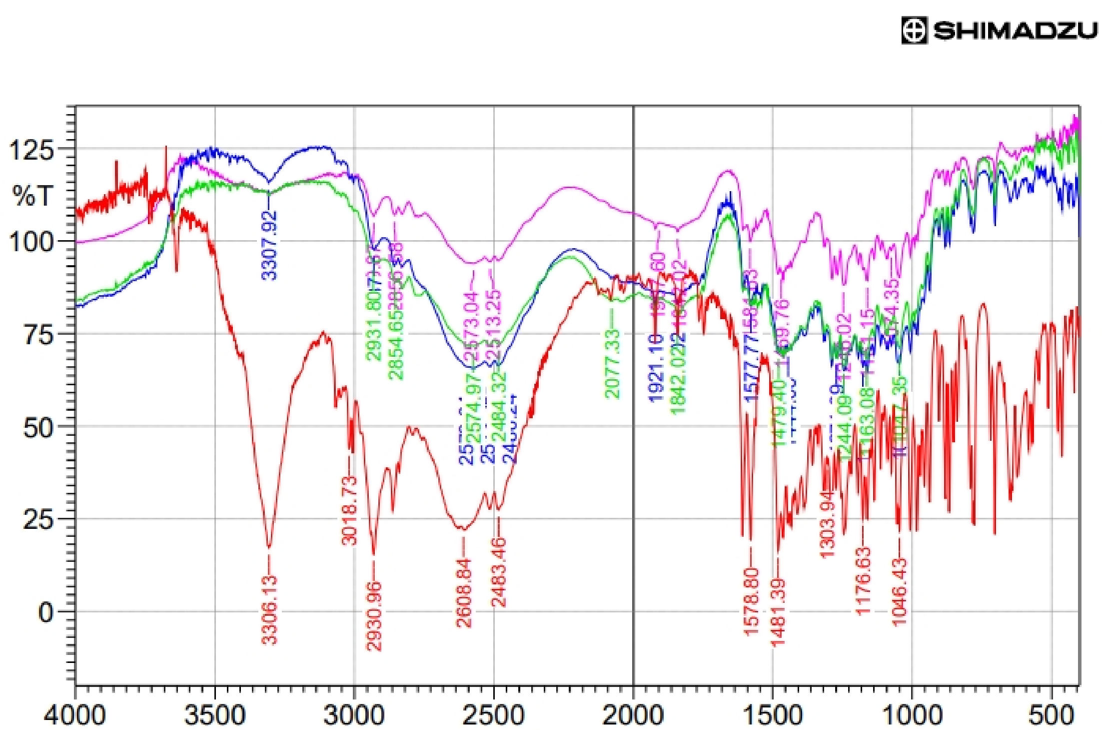

Figure 2: IR Spectra of (A) Tramadol HCl (B) Tramadol HCl and HPMC K 100 M CR (C) Tramadol HCl and Xanthan gum (D) Tramadol HCl,HPMC K 100 M CR and Xanthan gum.

Factors used in experimental design i.e., HPMC K-100 CR, Sodium bicarbonate and Citric acid are numeric variables with defined minimum and maximum values. The coded values (+1 and -1) represent the low and high levels for each factor and is given in Table 6.

The ANOVA results for Response 1 (% drug release) are summarized in Table 7. The overall model is statistically significant ($p = 0.0353$), confirming the influence of formulation factors on % drug release.

The model showed a high degree of accuracy with a coefficient of determination ($R^2 = 0.998$) and an adjusted R^2 of 0.997confirming a strong agreement between experimental and predicted values. The standard deviation (5.90) and coefficient of variation (7.10%) were within acceptable limits, supporting model reliability. The fit statistics for the response (% drug release) are presented in Table 8.

The half normal plot indicates that there are no errors in the statistical F test and the probability of reaching the drug release is high. The dissolution rate also increased significantly by using the materials. The half-normal plot allows us to visually distinguish between the effects that are small (and normally distributed) versus large (and likely to be statistically significant). Normal plot shows that the ANOVA follows normal distribution as there is no negative effect and determines the assumptions of the ANOVA are met. A comparative representation for the plots is given in Figure 4.

The Pareto chart in Figure 5 describes the priority of the factors (excipients) used for the design and found that the factor HPMC K100 has higher priority than the other factor.

Interaction chart shows that there is no interaction of other factors in the design and also there is no interaction between the factors and it was observed that the actual value of the ANOVA is higher than the predicted value which shows that the design is significant and it is represented in Figure 6.

The cubical graph shown in Figure 7 suggests that the release of the drug from the designed dosage form is more when the concentration of HPMC K100 and sodium bicarbonate is optimal.

The statistical analysis of using the QbD approach revealing a good correlation between actual and predicted values of drug release with relatively low residuals. The low Cook's distance and DFFITS values indicate no highly influential points affecting model stability. The results confirm that the developed model is reliable for predicting drug release, supporting its use in optimizing the floating formulations it is given in Table 9.

DISCUSSION

In this study, floating formulations were developed to improve the residence time and sustained drug release of tramadol HCl in the stomach. The drug-excipient compatibility was confirmed by the IR and DSC analysis which suggest no interaction. Drug release kinetics analysis of the optimised formulations F3,

Table 5: 2^3 factorial fractional design.

Std	Run	Fac 1	Fac 2	Fac 3	Resp 1
		A:HPMC K-100 CR	B:Sodium bicarbonate	C:Citric acid	% Drug Release
9	1	60	60	20	96.68
3	2	40	90	10	80.14
6	3	80	30	30	82.95
4	4	80	90	10	81.56
8	5	80	90	30	86.38
5	6	40	30	30	75.41
7	7	40	90	30	79.53
2	8	80	30	10	83.44
1	9	40	30	10	82.41

Table 6: Factors.

Factor	Name	Units	Type	Min	Max	C- Low	C- High	Mean	Std. Dev.
A	HPMC K-100 CR	60	Numeric	40.00	80.00	-1 ↔ 40.00	+1 ↔ 80.00	60.00	20.00
B	Sodium bicarbonate	60	Numeric	30.00	90.00	-1 ↔ 30.00	+1 ↔ 90.00	60.00	30.00
C	Citric acid	20	Numeric	10.00	30.00	-1 ↔ 10.00	+1 ↔ 30.00	20.00	10.00

Table 7: Response 1: % Drug Release.

Source	SoS	d_f	MS	F-value	*p*-value	
Model	38.24	3	8.77	0.687	0.03531	Significant
A-HPMC K-100 CR	35.45	1	35.45	4.04	0.1148	
B-Sodium bicarbonate	1.44	1	1.44	0.1647	0.7056	
C-Citric acid	1.34	1	1.34	0.1533	0.7154	
Curvature	205.44	1	205.44	23.42	0.0084	
Residual	35.09	4	12.75			
Core Total	278.76	8				

Coded with Factor codings. Where, SoS is Sum of Squares; MS is Mean Square.

Table 8: Fit Statistics.

SD	5.90		R^2	0.998
Mean	83.17		Adj. R^2	0.997
C.V. %	7.10		Pred. R^2	-0.2656
			Adeq Precision	NA(1)

Table 9: Table showing results of statistical analysis by QbD.

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	96.68	98.77	2.09	0.111	2.067	4.839	0.133	1.711	9
2	80.14	81.90	-1.76	0.486	-0.353	-0.320	0.030	-0.311	3
3	82.95	84.44	-1.49	0.486	-0.299	-0.270	0.021	-0.262	6
4	81.56	86.11	-4.55	0.486	-0.914	-0.896	0.198	-0.872	4
5	86.38	85.29	1.09	0.486	0.220	0.198	0.011	0.192	8
6	75.41	80.23	-4.82	0.486	-0.969	-0.961	0.222	-0.935	5
7	79.53	81.08	-1.55	0.486	-0.311	-0.281	0.023	-0.273	7
8	83.44	85.26	-1.82	0.486	-0.365	-0.331	0.032	-0.322	2
9	82.41	81.05	1.36	0.486	0.274	0.247	0.018	0.240	1

Current Transform: % Drug Release; Recommended Transform: None; Best Lambda 95% CI Low 95% CI High -3.00.

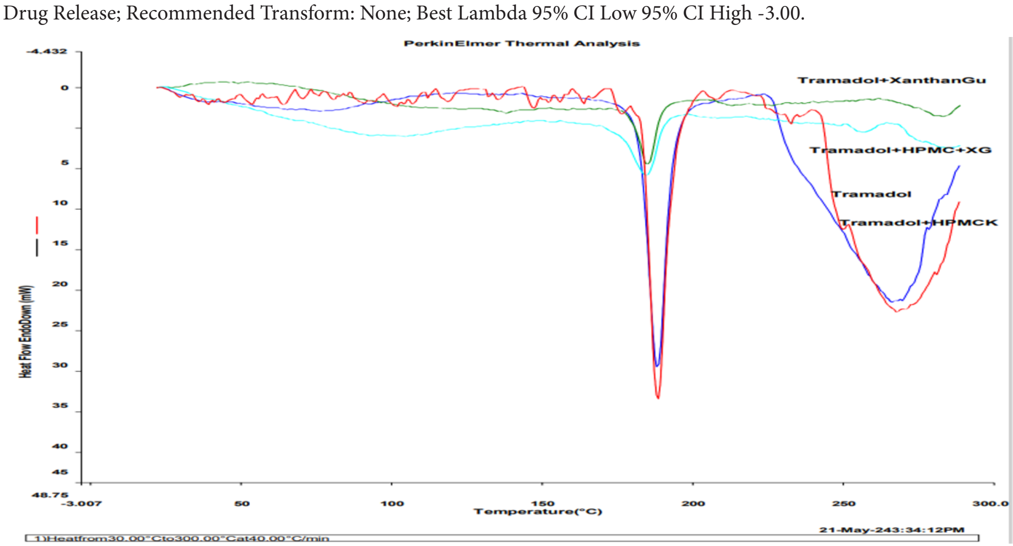

Figure 3: DSC thermogram of (A) Tramadol HCl (B) Tramadol HCl and HPMC K 100 M CR (C) Tramadol HCl and Xanthan gum (D) Tramadol HCl, HPMC K 100 M CR and Xanthan gum.

F7, F8, and F9 further revealed that the drug release from the formulations followed zero-order kinetics, i.e., the release rate was constant regardless of drug concentration, and exhibited a non-Fickian type release pattern with a value of n greater than 0.5 under the K-P model, which is advantageous for achieving sustained plasma levels.

Among all the formulations, F8 is considered the best one which contains a combination of HPMC K100M, xanthan gum and sodium bicarbonate at a defined proportion and was identified as the better formulation based on the drug release of 96.58%, a buoyancy lag time of less than 1 min and total buoyancy time of over 24 hr. The addition of polymer effectively increased the drug release with minimal lag time and enhanced floating period. Moreover, formulation F8 displayed a desirable swelling index. A stability study conducted on Batch F8 tablets at 40 ± 2℃ for one month revealed no significant changes in drug release, floating properties or dissolution.

The QbD approach and factorial design was used to optimize the tramadol HCl floating tablets by identifying of critical factors and their interactions. A 2^3 factorial design studied the effects of HPMC K100M, sodium bicarbonate, and citric on drug release. Statistical analysis and diagnostic plots confirmed model adequacy, and the optimal formulation F8 was achieved at mid-level concentrations. The design space demonstrated high predictability ($R^2 = 0.998$), with minimal residual error. The QbD driven optimization ensured robust formulation performance, enhanced drug release, and regulatory aligned development.

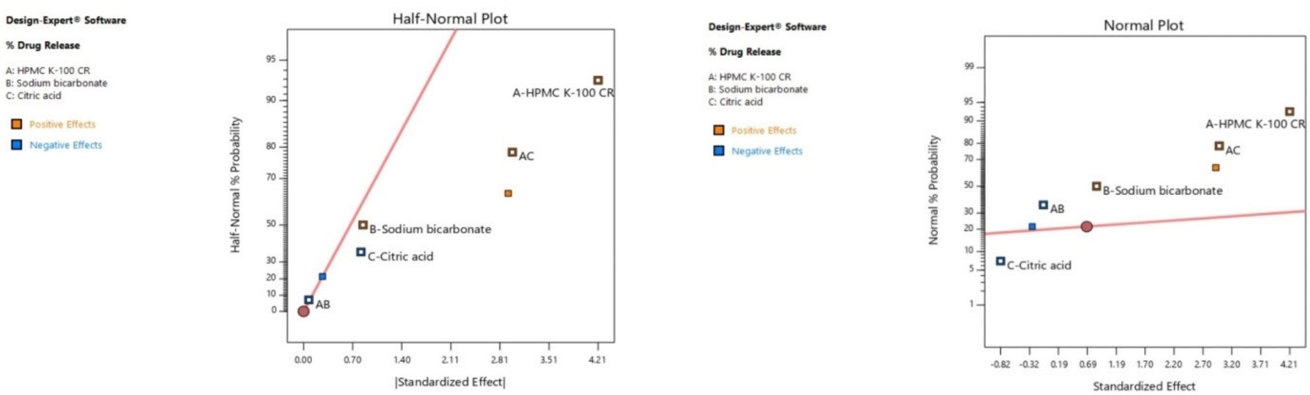

Figure 4: Half-Normal Plot and Normal Plot.

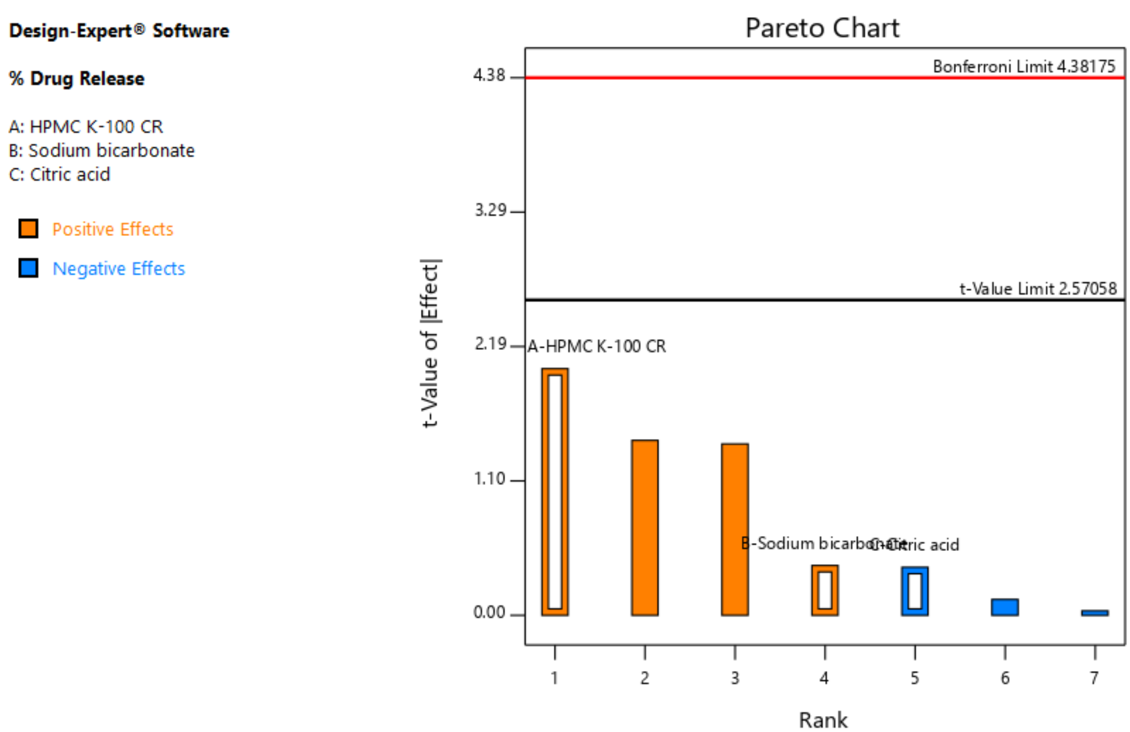

Figure 5: Pareto Chart.

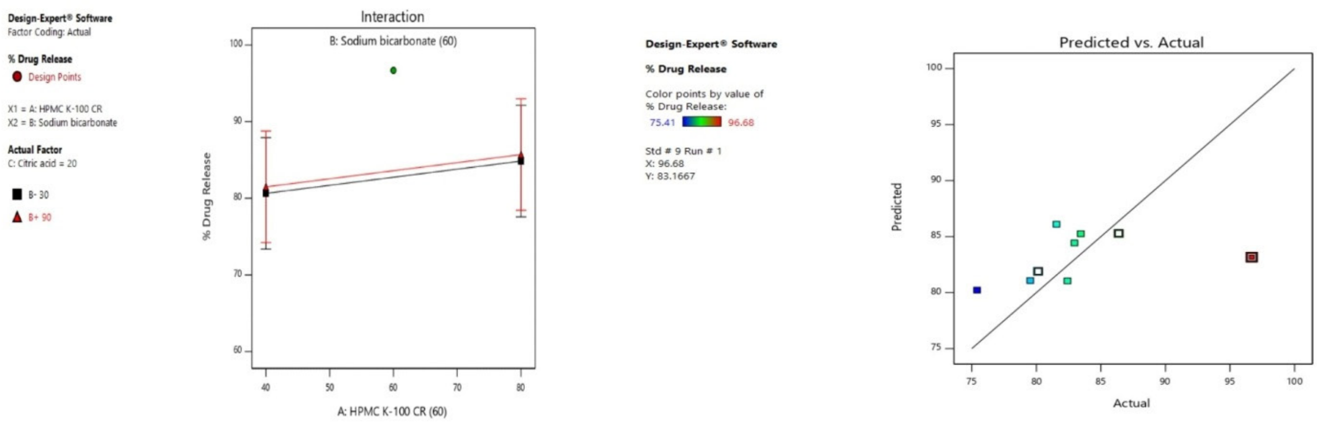

Figure 6: Interactions and Predicted vs Actual.

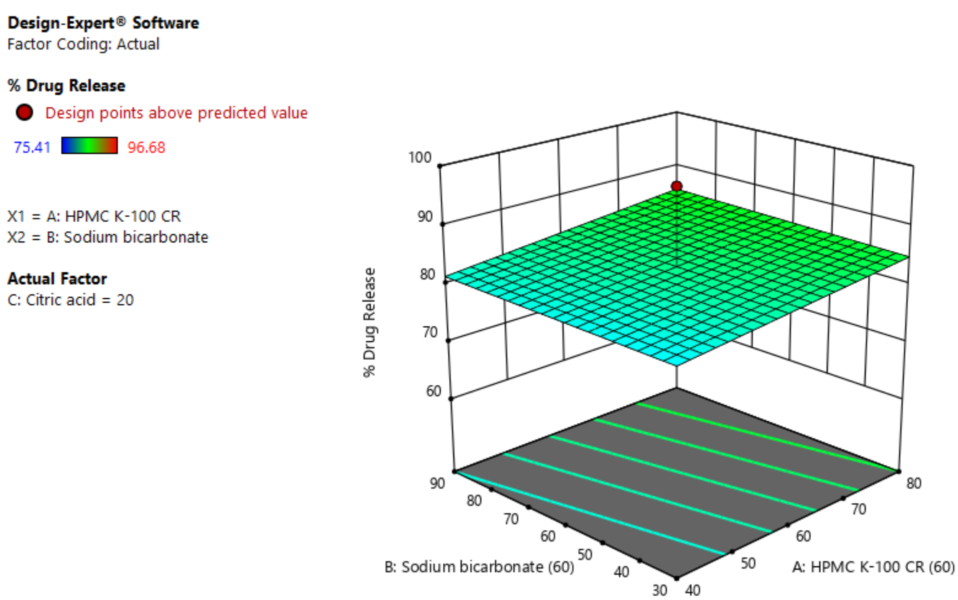

Figure 7: Cubical Design.

CONCLUSION

Floating tablets of tramadol HCl can be developed and optimized using a QbD approach by incorporating a combination of specific concentrations of HPMC K 100 M CR and xanthan gum along with other important excipients like sodium bicarbonate and citric acid, making them ideal for floating drug delivery systems. Out of all the formulations, F8 was considered the best formulation as it has total floating time of over 24 hr with a faster lag time (< 10 sec) and showed a dissolution rate over 96%. Kinetic drug release analysis indicated non-Fickian diffusion as the value of 'n' is more than 0.5 (i.e., 0.605) in the optimized formulation, suggesting a combination of diffusion and erosion mechanism, enhancing the effectiveness of formulations. The application of statistical modelling provided insights into critical formulation variables, identifying HPMC K100M as the most significant factor influencing drug release. Stability studies confirmed the physical and chemical robustness of the optimized formulation. Overall development of FDDS with QbD implementation presents a unique approach for improving drug absorption and bioavailability for drugs absorbed in the stomach, thus enhancing therapeutic effectiveness.

ACKNOWLEDGEMENT

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ABBREVIATIONS

GRDDS: Gastro Retentive Drug Delivery System; **FDDS:** Floating Drug Delivery System; **QbD:** Quality by Design; **IR:** Infra Red Spectroscopy; **DSC:** Differential scanning calorimeter; **KBr:** Potassium Bromide; **DC:** Drug Content; **WV:** Weight Variation;

BLT: Buoyancy Lag Time; **TFT:** Total Floating Time; **SI:** Swelling Index; **Fac:** Factor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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