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Quality by Design Approach for Development of Verapamil Hydrochloride Floating Matrix Tablet.

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ABSTRACT

Verapamil hydrochloride has a short half-life 2.8 to 7.4 hours, a narrow absorption window and is mainly absorbed in proximal areas of GIT. The present investigation aimed to formulate a floating drug delivery system of Verapamil Hydrochloride by Quality by design approach. In risk assessment, the effects of process and formulation variables on particle drug release and floating lag time were investigated. Design of experiments (DoE) and multivariate data analysis were used to identify important process and formulation parameters. A 2^2 factorial design in replicate was employed to produce controlled release floating tablet. The effect of critical formulation variables i.e. levels of HPMC K15M and gas generating agent (i. e. Sodium bicarbonate and citric acid) on % Drug release after 12 hr (% $DRel_{12}$) and floating lag time (FLT) were analyzed. Verapamil HCl tablets were evaluated for hardness, friability, weight variation, drug content, floating behavior and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5^{O}C. The tablets showed acceptable physicochemical properties. The two independent variables studied exhibited a significant influence ($P < 0.05$) on % DR 12 Hr and FLT. Numerical and graphical optimization technique employing design space approach was used to develop a new formulation by setting constrains on the dependent and independent variables. The experimental values of % DR 12 Hr and FLT for optimized batch were found to be in close agreement with those predicted by mathematical model. Experimental values obtained from the optimized formulations were in both cases close to the predicted values, thus confirming the validity of the generated mathematical model. These results demonstrated the effectiveness of the proposed floating tablet, as well as the usefulness of the QbD approach for the development of Verapamil floating tablet with optimized properties.

Keywords: Floating drug delivery system, Quality by design, Verapamil Hydrochloride, HPMCK15M, factorial design, Design space.

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INTRODUCTION

The majority of drugs are preferentially absorbed in the upper part of the small intestine, whereas retention period of DDS in humans, averages 2–3 h becomes the major contractions[1,2]. Gastro retentive drug delivery helps provide better availability of dosage form in stomach with new therapeutic possibilities and substantial benefits for patients[3,4,5]. Gastric retention of solid dosage forms may be achieved by different approaches such as floating[6,7], mucoadhesion[8], sedimentation[9,10], modified shape systems[11], or by the simultaneous administration of pharmacological agents that delay gastric emptying[12,13]. Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period [7,14]. The various buoyant preparations include hollow microspheres (microballoons), granules, powders, capsules, tablets (pills), and laminated films[1,19]. Most of the floating systems reported in literature is single-unit system, floating tablets [15]. Verapamil HCl a calcium channel blocker, used in treatment angina pectoris, hypertension, and supraventricular tachyarrhythmia. It is weakly basic in nature and pH-dependent solubility (poorly soluble at high pH values, highly soluble at low pH values) [16, 17]. However, due to first-pass effect, only 10–20% of total dose absorbed from the digestive tract penetrates to the systemic circulation in an unchanged from and short half-life (4 h) making its dosing frequency high. Hence, Verapamil HCl is good candidates for sustained release formulations [18, 20, 21].

The US Food and Drug Administration introduced the quality by design (QbD) approach which encourages the use of statistical designs to understand and optimize pharmaceutical product with high anticipated quality [22]. The International Conference on Harmonization described different tools for implementing the Quality by Design approach. Design of Experimentation or DoE is one of the tools, provides scientific understanding of the effects of multiple process parameters and raw material attributes on product CQAs and leads to establishment of a “design space” and manufacturing control strategy [23]. The “design space” is the region of experimental space where multifactorial combination and interaction of them demonstrated to provide quality of product and assurance thereof. To understand the variables and their interactions, many statistical experimental designs have been recognized as useful techniques. Factorial design, Response surface methodology (RSM) and Mixture designs were used for selected significant factors involved in optimization [23, 24, 25]. DoE was previously used in formulation studies to observe effect of different formulation and process variables and further optimize those [24, 25, 26].

The present investigation deals with optimization of Verapamil HCl floating tablet in terms of floating lag time, buoyancy time and drug release using QbD approach. Risk assessment was carried based on understanding of effect of different process and formulation variables on floating lag time and drug release from floating tablet. DoE was used in the development, since it enables simultaneous evaluation of critical parameters with respect to their actual significance on the considered responses and possible interrelationships among them. The critical parameters were amount of HPMC K15M and sodium bicarbonate: citric acid ratio to formulate floating tablet.

The 2^2 factorial designs in replicate were employed for DoE. Regression analysis was performed to identify the best formulation and to validate the model by comparing the experimental results with the theoretical values of the responses [27, 28]. The selected design and QbD approach allowed an efficient selection of the best formulation composition and of the most suitable experimental conditions in the shortest time and with the minimum number of experiments.

MATERIALS AND METHOD

Materials

Verapamil HCl was received as gift sample from Ajanta Pharma, Mumbai, India. HPMC (K4M, K15M, and K100M) and PVP K30 were gifts from Medley Pharmaceuticals, Mumbai. All other chemicals were of analytical grade

Compatibility studies

Compatibility studies of drug and polymers were studied using Differential scanning Calorimetry (DSC) techniques. DSC thermograms were recorded at a standard heating rate of 10ºC/min over a temperature range 50-400 ºC under nitrogen atmosphere in order to eliminate oxidative and pyrolytic effects.

Risk assessment of Critical Quality Attributes:

ICH Q 9 guidance document introduced the concept of quality risk management for assessing, controlling, communication and reviewing risks to the Quality Target Product Profile (QTPP) across product life cycle. The risk assessment for the floating tablet experiment was carried out; the key parameters called critical quality attributes (CQA) that could impact floating tablet formulation were identified shown in table 1. Concentration of polymer and concentration of gas generating agent was high risk parameters and were considered for design of experimentation for the Verapamil HCl Floating tablet.

Table 1: Risk assessment of formulation and process parameters

DP CQA	Drug substance particle size	HPMC grade &concentration	Gas generating agent ratio	Granulation	Blending
Assay	Low	Low	Low	Low	High
Content Uniformity	High	Low	Low	Low	High
Dissolution	High	High	Medium	High	Low
Floating Lag time	Low	High	High	High	Low
Total Floating time	Low	High	High	High	Low
Hardness of tablet	Low	Medium	Low	Low	Low

Preparation of Verapamil HCl Floating Matrix (VFM) Tablets

Verapamil HCl Floating matrix (VFM) tablets were prepared by wet granulation method. Verapamil HCl was mixed with required quantity of HPMC K15M, sodium bicarbonate, MCC for 4-5 mins, the blend was granulated using 4% of PVP K30 (w/v) in Isopropanol solution as binder. The wet mass was sieved (sieve # 22) and granules were dried at 40^0C. Further dried granules were sieved (sieve # 25) and mixed with 0.5 % magnesium stearate and talc. The resultant granules were then compressed into tablets using a 12 station tablet punching machine with 10 mm diameter concave punches. [29, 30, 31]

Table 2: Experimental design of Verapamil HCl Floating matrix tablets as per 2^2 factorial

Formulation code	Independent Variables		Dependent Variables	
	X_1 (HPMC K15M)	X_2 (Gas generating agent)	Drug release (%) Y_1	Floating lag time (sec.)Y_2
DF1	-1(60mg)	-1(40:20)	55.40	39.33±1.52
DF1R	-1(60mg)	-1(40:20	53.28	40.66±1.52
DF2	-1(60mg)	1(50:25)	56.67	32.00±2.00
DF2R	-1(60mg)	1(50:25)	62.85	32.66±1.52
DF3	1(70mg)	-1(40:20)	52.36	56.33±1.52
DF3R	1(70mg)	-1(40:20)	52.91	58.00±1.00
DF4	1(70mg)	1(50:25)	54.59	48.33±1.52
DF4R	1(70mg)	1(50:25)	56.83	49.33±1.52

Each tablet contains Verapamil HCl 120mg, MCC 20mg, PVPK30 20mg, Talc 5mg, Magnesium Stearate 5mg.

Design for Experimental for Verapamil HCl Floating matrix tablets:

In present investigation, 2^2 full factorial designs with 2 replicates were selected for design of experimentation of Verapamil HCl Floating matrix tablet[32, 33]. HPMC K15M concentration (X_1) and gas generating agent (X_2) were selected as independent variables whereas Drug release at 12 Hr (Y_1) and Floating lag time (Y_2) were chosen as dependent variables. HPMC K15M was evaluated at60 mg (-1) and 70 mg (1). While content of gas generating agent (sodium

bicarbonate and citric acid in 2:1 ratio) evaluated at 40mg: 20mg (-1) and 50mg: 25mg (1) of total tablet weight. The levels of these two formulation parameter were determined from preliminary study.

Post compression parameters*:*

The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity [34]

In Vitro Buoyancy studies:

The in vitro buoyancy was determined by buoyancy lag time per the method. The test was performed by placing each of the tablets in a 250-mL beaker, containing 200 mL of 0.1 N HCl, pH 1.2, maintained at 37±0.5°C in a water bath. Their physical state was observed for 24 h. The time between introduction of the dosage form and its buoyancy on the 0.1 N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were observed visually. Test was carried out in triplicate.[31, 35]

In Vitro Dissolution studies:

The in vitro dissolution study was performed by using a USP XXII paddle apparatus (Elecrolab-TDT 06L, Mumbai) at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 N HCl used as the dissolution medium and was maintained at 37±1°C. Then, 5 ml of the dissolution medium was withdrawn at specified time interval until 12 h. The samples were filtered through a membrane filter (0.45-µm), suitably diluted and exact 5 ml of fresh medium was replaced to the dissolution vessel after each withdrawal to maintain a constant quantity. Absorbance of these solutions was measured by using a UV spectrophotometer (UV-1800, Shimadzu, Japan) at 278 nm. [31, 35]

Mechanism of drug release:

To analyze the mechanism of drug release from the floating tablets, the *in vitro* dissolution data of the formulations were fitted to the zero order, first order, Higuchi model and Korsmeyer-Peppas model as per the method described.[35, 38]

Statistical analysis and optimization:

Data obtained from all Floating matrix tablet formulations were analyzed using Design Expert software and used to generate the study design and the surface response plots. The best fitting model was selected based on comparisons of several statistical parameters, provided by Design Expert software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F test and P values were also calculated using the software. The relationship between the dependent and independent variables was further elucidated using response surface plots. Subsequently, a graphical optimization

technique using overlay plots were used to generate new formulations with the desired responses.[24, 33,]

Validation of the experimental design [33]

To validate the chosen experimental design, the checkpoints were selected from the design space and the experimental values of the responses were quantitatively compared with predicted values and the relative error (%) was calculated.

RESULTS AND DISSCUSSION

Based on QbD principles, risk assessment was carried as shown in table 1 and high risk parameters, i.e. Critical Quality Attributes (CQAs) based on their strong correlation to Total Quality Product Profile (TQPP) were considered for Design of experimentation to ensure a predefined quality of the product. In order to define the ‘‘design space’’ the critical formulation variables (independent variables) and the responses able to measure the product quality were defined based on prior knowledge and preliminary studies. The independent variables considered for Floating matrix tablet formulations were Concentration of HPMC K15M polymer and gas generating agent quantity since they were considered critical in determining responses DR12 hr, and Floating lag time (FLT). Based on the number of parameters or variables and their levels, 2^2 full factorial design with 2 replicates with ‘8-runs’ was selected for Verapamil HCl Floating matrix tablet optimization, as it reduces the number of experiments that are required to evaluate the effect on TQPP. Floating matrix tablets were prepared by wet granulation method using HPMC K15M polymer at different concentration.

Drug polymer compatibility studies using DSC

DSC studies revealed that the drug exhibit sharp melting endothermic peak at 146°C and thermograms of the physical mixture of Verapamil HCl with polymers exhibited endothermic peak in the vicinity of its melting point range indicates absence of any drug-polymer interactions as shown in (figure 1).

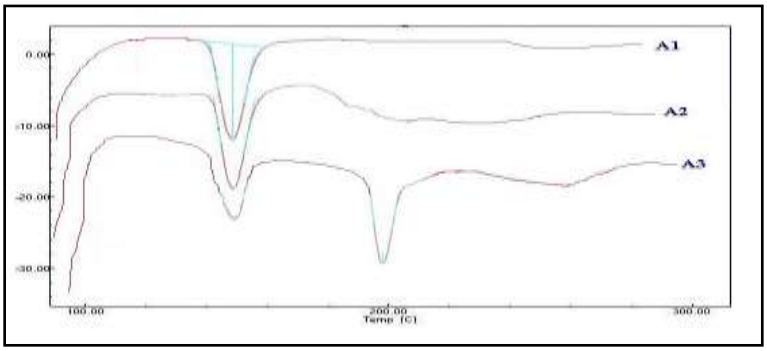


Figure 1: DSC thermograms of pure drug (A1), physical mixture (A2) and tablet (A3)

Evaluation of Floating matrix tablet

All prepared floating matrix tablets were evaluated for thickness, hardness, friability, weight variation, Drug content represented in Table 4. The hardness of Floating matrix tablets were from 6.0 - 6.6kg/cm^2 and increased due to increasing weight of the tablet. The average thickness of the floating matrix tablets (DF1-DF4R) was observed in the range of 4.27 to 4.37 mm. All the floating matrix tablets complies the Indian Pharmacopoeia standard for weight variation and friability as presented in Table 3.The Drug content of the Floating matrix tablet (DF1 to DF4R) was evaluated and the results are presented in Table 3. The maximum percentage of drug content from the different formulations was found to be 101.9 %and minimum percentage of drug content was found to be 97.6%.Hence it is concluded that all the formulations are falling within the Pharmacopoeial limits

Table 3: Physicochemical Parameter

Formulation Code	Physicochemical Parameter				
	Weight variation**(mg)	Thickness* (mm)	Hardness* (kg/cm2)	Friability** (%)	Content uniformity** (%)
DF1	292±1.15	4.27±0.035	6.0±0.42	0.74±0.083	97.6±.039
DF1R	293±1.15	4.32±0.021	6.1±0.29	0.73±0.088	98.3±0.90
DF2	307±1.52	4.36±0.037	6.6±0.26	0.72±0.081	98.6±0.96
DF2R	306±0.57	4.37±0.020	6.5±0.27	0.73±0.020	99.0±0.72
DF3	302±1.52	4.32±0.022	6.4±0.17	0.59±0.098	97.5±0.98
DF3R	303±1.52	4.36±0.024	6.5±0.29	0.69±0.098	98.2±0.95
DF4	316±1.15	4.35±0.017	6.5±0.44	0.42±0.077	96.4±0.50
DF4R	315±1.52	4.35±0.025	6.4±0.36	0.47±0.116	101.93±0.51

All values are mean ± SD: - * n = 6; ** n = 20

Data analysis:

All the formulations were then evaluated in a randomized order for Floating lag time and % Drug release at 12 Hr. Analysis of variance (ANOVA) was applied for testing the significance and validity of the postulated model, using a 1% significance level. ANOVA results shown in Table 4 indicated that the assumed regression model was significant and valid for the examined responses.

Table 4: ANOVA results for formulation variables of Verapamil HCl Floating matrix Tablets

	Source	Sum of Squares	df	Mean square	F value	P value Probe ⟩F	Comment
Response (Y1) Drug Release at 12 hr	Model	119.4	3	39.8	19.19	0.0077	Significant
	A-HPMC K15M	69.38	1	69.38	33.45	0.0044	Significant
	B-Gas Generating Agent	35.11	1	35.11	16.93	0.0147	Significant

	AB	14.91	1	14.91	7.19	0.0552	Not significant
	Pure Error	8.3	4	2.07			
	Cor Total	127.7	7				
Response(Y2)	Model	514.37	3	171.46	31.9	0.003	Significant
Floating lag time	A-HPMC K15M	435.12	1	435.12	80.95	0.0008	Significant
	B-Gas Generating Agent	78.13	1	78.13	14.53	0.0189	Significant
	AB	1.13	1	1.13	0.21	0.6711	Not- Significant
	Pure Error	21.5	4	5.38			
	Cor Total	535.88	7				

Effect on Drug release at 12 hr

The *in-vitro* drug release of Floating matrix tablets was presented in Table 6. Release of drug from Floating matrix tablet varied according to the concentration of HPMC K15M polymer and gas generating agent quantity. From polynomial equation (1) it was observed that drug release was decreased as polymer concentration increased. Also, it was observed that drug release decreased with increase HPMC K15M polymer concentration .It has excellent, gelling properties and also helps in controlling drug release.

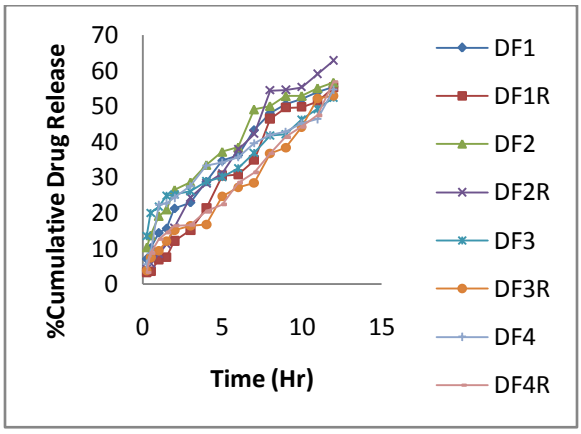


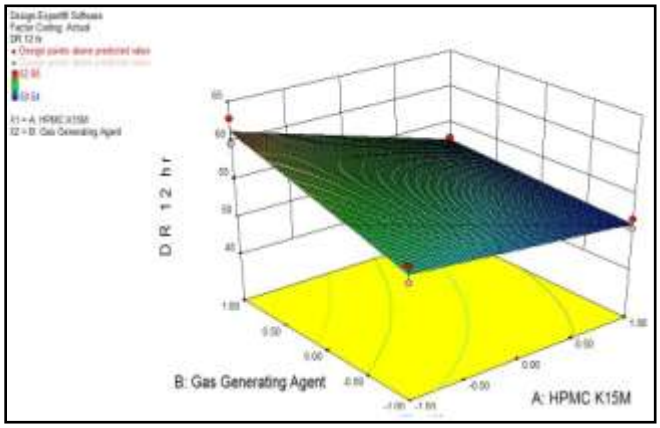
Figure 4: *In-Vitro* dissolution study of Verapamil HCl Floating tablets.

It was reverse in case of gas generating agent quantity; drug release was increased at high level of gas generating agent quantity, as gas generating agent helped to swell HPMC at low level but at high level gas generating agent might have formed pores in matrix resulting into increased drug release.

$$Y_1 = 54.86 - 2.95\ X_1 + 2.09\ X_2 - 1.36\ X_1X_2$$ .....Equation (1)

The relationship between variables was further elicited using Half-normal plots/Pareto charts as shown in figure 2. In Half-normal plot, large effects or absolute effects appear in the upper-right corner of the plot i.e. polymer concentration has more significant effect on drug release as compared to gas generating agent. In Pareto chart, effects above the Bonferroni Limit are almost

certainly significant indicating importance of polymer and gas generating agent quantity. The effect of independent variables on drug release indicates the linearity in surface response and contour plot shown in figure 2 The calculated F-value and p-value for main response Y_1 as shown in ANOVA table 4 and individual terms of equation, indicates a significant effect of the two factors on the response Y_1 i.e. Drug release



(a) **(b)**

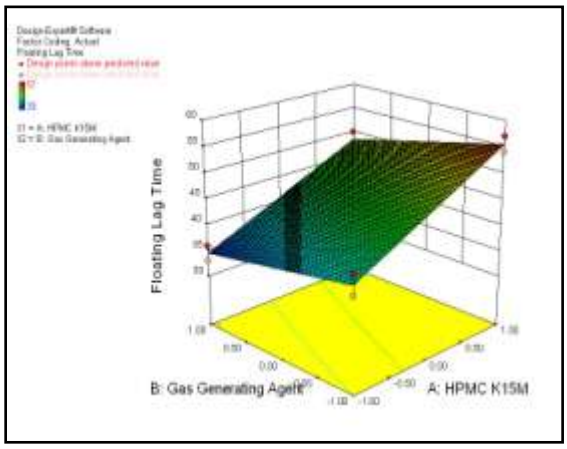
Figure 2: Surface response plot (a) and Contour plot (b) demonstrating influence of polymer concentration and gas generating agent on drug release at 12 hr.

Effects on Floating lag time:

The Floating lag time of Verapamil HCl floating matrix tablet was found to be in between 32.00 to 58.00 second. The increase in concentration of HPMC K15M showed a gradual rise in floating lag time. This is because of the gelling nature of the polymers. Formulation DF3R show high Floating lag time were DF2 had low Floating lag time as shown in Table 3.

$$Y_2 = 44.63 + 7.37X_1 - 3.13X_2 - 0.37X_1X_2 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{Equation(2)}$$

The positive value for the coefficient of X1 and negative value for X2 in the equation (2) indicates increase in the Floating lag time with increase in the polymer concentration of HPMC K15M , whereas gas generating agent quantity showed negative effect on Floating lag time . In half-normal plots for Floating lag time, it was confirmed that polymer has large (absolute) effect as compared to gas generating agent ratio as shown in figure 3 .In Pareto chart effect above the Bonferroni Limit i.e. Polymer and gas generating agent is certainly significant, while effect above the T-Value Limit, gas generating agent quantity is possibly significant. The effect of two independent variables was found to be linear in surface response of Floating lag time.



(a) **(b)**

Figure 3: Surface response plot (a) and Contour plot (b) demonstrating influence of polymer concentration and gas generating agent on Floating Lag Time.

Drug release kinetics:

The release data obtained was fitted into various mathematical models using PCP Disso - V2.08 software. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression co-efficient were determined by Korsmeyer - Peppas equation to understand the release mechanism. Drug release kinetics results are shown in Table 5.

Table 5: Model fitting data of Verapamil HCl floating tablets for drug release kinetics

Formulation Code	Korsmeyer-Peppas		Zero Order	First Order	Matrix Model	Hix.Crow.	Mechanism of release kinetics	Best fit model
	n	R^2	R^2	R^2	R^2	R^2		
DF1	0.5548	0.9953	0.9342	0.9489	0.9913	0.9443	Non Fickian	Peppas
DF1R	0.8209	0.9886	0.9863	0.9886	0.9478	0.9879	Non Fickian	Peppas
DF2	0.4572	0.9957	0.8490	0.8778	0.9944	0.8687	Fickian	Peppas
DF2R	0.7571	0.9944	0.9814	0.9867	0.9649	0.9851	Non Fickian	Peppas
DF3	0.5138	0.9673	0.7745	0.8065	0.9835	0.7963	Non Fickian	Matrix
DF3R	0.6227	0.9772	0.9705	0.9758	0.9601	0.9742	Non Fickian	Peppas
DF4	0.3110	0.9670	0.6741	0.7320	0.9538	0.7139	Fickian	Peppas
DF4R	0.6360	0.9845	0.9811	0.9838	0.9512	0.9831	Non Fickian	Peppas

Establishing Design Space and Control Strategy:

In general, the knowledge space within the QbD-approach represents the whole range of interactions between Critical Process parameters and their effects on Critical Quality Attributes that has been examined during process characterization studies. During the process and formulation variable characterization study, the impact of the input parameters HPMC K15M polymer and gas generating agent quantity was assessed. The criteria considered of responses, drug release at 12 hr in range of 50-55 %.Floating lag time in range of 40-50 Second. This study lead to the knowledge space and ultimately design space from multidimensional combination of

HPMC K15M polymer and gas generating agent leads to the acceptable operating ranges for formulating Floating matrix tablet with respect to target product profile. The variables ranked as high risk in the initial risk assessment are included in the control strategy. Design space shown in figure 5 also called as overlay plot which is shaded region with yellow color indicates that region of successful operating ranges.

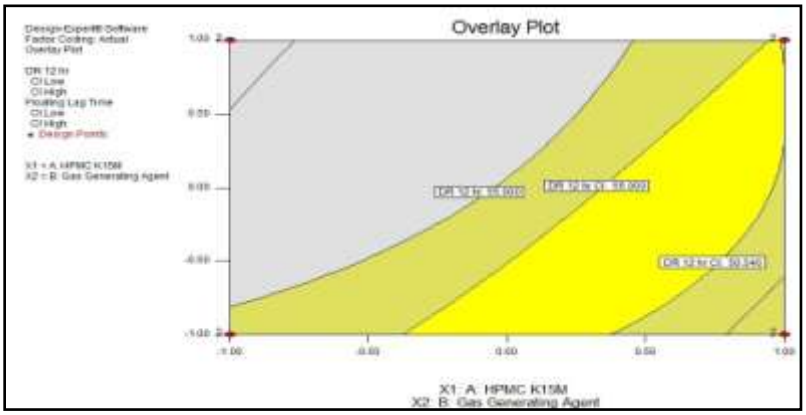


Figure 5: Design space (Overlay Plot) for Verapamil HCl floating tablets

Validation of optimized formulations of floating matrix tablets:

From the polynomial equations generated for each responses using Design Expert Software (8.0.4), intensive grid and integrated search was performed over the experimental domain and three optimized formulations were selected (DXF1, DXF4 and DXF6).The statistically optimized formulation fulfilled all the physicochemical criteria. In *vitro* buoyancy study and dissolution studies were carried out on the prepared optimized formulation to verify the theoretical prediction. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within 3%. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model Table 6.

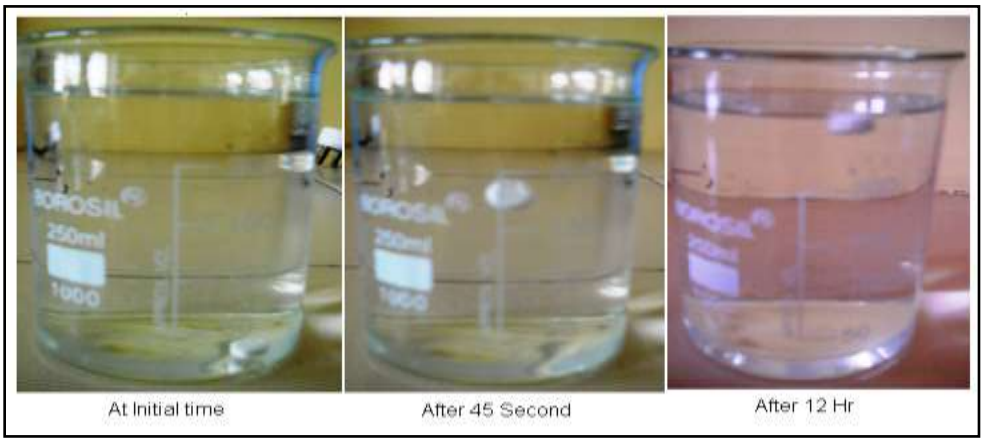


Figure 6: *In Vitro* buoyancy study of Optimized Floating Matrix Tablet

Table 6: Comparison of experimental results with predicted responses of Verapamil HCl Tablets formulation

Formulation Code	Composition (mg/tab)		Response	Predicted Value	Experimental Value	Standard Error
	X1	X2				
DXF1	68.6	48.1/24.05	Y1 (%DR_{12})	53.41	52.12	2.415%
			Y2(FLT) (Sec)	47.84	46.50	2.801%
DXF4	68	41.3/20.6	Y1 (%DR_{12})	52.15	50.90	2.39%
			Y2 (FLT) (Sec)	51.5	50.00	2.912%
DXF6	63.9	40.0/20.0	Y1 (%DR_{12})	53.12	52.23	1.67%
			Y2 (FLT) (Sec)	46.02	45.00	2.21%

CONCLUSION:

It can be concluded that QbD approach can be successfully implemented in the development of Verapamil HCl floating matrix tablet formulation with predictable drug release and floating lag time. All Critical parameters ranked as high risk in the initial risk assessment are included in the control strategy because the conclusion of the experiments was dependant on the range studied and the complex multivariate relationship between variables. Thus, the control strategy is an integrated overview of how quality is assured based on knowledge space. Design space was defined as per to ICH Q8 guideline. From this study it can be concluded that formulation prepared within design space can produce formulation with acceptable *in vitro* drug release and floating lag time. It can be expected that this application of the DoE tools in QbD approach could be useful for further formulation studies especially related to process parameters which contribute significantly to the product quality, but these are beyond the current experimental work.

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ABBREVIATIONS:

HPMC = Hydroxypropyl methylcellulose

MCC = Microcrystalline cellulose

FLT = Floating lag time

QbD = Quality by Design

CMAs = Critical Process Parameters

CPAs = Critical Process Parameters

CQA_S	=	Critical Quality Attributes
QTPP	=	Quality Target Product Profile
DR 12 hr	=	Drug release after 12 hr
USP	=	United State Pharmacopoeia
ANOVA	=	Analysis of Variance
ICH	=	International Conference Harmonization

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