ORIGINAL ARTICLE

Formulation developement and evaluation of floating matrix tablet of Verapamil HCl

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The objective of this study was to develop the Verapamil hydrochloride sustained-release floating matrix tablets using gas-generation approach to prolong the gastric residence time. Floating tablets were prepared using hydroxypropyl methylcellulose K4M (HPMC) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and Citric Acid as floating assistant agent. A 3^2 factorial design was used to select the optimized formulation wherein HPMC K4M (X1) and Citric Acid (X2) were taken as independent variables and Floating lag time (FLT), amount of drug release after 24hrs. (Q_{24}) were taken as dependent variables. The release data were evaluated by the model-dependent (curve fitting) method using PCP Disso v2.08 software. Optimisation studies were carried out by using the Design Expert software (version 8.0.1). The floating tablets were evaluated for uniformity of weight, hardness, thickness, swelling index, friability, drug content, FLT, and *in vitro* release. The *in vitro* drug release followed Hixson-Crowell model and mechanism of drug release was found to be anomalous or non-fickian type. The optimized formulation was F3 containing HPMC K4M 15%, and Citric acid 3% having minimum FLT and maximum drug release after 24 hrs.

Key words: *Floating lag time, sustained release, verapamil hydrochloride*

INTRODUCTION

Oral delivery of drugs is the most preferred route of administration due to ease of administration. Drug bioavailability of pharmaceutical oral dosage forms is influenced by various factors. One important factor is the gastric residence time (GRT) of these dosage forms.[1] A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments.

Under certain circumstances prolonging the gastric retention of a delivery system for achieving greater therapeutic benefit of the drug substance is desirable.[2] A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs.[3] The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of flotation,[4] mucoadhesion,[5] sedimentation,[6] expansion,[7] modified shape systems[8] or by the simultaneous administration of pharmacological agents that delay gastric emptying.[9,10] Verapamil HCl is a calcium channel blocker used in the treatment of several cardiovascular disorders, particularly angina pectoris supraventricular tachycardia and hypertension.[11] It is established that 90% of Verapamil HCl is absorbed following its oral administration and then it reaches maximum plasma concentration within 1-2 hrs.

However, due to first pass effect it has low bioavailability (10-20%).[12] It has short half-life of 4 hrs, so dosing frequency is high. The physicochemical properties of Verapamil HCl and its short half-life make its suitable candidate for preparation of gastroretentive tablets.[13,14] Gastroretentive drug delivery systems can improve the controlled delivery of drugs that have an absorption window in the stomach by continuously releasing the drug for a prolonged period of time, thus ensuring its optimal bioavailability.[15] The objective of present investigation is to prepare and evaluate gastroretentive tablets of Verapamil HCl based on gas generation approach using hydroxyl propyl methyl cellulose K4M and Citric acid.

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MATERIALS AND METHODS

Materials

Verapamil HCl was procured as a gift sample from (Nicholas Piramal, Mumbai), polymer Hydroxy propyl methyl cellulose K4M (HPMC K4M), Sodium bicarbonate, Citric acid, Povidone K-30, Magnesium stearate were procured as gift samples from Concept pharmaceuticals Ltd. Aurangabad, Lactose was procured from Loba Chemicals. All other chemicals and solvents used were of analytical grade.

Methods

Preparation of floating matrix tablets

The nine formulations bearing 120mg of drug Verapamil HCL were prepared by wet granulation method. HPMC K4M was used as rate retarding polymer, sodium bicarbonate as a gas generating agent, PVP K30 was used as a binding agent, magnesium stearate as lubricating agent, talc as glidant and isopropyl alcohol was used as granulating agent respectively. Verapamil HCl, HPMC K4M, sodium bicarbonate and citric acid were mixed thoroughly in mortar and pestle for five min to obtain a homogeneous blend. The blend was granulated using PVP K-30 solution into IPA and the wet mass obtained was passed through sieve # 16 to obtain the granules. The granules were dried at 50°C for 1 hr. The dried granules were lubricated with magnesium stearate and talc then passed through sieve # 22. The granules compressed using Labpress rotary tablet machine using 12 mm flat faced punches [Table 1].

Evaluation of granules flow properties

The prepared granules were evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio as per official procedures.[16]

Evaluation of floating tablets

The compressed tablets were evaluated for appearance, thickness, hardness, and friability, FLT and FT.[17]

Drug content and weight variation

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing 0.1 g of Verapamil Hydrochloride, shake with 150 ml of 0.1 M hydrochloric acid for 10 minutes, add sufficient 0.1 M hydrochloric acid to produce 200.0 ml and filter. Dilute 10.0 ml of the filtrate to 100.0 ml with water and measure the absorbance of the resulting solution at the maximum at about 278 nm. Calculate the content of C27H38N2O4, HCl taking 118 as the specific absorbance at 278 nm.[18] The tablets were also evaluated for weight variation as per official method.

In vitro buoyancy study

All formulations were subjected to buoyancy test. Buoyancy test was done using USP Type II apparatus at 50 rpm maintained at 37± 5°C. Tablets were placed in 900 ml jar containing 0.1N HCl as dissolution medium. The FLT and FT was noted.[19]

Dissolution studies

The release rate of Verapamil HCl from floating matrix tablet ($n = 3$) was determined using USP dissolution test apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 50 rpm. The temperature of the medium was maintained at 37 ± 0.5°C and the study was carried out for 24 hr. Aliquot of 5 ml were withdrawn at an interval of 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hrs respectively. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatmann filter paper no.41 and the volume made up to 10 ml with 0.1N HCL. The samples were analyzed spectrophotometically (SHIMADZU-1700) at 278 nm.

Dissolution efficiency

The % dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain limit, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It is calculated by the following equation,

$$D.E. = \frac{\int_0^t y \pm \times dt}{y_{100} \times t} \times 100 \quad (1)$$

Where y is drug percent dissolved at time t

Swelling study

The previously weighed tablets were placed in dissolution vessels containing 0.1 N HCl at 37± 0.5°C. At selected time interval (30 min, 1, 2, 4, 6, 8, 12 and 24 hr respectively) tablets were withdrawn using the basket. The tablet and basket were blotted to remove excess water and then weighed. The swelling index was calculated by the following equation,

$$\text{Swelling index} = \frac{W_t - W_0}{W_0} \quad (2)$$

Where, W_0 - initial weight of tablet.
W_t - weight of tablet at time t

Kinetics of drug release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model. In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e., release exponent was calculated.

Analysis of data by design expert software

A 32 full factorial design was selected and the two factors were evaluated at three levels, respectively [Table 2]. The statistical treatment and interpretation of data was done by Stat Ease Design Expert 8.0.1 software. The data were also

subjected to analysis of variance (ANOVA) and 3-D response surface methodology to study the interaction of independent variables.

Grid analysis

The grid analysis was performed for selection of the optimized level for FLT, and Q_{24}. The formulation F3 was selected as optimized formulation.

Stability study

The optimized formulation (F3) which gave desired drug release for extended period of time was selected, packed in aluminum foil and subjected to stability studies as per ICH guidelines, 40 ± 2°C and 75 ± 5% RH. Samples were withdrawn at time intervals of one to three months. The samples were evaluated for appearance, hardness, friability, weight variation, swelling index FLT, FT, assay and *in vitro* release profile.

Table 1: Formulation of factorial design batches

Ingredients (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil HCl	120	120	120	120	120	120	120	120	120
HPMC K4M (X1)	75	75	75	100	100	100	125	125	125
Citric acid (X2)	05	10	15	05	10	15	05	10	15
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Poly vinyl pyrrolidone K30	60	60	60	60	60	60	60	60	60
Magnesium stearate	05	05	05	05	05	05	05	05	05
Talc	05	05	05	05	05	05	05	05	05
Total weight (mg)	360	365	370	385	390	395	410	415	420

Table 2: Amount of variables in 3^2 factorial design batches

Coded values	Actual values (%)	
	X1	X2
-1	15	1
0	20	2
+1	25	3

RESULTS AND DISCUSSION

Evaluation of granules flow properties

The angles of repose of all the formulations were within the range of 27.70-30.81, of good flowability. The bulk density of granules was found to be between 0.43-0.48 gm/cm^3. The values indicate good packing capacity of granules. The tap density of the granules of factorial design batches were found in the range of 0.48-0.56 gm/cm3. The bulk density and tap density was used to calculate the percent compressibility of the granules.

Good compressibility of the granules indicated in the Carr's index of the granules was observed between 11.32 and 18.76. The values of the Hausner's ratio were found to be between 1.04-1.23, indicating good flowability. The results were shown in Table 3.

Evaluation of floating tablets

All tablets of the factorial design batches were off white colored with smooth surface, circular flat faced with good texture.

There were no marked variations in the thickness of tablets within each formulation (<5%) indicating uniform behavior of granules throughout the compression process. The thickness of the factorial design batches were found in range of 3.68-3.89 mm. The hardness of the tablet was found to be in the range of 6.5-7.8 kg/cm^2. This ensures good mechanical strength. This resulted due constant tablet press setting across all batches of factorial design irrespective of weight variation.

The tablet density close to one results in good floating characteristics *in vitro*. The tablet densities of the factorial design batches were found to be between 1.13-1.19 gm/cm^3.

Friability of the tablet is the measure of the tablets strength. Tablets with friability less than 1% of their weight are acceptable. The friability of the factorial design batches were in the range of 0.13-0.40%, which was within the specified limits. The results were summarized in Table 4.

Table 3: Flow properties of granules

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Angle of repose		Hausner's ratio
				Before lubrication	After lubrication	
F1	0.431±0.002	0.486±0.005	11.32±0.12	31.23±1.14	28.22±1.06	1.13±0.05
F2	0.448±0.003	0.512±0.010	12.50±0.32	32.60±1.54	29.86±1.22	1.04±0.05
F3	0.438±0.130	0.532±0.016	17.67±1.08	32.57±1.44	30.81±1.09	1.21±0.09
F4	0.452±0.015	0.547±0.023	17.37±1.03	30.07±1.10	27.70±1.05	1.21±0.05
F5	0.470±0.020	0.559±0.021	15.92±1.42	31.41±1.22	29.35±1.34	1.19±0.07
F6	0.481±0.004	0.566±0.011	15.02±0.78	30.86±1.26	28.57±1.12	1.18±0.05
F7	0.430±0.007	0.508±0.013	15.35±0.44	32.35±1.08	30.19±1.45	1.18±0.03
F8	0.434±0.006	0.530±0.005	18.11±0.30	31.18±1.08	28.20±1.40	1.22±0.09
F9	0.459±0.021	0.565±0.016	18.76±0.90	31.21±1.32	29.52±1.23	1.23±0.02

Table 4: Evaluation of tablet properties of factorial design batches

Formulation	Appearance	Thickness* (mm)	Hardness* (kg/cm²)	Tablet density*	Friability (%)*
F1	Off white, circular,12 mm flat faced	3.68±0.02	7.8±1.23	1.19±0.01	0.27±0.04
F2	Off white, circular,12 mm flat faced	3.7±0.01	7.3±0.59	1.19±0.01	0.18±0.03
F3	Off white, circular,12 mm flat faced	3.79±0.01	7.0±0.48	1.16±0.01	0.31±0.05
F4	Off white, circular,12 mm flat faced	3.77±0.06	7.2±1.14	1.17±0.03	0.21±0.06
F5	Off white, circular,12 mm flat faced	3.77±0.05	7.3±1.65	1.18±1.18	0.33±0.03
F6	Off white, circular,12 mm flat faced	3.84±0.04	7.1±0.42	1.16±0.01	0.40±0.06
F7	Off white, circular,12 mm flat faced	3.89±0.03	6.5±0.35	1.13±0.01	0.18±0.12
F8	Off white, circular,12 mm flat faced	3.88±0.02	6.8±1.65	1.14±0.01	0.22±0.02
F9	Off white, circular,12 mm flat faced	3.78±0.02	7.2±1.12	1.15±0.01	0.13±0.05

*All values are expressed as mean±SD, *n*=3, †All values are expressed as mean±SD, *n*=20

Drug content and weight variation

The drug content of the nine formulations was found to be between 97-101%. The value ensures good uniformity of the drug content in the tablet.

The average weight of tablets within each formulation was found to be uniform. This indicates uniform filling of die cavity during tablet compression. Since the average weight of tablet is more than 250 mg, the test requirements are met if none of the individual tablet weights are less than 95% or more than 105% of the average weight.

In vitro buoyancy study

The preliminary studies revealed polymer HPMC K4M below 15% was not able to float for 24 hr. and possessed poor tablet integrity. Thus, polymer HPMC K4M was used above 15% and Citric acid was incorporated to reduce floating lag time (FLT).

The factorial design batches were formulated and *in vitro* buoyancy was studied. As amount of HPMC K4M increased from formulations F1-F3 (15%), F4-F6 (20%) and F7-F9 (25%) resulted in overall increase in FLT. This could be accounted to the fact that an increase in polymer concentration lead to delay in hydration of polymer and subsequently CO_2 gas generation.

The factorial formulations containing different concentrations of citric acid were then studied to find out its effect on the FLT. It is observed that significant effect of the citric acid concentration on the FLT within batches (F1, F4, F7), (F2, F5, F8) and (F3, F6, F9) containing 1, 2 and 3% of citric acid concentration, respectively. Thus, decreased trend in FLT after increase in citric acid concentration was observed. Higher citric acid concentration leads to more CO_2 gas generation after reaction with sodium bicarbonate and caused the tablet to float within a shorter period of time.

The most successful formulation was F3 containing 15% of polymer HPMC K4M and 3% of citric acid which took 19 sec to float and given drug release of about 103.9% after 24 hr.

Dissolution studies

The factorial design batches were then formulated and *in vitro* release was studied. Formulations F1-F3 containing 15% of polymer concentration showed higher drug release after 24 hr.

Table 5: A 3^2 factorial design and level of independent variables

Formulation code	Coded values		FLT (sec)±SD	Q_{24} (%)±SD	Tablet integrity
	X1	X2			
F1	-1	-1	22.33±2.08	96.36±0.27	+
F2	-1	0	20.67±2.31	97.87±1.05	+
F3	-1	+1	19.00±2.00	103.9±1.61	+
F4	0	-1	32.67±3.06	94.08±1.59	+
F5	0	0	30.67±1.53	94.98±1.23	+
F6	0	+1	25.67±3.06	97.57±0.53	+
F7	+1	-1	58.00±2.00	87.95±2.10	+
F8	+1	0	49.00±2.65	90.82±1.45	+
F9	+1	+1	43.33±2.08	92.90±1.11	+

The response from the dissolution study taken was Q_{24}. The response Q_{24} of the formulations F1, F4 and F7 containing 15%, 20% and 25% of the polymer showed significant difference indicating the rate retarding effect of polymer. The Q_{24} i.e., drug release after 24hrs for formulations F1, F4 and F7 were 96.36 ± 0.27, 94.08 ± 1.59 and 87.95 ± 2.10% respectively.

However, with constant polymer concentration F1-F3 (15%) and increased citric acid concentration (1%, 2% and 3% respectively) showed increased Q_{24}. Same trend was observed for formulations bearing 20% polymer (F4-F6) and 25% polymer (F7-F9). This may be due to erosion of the tablet because of presence of citric acid. The release profile of the drug from the formulation was as follows, F3> F2> F1, F6> F5> F4 and F9> F8> F7 which depicts the significant effect of citric acid.

Most successful batch was F3 with 15% HPMC K4M and Citric acid 3%. The result of cumulative drug release (%) of all formulation batches were shown in Table 5. The comparative drug release shown in Figure 1.

Dissolution efficiency

The dissolution efficiency of the all factorial design batches were found between 5.23 to 72.75%.

Swelling study

The swelling behavior of all the factorial design batches was studied. The study was carried out for 24hrs and the swelling indices at time interval of 0.5, 1, 2, 4, 6, 8, 12, and 24 hrs respectively, was determined. The release study carried out for the 24 hrs, hence swelling behavior was also studied for 24 hr.

A characteristic behavior was found within the formulations F1-F3, F4-F6 and F7-F9 containing 15, 20 and 25% of polymer concentration, respectively. The swelling studies revealed that the swelling index is increased with an increase in the polymer concentration. A significant increase in the swelling index was observed within the formulations F1-F3, since the concentration of citric acid is increased. The increase concentration of citric acid could have caused erosion of the tablet with increased liquid media penetration and thus fast swelling. A similar trend was observed within batches F4-F6 and F7-F9 respectively. The higher swelling index was observed with the formulation F9 (S.I. = 2.227) containing 25% of the polymer and 3% of the citric acid. The swelling behavior of the polymer HPMC K4M at different concentration also affects the drug release profile. Higher swelling leads to imbition of more liquid medium, thus leading to polymer chain relaxation with volume expansion and subsequently affecting drug release profile. The higher penetration rate of gastric fluid into the tablet leads to faster CO_2 gas generation and thereby reducing the FLT. The result of swelling index of all formulation batches were shown in Table 6. The comparative swelling shown in Figure 2.

Kinetics of drug release

The results showed that most of the factorial design batches followed Hixon-Crowell model. The R2 value of Hixon-Crowell model was found close to one as shown in Table 7.

Hixon-Crowell proposed that the particle regular area is proportional to the cubic root of its volume and derived an equation that can be described in the following manner,

$$W_0^{1/3} - W_t^{1/3} = K_s T \quad (3)$$

Where,

W_0 is the initial amount of drug in pharmaceutical dosage form,

Wt is the remaining amount of drug in pharmaceutical dosage form at time *t* and

K_s is a constant incorporating the surface volume relationship.

The above expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimension diminishes proportionally in such a manner that the initial geometrical form is constant all the time. When this model

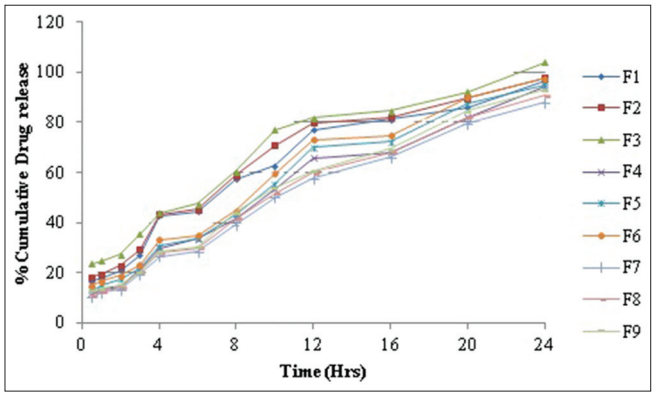

Figure 1: Percentage cumulative drug release of factorial design batches

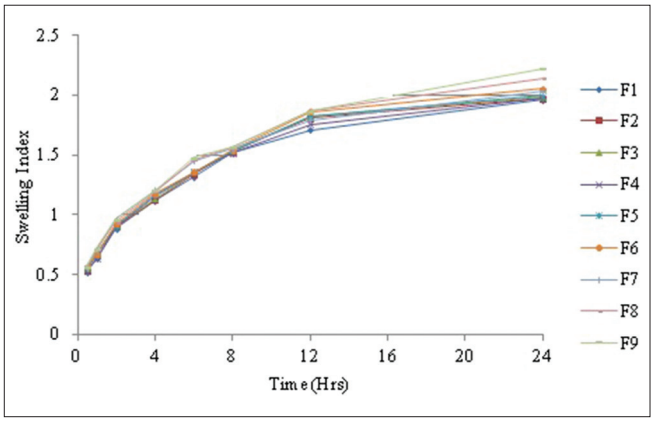

Figure 2: Swelling index of factorial design batches

Table 6: Swelling Index of factorial design batches

Time (Hr)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	0.520	0.542	0.553	0.528	0.552	0.563	0.560	0.565	0.569
1	0.631	0.664	0.672	0.636	0.663	0.669	0.703	0.713	0.719
2	0.887	0.905	0.912	0.901	0.906	0.925	0.965	0.944	0.969
4	1.120	1.125	1.137	1.153	1.169	1.175	1.206	1.194	1.205
6	1.319	1.339	1.360	1.357	1.358	1.361	1.455	1.465	1.483
8	1.517	1.530	1.534	1.516	1.537	1.542	1.553	1.563	1.569
12	1.710	1.807	1.827	1.755	1.820	1.864	1.792	1.872	1.869
24	1.961	1.972	1.987	1.975	1.994	2.056	2.033	2.143	2.227

is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e., release exponent was calculated. The n value is used to interpret the release mechanism. The n values were found to be between 0.5-1, indicating non-fickian diffusion or anomalous transport.

Analysis of data by design expert software

The 3^2 full factorial designs were selected to study the effect of independent variables HPMC K4M (X1) and Citric Acid (X2) on dependent variables FLT and Q_{24}. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22} \quad (4)$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs and bi (b_1,b_2,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1 X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity. The FLT and Q_{24} for the nine batches (F1-F9) showed a wide variation (i.e., 19.00-58.00 sec, and 87.95-103.90%, respectively). The responses of the formulations prepared by 3^2 factorial design batches are indicated in Table 5. The data clearly indicate that the FLT and Q_{24} values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses FLT and Q_{24} are shown in the following equations, respectively.

Final equations in terms of coded factors:

$$FLT = 29.63 + 14.72*A - 4.17*B - 2.84*A*B + 5.72*A2 + 0.053*B2 \quad (5)$$

Final equations in terms of actual factors:

$$FLT = 29.63444 + 14.72167*HPMC\ K4M - 4.16667*\ Citric\ Acid - 2.83500*\ HPMC\ K4M*\ Citric\ Acid + 5.718333*\ HPMC\ K4M^2 + 0.053333*\ Citric\ Acid^2$$

$$(r^2 = 0.969778) \quad (6)$$

Final equations in terms of coded factors:

$$Q_{24} = 94.94 - 4.41*A + 2.66*B - 0.65*A*B - 0.58*A^2 + 0.90*B^2 \quad (7)$$

Final equations in terms of actual factors:

$$Q_{24} = 94.94111 - 4.41*HPMC\ K4M + 2.663333*\ Citric\ Acid - 0.6475*\ HPMC\ K4M*\ Citric\ Acid - 0.57667*\ HPMC\ K4M^2 + 0.903333*\ Citric\ Acid^2$$

$$(r^2 = 0.929749) \quad (8)$$

The information the equation conveyed was the basis to study the effects of variables. The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e., positive or negative.

The positive coefficient of variable X1 i.e., HPMC K4M in case of response FLT indicates that as the HPMC concentration was increased the FLT value was also increased. However, the negative coefficient for Q_{24} shows opposite effect indicating the increased concentration of HPMC K4M leads to decreased Q_{24} value.

The second variable X2 showed positive coefficient for response Q_{24} while negative coefficient value for the responses FLT.

ANOVA study

Table 8 and 9 shows ANOVA for the dependent variables FLT and Q_{24} respectively. The coefficients of X1 and X2 were found to be significant at $P < 0.05$, hence confirmed the significant

Table 7: Kinetics of drug release

Formulation code	R^2					*n*	k
	Zero order	1st order	Matrix	Peppas	Hixson crowell		
F1	0.8620	0.9549	0.9896	0.9799	0.9863	0.5073	19.9466
F2	0.8489	0.7966	0.9901	0.9741	0.9354	0.4768	22.0426
F3	0.8122	0.9548	0.9484	0.9674	0.9832	0.5285	25.9652
F4	0.9608	0.9548	0.9690	0.9701	0.9879	0.5963	13.1285
F5	0.9526	0.9636	0.9699	0.9742	0.9886	0.5875	13.9745
F6	0.9445	0.9068	0.9731	0.9693	0.9797	0.5585	15.6454
F7	0.9658	0.9856	0.9724	0.9762	0.9951	0.6047	11.7619
F8	0.9663	0.9734	0.9723	0.9737	0.9931	0.5995	12.3804
F9	0.9636	0.9623	0.9730	0.9721	0.9907	0.5919	13.0071

Table 8: Analysis of variance for floating lag time

Source	Sum of squares	Degrees of freedom	Mean square	F value	*P* value	Model significant/Non
Model	1502.085	5	300.4169	192.7475	0.0006	Significant
X1	1300.365	1	1300.365	834.314	<0.0001	Significant
X2	104.1667	1	104.1667	66.83332	0.0038	Significant
X1X2	32.1489	1	32.1489	20.62673	0.0200	Significant
(X1)2	65.39867	1	65.39867	41.95978	0.0075	Significant
(X2)2	0.005689	1	0.005689	0.00365	0.9556	Non-significant
Residual	4.675811	3	1.558604	-	-	-
Core total	1506.761	8	-	-	-	-

Table 9: Analysis of variance for Q_{24}

Source	Sum of squares	Degrees of freedom	Mean square	F value	*P* value	Model significant/Non
Model	163.2228	5	32.64456	20.05569	0.0164	Significant
X1	116.6886	1	116.6886	71.68946	0.0035	Significant
X2	42.56007	1	42.56007	26.14744	0.0145	Significant
X1X2	1.677025	1	1.677025	1.030306	0.3848	Non-significant
(X1)2	0.665089	1	0.665089	0.408608	0.5681	Non-significant
(X2)2	1.632022	1	1.632022	1.002658	0.3905	Non-significant
Residual	4.883086	3	1.627695	-	-	-
Core total	168.1059	8	-	-	-	-

effect of both the variables on the selected responses. Increasing the concentration of the HPMC K4M resulted in the decrease in the release of Verapamil and increase in FLT of the tablet. However, the increase in concentration of the citric acid resulted in decrease in FLT and increase in drug release. Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 8.0.1 software. However, both the variables favor the preparation of controlled release floating tablets of Verapamil HCl.

Response surface plot

The quadratic model obtained from the regression analysis used to build a 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

The response surface plots were generated using Design Expert 8.0.1 software presented in Figures 3 and 4 to observe the effects of independent variables on the response studied such as FLT and Q_{24} respectively.

Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis.

The response surface plots showed that various combinations of independent variables X1 and X2 may satisfy any specific requirement (i.e., maximum drug release with minimum FLT) while taking into consideration of various factors involved in dosage form.

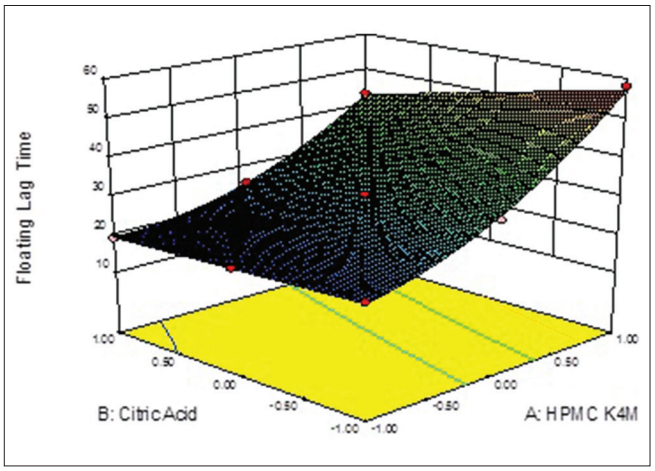

Figure 3: Response surface plot for FLT

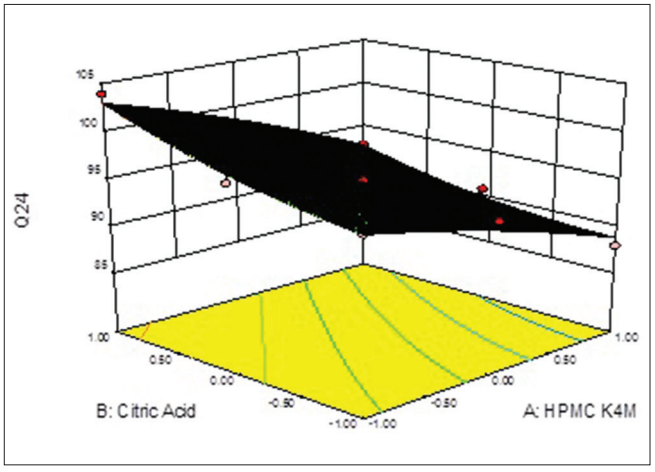

Figure 4: Response surface plot for Q_{24}

Table 10: Search for optimized level for floating lag time

	FLT										
C/H	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	22.01	23.47	25.38	27.74	30.57	33.85	37.59	41.79	46.45	51.56	57.13
-0.8	21.73	23.07	24.86	27.12	29.83	33.00	36.63	40.71	45.25	50.25	55.71
-0.6	21.45	22.67	24.36	26.50	29.10	32.15	35.66	39.64	44.06	48.95	54.30
-0.4	21.17	22.28	23.85	25.88	28.36	31.31	34.71	38.56	42.88	47.65	52.88
-0.2	20.90	21.90	23.35	25.27	27.64	30.47	33.75	37.50	41.70	46.36	51.47
0	20.63	21.51	22.86	24.66	26.91	29.63	32.80	36.43	40.52	45.07	50.07
0.2	20.37	21.14	22.37	24.05	26.20	28.80	31.86	35.37	39.35	43.78	48.67
0.4	20.11	20.76	21.88	23.45	25.48	27.97	30.92	34.32	38.18	42.50	47.27
0.6	19.85	20.40	21.40	22.86	24.77	27.15	29.98	33.27	37.02	41.22	45.88
0.8	19.60	20.03	20.92	22.26	24.07	26.33	29.05	32.22	35.86	39.95	44.50
1	19.35	19.67	20.44	21.68	23.37	25.51	28.12	31.18	34.70	38.68	43.11

Table 11: Search for optimized level for Q_{24}

	Q_{24}										
C/H	**-1**	**-0.8**	**-0.6**	**-0.4**	**-0.2**	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
-1	96.36	95.82	95.23	94.59	93.91	93.18	92.40	91.58	90.72	89.80	88.84
-0.8	96.70	96.13	95.51	94.85	94.14	93.39	92.59	91.74	90.85	89.90	88.92
-0.6	97.11	96.51	95.87	95.18	94.45	93.67	92.84	91.97	91.05	90.08	89.07
-0.4	97.59	96.97	96.30	95.59	94.83	94.02	93.17	92.27	91.32	90.33	89.29
-0.2	98.14	97.50	96.80	96.06	95.28	94.44	93.56	92.64	91.67	90.65	89.58
0	98.77	98.10	97.38	96.61	95.80	94.94	94.03	93.08	92.09	91.04	89.95
0.2	99.47	98.77	98.02	97.23	96.39	95.51	94.58	93.60	92.58	91.50	90.39
0.4	100.24	99.51	98.74	97.92	97.06	96.15	95.19	94.19	93.14	92.04	90.90
0.6	101.08	100.33	99.53	98.69	97.80	96.86	95.88	94.85	93.77	92.65	91.48
0.8	101.99	101.22	100.39	99.52	98.61	97.64	96.63	95.58	94.48	93.33	92.13
1	102.98	102.18	101.33	100.43	99.49	98.50	97.46	96.38	95.26	94.08	92.86

Table 12: Stability study of gastroretentive tablets of verapamil HCl

Tests	**Initial**	**1 month**	**2 months**	**3 months**
Appearance	Off white, circular, 12 mm flat faced	Off white, circular, 12 mm flat faced	Off white, circular, 12 mm flat faced	Off white, circular, 12 mm flat faced
Hardness (Kg/cm^2)	7.0	7.4	7.2	7.1
Friability (%)	0.31	0.30	0.31	0.33
Weight variation	497	499	499	498
Swelling index	1.987	1.785	1.923	1.975
Assay	99.55	100.69	100.85	101.12
FLT (Sec)	19	22	21	20
FT (Hr)	24	24	24	24
In vitro release (%)	103.9	102.36	103.25	102.45

Grid analysis

The grid analysis was performed for selection of the optimized level for FLT and Q24. The best results for FLT and Q_{24} was obtained at the lower level concentration of HPMC K4M (15%) and upper level concentration of Citric Acid (3%) which revealed the release profile within acceptance criteria. The formulation F3 was selected as optimized formulation. The results were shown in Tables 10 and 11.

Stability study

The optimized formulation F3 was subjected to the accelerated stability study at 40 ± 2°C and 75 ± 5% RH for three months as per ICH guidelines. Drug release profile and visual appearance, hardness, friability, weight variation, swelling index, assay, FLT and FT were monitored for three months. The results of the accelerated stability studies revealed no significant change in the parameters. From the data presented in the Table 12 the drug content remained more than 100% for three months. Therefore the formulation F3 is considered to be stable.

CONCLUSION

A 3^2 factorial design was performed to study the effect of

formulation variables on FLT and *in vitro* drug release.

Further the release from the floating studies suggested that the desired floating profile of gastroretentive floating drug delivery system could be achieved while maintaining the desired release properties of formulation. The statistical approach for formulation optimization is useful tool, particularly when two or more variables are to be evaluated simultaneously.

The variables HPMC K4M and citric acid evaluated in this study exhibited significant effect on the responses FLT and Q_{24} of the formulations; however the citric acid markly affected the FLT while the HPMC K4M affected the release profile.

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