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Formulation, evaluation and optimization of floating tablets of Valacyclovir Hydrochloride

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ABSTRACT

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract (GIT) for local and systemic effect. The present study has been a satisfactory attempt to formulate floating drug delivery system of Valacyclovir, an orally administrated antiviral drug with a view of improving its oral bioavailability and giving sustained release of the drug. In present study design expert trial 8.0.6.1 software is used for designing of experiment. In central composite design based on response surface methodology yielded nine experimental runs. These nine formulations are evaluated for precompressional parameters like bulk density, tapped density, angle of repose and carr's index. Formulations are also evaluated for postcompressional parameters like hardness, thickness, weight variation etc. all the formulations shows results in the acceptable range. All preliminary formulations are subjected to *invitro*bouyancy and dissolution study. The data obtained from the in vitro release study was fit to various kinetic models to explain the release profile of the drug. Kinetic models used were zero and first-order equations, Krosmeyersand peppas and Higuchi models. Based on results obtained from the prelimimary formulations five optimized formulations are selected and validated. Short-term stability study was done for optimized formulations.

Keywords: Valacyclovir, floating drug delivery, *In vitro* release, kinetic models, *in vitro* buoyancy, optimization.

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INTRODUCTION

Oral administration is the most convenient and preferred means of any delivery to the systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in Pharmaceutical field to achieve improved therapeutic advantages such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half-life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is required to achieve therapeutic activity. To avoid these limitations, the development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long time.

After oral administration, such a drug delivery would be retain in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption site in gastro intestinal tract.

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract (GIT) for local and systemic effect. Gastro retentive dosage form can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades several gastro retentive drug delivery approaches been designed and developed, including high density (sinking) system that is retained in the bottom of the stomach, low densitysystems that causes buoyancy in gastric fluids, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendable or swellablesystem which limits emptying of the dosage forms through the pyloric sphincter of the stomach, super porous hydrogel system, magnetic system etc[1].

In present study Valacyclovir, an antiviral drug is used to formulate and optimize the floating tablets. Valacyclovir is L-valine 2 [(2amino 1, 6 di hydro 6-oxo-9H- purin- 9yl) methoxy]ethyl ester. After oral administration Valacyclovir is rapidly converted to acyclovir, which has demonstrated antiviral activity against Herpes simplex virus-1(HSV-1), Herpes simplex virus-2 and Varicella zoster virus[5].

MATERIALS AND METHOD

Valacyclovir Hydrochloride, HPMC K4M, HPMC K15M, citric acid, sodium bicarbonate, magnesium stearate and talc, all chemicals are purchased from Yarrow chemicals Mumbai.

Methods:

FTIR studies:

FTIR spectra help to confirm the identity of drug and to detect the interaction of the drug with the carriers. FTIR spectroscopy of pure drug and physical mixture of drug with polymers was carried out using shimadzu FTIR to check the compatibility between drug and polymers. The FTIR spectra of drug with polymers were compared with the standard FTIR spectrum of the pure drug.

Designing of Formulations:

Formulation of floating tablets of Valacyclovir Hcl was designed using design expert software trial version 8.0.1 by applying 2^2factorial design by central composite design using response surface methodology. Amount of polymer used was taken as an independent variables i.e, amount of HPMC K4M(X_1) and HPMC K15M (X_2) as independent variables and percentage drug release at 6Hrs(Y_1) and at 12Hrs(Y_2) was considered as dependent variables or responses. By using this data total nine preliminary formulations were prepared (i.e, PF1 to PF9).

Method of Formulation of Floating Tablets:

Floating tablets of Valacyclovir Hcl were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine**.**

Precompressionalparameters:

Bulk density and tapped density:

It is the ratio of total mass of powder to the bulk volume of powder. Accurately weighed 5 g of the granules was placed in a 10 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 100 times the tapped volume was measured to the nearest graduated unit, then once again cylinder was tapped for 100 times the tap volume was measured to the nearest graduated unit. Process was repeated until we get concordant readings. The $D_b$and $D_t$were calculated in g/ ml using following formulae,

$D_b = M/V_b$

$D_t = M/V_t$

Where M = mass of the powder

V_b= bulk volume of powder

V_t = tapped volume of the powder

D_b = bulk density

D_t = tapped density

consolidation index:

Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated using the given formula.

Carr's index (%) = $[(D_t - D_b) \times 100]/D_t$

Angle of repose:

Good flow properties are critical for the development of any pharmaceutical tablets, capsule or powder formulations. Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. It is performed to determine the flow property of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on horizontal surface, giving a heap angle of powder on a paper. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\theta = \tan^{-1} (h / r)$$

Where, h and r are the height and radius of the powder cone, respectively. Flow properties for different values of angle of repose were given below.

Post compressional parameters:

1) Appearance:

The tablets were checked for presence of cracks, depressions, pinholes etc if any, uniformity of the color and the polish of the tablets

2) Hardness:

In this five tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

3) Friability test:

In Roche friabilator, 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

4) Weight variation:

This test was performed to maintain the uniformity of weight of each tablet, which should be in

the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analysed for sample mean and percentage deviation. IP limit for weight variation in case of tablets weighing 130 - 324 mg is ± 7.5 % and more than 324 mg is ± 5%

5) Thickness:

Thickness of tablet was important for uniformity of the tablet size. Thickness was measured using vernier callipers.

6) Drug Content Estimation:

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N Hcl, followed by stirring for 30 minutes. The solution was filtered through a Whatman's filter paper, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 255nm using 0.1N Hcl as blank.

7) *In vitro* studies[6]:

a) *In vitro buoyancy studies*

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 100-ml beaker containing 0.1N Hcl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

b) *In vitro* dissolution studies

The release rates of Valacyclovir from floating tablets were determined using Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml 0f 0.1N Hcl at 37° ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman's filter and diluted to a suitable concentration with 0.1N Hcl. Absorbance of these solutions were measured at 255 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

Optimization:

Results obtained from the preliminary formulations are applied in design expert software and analysed for two responses i.e release rate at 6 Hrs (Y_1) and Release rate at12 Hrs (Y_2). A

statistical model (see equation) incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$\mathbf{Y = b_0 + b_1X_1+b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_2^2X_2^2.}$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high

value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit.

Then responses are analysed for statistics. ANOVA was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant if the p-value is less than 0.05. Test on lack of fit is done to get an empirical mathematical model for each individual response. After generating the model polynomial equations to relate the dependent and independent variables, the process was optimized for two responses (Y_1, Y_2). Optimum formulation was selected based on the constraints set on independent variables. The final optimal experimental parameters were calculated using the extensive grid search and feasibility search provided in the Design Expert software.

Stability studies:

Short-term accelerated stability study was performed on the optimized formulations. The samples were tested for any changes in physical appearance, drug content, *in vitro* floating ability and *in vitro* drug release studies.

Following conditions were used for stability studies

30 ± 2^0C/65±5 % RH analyzed at a time interval of 30 days till a period of 90days.

40 ± 2^0C/75±5 % RH analyzed at a time interval of 30 days till a period of 90 days.

Formulation chart

Table; formulation chart

Formulation	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
Valacyclovir	500	500	500	500	500	500	500	500	500
HPMC K4M	75	50	100	75	75	110.3	50	39.64	100
HPMC K15M	75	100	50	110.3	39.64	75	50	75	100
Sodium Bicarbonate	75	75	75	75	75	75	75	75	75
Citric Acid	25	25	25	25	25	25	25	25	25
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10	10

***each values are in milligrams**

RESULTS AND DISCUSSION:

Preformulation Studies:

Determination of λ max:

This is performed by using UV spectrophotometer by using 0.1N Hcl as medium. Maximum absorbance was found at 255nm.

FTIR Studies

Following are the spectra obtained from FTIR spectrophotometer. Kbr was admixed with the different samples.

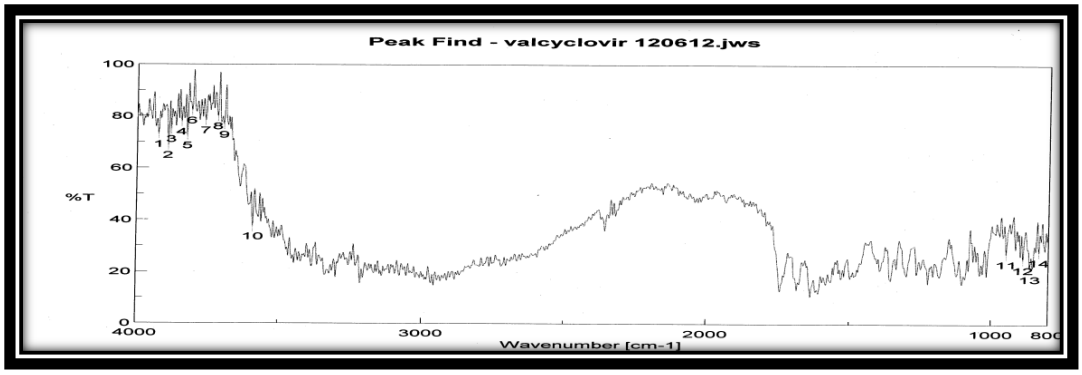

Figure 1- FTIR spectra of Valacyclovir

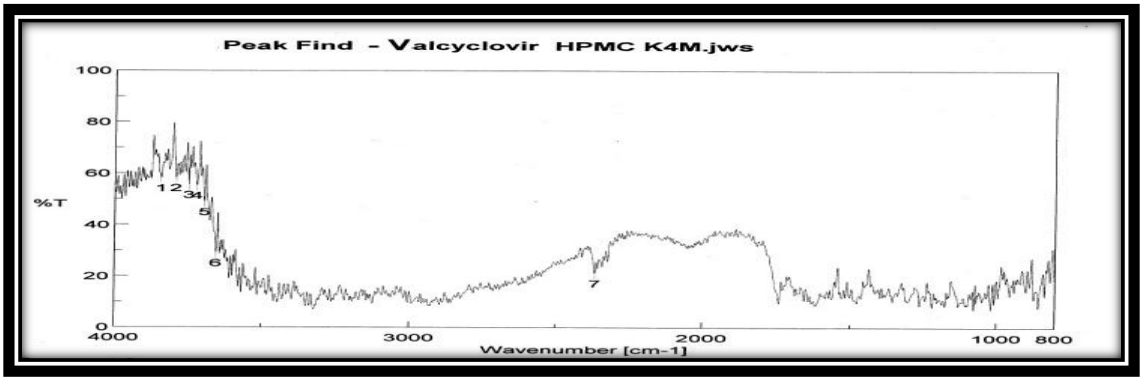

Figure 2- FTIR spectroscopy of Valacyclovir with HPMC K4

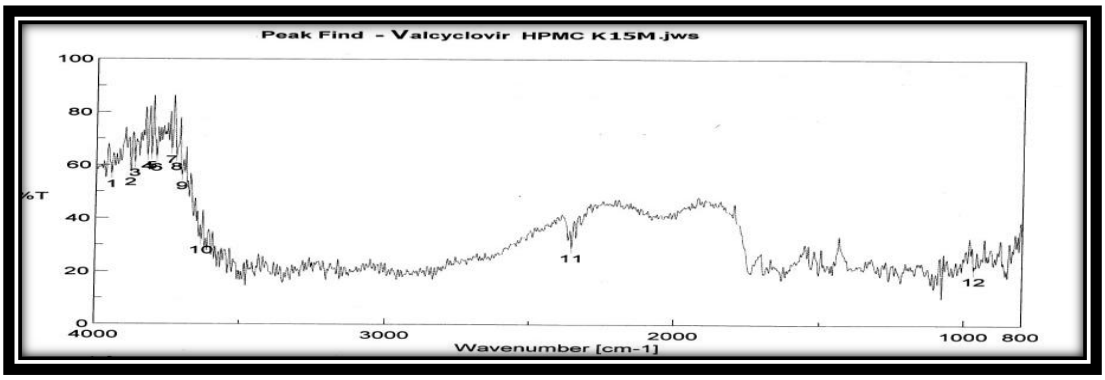

Figure 3- FTIR spectroscopy of Valacyclovir with HPMC K15M

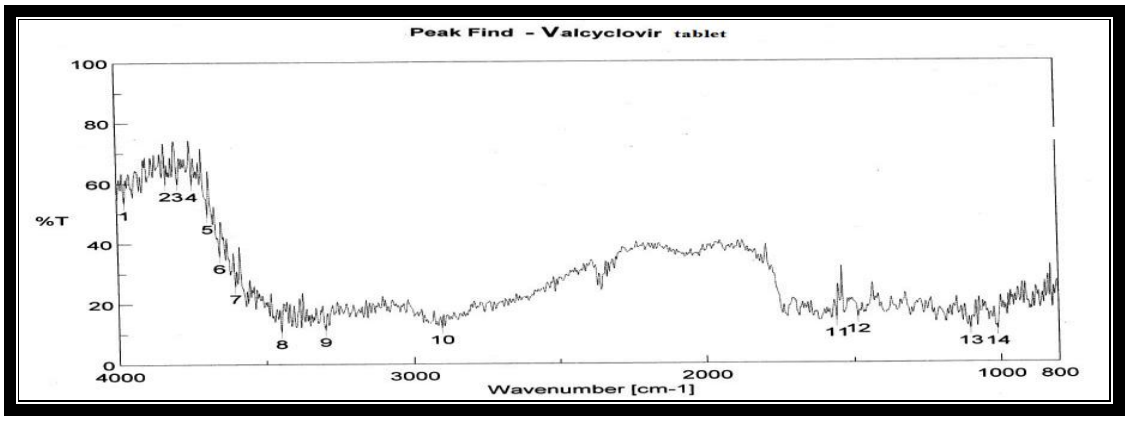

Figure 4 FTIR spectra of formulated tablet.

Pre-compressional parameters

The powders of formulations are evaluated for bulk density, tapped density, compressible index and Angle of repose. The results of bulk density and tapped density were showed good flow properties of the powder, this was further supported by lower compressibility index and angle of repose value. The results were showed in the table 2

Table 2 pre-compression parameters

	Bulk density ±SD* (gm/cc)	Tapped density ±SD* (gm/cc)	Carr's index ±SD* (%)	Angle of repose ±SD* (θ)
PF1	0.37±0.032	0.38±0.023	4.3±0.021	$24^0$94'±0.26
PF2	0.38±0.028	0.40±0.032	5.2±0.033	26^0 56'±0.27
PF3	0.39±0.038	0.41±0.028	4.8±0.016	28^0 81'±0.34
PF4	0.36±0.042	0.39±0.034	7.69±0.038	$27^0$02'±0.42
PF5	0.40±0.033	0.44±0.052	9±0.022	27^0 47'±0.16
PF6	0.38±0.036	0.48±0.033	20±0.030	25^0 64'±0.20
PF7	0.37±0.032	0.44±0.012	15±0.028	27^0 92'±0.28
PF8	0.39±0.022	0.55±0.019	13.22±0.042	27^0 92'±0.30
PF9	0.38±0.026	0.43±0.022	11.62±0.042	28^0 20'±0.34

***** Each value is an average of three determinations

Post compressional parameters

Formulated tablets are evaluated for post compressional parameters like hardness, friability weight variation, thickness and uniformity of drug content.. The hardness value ranges from 3.94 ±0.040 kg/cm^{2}to 5.04±0.044 kg/cm^2. Hardness of all floating tablets was maintained within the limit 3.5 to 6 kg/cm^2.Percentage friability value ranges from 0.25±0.075% to 0.72±0.055%. The percentage friability for all the formulations was below 1% indicating that the friability was within the prescribed limits.The results of friability test indicate that the tablet possesses good mechanical strength.Weight variation value of all formulations ranges from 0.4%. to 1.28%. All the tablets were passed weight variation test as the average weight variation was within the

pharmacopoeial limit ±5%. The weight of all the tablets was found to be uniform with low standard deviation value. Thickness of all formulations ranges from 4.02±0.0037mm to 4.10±0.04mm.Percentage drug content of Valacyclovir in all the formulated tablets were found within the limits. The results within the range 97-99.67% indicate uniform of mixing. Results were tabulated in the Table 3

Table 3 post compressional parameters

Formulation code	Hardness* (kg/cm^2)	Friability* (%)	Thickness* (mm)	Weight variation* (mg)	Drug content* (%)
PF1	5.04±0.044	0.50±0.036	4.07±0.084	714±1.28	98±0.061
PF2	4.84±0.044	0.27±0.029	4.07±0.05	764±0.85	99.32±0.08
PF3	4.18±0.052	0.40±0.055	4.06±0.037	764±0.85	98.42±0.05
PF4	4.0±.06	0.50±0.09	4.02±0.037	729±0.41	98.98±0.09
PF5	4.04±.044	0.72±0.055	4.08±0.060	801±0.75	97.0±0.082
PF6	3.94±.04	0.35±0.054	4.02±0.037	729±0.42	98.92±0.09
PF7	3.82±.032	0.32±0.070	4.04±0.03	715±0.45	99.10±0.086
PF8	4.38±.052	0.25±0.072	4.09±0.05	801±0.55	99.56±0.09
PF9	4.72±0.052	0.25±0.075	4.10±0.04	815±0.45	99.67±0.08

***** Each value is an average of three determinations

Table 4 *In-vitro* buoyancy studies:

Formulation code	Floating lag time(seconds)	Total floating time(hours)
PF1	180	5.00
PF2	270	5.45
PF3	30	8.00
PF4	45	6.10
PF5	311	1.45
PF6	93	4.00
PF7	15	1.35
PF8	14	12.0
PF9	20	13.0

The floating lag time and total floating time of the different tablet formulations are showed in the Table 4. Floating lag time of all formulation is in the range of 14-311seconds. Total floating time of all formulations ranges from 1.45-13 hours. To decrease the floating lag time citric acid and sodium bicarbonate was added.

***In-vitro* dissolution study of preliminary formulations**

In vitro drug release study was performed using USP XXIII dissolution test apparatus at 50 rpm using 900 ml of 0.1N Hcl maintained at 37±0.5ºC as the dissolution medium.

Dissolution profile of preliminary formulations compared at two check points i.e percentage cumulative drug release at 6 hours and percentage cumulative drug release at 12 hours.

Formulation PF9 showed least percentage cumulative drug release value 53.57 ±0.15% at 6 hours and formulation PF7 showed highest percentage of drug release value 96.4 ±0.11 % in 6 hours. Percentage cumulative drug release value of all formulations ranges from 53.57±0.15 % to 96.4 ±0.11% at 6 hours.

Formulation PF9 showed least percentage cumulative drug release value 85.71±0.12% at 12 hours and formulation PF7 showed highest percentage of drug release value 99.1±0.15 % in 12 hours. Percentage cumulative drug release value of all formulations ranges from 85.71±0.12% to 99.1 ±0.15 % at 12 hours.

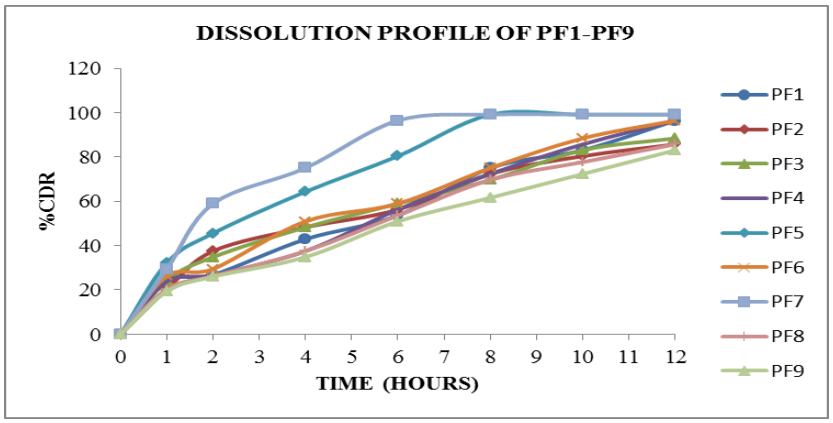

Figure 5 *In vitro* dissolution studies of preliminary formulations

Data fitting to the model and ANOVA

For the response surface methodology based on central composite design nine experimental runs are conducted and responses for the nine formulations are given in the Table 5. Range of responses Y_1, the cumulative % drug release after 6 Hrs was 53.5%(minimum) in formulation No.1(PF1) and 96.4% (maximum) in formulation No.7 (PF7). Simillarly response Y_2 was 99.1%(maximum) in formulation No7 (PF7) and 85.71% (minimum) in formulation No.9 (PF9).

Table 5- Observed responses in central composite design and release parameters

Run	Response (percentage release)		Release parameter	
	Y_1 (at 6 Hrs)(%)	Y_2 (at 12Hrs)(%)	n	R^2
1(PF1)	53.5	96	0.594	0.960
2(PF2)	56	85.7	0.678	0.991
3(PF3)	58.9	88.3	0.678	0.990
4(PF4)	56.2	96.4	0.681	0.990
5(PF5)	80.3	99.1	0.711	0.980
6(PF6)	58.9	96.4	0.688	0.990
7(PF7)	96.4	99.1	0.720	0.972
8(PF8)	53.57	99.1	0.672	0.995
9(PF9)	53.57	83.03	0.661	0.995

Regression equations of the fitted model

$$Y_1 = 53.50 - 12.15\ X_1 - 8.62\ X_2 + 8.22\ X_1X_2 + 8.52X_1^2 + 6.62X_2^2.$$

$$Y_2 = 96 - 5.53X_1 - 1.14X_2 + 0.0025X_1X_2 - 2.98X_1^2 + 0.37X_2^2.$$

Mathematical relationship in the form of polynomial equations for the measured responses obtained with the statistical package Design Expert version 8.0.6 . These equations represent the quantitative effect of variables (X_1, X_2) and their interactions on the response $Y_1$and Y_2. Coefficients with more than one factor term and those with higher order terms represent interaction terms and quadratic relationships respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect. The values of X_1,X_2 were substituted in the equation to obtain the theoretical values of Y_1 and Y_2.

Table 6 - ANOVA summary of responses Y_1 and Y_2

Source	Y_1(Quadratic)		Y_2(Quadratic)	
	F value	p-value	F value	p-value
Model	20.21	0.0005	51.43	< 0.0001
X_1	43.15	0.0003	196.17	< 0.0001
X_2	21.71	0.0023	8.34	0.0234
X_1X_2	18.44	0.0163	2.006	0.9655
X_1^2	11.13	0.0036	49.42	0.0002
X_2^2	27.38	0.0125	0.75	0.4148

ANOVA was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant if the p-value is less than 0.05. The ANOVAanalysis for both the responses are shown in Table

ANOVA analysis of Y_1 showed that The Quadratic Model was found to be significant with an F-value of 20.21. There is only a 0.05% chance that a "Model F-Value" This large could occur due to noise. Values of "Prob> F" less than 0.05 indicate model terms are significant and coeffiecients b_1, b_2 and their interaction coeffiecients b_1b_2, b_1^2, b_2^2 had significance effects withP- Value less than 0.05. Similarly ANOVA analysis of Y_2 showed that the model F-value of 51.43 implies the model is significant. There is only a 0.0001% chance that a "Model F- Value" this large could occur due to noise. Values of "Prob>F" less than 0.05 indicate model term are significant and coeffiecients b_1, b_2 and their interaction coeffecient b_1^2 showedsignificance effects withP- Value less than 0.05.

Response surface analysis:

A response surface model factorial design with two independent variables was used to study the effects on dependent variables. The dependent variables (percentage drug release at 6 Hrs and percentage drug release at 12Hrs) obtained at various levels of the 2 independent variables(X1

and X2) were subjected to multiple regression to yield polynominal equation. The response values subjected for this analysis are;

1. Percentage drug release at 6 Hrs.
2. Percentage drug release at 12 Hrs.

These responses were chosen for the analysis of the following relationship:

1. To study the effect of amount of HPMC K4M
2. To study the effect of amount of HPMC K15M.
3. To study the combined effect of HPMC K4M and HPMC K15M.

Effects of formulation variables on percentage drug release at 6 Hours.

The relationship between the variable was elucidated using response surface (Figure 6) along with contour plot (Figure 7). At lower level of X_1 and X_2, the Y_1(percentage drug release at 6 Hrs) was found to be 96.42% s and at higher concentration of X_1 and X_2, theY_1(percentage drug release at 6 Hrs) was decreased to 58.92%.

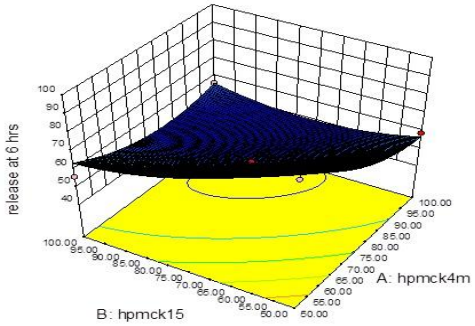

Figure 6 Response surface plot showing effects of X_1, X_2 on response Y_1

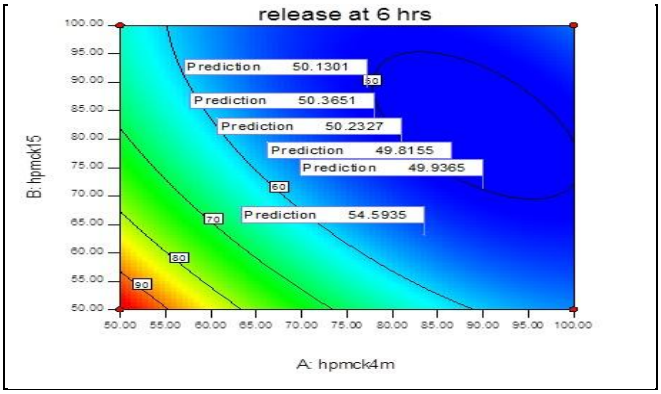

Figure 7 Contour plot showing effects of X_1, X_2 on response Y_1

Effects of formulation variables on percentage drug relese at 12 Hours

The relationship between the variable was elucidated using response surface plot (Figure 8) along with contour plot (Figure 9) At lower level of X_1 and X_2 the percentage drug release at 12

Hrs was found to be 99.10% and higher concentration of X_1 and X_2 the percentage drug release at 12 Hrs decreased to 85.71%.

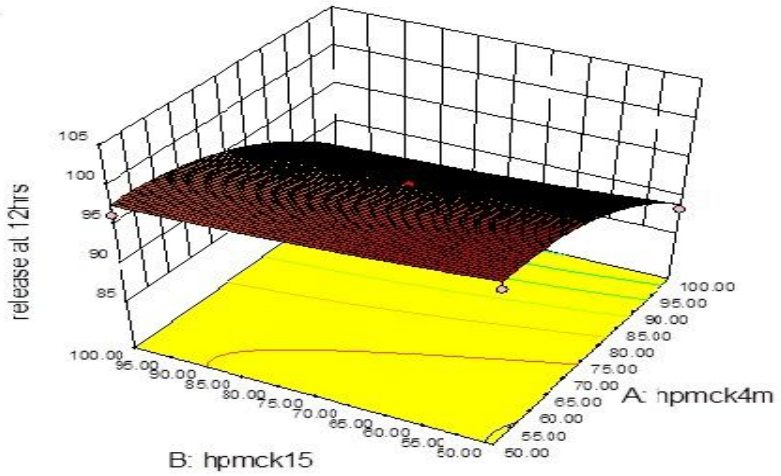

Figure 8 Response surface plot showing effects of X_1, X_2 on response Y_2

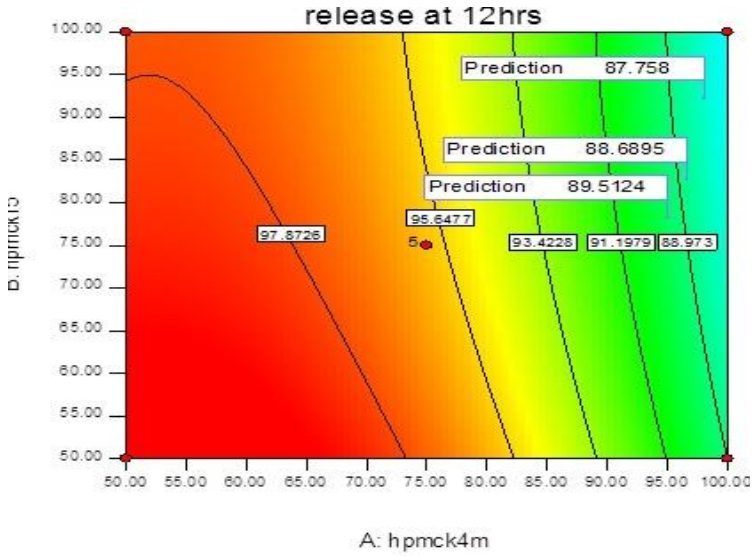

Figure 9 Contour plot showing effects of X_1, X_2 on response Y_2

Effect of individual variable.

On increasing the concentration of HPMC K4M (X_1) a decrease in percentage drug release is observed. At low concentration of HPMC K4M the percentage drug release were found to be 58.92 %.When the concentration of HPMC K4M is increased by keeping concentration of HPMC K15M(X_2) constant, the percentage drug release decreases to 53.92%.

Similarly at low concentration of HPMC K15M the percentage drug release were found to be 80.35 %.When the concentration of HPMC K15M is increased by keeping concentration of HPMC K4M constant, the percentage drug release decreases to 56.10%. The result conveyed us

that factor X_1 has significant effect on percentage drug release than that of X_2.

Optimization

After generating the model polynomial equations to relate the dependent and independent variables, the process was optimized for two responses (Y_1 and Y_2). Optimum formulation was selected based on the constraints set on independent variables: Y_1 (45 – 96%), Y_2 (83 – 100%). The final optimal experimental parameters were calculated using the extensive grid search and feasibility search provided in the Design Expert software. The 35 solutions provided by the software from which 5 formulations are randomly selected which was tabulated in the Table 7.

Table 7 - Randomly selected Solutions from design expert software.

Number	HPMC K 4M (mg)	HPMC K 15 M (mg)	Percentage drug release At 6 Hours	Percentage drug release At 12 Hours	Desirability
1	94.43	75	49.17	89.73	1
2	84.58	94.72	49.91	91.07	1
3	95.94	86.96	49.98	88.39	1
4	98.51	88.05	50.94	87.58	1
5	65.29	91.49	54.59	96.96	1

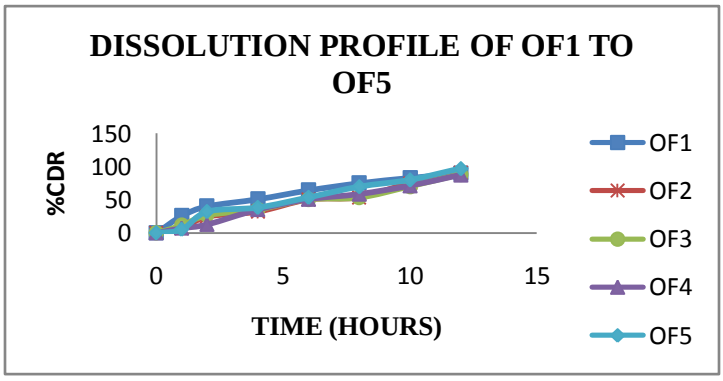

Figure 10 *In vitro* dissolution of optimized formulation:

Dissolution profile of Optimized formulations compared at two check points i.e percentage cumulative drug release at 6 hours and percentage cumulative drug release at 12 hours.

In Optimized formulations OF1,OF2, OF3 show 50.89%, 50.35%, 50.62% and OF4, OF5 shows 50.89%, and 53.57% at 6 hours. Formulations OF1, OF2, OF3 show 89.73, 91.07 and 88.39% and OF4 and OF5 shows 87.58 and 96.96% respectively at 12 hours. Values obtained are nearer to the predicted values.

Validation of the RSM results:

Five check point formulations were selected, for which the results of all the dependent variables were found to be within the limits. Table 8 lists the obtained and predicted values of the check

point formulations along with the % prediction error. Linearity correlation plots between the observed experimental values and the predicted values are shown in Figure 11 and Figure 12

Table 8 - Comparison of predicted and actual experimental values:

Optimized formulation	Release at 6 hours			Release at 12 hours		
	Predicted	Actual	%Error	Predicted	Actual	%Error
OF1	49.17	50.89	3.37	89.81	89.73	-0.08
OF2	49.91	50.35	0.87	92.68	91.07	-1.76
OF3	49.98	50.62	1.26	88.83	88.39	-0.49
OF4	50.94	50.89	-0.09	87.68	87.58	-0.114
OF5	54.59	53.57	-1.09	97	96.96	-0.04

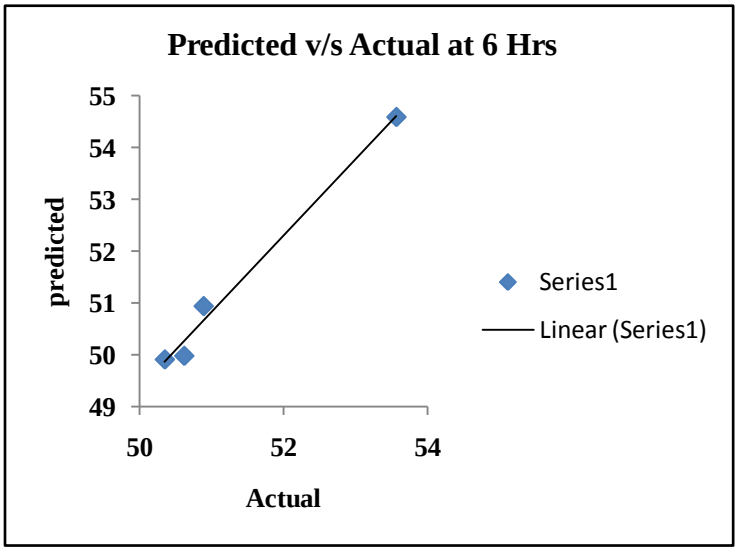

Figure 11 Predicted v/s actual graph of optimized formulation at 6 Hours

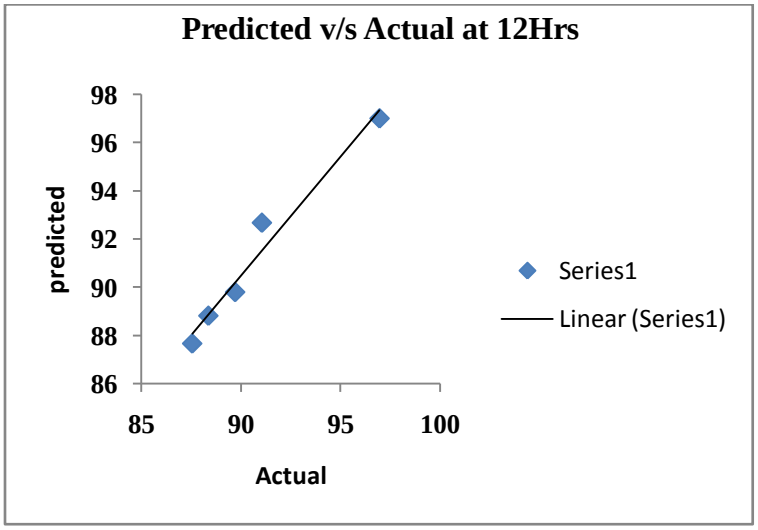

Figure 12 Predicted v/s actual graph of optimized formulation at 12 Hours

Linearity correlation plots between the observed experimental values and the predicted values we can clearly showed there is no much deviations between predicted and experimental values**.**

Table 9 Stability study of optimized formulation

Time (months)	Drug content (%)		Floating behaviour				Drug release at the end of 12 Hrs (%)	
			Floating lag time (sec)		Floating duration (Hrs)			
	*	**	*	**	*	**	*	**
Zero	98.98	98.01	60	60	> 12Hrs	>12Hrs	89.73	89.67
First	98.65	97.96	60	60	> 12Hrs	>12Hrs	90.10	90.25
Second	97.45	96.92	60	60	> 12Hrs	>12Hrs	88.8	89.0
Third	97.98	97.08	60	60	>12Hrs	>12Hrs	88.9	88.67

*** 30±2°C and 65±5% RH, ** 40±2°C and 75±5% RH**

Short-term accelerated stability study was performed on the optimized formulations by storing the samples at 30±2°C with 65±5% RH and 40±2ºC with 75±2% RH for 90 days. The samples were tested for any changes in physical appearance, drug content, *in vitro* floating ability and *in vitro* drug release studies at monthly intervals. The results of stability studies did not show any significant change in the physical appearance, drug content, floating lag time and *in-vitro* dissolution studies.

CONCLUSION:

From the experimental results it can be concluded that, Floating drug delivery systems of Valacyclovir with shorter lag time can be prepared by direct compression method using HPMC K4 M, HPMC K15M and NaHCO3 a gas generating agent. FTIR gave confirmation about the purity of the drug and showed no interaction between drug and the polymers. All the prepared tablet formulations were found to be good without capping and chipping. Nine preliminary formulations are prepared based on the results obtained from the preliminary formulations five optimized formulations are prepared. From this study, it was concluded that as the concentration of polymer increases, the drug release will decreases. All Most of the designed formulations of Valacyclovir FDDS displayed zero order release kinetics, and drug release follows non-Fickanian diffusion mechanism.

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