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FORMULATION AND EVALUATION OF GASTRORETENTIVE ACYCLOVIR FLOATING IN - SITU GELLING SUSPENSION

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Abstract: Acyclovir used in Herpes Simplex Infection (e.g. cold sores, genital herpes), Herpes Zoster Infection (e.g. shingles) and Vericella Infection (e.g. chicken pox), is absorbed mainly from stomach and upper gastrointestinal tract. Food does not affect absorption of acyclovir. The dose of Acyclovir is 200 mg, 400 mg and 800 mg. The gastroretentive in-situ gelling drug delivery system can incorporate high dose (750-1000 mg) of the drug. The tablet for such a high dose will be large in size. Thus, it will not be patient compliant for patients having difficulty in swallowing, pediatrics, and geriatrics. Thus, the liquid dosage form is preferable. Dispersible tablets, conventional coated and uncoated tablets, capsules, suspensions, ointments and parenteral of Acyclovir are available in market. All these dosage forms show the half-life of 2-3 hours. Thus, dosing frequency is more. To reduce the dosing frequency, sustained release dosage form will be helpful.

Index Terms - Site specific, Gastroretentive, Acyclovir, Floating, In-situ gel.

I. INTRODUCTION

Site specific drug delivery is an advanced method of delivering drugs to the patients in a sequences that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells). It in turn improves efficacy of treatment by reducing side effects of drug administration. Basically, site specific drug delivery is to support the drug molecule to reach its desired site. The advantage of this technique is reduced dose and reduced side effect of the drug. The goal of a site specific drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased organs/tissues/cells. [1]

The Gastroretentive Drug Delivery System (GRDDS) is retained in the stomach for prolonged period of time. GRDDS increases the gastric residence time of drug formulation and thus drug could be supplied to its site of absorption in GIT (mainly stomach and upper part of small intestine). The gastric residence time is an important factor for this system, as it significantly increases the time for which drugs may be released from the formulations. Dosing intervals will be prolonged thus improving patient compliance. The drugs having less half-life and/or bioavailability will be having less effectiveness. The drugs having short half-life will be eliminated from systemic circulation quickly, thus will require frequent dosing of the drug formulation to achieve desired therapeutic activity. [2]

In floating In-Situ Gelling system, the drug dosage from prepared is in a liquid state. When it reaches to the acidic gastric environment it will form a gel with the mechanism dependent on physiological changes (e.g. temperature, pH), chemical stimulations (e.g. ionic cross-linking) or physical changes (e.g. diffusion of solvent and swelling). The polymers used will gel and control the release rate of the drug from the dosage form. [2, 3, 4]

II. MATERIALS AND METHODS

2.1 MATERIALS

Acyclovir was purchased from Yarrow Chem. Products, Mumbai, India. Sodium alginate, Sodium citrate, Hydrochloric acid and Sodium hydroxide were obtained from Thomas Baker (Chemicals) Pvt. Ltd., India. HPMC K-100M, Calcium chloride and Sodium bicarbonate was obtained from Chem Dyes Corporation, Mumbai, India.

2.2 METHODS

2.2.1 Preparation of Gastroretentive Acyclovir Floating In - Situ Gelling Suspension:

The polymeric solution was prepared with continuous stirring in sufficient quantity of distilled water at 50 – 60 °C. The required quantities of sodium citrate and calcium chloride were added. The solution was cooled below 40 °C. The drug Acyclovir and sodium bicarbonate were added and formulation was homogenized for proper dispersion of the drug. Preservatives were finally added and formulation was stored. [4, 5, 6]

2.2.2 Fourier - Transform Infra Red [FT-IR] Study for identification of drug:

The FT-IR spectrum of Acyclovir was recorded using Jasco FTIR 4100 spectrometer. The sample for IR was prepared by KBr disc method in appropriate ratio of Acyclovir: Potassium bromide and examined in transmission mode. The spectrum was measured over the frequency range of 4000-400 cm^{-1}. [7, 8]

2.2.3 Determination of UV Absorbance Maxima (λ_{max}):

Drug acyclovir was dissolved in 0.1 N HCl and further diluted to appropriate concentration to prepare stock solution. This stock solution was scanned in the entire UV range of 400-200 nm wavelength on Shimadzu UV Spectrophotometer to obtain the absorbance spectra. [9]

2.2.4 Preparation of Standard Curve of Acyclovir in 0.1 N HCl:

100 mg of drug Acyclovir was dissolved in 40 mL 0.1 N HCl in a 100mL volumetric flask and sonicated for about 10 min. The final volume was adjusted with 0.1 N HCl. This solution was diluted with 0.1 N HCl to obtain solutions with concentration 2, 4, 6, 8, 10, 12, 14 and 16 µg/mL. The absorbance of resulting solutions was measured at λ_{max}. [9]

2.2.5 Solubility of Acyclovir in 0.1 N Hydrochloric Acid:

The drug was weighed and dissolved in 10 mL of 0.1 N HCl. This process was continued till the supersaturated point is achieved. The solution was filtered and diluted till appropriate concentration. The sample was analyzed spectrophotometrically for drug content. [9, 10]

2.2.6 3^2 Randomized Full Factorial Design:

A 3^2 randomized full factorial design was used in the present study. In this design, 2 factors were evaluated; each at 3 levels and experimental trials was performed for all 9 possible combinations. The concentration of HPMC K100M (X_1) and concentration of Sodium Bicarbonate ($NaHCO_3$) (X_2) were chosen as independent variables in 3^2 full factorial design, while cumulative percent drug release after 9 hours was taken as dependent variable. [4, 5, 11] [Table 1 (a) and Table 1 (b)]

Table 1: (a) Factorial Batches (In coded terms)

Batch Code		Variable levels in coded form	
		X_1	X_2
F1	I A	-1	-1
F2	I B	-1	0
F3	I C	-1	+1
F4	II A	0	-1
F5	II B	0	0
F6	II C	0	+1
F7	III A	+1	-1
F8	III B	+1	0
F9	III C	+1	+1

Coded Values	Actual Values	
	X_1: HPMC K100M	X_2: $NaHCO_3$
-1	1.0 %	1.5 %
0	1.5 %	1.7 %
+1	2.0 %	1.9 %

Table 1: (b) Factorial Batches (In actual terms)

	F1	F2	F3	F4	F5	F6	F7	F8	F9
	I A	I B	I C	II A	II B	II C	III A	III B	III C
Drug (Acyclovir)	4.000 gm	4.000 gm	4.000 gm	4.000 gm	4.000 gm	4.000 gm	4.000 gm	4.000 gm	4.000 gm
Sodium Alginate	1.250 gm	1.250 gm	1.250 gm	1.250 gm	1.250 gm	1.250 gm	1.250 gm	1.250 gm	1.250 gm
HPMC K100M	**0.500 gm**	**0.500 gm**	**0.500 gm**	**0.750 gm**	**0.750 gm**	**0.750 gm**	**1.000 gm**	**1.000 gm**	**1.000 gm**
Sodium Citrate	0.250 gm	0.250 gm	0.250 gm	0.250 gm	0.250 gm	0.250 gm	0.250 gm	0.250 gm	0.250 gm
Calcium Chloride	0.070 gm	0.070 gm	0.070 gm	0.070 gm	0.070 gm	0.070 gm	0.070 gm	0.070 gm	0.070 gm
Sodium Bicarbonate	**0.750 gm**	**0.850 gm**	**0.950 gm**	**0.750 gm**	**0.850 gm**	**0.950 gm**	**0.750 gm**	**0.850 gm**	**0.950 gm**
Distilled Water (q.s.)	50.0 mL	50.0 mL	50.0 mL	50.0 mL	50.0 mL	50.0 mL	50.0 mL	50.0 mL	50.0 mL

2.2.7 Floating Lag Time (FLT):

FLT is the time taken by the formulation to float after administration. The formulation is measured (i.e. dose = 10 mL) and poured in 0.1 N HCl from the walls of the container. The time taken by the formulation to come on surface and float is noted as FLT (Floating Lag Time). [4, 5]

2.2.8 Floating Time:

Floating time is the time for which formulation remains in floating state. [4, 5]

2.2.9 Drug Content:

10 mL formulation was added in 500 mL 0.1 N HCl and stirred continuously for 1 hr. the solution was filtered and diluted to appropriate concentration using 0.1 N HCl. The drug concentration was determined using UV Spectrophotometer at 255.6 nm. [6]

2.2.10 In Vitro Drug Release Study:

The in vitro drug release study of formulation was performed using USP II apparatus fitted with the paddle (50 RPM) at 37 ± 0.5 ^{0}C using 500 mL of 0.1 N HCl as a dissolution medium. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist in vivo. At the predetermined time intervals 5 mL samples were withdrawn, filtered through Whatman filter paper, diluted and assayed at 255.6 nm using Shimadzu UV 1800 double-beam spectrophotometer. Cumulative percentage drug release (CPR) was calculated using an equation obtained from a standard calibration curve. [12]

2.2.11 Kinetic Modeling of Drug Dissolution Profiles:

The release profile of all the batches was fitted to zero order, first order, Higuchi, Korsemeyer - Peppas, and Hixson – Crowell model to ascertain the kinetic modeling of the drug release. [4, 5]

2.2.12 Stability Study of Optimized Batch:

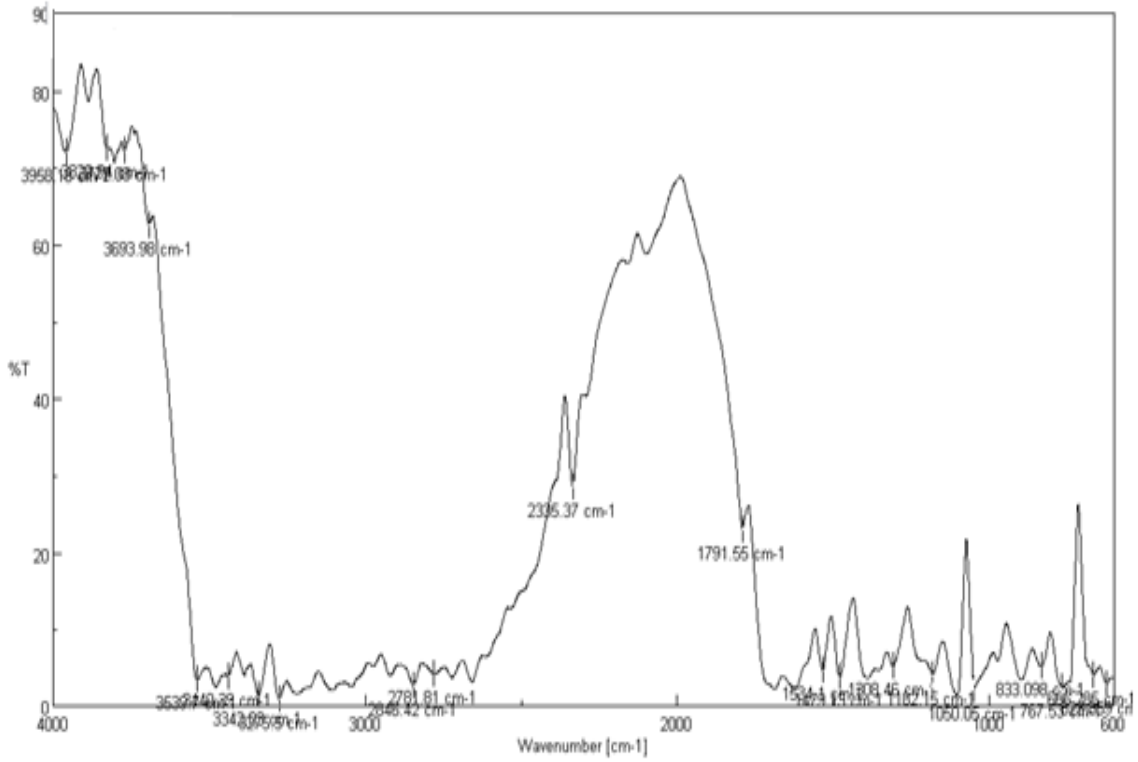
The optimized formulation was subjected to the stability studies for the period of 2 months at 25± 2°C/60± 5% RH, 30± 2°C/65± 5% RH and 40± 2°C/75± 5% RH as per ICH guidelines. [4]

III. RESULTS

3.1 Fourier - Transform Infra Red [FT-IR] Study for identification of drug

The IR spectrum of pure drug was found to be similar to the standard spectrum of Acyclovir. [Figure 1]

Figure 1: FTIR Spectrum of Pure drug Acyclovir



The spectrum of Acyclovir shows the following functional groups at their frequencies. [Table 2]

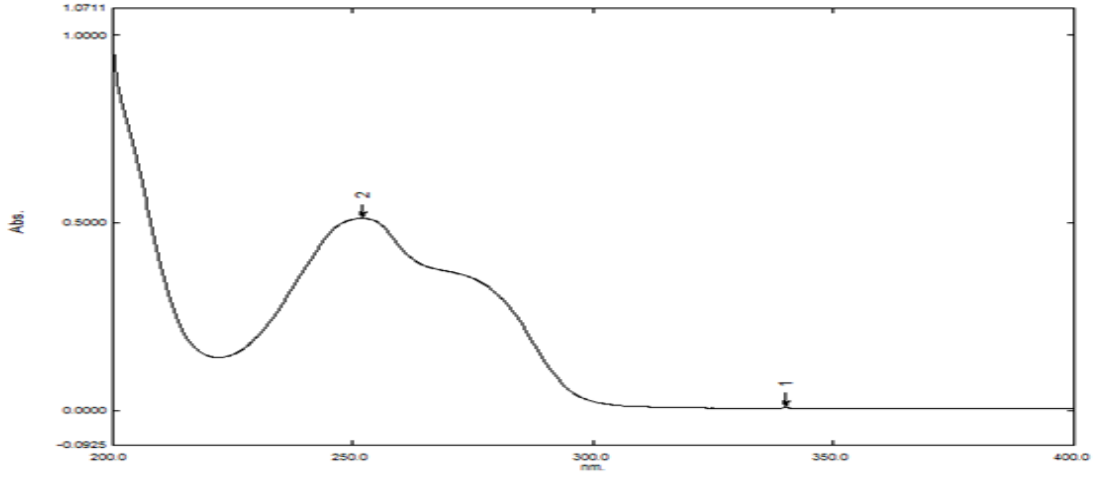
Table 2: Functional groups and their frequencies for FTIR Spectrum of drug Acyclovir

Wave number	Functional Group
3563.81 cm^{-1}	O-H stretching
3444.24 cm^{-1}	N-H stretching
2927.94 cm^{-1}	aliphatic C-H stretching anti symmetric
2856.06 cm^{-1}	aliphatic C-H stretching symmetric
1714.41 cm^{-1}	C=O stretching
1608.63 cm^{-1}	O-H deformation
1482.99 cm^{-1}	aliphatic C-H deformation
1143.8 cm^{-1}	C-O stretching

3.2 Determination of UV Absorbance Maxima (λ_{max})

The drug shows maximum absorption at 255.6 nm. Thus λ_{max} of Acyclovir is 255.6 nm. [Figure 2]

Figure 2: Determination of λ_{max}



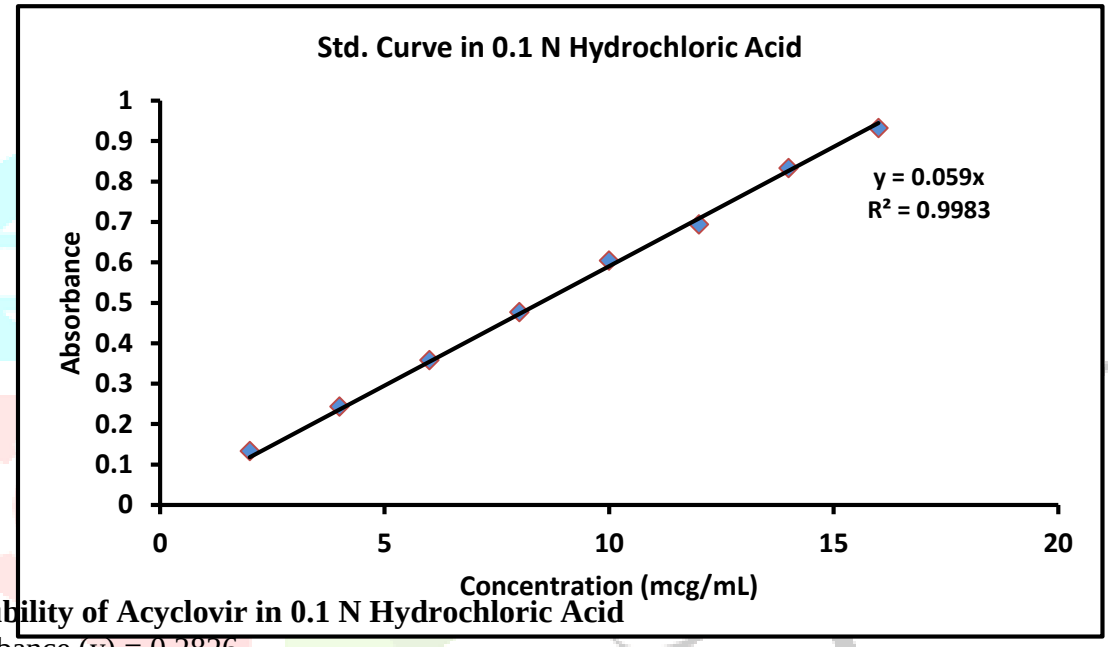
3.3 Preparation of Standard Curve of Acyclovir in 0.1 N HCl

The standard curve of Acyclovir was prepared in 0.1 N HCl. [Table 3 and Figure 3]

Table 3: Standard curve in 0.1 N HCl

Concentration (µg/mL)	Absorbance
2	0.1337
4	0.2439
6	0.3582
8	0.4772
10	0.6047
12	0.6942
14	0.8338
16	0.9321

Figure 3: Standard curve in 0.1 N HCl



3.4 Solubility of Acyclovir in 0.1 N Hydrochloric Acid

Absorbance (y) = 0.2826

Standard Curve Equation for 0.1 N Hydrochloric Acid is:

$y = 0.059\ x$

$0.2826 = 0.059\ x$

$x = 4.7898$ µg/mL.

Solubility of Acyclovir = x X Dilution factor

= 4.7898 X 4000

= 19.159 mg/mL.

3.5 3^2 Randomized Full Factorial Design

The prepared batch was evaluated for colour, consistency, pH, Floating lag time and floating time. [Table 4]

Table 4: Evaluation Parameters

Batch		pH	FLT	Floating Time	Colour	Consistency
F1	IA	7.98	13 sec	>12 hrs	White	Easily pourable
F2	IB	8.60	11 sec	>12 hrs	White	Easily pourable
F3	IC	8.69	08 sec	>12 hrs	White	Easily pourable
F4	IIA	8.18	15 sec	>12 hrs	White	Pourable
F5	IIB	8.23	12 sec	>12 hrs	White	Pourable
F6	IIC	8.67	10 sec	>12 hrs	White	Pourable
F7	IIIA	8.28	17 sec	>12 hrs	White	Difficult to pour
F8	IIIB	8.36	14 sec	>12 hrs	White	Difficult to pour
F9	IIIC	8.56	13 sec	>12 hrs	White	Difficult to pour

The Model F-value of 34.26 implies the model is significant. There is only a 0.05% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case, A and B are significant model terms. [Table 5]

Table 5: Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	828.88	2	414.44	34.26	0.0005	Significant
A-HPMC K100M	401.47	1	401.47	33.19	0.0012	
B-Sodium Bicarbonate	427.40	1	427.40	35.34	0.0010	
Residual	72.57	6	12.10			
Cor Total	901.45	8				

The "Pred R-Squared" of 0.8054 is in reasonable agreement with the "Adj R-Squared" of 0.8927; i.e. the difference is less than 0.2. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 16.554 indicates an adequate signal. This model can be used to navigate the design space. [Table 6 (a)]

Table 6: (a) Parameters of ANOVA

Std. Dev.	3.48	R-Squared	0.9195
Mean	72.91	Adj R-Squared	0.8927
C.V. %	4.77	Pred R-Squared	0.8054
PRESS	175.40	Adeq Precision	16.554
-2 Log Likelihood	44.33	BIC	50.92
		AICc	55.13

Final Equation in Terms of Coded Factors:

% Drug Release = +25.70556 - 16.36000 * A + 42.20000 * B

Final Equation in Terms of Actual Factors:

% Drug Release = +25.70556 - 16.36000 * HPMC K100M + 42.20000 * Sodium Bicarbonate

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. [Table 6 (b)]

Table 6: (b) Parameters of ANOVA

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	72.91	1	1.16	70.07	75.74	
A-HPMC K100M	-8.18	1	1.42	-11.65	-4.71	1.00
B-Sodium Bicarbonate	8.44	1	1.42	4.97	11.91	1.00

Here, the levels should be specified in the original units for each factor.

This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space. [Figure 4, 5 and 6]

Figure 4: Effect of factors on Response

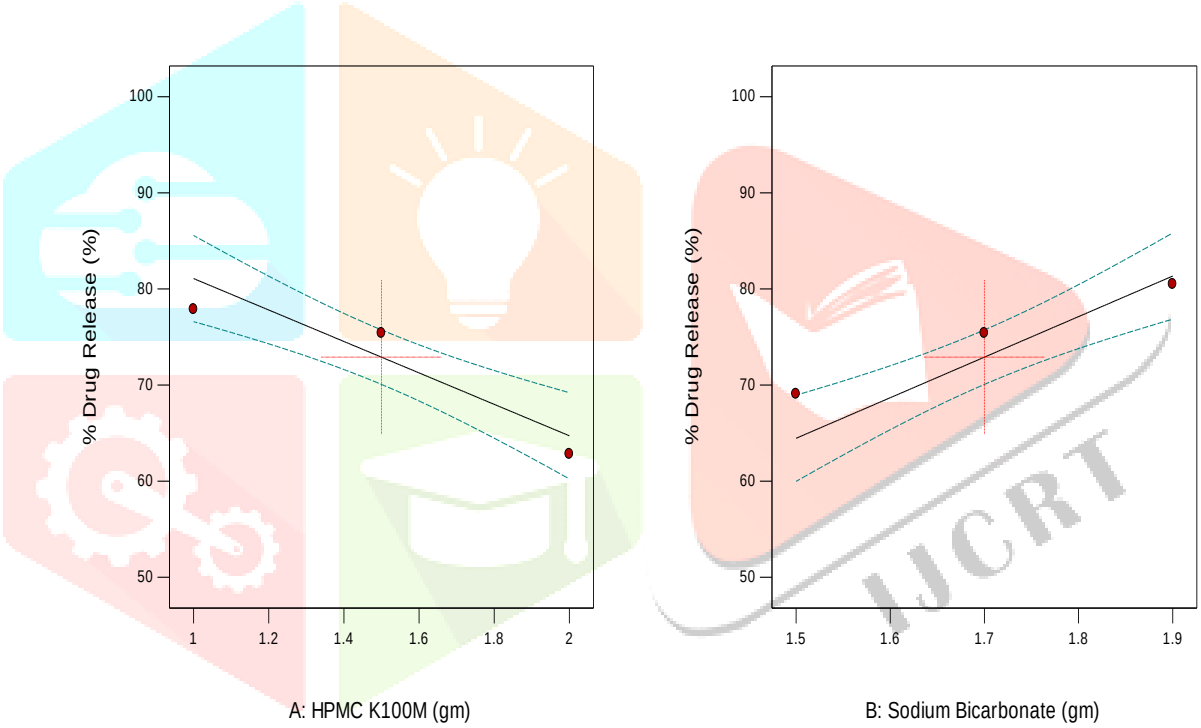


Figure 5: Interaction Plot

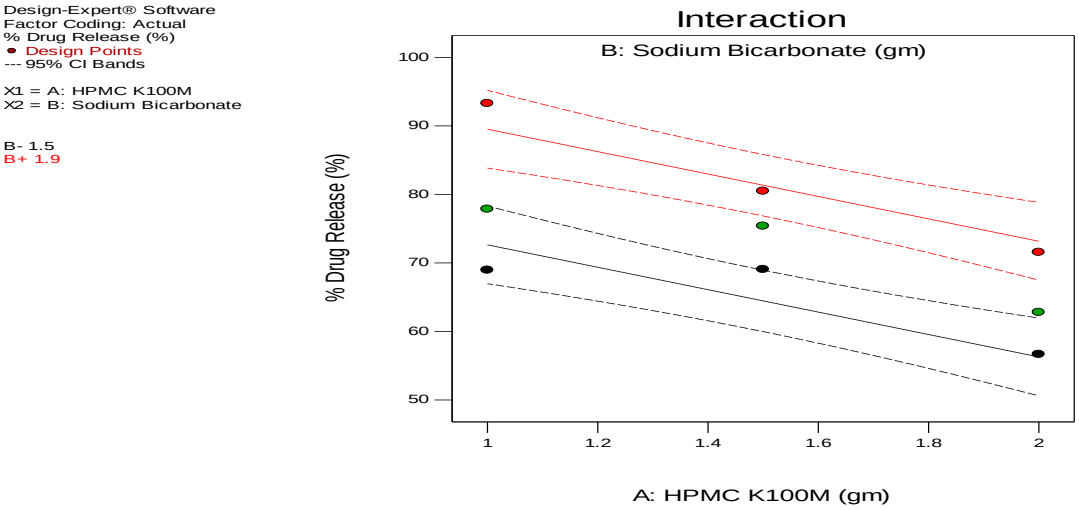
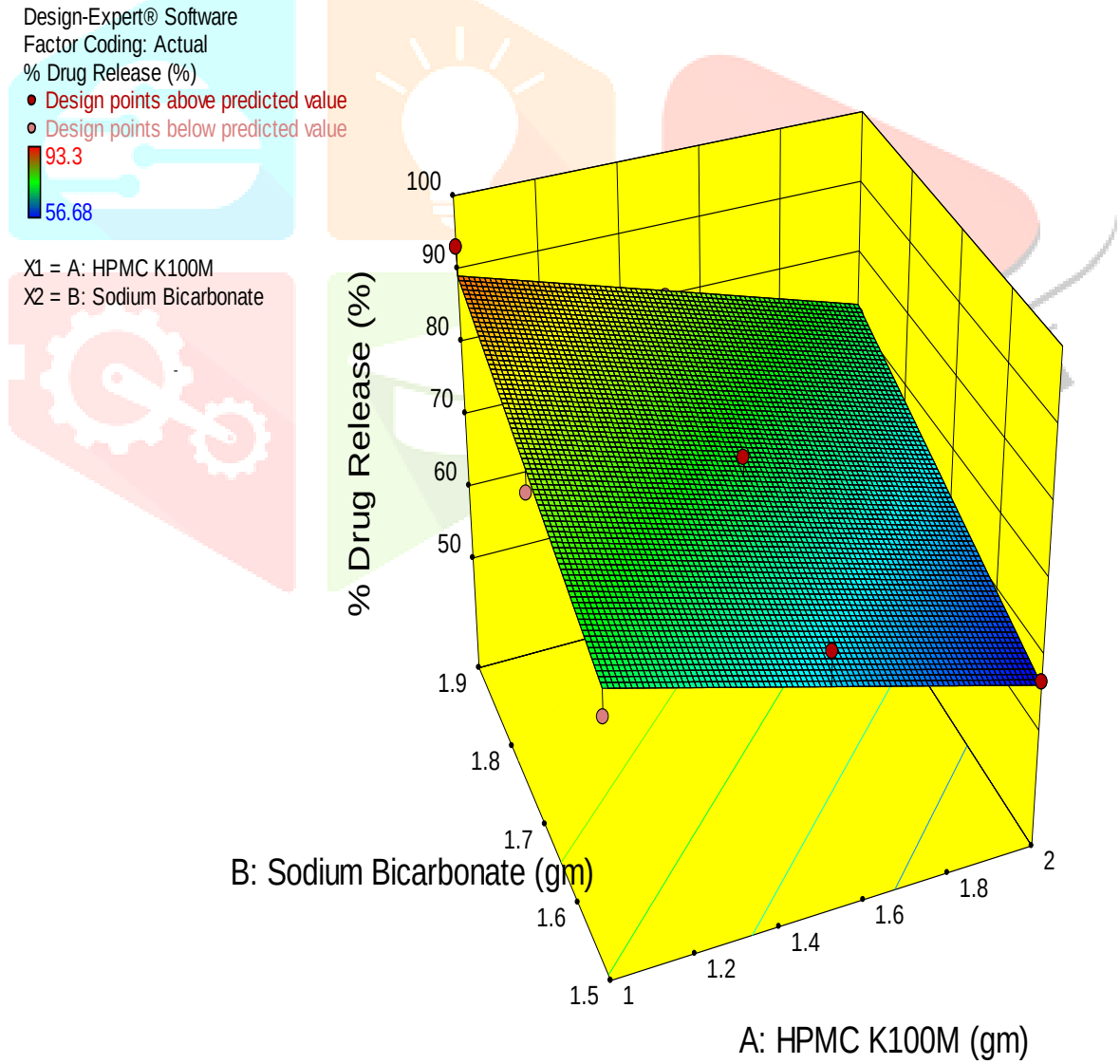


Figure 6: Factorial Plot



3.6 Drug Content

The % Drug Content of optimized batch was found to be 99.95 %.

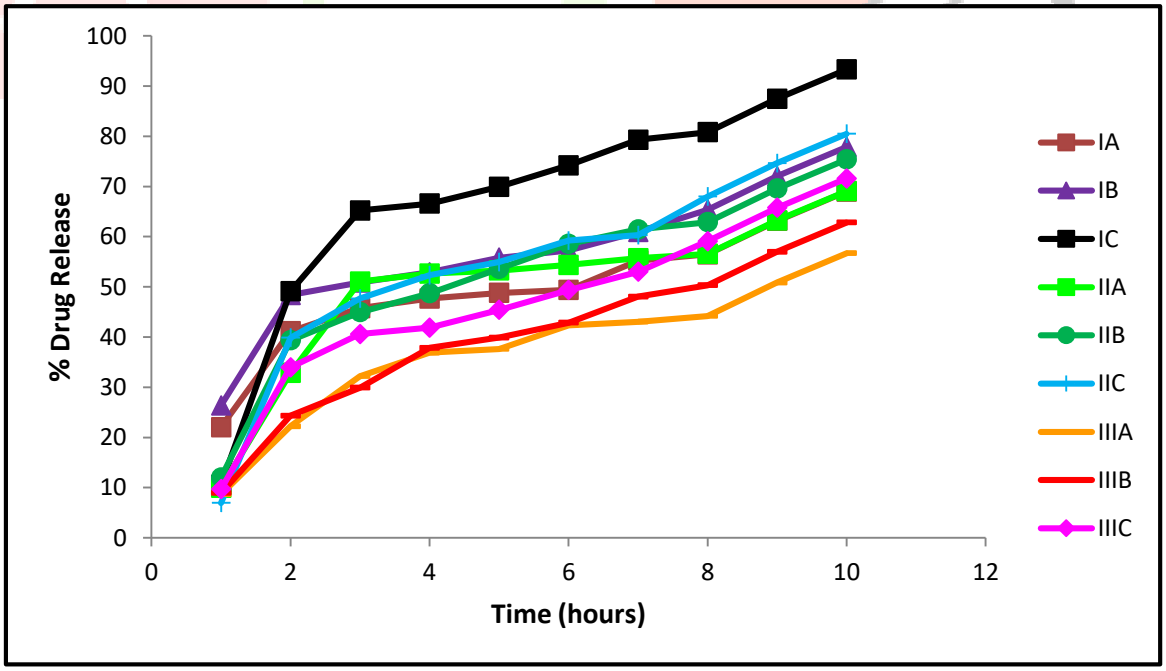
3.7 In Vitro Drug Release Study

It was observed from regression coefficient value that the optimized batch follows Higuchi release kinetics. [Table 7 and Figure 7]

Table 7: Factorial Design-CPR (Cumulative % Drug Release)

Time (hrs)	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
	IA	IB	IC	IIA	IIB	IIC	IIIA	IIIB	IIIC
0	22.03 ± 0.043	26.36 ± 0.029	10.55 ± 0.024	09.99 ± 0.051	12.01 ± 0.051	06.96 ± 0.043	08.67 ± 0.029	08.93 ± 0.036	09.70 ± 0.045
1	41.14 ± 0.059	48.37 ± 0.028	49.09 ± 0.022	32.83 ± 0.045	39.34 ± 0.028	39.85 ± 0.016	22.22 ± 0.037	24.34 ± 0.022	33.96 ± 0.022
2	45.77 ± 0.033	50.87 ± 0.029	65.22 ± 0.029	51.04 ± 0.073	44.97 ± 0.041	47.68 ± 0.045	32.21 ± 0.033	29.91 ± 0.051	40.59 ± 0.043
3	47.66 ± 0.022	52.91 ± 0.047	66.57 ± 0.037	52.63 ± 0.041	48.73 ± 0.022	52.33 ± 0.033	36.89 ± 0.037	37.84 ± 0.033	41.88 ± 0.033
4	48.78 ± 0.037	55.79 ± 0.036	69.92 ± 0.036	53.25 ± 0.033	53.60 ± 0.022	54.95 ± 0.028	37.63 ± 0.036	39.89 ± 0.051	45.41 ± 0.029
5	49.39 ± 0.051	57.22 ± 0.029	74.21 ± 0.033	54.38 ± 0.041	58.55 ± 0.022	59.22 ± 0.022	42.36 ± 0.028	42.87 ± 0.024	49.36 ± 0.022
6	55.23 ± 0.033	60.95 ± 0.033	79.30 ± 0.028	55.72 ± 0.045	61.46 ± 0.022	60.30 ± 0.036	43.03 ± 0.043	48.05 ± 0.033	52.99 ± 0.051
7	56.47 ± 0.045	65.37 ± 0.029	80.80 ± 0.043	56.57 ± 0.051	62.89 ± 0.036	67.99 ± 0.051	44.18 ± 0.037	50.31 ± 0.043	59.07 ± 0.037
8	63.14 ± 0.024	72.04 ± 0.029	87.47 ± 0.033	63.24 ± 0.036	69.56 ± 0.028	74.66 ± 0.036	50.85 ± 0.033	56.98 ± 0.050	65.74 ± 0.022
9	68.97 ± 0.029	77.87 ± 0.037	93.30 ± 0.042	69.07 ± 0.037	75.39 ± 0.029	80.49 ± 0.037	56.68 ± 0.037	62.81 ± 0.036	71.57 ± 0.016

Figure 7: Graphs of Time (hours) vs. Cumulative Percent Drug Release (%)



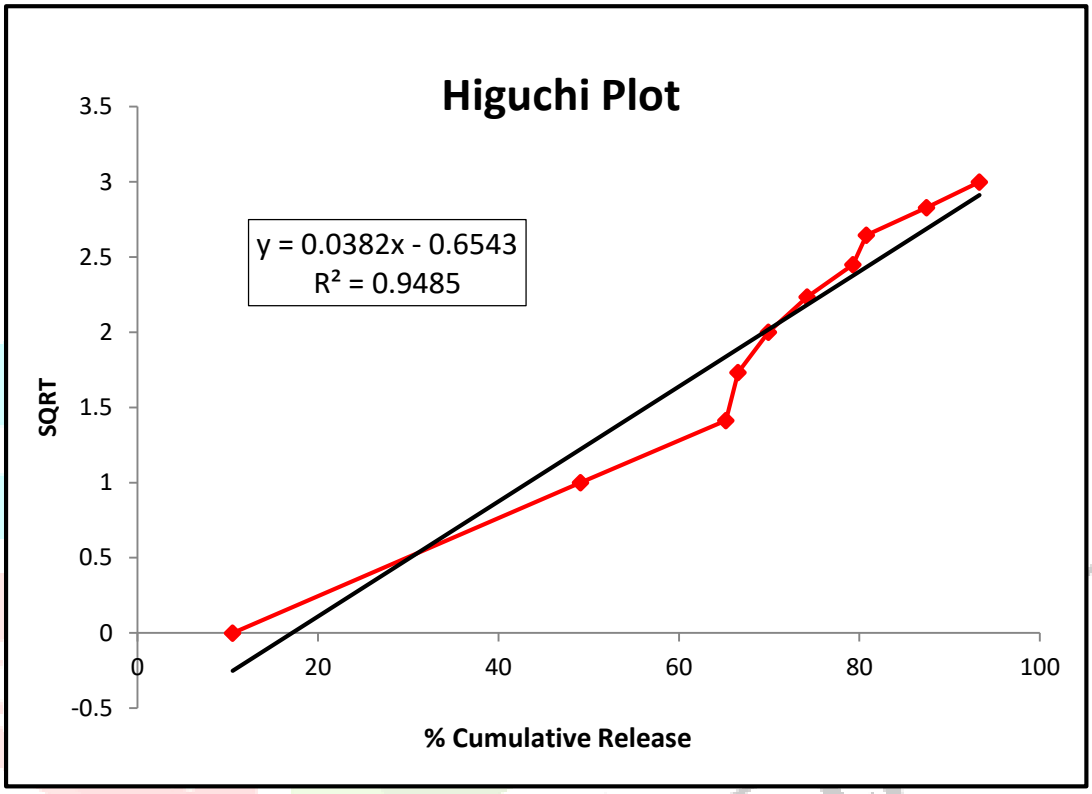
3.8 Kinetic Modeling of Drug Dissolution Profiles

The release profile of all the batches was fitted to zero order, first order, Higuchi, Korsemeyer - Peppas, and Hixson – Crowell model to ascertain the kinetic modeling of the drug release. The optimized batch was found to be following Higuchi model of drug dissolution. [Table 8 and Figure 8]

Table 8: Regression Coefficient Values of Optimized Batch

Model	Equation	Regression Coefficient (R^2)
Zero order	y = 6.871x + 36.72	0.776
First order	y = - 0.099x + 1.860	0.923
Higuchi	y = 0.038x – 0.654	0.948
Hixson-Crowell	y = - 0.174x + 1.442	0.613
Korsemeyer-Peppas	y = 0.971x – 1.172	0.578

Figure 8: Release Kinetics followed by Optimized Batch



3.9 Stability Study of Optimized Batch

The optimized formulation batch IC was evaluated for stability studies for the period of 2 months stored at 25±2°C/60±5% RH, 30±2°C/65±5% RH and 40±2°C/75±5% RH as per ICH guidelines, in environmental test chamber. The parameters studied were pH, FLT, floating time, colour, consistency, total drug content and in-vitro drug release. The optimized formulation batch IC was found stable at specified conditions for these parameters. [Table 9]

Table 9: Stability Studies Data

Sr. No.	Parameters	Initial	After 1 month			After 2 months		
			25±2° C/ 60±5% RH	30±2° C/ 65±5% RH	40±2° C/ 75±5% RH	25±2° C/ 60±5% RH	30±2° C/ 65±5% RH	40±2° C/ 75±5% RH
	pH	8.69	8.94	8.64	8.25	8.34	8.46	8.76
	FLT (sec)	08	11	10	15	12	13	17
	Floating Time	>12 hrs	>12 hrs	>12 hrs	>12 hrs	>12 hrs	>12 hrs	>12 hrs
	Colour	White	White	White	White	White	White	White
	Consistency	Easily pourable	Easily pourable	Easily pourable	Easily pourable	Easily pourable	Easily pourable	Easily pourable
	Total Drug Content (%)	99.95	99.75	99.67	98.43	98.92	98.68	97.78
	In-vitro Drug Release	93.30 ± 0.042	92.64 ± 0.087	92.79 ± 0.054	90.45 ± 0.078	91.75 ± 0.019	91.45 ± 0.085	88.94 ± 0.021

IV. DISCUSSION

The Acyclovir Floating In - Situ Gelling Suspension was successfully formulated under the thesis work entitling "FORMULATION AND EVALUATION OF GASTRORETENTIVE ACYCLOVIR FLOATING IN - SITU GELLING SUSPENSION". The prepared formulation showed good physicochemical characteristics and good cumulative % drug release profile. From stability studies it can be concluded that, the formulation was stable even after 2 months.

V. CONCLUSION

Acyclovir Floating In - Situ Gelling Suspension can be a good alternative for the conventional tablets and syrups to reduce dosing frequency and sustain effect. The formulation will thus improve patient compliance especially in pediatric and geriatric patients.

VI. ACKNOWLEDGMENT

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